

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: A total of 147 children (aged 8–16 years, 77 with CT) completed a fear conditioning procedure during a functional magnetic resonance imaging 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 2-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 the conditioned threat versus safety stimuli (CS+>CS−) in the right amygdala. In addition, trauma was associated with reduced functional connectivity of right amygdala with the hippocampus, posterior parahippocampal gyrus, and posterior cingulate cortex and with elevated connectivity with the anterior cingulate cortex to CS+>CS−. The longitudinal association between CT and later externalizing symptoms was mediated by blunted activation in the right amygdala. Reduced amygdala-hippocampal connectivity mediated the association of CT with transdiagnostic anxiety symptoms, and elevated amygdala–anterior cingulate cortex connectivity mediated the association of CT with generalized anxiety symptoms.

CONCLUSIONS: CT 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.

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Childhood trauma (CT) is common, with more than half of children in the United States 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 an elevated risk for onset and persistence of multiple forms of psychopathology, including mood, anxiety, posttraumatic stress, and behavioral 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 with conditioned stimuli (CS), where a previously neutral stimulus is associated with threat (CS+, threat cue) by 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). Saliency network regions—particularly the right amygdala, anterior insula, and dorsal anterior cingulate cortex (ACC)—preferentially respond to conditioned threat cues, whereas default mode regions—particularly the hippocampus and ventromedial prefrontal cortex—preferentially respond to conditioned safety cues (14).

Animal studies have identified changes in neural function during fear conditioning after early-life adversity (15), but we are unaware of previous 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 after 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 are associated with anxiety (18,19), and blunted response to threat cues and reduced threat-safety discrimination are associated with both post-traumatic 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 after CT is unknown.

This 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 AND MATERIALS

Participants

A sample of 159 participants aged 8 to 16 years (mean = 12.63, SD = 2.68) was 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 toward 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 magnetic resonance imaging (MRI) (e.g., braces). Participants completed a baseline assessment and returned approximately 2 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 owing to failure to complete the task ($n = 8$), technical issues ($n = 2$), or excessive motion ($n = 2$) (see [Supplemental Methods](#)). The final analytic sample included 147 participants (77 trauma-exposed). See [Table 1](#) for sociodemographic characteristics. A total of 121 of these participants (59 trauma-exposed) returned for follow-up assessments (mean = 20.42 mo, SD = 6.97 mo, 82.3% retention rate).

Measures

Trauma Exposure. Trauma was assessed with a multi-informant, multimethod 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 interview (21), UCLA PTSD Reaction Index (PTSD-RI) trauma screen (22), or was 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 Childhood Experiences of Care and Abuse, 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 (26,27). Generalized anxiety disorder (GAD) and panic symptoms were assessed using the Screen for Child Anxiety Related Emotional Disorders (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 2 reporters was used for PTSD and externalizing symptoms (see [Supplemental 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 functional MRI with children and adolescents (31) (see [Supplemental Methods](#), [Figure S1](#)). The US was an aversive grating sound, and the CS were counterbalanced colored shapes. Four block types were pseudorandomly presented 4 times each: CS−, reinforced CS+ (CS+R) with an 80% US reinforcement rate, nonreinforced CS+ (CS+) in which the US did not occur and was included for use in analyses of response to the

Table 1. Sociodemographic Characteristics of the Sample

Characteristics	Control (<i>n</i> = 70)		Trauma (<i>n</i> = 77)		χ^2	<i>p</i>
	Percent	<i>n</i>	Percent	<i>n</i>		
Sex, Female	47.1%	33	51.9%	40	0.17	.68
Race/Ethnicity					42.39	<.001
Asian	15.7%	11	7.8%	6		
Black	5.7%	4	40.3%	31		
Hispanic/Latino	7.1%	5	11.7%	9		
Other/Multiracial	4.3%	3	16.9%	13		
White	67.1%	47	23.4%	18		
	Mean	SD	Mean	SD	<i>t</i>	<i>p</i>
Age, Years	12.50	2.58	12.80	2.73	−0.67	.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 χ^2 tests. PTSD, posttraumatic stress disorder.

CS+ without the US confound, and baseline/intertrial interval consisting of a fixation cross during which participants were instructed to press a button to a single cue as an attention check.

Analyses

Functional MRI Whole-Brain Analysis. For neuroimaging acquisition and preprocessing details, see [Supplemental Methods](#). Functional MRI data analysis was carried out using FEAT version 6.00 in FSL (<http://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 blood oxygen level-dependent activity were submitted to group-level random effects models using FSL's FLAME 1, 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 blood oxygen level-dependent 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 region of interest (ROI) analyses in R, version 3.5.1. We examined three ROIs each from the salience network (the amygdala, insula, and dorsal ACC) and default mode network (the hippocampus, posterior parahippocampal gyrus [PHG], and ventromedial prefrontal cortex) ([Figure S2](#)). Amygdala and hippocampus ROIs were lateralized owing 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 [Supplemental 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 stepwise models; the best-fitting model was selected based on Akaike information criterion (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 (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 three regressors for the seed time series and the interactions of this time series 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, generalized psychophysiological interaction isolates which voxels are differentially functionally coupled with the 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 [Supplemental 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 2-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 [Supplemental Methods](#)). To examine associations between functional connectivity and psychopathology, extracted connectivity z scores were used as predictors in similar models.

Finally, 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 false discovery rate 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 here: <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 the amygdala, insula, and dorsal ACC. The $CS- > CS+$ contrast elicited activation in the 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 the amygdala, insula, dorsal ACC, hippocampus, PHG, ventromedial prefrontal cortex, and posterior cingulate cortex. 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 CT

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 the right amygdala, as evidenced by a significant three-way interaction of stimulus $\times$ block $\times$ group ($F_{1,878} = 6.95, p = .034$) ([Figure 2](#)). A similar pattern was observed in the right hippocampus, but did not survive correction for multiple

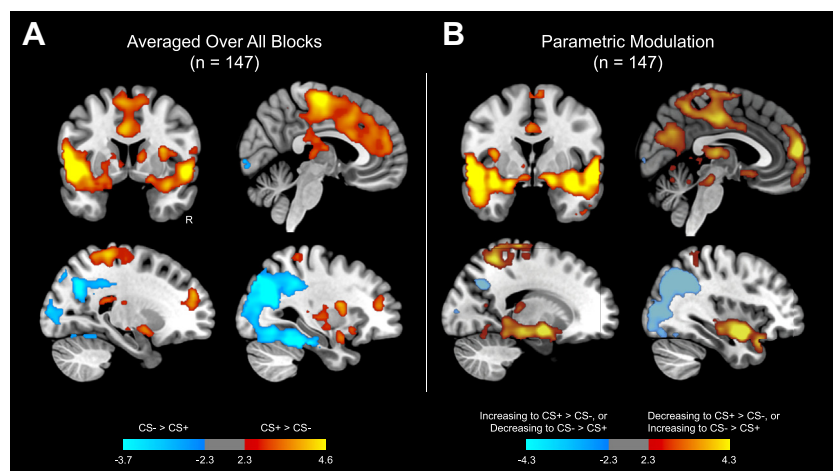


Figure 1. Activation maps for whole-brain analyses in the whole group. Whole-brain maps in the whole group ($n = 147$) for the $CS+ > CS-$ and $CS- > CS+$ contrasts averaged over the entire task (**A**) and parametrically modulated to model increasing and decreasing patterns of activation across blocks (**B**). Slice selection clockwise from top left: in panel (**A**), $y = 4, x = 4, x = 30, x = 22$; in panel (**B**), $y = 0, x = 3, x = 34, x = 18$. R, right.

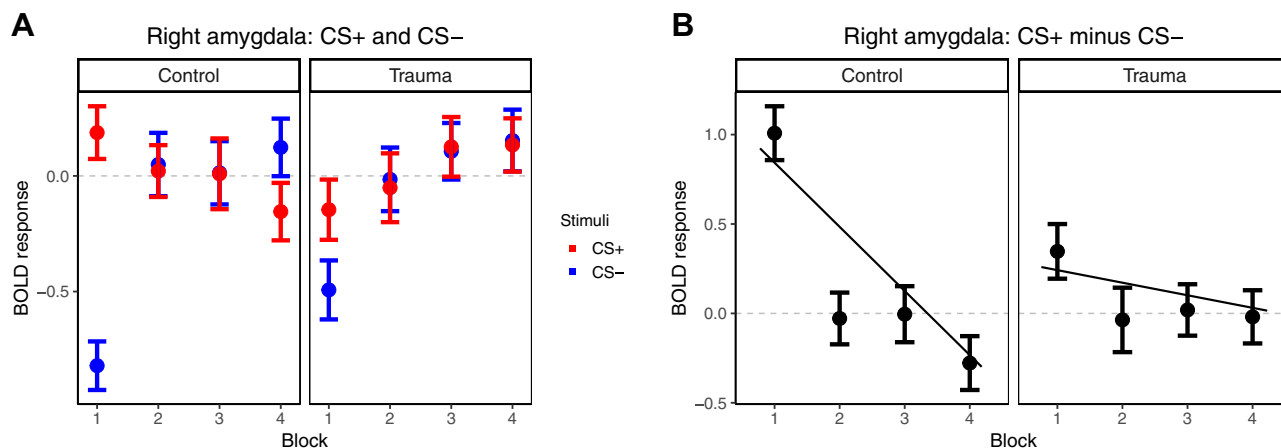


Figure 2. Childhood trauma is associated with blunted dynamic neural activation patterns during aversive learning. Region of interest analyses depicting significantly different patterns of response over time between the control and trauma groups in the right amygdala. Responses to the CS+ (red) and CS- (blue) during each block are shown in panel (A), and the differential responses for each block are shown in panel (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 $\times$ block $\times$ group interaction ($F_{1,878} = 6.95$, $p = .034$) corrected for multiple comparisons. BOLD, blood oxygen level-dependent; CS, conditioned stimuli.

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 generalized psychophysiological interaction analyses, we observed functional coupling of the right amygdala with the cerebellum in the whole group (Table S1C) and multiple differences in connectivity of the right amygdala to CS+ > CS- as a function of trauma (Table S2A). Trauma was associated

with reduced connectivity of the right amygdala with bilateral hippocampus, PHG, and posterior cingulate cortex. This was driven by lower amygdala connectivity with these regions in children exposed to trauma specifically during the CS+ (Figure 3A and Figure S5A). Trauma was also associated with elevated connectivity of the right amygdala with dorsal ACC and frontoparietal regions (Figure 3B and Figure S5B).

Age and puberty stage were unrelated to connectivity, and there were no interactions of trauma with age or puberty. However, a trauma $\times$ sex interaction predicted connectivity of the amygdala with the hippocampus ($b = 0.33$, $p = .030$) and PHG ($b = 0.63$, $p = .010$) (Figure S6A). Trauma was associated with reduced connectivity regardless of sex; in control subjects, females had lower connectivity than males. Trauma also

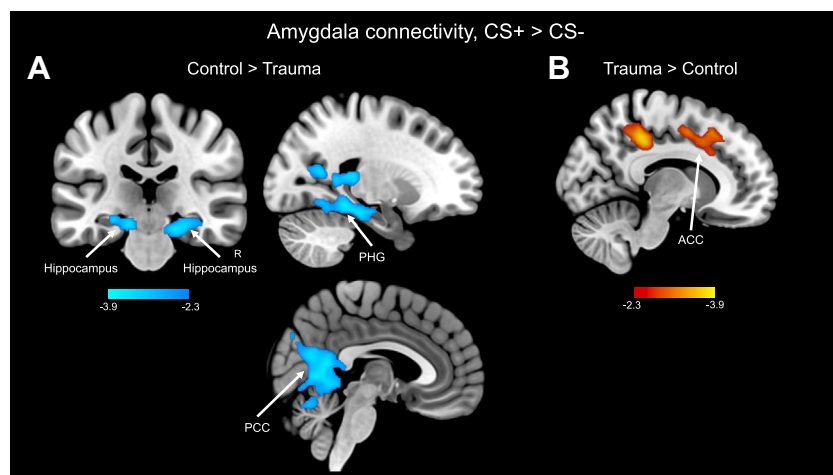


Figure 3. Childhood trauma is associated with altered functional connectivity of the right amygdala during aversive learning. During CS+ > CS-, the trauma group compared with the control group showed reduced connectivity of the right amygdala with the bilateral hippocampus, parahippocampal gyrus (PHG), and posterior cingulate cortex (PCC), shown in panel (A). The trauma group showed elevated connectivity between the right amygdala and bilateral anterior cingulate cortex (ACC) compared with the control group, shown in panel (B). See Figure S5 for evidence demonstrating that the group differences visualized by the interaction depicted in panel (A) arise from blunted strength of functional connectivity between the right amygdala and these regions during the CS+ in the trauma group compared with the control group, while the magnitude of functional connectivity during the CS- is comparable between groups; findings depicted in panel (B) result from similar magnitude of functional connectivity of the right amygdala with the 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 panel (A), $y = -26$, $x = 21$, $z = 3$; in panel (B), $x = 10$. CS, conditioned stimuli; R, right.

interacted with sex in predicting amygdala-ACC connectivity ($b = 0.47, p = .030$), 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 ($b = 0.73, p < .001$), panic ($b = 0.61, p = .003$), PTSD ($b = 2.36, p < .001$), and externalizing ($b = 0.24, p < .001$) 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 the insula was associated with greater increases in PTSD symptoms ($b = -0.29, p = .047$). Blunted learning slopes (i.e., reduced habituation) to $CS+ > CS-$ in the right amygdala were associated with greater increases in externalizing symptoms over the 2-year follow-up ($b = 0.07, p = .011$).

In contrast, functional connectivity to $CS+ > CS-$ was associated with psychopathology only at baseline. Reduced right amygdala-hippocampus connectivity was associated with higher depression ($b = -0.45, p = .004$), GAD ($b = -0.43,$

$p = .015$), panic ($b = -0.51, p = .004$), PTSD ($b = -0.62, p = .017$), and externalizing ($b = -3.86, p = .015$) symptoms. Elevated right amygdala-ACC connectivity was associated with higher depression ($b = 0.26, p = .028$), GAD ($b = 0.32, p = .028$), and panic ($b = 0.35, p = .016$) symptoms.

Neural Mediators Linking CT and Psychopathology

Critically, the association of trauma with externalizing symptoms at the 2-year follow-up was mediated by blunted habituation in the right amygdala (indirect effect = 1.31, 95% CI 0.34–2.72), controlling for baseline symptoms (Figure 4A). The association of trauma with GAD (indirect effect = 0.70, 95% CI 0.06–1.49) and panic symptoms (indirect effect = 0.77, 95% CI 0.24–1.56) at baseline was mediated by reduced connectivity of the right amygdala with the bilateral hippocampus (Figure 4B). Finally, the association of trauma with GAD symptoms at baseline was mediated by elevated right amygdala connectivity with the bilateral dorsal ACC (indirect effect = 0.42, 95% CI 0.05–1.07) (Figure 4C).

DISCUSSION

CT is associated with altered dynamic patterns of neural activation and connectivity during aversive learning in children. Children exposed to trauma exhibited reduced discrimination

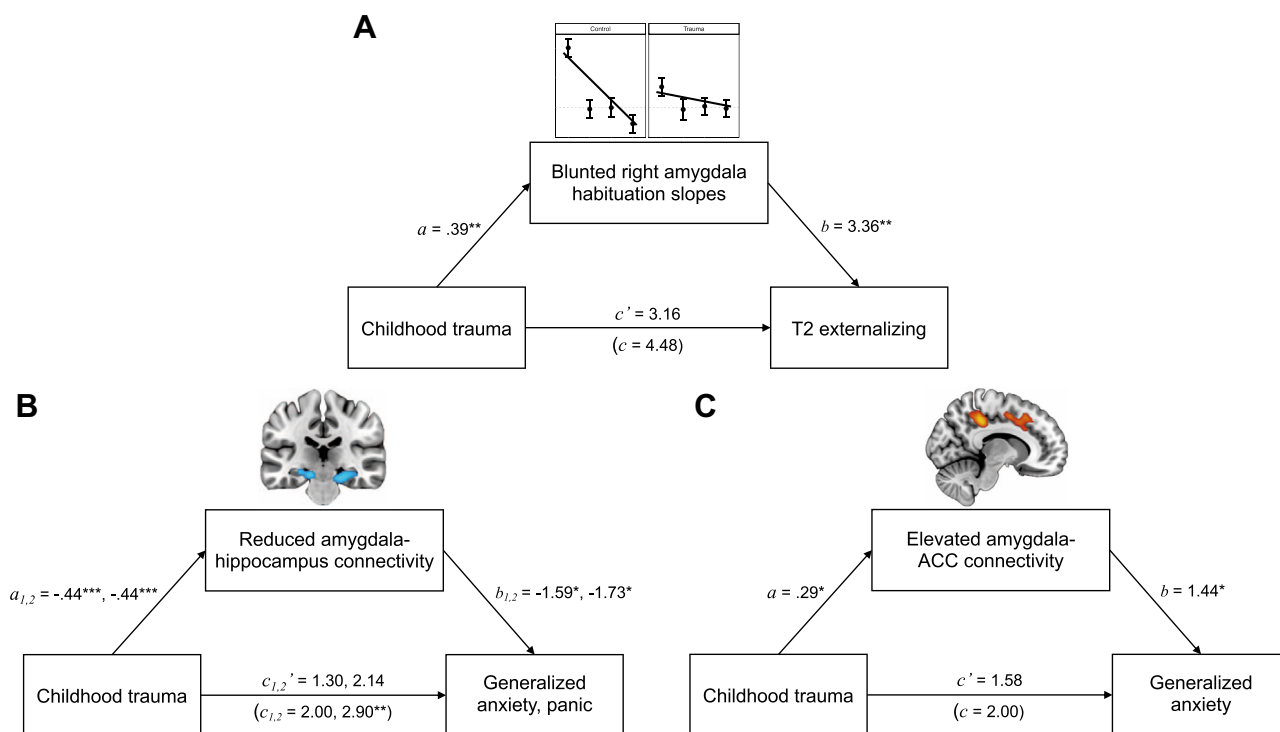


Figure 4. Altered patterns of neural activation and connectivity during aversive learning mediate the associations between childhood trauma and distinct forms of psychopathology. In panel (A), the association between childhood trauma and externalizing symptoms at 2-year follow-up was mediated by blunted right amygdala habituation slopes, controlling for baseline symptoms (indirect effect = 1.31, 95% CI 0.34–2.72). In panel (B), the associations between childhood trauma and generalized anxiety and panic at baseline were both mediated by reduced right amygdala–bilateral hippocampus connectivity (indirect effect = 0.70, 95% CI 0.06–1.49 and indirect effect = 0.77, 95% CI 0.24–1.56, respectively). Generalized anxiety mediation statistics are reported with subscript 1, and panic mediation statistics are reported with subscript 2. In panel (C), the pathway between childhood trauma and generalized anxiety was mediated by elevated amygdala–bilateral anterior cingulate cortex (ACC) connectivity (indirect effect = 0.42, 95% CI 0.05–1.07). *** $p < .001$; ** $p < .01$; * $p < .05$. T2, 2-year follow-up.

between threat and safety cues and blunted learning slopes to the threat versus safety cue (i.e., blunted habituation) in the 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 the right amygdala with the hippocampus mediated the association between trauma and transdiagnostic anxiety symptoms, and elevated connectivity of the 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+, although 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 and safe stimuli. These results replicate and extend previous work on the temporal dynamics of learning after CT using physiological indicators of learning, finding reduced differential SCR to the threat versus safety cue and attenuated habituation across learning (16). We found 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 after 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+ after 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 the right amygdala with multiple default mode regions, including the hippocampus, PHG, and posterior cingulate cortex 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 the 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 the 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 frontoparietal 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 over-generalized 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 2 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 the right amygdala with the hippocampus and other default mode regions involved in context processing mediated the association between trauma

and transdiagnostic anxiety symptoms, and elevated connectivity of the right amygdala with the ACC mediated the 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 this research. We were unable to examine associations with timing or duration of trauma owing to substantial missing data on age of first exposure. The fear conditioning paradigm used 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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ARTICLE INFORMATION

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