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Dynamic Alterations in Neural Networks Supporting Aversive Learning in Children Exposed to Trauma: Neural Mechanisms Underlying Psychopathology

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ABSTRACT

Background: Altered aversive learning represents a potential mechanism through which childhood trauma (CT) might influence risk for psychopathology. This study examines the temporal dynamics of neural activation and patterns of functional connectivity during aversive learning in children with and without exposure to CT involving interpersonal violence, and evaluates whether these neural patterns mediate the association of CT with psychopathology in a longitudinal design.

Methods: 147 children (aged 8-16 years, 77 with CT) completed a fear conditioning procedure during an fMRI scan. Dynamic patterns of neural activation were examined, and functional connectivity was assessed with generalized psychophysiological interaction analyses. We evaluated whether the associations between CT and psychopathology symptoms at baseline and two-year follow-up were mediated by neural activation and connectivity during aversive learning.

Results: Children exposed to trauma displayed blunted patterns of neural activation over time to CS+>CS- in right amygdala. Additionally, trauma was associated with reduced functional connectivity of right amygdala with hippocampus, posterior parahippocampal gyrus, and posterior cingulate cortex and elevated connectivity with anterior cingulate cortex (ACC) to CS+>CS-. The longitudinal association between CT and later externalizing symptoms was mediated by blunted activation in right amygdala. Reduced amygdala-hippocampal connectivity mediated the association of CT with transdiagnostic anxiety symptoms, and elevated amygdala-ACC connectivity mediated the association of CT with generalized anxiety symptoms.

Conclusions: Childhood trauma is associated with poor threat-safety discrimination and altered functional coupling between salience and default mode network regions during aversive learning.

These altered dynamics may be key mechanisms linking CT with distinct forms of psychopathology.

INTRODUCTION

Childhood trauma (CT) is common, with more than half of U.S. children experiencing a traumatic event by the time they reach adulthood and approximately 20% experiencing serious forms of interpersonal violence(1,2). CT is associated with elevated risk for onset and persistence of multiple forms of psychopathology, including mood, anxiety, posttraumatic stress, and behavior disorders(3–5). Children exposed to trauma, defined here as interpersonal violence, encounter an early environment characterized by a high degree of threat. Chronic threat experienced during periods of enhanced brain plasticity early in life may fundamentally alter neural circuits that detect, interpret, and respond to aversive stimuli and other potential threats. As such, altered aversive learning represents a potential mechanism linking CT with psychopathology. Conceptual models argue that aversive learning is altered in children exposed to trauma(6) and that trauma-related psychopathology arises through changes in aversive learning(7,8), but surprisingly little research has investigated aversive learning as a mechanism linking CT to psychopathology(9).

Aversive learning is studied using fear conditioning paradigms, where a previously-neutral stimulus is associated with threat (CS+, threat cue) through repeated pairing with an aversive unconditioned stimulus (US), while another previously-neutral stimulus is never associated with the US and thereby signals safety (CS-, safety cue). The neural correlates of aversive learning have been extensively characterized in animals, adults, and more recently children and adolescents(10–13). Two primary neural networks are engaged during fear conditioning in humans: the salience network, subserving detection of motivationally salient stimuli, including threats, and the initiation of defensive responses; and the default mode network, which is associated with the inhibition of fear responses during fear conditioning(14).

Salience network regions—particularly right amygdala, anterior insula, and dorsal anterior cingulate cortex (ACC)—preferentially respond to conditioned threat cues, whereas default mode regions—particularly hippocampus and ventromedial prefrontal cortex (vmPFC)—preferentially respond to conditioned safety cues(14).

Animal studies have identified changes in neural function during fear conditioning following early-life adversity(15), but we are unaware of prior studies examining the neural correlates of fear conditioning in children exposed to trauma. However, one study investigated physiological responses during fear conditioning in children with trauma exposure. Trauma was associated with blunted skin conductance response (SCR) to the threat cue and reduced SCR discrimination between threat and safety cues(16). The rapid discrimination between threat and safety cues, followed by habituation to the threat cue observed in children without trauma was both delayed and attenuated in trauma-exposed children, indicating changes in the temporal dynamics of aversive learning following CT. This blunted threat-safety discrimination was associated concurrently with externalizing psychopathology (i.e., anger, aggression, and impulsive behaviors)(16).

Fear mechanisms have long served as models for processes underlying anxiety and stress-related disorders(17). In children, elevated physiological responses to both threat and safety cues during conditioning is associated with anxiety(18,19) and blunted response to threat cues and reduced threat-safety discrimination is associated with both posttraumatic stress disorder (PTSD)(16) and externalizing problems(16,20). The degree to which the neural mechanisms underlying aversive learning contribute to the emergence of psychopathology following CT is unknown.

The current study leverages a longitudinal design to investigate the neural correlates of aversive learning in children exposed to trauma by examining the temporal dynamics of neural activation and functional connectivity during fear conditioning. We expected that children exposed to trauma would exhibit patterns of activation and connectivity consistent with poor discrimination between threat and safety cues, and that these changes would mediate the longitudinal associations between CT and multiple forms of psychopathology, including anxiety, PTSD, and externalizing symptoms.

METHODS

Participants

A sample of 159 participants aged 8-16 years ($M=12.63$, $SD=2.68$) were recruited between January 2015 and June 2017. Recruitment efforts were targeted at schools, after-school and prevention programs, adoption programs, food banks, shelters, parenting programs, medical clinics, and the general community in Seattle, Washington. Inclusion criteria for the trauma group included exposure to physical or sexual abuse or direct witnessing of domestic violence (i.e., violence directed towards a caregiver). Children in the control group had no history of violence exposure and were matched to the trauma group on age, sex, and handedness. Exclusion criteria for both groups included $IQ < 80$, pervasive developmental disorder, psychosis, mania, substance abuse, safety concerns, and contraindications for MRI (e.g., braces). Participants completed a baseline assessment and returned approximately two years later for a follow-up assessment. Written informed consent in accordance with the University of Washington Institutional Review Board was obtained from legal guardians; children provided written assent. All cases of abuse not previously reported were referred to child protective services, as required by law.

Of the 159 participants with neuroimaging data, 12 were excluded due to failure to complete the task ($n=8$), technical issues ($n=2$), or excessive motion ($n=2$; see Supplementary Methods). The final analytic sample included 147 participants (77 trauma-exposed). See Table 1 for socio-demographic characteristics. A total of 121 of these participants (59 trauma-exposed) returned for follow-up assessments ($M=20.42$ months, $SD=6.97$ months, 82.3% retention rate).

Measures

Trauma Exposure. Trauma was assessed with a multi-informant, multi-method approach. Children were classified as experiencing physical or sexual abuse if abuse was endorsed by the child on the Childhood Experiences of Care and Abuse (CECA) interview(21), UCLA PTSD Reaction Index (PTSD-RI) trauma screen(22), or above the validated threshold on the Childhood Trauma Questionnaire(23); or reported by the caregiver on the Juvenile Victimization Questionnaire(24) or PTSD-RI trauma screen. Domestic violence was assessed by child-report on the CECA, PTSD-RI, and Violence Exposure Scale for Children-Revised(25). A total of 77 children were exposed to trauma, and 70 comprised the control group, never exposed to trauma.

Psychopathology. Depression symptoms were measured using the Children's Depression Inventory-2 (CDI)(26,27). Generalized anxiety disorder (GAD) and panic symptoms were assessed with the Screen for Child Anxiety Related Emotional Disorders (SCARED)(28). PTSD symptoms were assessed using both child- and caregiver-report on the PTSD-RI(29). Externalizing symptoms were assessed using child-report on the Youth Self-Report and caregiver-report on the Child Behavior Checklist(30). The highest score of the two reporters was used for PTSD and externalizing symptoms (see Supplementary Methods). All measures of psychopathology reflect dimensional symptom levels, rather than categorical diagnoses.

Fear Conditioning Task. Participants completed a fear conditioning paradigm assessing aversive associative learning previously validated for fMRI with children and adolescents (31) (see Supplementary Methods, Figure S1). The unconditioned stimulus (US) was an aversive grating sound, and the conditioned stimuli (CS) were counterbalanced colored shapes. Four block types were pseudo-randomly presented 4 times each: CS-, reinforced CS+ (CS+R) with an 80% US reinforcement rate, non-reinforced CS+ (CS+) in which the US did not occur and is included for use in analyses of response to the CS+ without the US confound, and baseline/inter-trial interval (ITI) consisting of a fixation cross during which participants were instructed to press a button to a single cue as an attention check.

Analyses

fMRI Whole-Brain Analysis. For neuroimaging acquisition and preprocessing details, see Supplementary Methods. fMRI data analysis was carried out using FEAT, version 6.00 in FSL (www.fmrib.ox.ac.uk/fsl). Regressors were created by convolving a boxcar function of phase duration with the standard double-gamma hemodynamic response function for each phase of the task and the attention check. A general linear model was constructed for each participant, including two contrasts of interest: CS+>CS- and CS->CS+. These contrasts include only CS+ trials that did not also include the US. Individual-level estimates of BOLD activity were submitted to group-level random effects models using FSL's FLAME1, and results are reported after cluster-level correction of $z > 2.3$, $p < .01$.

We examined contrasts of interest in whole-brain analyses averaged across all blocks of the task, and investigated differences in BOLD response for these contrasts as a function of trauma. Next, we conducted a parametrically-modulated analysis to examine dynamic changes in neural activation over time (i.e., learning), weighting the four blocks within each task phase to

model linearly decreasing or increasing neural response, and then repeated the models described above. Supplemental analyses examined CS+R>CS+ to investigate potential group differences in response to the US.

Region-of-Interest Analyses. To examine how dynamic neural response during fear conditioning varied as a function of trauma, we conducted regions-of-interest (ROI) analyses in R, version 3.5.1. We examined 3 ROIs each from the salience network (amygdala, insula, and dorsal ACC) and default mode network (hippocampus, posterior parahippocampal gyrus [PHG], and vmPFC) (Figure S2). Amygdala and hippocampus ROIs were lateralized due to evidence of differential activation during fear learning across hemispheres(32–35). Subcortical ROIs were defined anatomically based on the Harvard-Oxford Atlas (50% threshold), and cortical ROIs were defined based on anatomically-constrained meta-analytic results(14) (see Supplementary Methods). ROIs were warped into native space, and z-scores of activation in these regions for each stimulus (CS+, CS-) during each of the four blocks were extracted for each participant. Mixed effects models using the lme4 package in R were used to test whether trauma was associated with patterns of neural response to the stimuli across blocks, including a random intercept and random slope of activation across blocks in step-wise models; the best-fitting model was selected based on AIC(36). We conducted additional analyses to determine whether age, sex, puberty stage (assessed with the Tanner scale), or an interaction between trauma and these variables predicted the pattern of neural response.

Task-Based Functional Connectivity. We used generalized psychophysiological interaction (gPPI)(37) to examine functional connectivity of the right amygdala—the region where the binding of CS+ and US occurs(15)—with other regions during the task. We defined the right amygdala seed anatomically, from the Harvard-Oxford Atlas (50% threshold).

Individual-level analyses were modeled as before, with the addition of 3 regressors for the seed timeseries and the interactions of this timeseries with task regressors for CS+ and CS-. In this model, significant results represent task-dependent activity in voxels significantly correlated with right amygdala activity, over and above task-independent correlated activity. In other words, gPPI isolates which voxels are differentially functionally coupled with right amygdala during different phases of the task. We conducted whole-brain analyses in the whole group and as a function of trauma.

Mean z-scores of connectivity were extracted from ROIs demonstrating differential connectivity between groups for use in psychopathology analyses, defined anatomically for subcortical ROIs and based on anatomically-constrained meta-analytic results for cortical ROIs, as before (see Supplementary Methods). We also examined whether age, sex, puberty stage (assessed with the Tanner scale), or an interaction of these variables with trauma predicted connectivity.

Psychopathology. We determined whether patterns of neural activation and connectivity were associated with symptoms of depression, GAD, panic, PTSD, and externalizing at baseline and at two-year follow-up controlling for baseline symptom levels. Based on prior evidence of initially blunted threat-safety discrimination during learning and reduced habituation over time(16), we examined two neural activation metrics using regression models. We calculated the differential response to CS+>CS- in the first block as a measure of initial threat-safety discrimination in salience network regions. To examine changing activation over time, we fit a linear regression to each participant's data and used the linear beta values (slopes) as predictors (referred to as "learning slopes" hereafter; see Supplementary Methods). To examine

associations between functional connectivity and psychopathology, extracted connectivity z-scores were used as predictors in similar models.

Lastly, to test whether the relationship between trauma and psychopathology was mediated by measures of neural activation and connectivity during fear conditioning, nonparametric mediation models with 10,000 simulations were run using the mediation package in R for models where the *a* and *b* arms of the mediation were each $p < .10$ or less, a conservative approach to estimating the indirect effect and in line with modern approaches to mediation that do not require a significant direct effect, particularly for distal associations(38–40). Longitudinal mediation models controlled for baseline symptom levels.

All models were corrected for multiple comparisons using FDR-correction at the level of the hypothesis(41). All analyses examining trauma controlled for race/ethnicity and income-to-needs ratio, which differed among children with and without trauma exposure.

All data and code are posted at: <https://doi.org/10.17605/OSF.IO/R8BW9>.

RESULTS

Whole-Brain Task-Related Activation

In the entire sample, the CS+>CS- contrast elicited activation in amygdala, insula, and dorsal ACC. The CS->CS+ contrast elicited activation in dorsal and ventral visual streams, PHG, and hippocampus (Figure 1A, Table S1A). In the parametric modulation analysis, the contrast representing either linearly decreasing activation to CS+>CS- or linearly increasing activation to CS->CS+ across the four blocks revealed activation in amygdala, insula, dorsal ACC, hippocampus, PHG, vmPFC, and posterior cingulate cortex (PCC). Activation in dorsal visual stream was observed in the reverse contrast, representing linearly increasing activation to CS+>CS- or decreasing activation to CS->CS+ (Figure 1B, Table S1B).

Differences in Neural Activation as a Function of Childhood Trauma

There were no trauma-related differences for either contrast in the averaged or parametrically-modulated whole-brain analysis.

We next examined the planned ROIs. Mixed effect models revealed that trauma predicted dynamic fear response across blocks in right amygdala, as evidenced by a significant three-way interaction of stimulus x block x group, $F(1, 878)=6.95$, $p=.034$ (Figure 2). A similar pattern was observed in right hippocampus, but did not survive correction for multiple comparisons (Figure S3). Age, sex, and puberty stage were unrelated to amygdala responses, either directly or in interaction with trauma exposure.

To examine group differences in response to the US, we examined $CS+R>CS+$. No significant group differences were observed in whole-brain or ROI analyses of left and right amygdala (Figure S4).

Functional Connectivity

Using gPPI analyses, we observed functional coupling of right amygdala with cerebellum in the whole group (Table S1C) and multiple differences in connectivity of right amygdala to $CS+>CS-$ as a function of trauma (Table S2A). Trauma was associated with reduced connectivity of right amygdala with bilateral hippocampus, PHG, and PCC. This was driven by lower amygdala connectivity with these regions in children exposed to trauma specifically during the $CS+$ (Figure 3A, Figure S5A). Trauma was also associated with elevated connectivity of right amygdala with dorsal ACC and fronto-parietal regions (Figure 3B, Figure S5B).

Age and puberty stage were unrelated to connectivity, and there were no interactions of trauma with age or puberty. However, a trauma x sex interaction predicted connectivity of amygdala with hippocampus ($b=.33$, $p=.030$) and PHG ($b=.63$, $p=.010$) (Figure S6A). Trauma

was associated with reduced connectivity regardless of sex; in controls, females had lower connectivity than males. Trauma also interacted with sex in predicting amygdala-ACC connectivity ($b=.47$, $p=.030$), such that connectivity was elevated specifically among trauma-exposed females (Figure S6B).

Neural Responses During Aversive Learning and Psychopathology

Trauma was associated with higher baseline depression ($b=.73$, $p<.001$), panic ($b=.61$, $p=.003$), PTSD ($b=2.36$, $p<.001$), and externalizing ($b=.24$, $p<.001$) symptoms and greater increases across the longitudinal follow-up in PTSD and externalizing symptoms, although these longitudinal findings did not survive correction.

Initial threat-safety discrimination and learning slopes predicted symptoms longitudinally while controlling for baseline levels, corrected for multiple comparisons. Blunted initial threat-safety discrimination in insula was associated with greater increases in PTSD symptoms ($b=-.29$, $p=.047$). Blunted learning slopes (i.e., reduced habituation) to CS+>CS- in right amygdala were associated with greater increases in externalizing symptoms over the two-year follow-up ($b=.07$, $p=.011$).

In contrast, functional connectivity to CS+>CS- was associated with psychopathology only at baseline. Reduced right amygdala-hippocampus connectivity was associated with higher depression ($b=-.45$, $p=.004$), GAD ($b=-.43$, $p=.015$), panic ($b=-.51$, $p=.004$), PTSD ($b=-.62$, $p=.017$), and externalizing ($b=-3.86$, $p=.015$) symptoms. Elevated right amygdala-ACC connectivity was associated with higher depression ($b=.26$, $p=.028$), GAD ($b=.32$, $p=.028$), and panic ($b=.35$, $p=.016$) symptoms.

Neural Mediators Linking Childhood Trauma and Psychopathology

Critically, the association of trauma with externalizing symptoms at two-year follow-up was mediated by blunted habituation in right amygdala (indirect effect=1.31, 95% CI .34-2.72), controlling for baseline symptoms (Figure 4A). The association of trauma with GAD (indirect effect=.70, 95% CI .06-1.49) and panic symptoms (indirect effect=.77, 95% CI .24-1.56) at baseline was mediated by reduced connectivity of right amygdala with bilateral hippocampus (Figure 4B). Lastly, the association of trauma with GAD symptoms at baseline was mediated by elevated right amygdala connectivity with bilateral dorsal ACC (indirect effect=.42, 95% CI .05-1.07) (Figure 4C).

DISCUSSION

Childhood trauma (CT) is associated with altered dynamic patterns of neural activation and connectivity during aversive learning in children. Children exposed to trauma exhibited reduced discrimination between threat and safety cues and blunted learning slopes to the threat vs. safety cue (i.e., blunted habituation) in right amygdala. Children exposed to trauma also showed reduced functional connectivity between regions of the salience and default mode networks and elevated functional connectivity within regions of the salience network during aversive learning. Blunted right amygdala habituation mediated the longitudinal association between trauma and externalizing symptoms. Reduced functional connectivity of right amygdala with hippocampus mediated the association between trauma and transdiagnostic anxiety symptoms, and elevated connectivity of right amygdala and dorsal ACC mediated the association between trauma and GAD symptoms. These findings demonstrate that alterations in neural activation versus connectivity may constitute different mechanisms associated with distinct forms of psychopathology.

The right amygdala is a key region within the salience network that exhibited strong activation to the threat cue early in learning, followed by habituation over time. The amygdala plays an essential role during fear conditioning, binding the US with the CS+, though there are inconsistencies in reported findings(14) which may be related to methodological choices that disregard temporal aspects of learning. Children with trauma exhibited two key differences in the observed dynamic pattern of neural activation: 1) blunted initial threat-safety discrimination; and 2) blunted learning slopes over time, which together indicate a reduced degree of learned differentiation between threatening vs. safe stimuli. These results replicate and extend previous work on the temporal dynamics of learning following CT using physiological indicators of learning, finding reduced differential SCR to the threat versus safety cue and attenuated habituation across learning(16). We find a similar pattern in the brain region most centrally involved in aversive learning, suggesting that an alteration in the capacity of the amygdala to predict threat following trauma may contribute to this pattern of response in the sympathetic nervous system.

The precise nature of environmental experiences that produce these patterns of neural activation is incompletely characterized. Acute exposure to violence may at first evoke elevated neural and sympathetic nervous system responses to potential threat cues. For example, a recent study induced acute threat exposure using violent images prior to fear conditioning, and found elevated SCR to the CS+ following this manipulation(42). In contrast, exposure to CT is often chronic and unpredictable (i.e., with low contingency between threat and environmental cues that predict that threat). Repeated experiences of unpredictable threat may contribute to the neural patterns observed here through several pathways. First, children exposed to trauma may begin to perceive the US itself as less threatening and salient over time. If this were true, we would

observe blunted response to the US in the trauma group. We do not find evidence for this pattern in our data (Figure S4). Second, exposure to chronic, unpredictable threat may decrease neural sensitivity to associative links between specific environmental cues and threat. This could arise through attentional mechanisms, such as attentional narrowing to the threat itself (i.e., the US), and decreased attention to environmental cues temporally prior to the threat (i.e., the CS+). Attentional narrowing to threat has been repeatedly observed in children exposed to trauma(43,44). While these patterns may be adaptive in the short term, decreased ability to discriminate cues that predict threat versus safety may have maladaptive long-term consequences. Adverse childhood experiences involve numerous experiences beyond those involving interpersonal violence (e.g., emotional abuse, neglect)(45). These observed neural patterns may be specific to children who have experienced threatening early environments; previous work does not find blunted threat-safety discrimination in previously-institutionalized children(31) and indicates that threat-related adversity but not deprivation is associated with physiological measures of aversive learning(46).

A reduced capacity of the amygdala to rapidly and robustly activate uniquely to the threat cue may contribute to a cascade of blunted learning across the brain, especially during this developmental period, where aversive learning is characterized by increased reliance on subcortical structures(11). Indeed, in trauma-exposed children we found reduced functional connectivity of right amygdala with multiple default mode regions, including hippocampus, PHG and PCC during CS+>CS-. These regions are all centrally involved in context processing(47,48). Failure to encode the specific context in which a cue is paired with an aversive outcome is associated with a decreased ability to disambiguate cues and therefore modulate responses to threat based on context(47,49). In line with this, CT is associated with reduced hippocampal

volume, reduced hippocampal activation to aversive cues, and poor memory for contexts paired with aversive cues(43). Reduced functional coupling of these regions with right amygdala during aversive learning may reflect reduced capacity to integrate contextual information with the presence of a threat cue, contributing to poor learning over time. Trauma was also associated with elevated functional connectivity of right amygdala with dorsal ACC—a key salience network region associated with fear expression(50) and more broadly with the evaluation of the expected value of exerting control(51)—and fronto-parietal regions associated with attentional direction and initiation of defensive responses during CS+>CS-. These findings arose from reduced modulation of amygdala functional coupling across different phases of the task in children exposed to trauma, who instead displayed similar degrees of amygdala functional connectivity with these regions regardless of task phase. This could reflect similar calculations of expected value of behavioral responses to threat without specific contextual predictions of when threat occurs, contributing to overgeneralized hypervigilance not modulated by context.

Critically, these patterns of neural activation and connectivity may be key mechanisms linking CT with distinct forms of psychopathology. Blunted right amygdala habituation mediated the longitudinal association between trauma and elevations in externalizing symptoms two years later, controlling for baseline symptoms, building on previous research highlighting blunted SCR to the threat cue during fear conditioning as a mechanism linking CT with externalizing problems(16). It is possible that poor threat-safety discrimination may contribute to self-protective, reactive aggression in the face of ambiguity. Meanwhile, blunted connectivity of right amygdala with hippocampus and other default mode regions involved in context-processing mediated the association between trauma and transdiagnostic anxiety symptoms, and elevated connectivity of right amygdala with ACC mediated to association between trauma and GAD

symptoms. A reduced capacity to integrate contextual information with threat and thereby evaluate appropriate responses may contribute to overgeneralized threat responses and hypervigilance, concepts closely related to anxiety, although greater research is needed. Females may be particularly susceptible to these changes in connectivity, which may contribute to sex differences in anxiety(52). These findings suggest that these neural alterations during aversive learning represent mechanisms linking CT with psychopathology. Many of our most successful behavioral interventions target learning processes(53), but are implemented after the development of psychopathology. Leveraging early interventions by targeting these learning processes after CT exposure with the goal of preventing or minimizing psychopathology is a promising possibility that merits investigation, as remarkably little work has been done in this area(9).

There are several limitations to the current research. We were unable to examine associations with timing or duration of trauma due to substantial missing data on age of first exposure. The fear conditioning paradigm utilized a block design and concurrent physiological measures and behavioral ratings were not obtained, precluding the possibility of trial-by-trial analyses and investigations of whether neural changes parallel changes in physiology and behavior. The CSs were colored shapes, which lack ecological validity, although they are commonly used in fear conditioning studies(31). The US was an aversive loud sound, which is a less potent US than electric shock. However, loud sounds evoke aversive learning, and avoid ethical concerns of using shock with children(54). Strengths of this study include a large, well-characterized sample of children exposed to trauma, longitudinal design, multimodal approach, and attention to the temporal aspects of learning.

We document altered patterns of neural activation and connectivity during aversive learning in children exposed to trauma. Trauma is associated with neural activation patterns indicating poor discrimination between threat and safety cues and with connectivity patterns suggesting poorer integration of contextual information that could serve to disambiguate these cues. These altered activation and connectivity patterns represent potential mechanisms linking trauma with distinct forms of psychopathology, and could be used to inform early interventions.

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TABLES

Table 1. Socio-demographic characteristics of the sample

	Control (n=70)		Trauma (n=77)		χ^2	p
	Percent	N	Percent	N		
Female	47.1%	33	51.9%	40	.17	.68
Race/ethnicity					42.39	<.001
White	67.1%	47	23.4%	18		
Black	5.7%	4	40.3%	31		
Hispanic/Latino	7.1%	5	11.7%	9		
Asian	15.7%	11	7.8%	6		
Other/multiracial	4.3%	3	16.9%	13		
	Control (n=70)		Trauma (n=77)		t	p
	Mean	SD	Mean	SD		
Age (years)	12.50	2.58	12.80	2.73	-.67	.50
Income-to-needs ratio	5.56	2.09	2.26	2.26	9.20	<.001
Depression	5.60	4.38	11.87	8.74	-5.57	<.001
Generalized anxiety	3.83	3.58	6.29	5.07	-3.40	<.001
Panic	3.13	3.39	6.36	5.55	-4.26	<.001
PTSD	2.69	5.17	29.30	15.68	-14.07	<.001
Externalizing	49.09	7.16	62.01	8.11	-10.26	<.001

Continuous variables were analyzed with independent t-tests and categorical variables were analyzed with chi-squared tests.

Figure 1. Activation maps for whole-brain analyses in the whole group

Whole-brain maps in the whole group (n=147) for the CS+>CS- and CS->CS+ contrasts averaged over the entire task (A) and parametrically modulated to model increasing and decreasing patterns of activation across blocks (B). Slice selection clockwise from top left: in A, y=4, x=4, x=30, x=22; in B, y=0, x=3, x=34, x=18.

Figure 2. Childhood trauma is associated with blunted dynamic neural activation patterns during aversive learning

ROI analyses depicting significantly different patterns of response over time between the control and trauma groups in right amygdala. Responses to the CS+ (red) and CS- (blue) during each block are shown in A, and the differential responses for each block are shown in B to better visualize the learning slope over time. Learning slopes are plotted for CS+ minus CS- because the amygdala is typically activated to CS+>CS-. The trauma group displays a blunted learning slope, as evidenced by a significant stimulus x block x group interaction ($X^2(1, N=147)=7.93, p=.034$), corrected for multiple comparisons.

Figure 3. Childhood trauma is associated with altered functional connectivity of right amygdala during aversive learning

During CS+>CS-, the trauma group compared to the control group showed reduced connectivity of right amygdala with bilateral hippocampus, parahippocampal gyrus (PHG), and posterior cingulate cortex (PCC), shown in A. The trauma group showed elevated connectivity between right amygdala and bilateral anterior cingulate cortex (ACC) compared to the control group, shown in B. See Figure S5 in the online supplement for evidence demonstrating that the group differences visualized by the interaction depicted in A arise from blunted strength of functional connectivity between right amygdala and these regions during the CS+ in the trauma group compared to the control group, while the magnitude of functional connectivity during the CS- is comparable between groups; findings depicted in B result from similar magnitude of functional connectivity of right amygdala with ACC regardless of the task phase in the trauma group, while the control group exhibits task-dependent functional coupling. Slice selection clockwise from top left: in A, y=-26, x=21, x=3; in B, x=10.

Figure 4. Altered patterns of neural activation and connectivity during aversive learning mediate the associations between childhood trauma and distinct forms of psychopathology

In A, the association between childhood trauma and externalizing symptoms at two-year follow-up was mediated by blunted right amygdala habituation slopes, controlling for baseline symptoms (indirect effect=1.31, 95% CI .34-2.72). In B, the association between childhood trauma and generalized anxiety and panic at baseline were both mediated by reduced right amygdala-bilateral hippocampus connectivity (indirect effect=.70, 95% CI .06-1.49 and indirect effect=.77, 95% CI .24-1.56, respectively). Generalized anxiety mediation statistics are reported with subscript 1, and panic mediation statistics are reported with subscript 2. In C, the pathway between childhood trauma and generalized anxiety was mediated by elevated amygdala-bilateral anterior cingulate cortex connectivity (indirect effect=.42, 95% CI .05-1.07). ACC, anterior cingulate cortex; T2, two-year follow-up; ***, $p < .001$; **, $p < .01$; *, $p < .05$.