Received: 21 July 2021 | Revised: 3 November 2021 | Accepted: 16 November 2021

DOI: 10.1002/da.23229

RESEARCH ARTICLE

ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA WILEY

Longitudinal hippocampal circuit change differentiates persistence and remission of pediatric posttraumatic stress disorder

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Funding information

National Institute of Mental Health, Grant/Award Numbers: K08 MH100267, R01MH115910, R01MH117141; National Alliance for Research on Schizophrenia and Depression; National Science Foundation; American Academy of Child and Adolescent Psychiatry

Abstract

Background: Previous studies have identified functional brain abnormalities in pediatric posttraumatic stress disorder (pPTSD) suggesting altered frontoparietal-subcortical function during emotion processing. However, little is known about how the brain functionally changes over time in recovery versus the persistence of pPTSD.

Methods: This longitudinal study recruited 23 youth with PTSD and 28 typically developing (TD) youth (ages: 8.07–17.99). Within the PTSD group, nine remitted by the 1-year follow-up (Remit) while the remaining 14 persisted (PTSD). At each visit, youth completed an emotional processing task in which they viewed threat and neutral images during functional magnetic resonance imaging (fMRI). Voxelwise activation analyses using linear mixed-effects regression were conducted using a group (TD, Remit, PTSD) by time (baseline, follow-up) by valence (threat, neutral) design. Based on activation findings, a subsequent analysis of hippocampal functional connectivity was performed using a similar model.

Results: PTSD youth showed significantly increasing hippocampal activation to threatening images compared to TD youth, while the Remit group showed more similar patterns to TD youth. Subsequent hippocampal functional connectivity analyses reveal the Remit group showed increasing functional connectivity between the hippocampus and visual cortex (V4) while viewing threat stimuli.

Conclusions: These findings represent one of the first preliminary reports of functional brain substrates of persistence and remission in pPTSD. Notably, increased hippocampal activation to threat and decreased connectivity in the hippocampal-V4 network over time may contribute to persistence in pPTSD. These findings suggest potential biomarkers that could be utilized to advance the treatment of pediatric PTSD.

KEYWORDS

adolescence, emotion, functional magnetic resonance imaging, neurodevelopment, posttraumatic stress disorder, remission

1 | INTRODUCTION

Pediatric posttraumatic stress disorder (pPTSD) is a debilitating and common illness, affecting an estimated 7% of youth by the age of 18 (Danese & Widom, 2020). While efficacious treatments for pediatric PTSD are available, they only achieve modest effect sizes (Dorsey et al., 2017). Advancing the diagnosis and treatment of PTSD in youth will require a more nuanced understanding of its developmental neurobiology and the neural mechanisms underlying recovery. In particular, functionally relevant biomarkers of persistence or remission of pPTSD have the potential to improve prediction of recovery or treatment response, and serve as treatment targets for novel interventions (Michopoulos et al., 2015).

One of the prevailing models of pPTSD involves disruption in the processing of threat, marked by enhanced neural and physiological reactivity to threat stimuli, impaired recognition of threat-related emotions and threat-safety discrimination, and impaired cognitive control of threat responses (Cisler & Herringa, 2020). Accordingly, cross-sectional neuroimaging studies of pPTSD suggest a pattern of neural responses including increased amygdala reactivity, altered hippocampal function, and decreased frontolimbic connectivity when processing emotional stimuli (Cisler & Herringa, 2020). These regions are notable for their role in threat detection and reactivity (e.g., amygdala), contextual gating of threat responses (e.g., hippocampus), and threat discrimination and regulation (e.g., hippocampus, prefrontal cortex [PFC]; Koseki et al., 2009; Morey et al., 2016; Rougemont-Bücking et al., 2011). Importantly, youth with PTSD also show altered cross-sectional age-related patterns in these same networks, suggesting a deviation from typical neurodevelopment which may exacerbate illness over time (Herringa, 2017). From the few neuroimaging studies of youth and adolescents, they exhibit increased emotional reactivity compared to adults with PTSD which may reflect differences in prefrontal and subcortical maturation (Gogtay et al., 2004; Uematsu et al., 2012). Generally, previous research shows age-related decreases in the amygdala and hippocampal to PFC connectivity over time which would indicate that young children may have differential brain correlates to trauma and that by late adolescence may show more similar patterns to adults (for a review, see Cisler & Herringa, 2020).

Little is known about how threat processing networks develop longitudinally in youth with PTSD and which developmental patterns are reflective of illness recovery or persistence. One recent study using an emotional faces task found that, over time, decreasing symptoms of PTSD were correlated with decreased activity in the hippocampus and cingulate cortex (Garrett et al., 2019). Additionally, a resting-state functional connectivity study found that increased connectivity between the PFC and hippocampus was inversely related to PTSD, depression, and anxiety severity (Heyn et al., 2019). Two studies examining changes in pPTSD symptoms associated with trauma-focused cognitive behavioral therapy found that decreased insular cortex volume, as well as increased functional connectivity to the amygdala over time, were predictive of nonresponse to therapy (Cisler et al., 2016; Zantvoord et al., 2020). Together these studies suggest that networks involved in both threat-safety discrimination and emotion regulation may be critical for recovery from pPTSD. However, it remains unclear which threat-related neurodevelopmental changes predict the persistence and remission of PTSD in youth over time.

In response to these knowledge gaps, the current study aimed to investigate preliminary threat-related neural substrates of naturalistic persistence and remission in pPTSD. More specifically, we analyzed differences in neurological function over time to threatening images in youth who remit from PTSD relative to persistent PTSD and typically developing (TD) youth. From our previous work, we predicted that longitudinal functional development of the amygdala, hippocampus, and PFC would be important biomarkers for youth with remitted PTSD. We expected to see decreased amygdala and hippocampal reactivity to threatening versus neutral images over time in the Remit group compared to the PTSD group. Finally, we hypothesized increased amygdala/hippocampus—PFC functional connectivity over time in the Remit group compared to the PTSD group when viewing threatening images compared to neutral images.

2 | METHODS AND MATERIALS

2.1 | Participants

Participants for this study were taken from the Youth PTSD Study, which enrolled 96 youth, TD youth free from any history of trauma or mental illness ($n = 48$) and youth with current PTSD ($n = 48$), between the ages of 8 and 18. A subset of the baseline sample ($n = 60$) of these participants also completed the 1-year follow-up study. At the time of follow-up, of the youth with PTSD, 9 remitted from PTSD (Remit) and 13 persisted with PTSD (PTSD). Informed assent and consent from both the child and parent, respectively, were obtained from all participants at both baseline and follow-up appointments. More details can be found in the Supporting Information Methods.

2.2 | Clinical and behavioral assessments

At both baseline and 1-year follow-up study visits, youth and their caregivers underwent comprehensive psychiatric and trauma interviews to assess for past and current mental health disorders in the youth participant. We assessed for PTSD, anxiety, and depression symptoms as well as the pubertal stage. We opted to focus on remission versus persistence, instead of continuous symptoms, for its clinical relevance in diagnostic status and to facilitate direct comparison with TD youth. Details on these assessments can be found in the Supporting Information Methods.

2.3 | Emotion processing task

Participants underwent functional magnetic resonance imaging (MRI) while completing an emotion processing task that has been described in detail previously and is summarized here (Schuyler et al., 2014;

Wolf & Herringa, 2016). During the task, youth viewed 16 threat and 16 neutral images from the International Affective Picture Schedule (IAPS) for a length of 4 s (Lang et al., 2008). Threat images were selected due to their trauma-relevant content, including depictions of interpersonal violence, injuries, or motor vehicle accidents. Half of the images, counterbalanced across threat and neutral images, were followed by a neutral male face presented for 500 ms. The eight neutral male face stimuli were derived from the NimStim face set, with each being presented twice with a single valence pairing (Messer et al., 2000; Tottenham et al., 2009). Participants were monitored for attention by assigning a valence (negative, positive, or neutral) to each image by pressing a button with their right hand. The task took approximately 8 min to complete. Finally, participants were asked to provide memory and likability ratings for the eight faces seen during the task, as well as eight novel faces about 1 h post-MRI.

2.4 | Image processing

Preprocessing for functional brain analyses was implemented using AFNI (Cox, 1996) and Freesurfer (Reuter et al., 2012). Activation and seed-based whole-brain connectivity analyses were conducted, see Supporting Information Methods for more details on image processing.

2.5 | Primary statistical analysis

From the emotion processing task, we conducted an analysis of variances on the memory and likeability of novel faces and faces previously viewed during the task for each group. We regressed the group on memory and likeability ratings that the participants gave outside of the scanner while covarying for age and sex.

Activation and hippocampal connectivity estimates were analyzed for group differences during the viewing of threat versus neutral IAPS images across time. Model parameters were estimated using AFNI's *3dLME*, which computed a group (TD, PTSD, Remit) by time (baseline, follow-up) by valence (threat, neutral) interaction, covaried for age at baseline and binary sex. For activation, we conducted whole-brain analyses in addition to using an a priori bilateral amygdala–hippocampal mask due to the small volume and relevance of these regions in pPTSD and emotion processing. Statistical maps were then extracted, and autocorrelation function estimates were calculated with AFNI's *3dFWHMx*. Finally, these maps were corrected for multiple comparisons using *3dClustSim* (*-acf* option) with an individual voxel-wise threshold of $p = .001$. The corrected whole-brain cluster threshold was 85 voxels, and the amygdala–hippocampal mask cluster threshold 12 voxels, for a corrected $\alpha < .05$.

Based on the results of the activation analysis, we used the significant Group by Time by Valence interaction cluster in the right hippocampus as a seed for connectivity analysis (voxelwise threshold of 0.005). Formal overlap analyses revealed 100% overlap between this region and the AAL3 atlas hippocampus segment (Rolls et al., 2020). The average time series of the hippocampus region of interest was extracted from the preprocessed statistical maps using *3dMaskDump*. Coefficient of determination (R^2) functional connectivity statistics were calculated as described above. We converted R^2 to the Pearson correlation coefficient (r), which were then Fisher Z-transformed for group analyses. Whole-brain family wise error (FWE) correction was conducted using the same method as described above, resulting in a cluster threshold of 78 voxels ($alpha_{fwe} < 0.05$).

2.6 | Post hoc statistical analyses

We conducted all post hoc analyses in R (R Core Team, 2013). We investigated all significant activation and functional connectivity findings to assess potentially confounding variables and relationships with clinical variables. To evaluate other potentially influential variables, models were rerun while including the following additional covariates: pubertal stage, IQ, age, binary sex, age of index trauma, maltreatment experiences (measured by the Childhood Trauma Questionnaire [CTQ] abuse subscore), therapy inclusion, and medication history. Results can be found in Analysis S1. Clinical measures, including PTSD symptoms, depressive symptoms, anxiety symptoms, and age at index trauma were also used to predict cluster averages to understand brain-behavior interactions.

3 | RESULTS

3.1 | Participant demographics and clinical characteristics

All participant demographics and clinical characteristics are summarized in Table 1. Among the three groups, there were no significant differences in age, sex, or Tanner stage ($p > .25$) at baseline or at follow-up. There were significant IQ differences between the TD and PTSD/Remit groups ($p = .009$), but not between the PTSD and Remit groups ($p = .074$). PTSD symptoms did not differ at baseline between the PTSD and Remit groups but did differ at follow-up for the clinician-administered PTSD scale (CAPS) ($p = .0006$). There was a significant difference in disorder comorbidities (higher for PTSD vs. Remit) at baseline ($p = .002$) and trending at follow-up ($p = .055$). Youth with PTSD reported higher abuse severity at baseline ($p = .007$) and at follow-up ($p = .012$) compared to the Remit group.

3.2 | Primary behavioral analyses

There were no significant group differences in memory between the three groups, but there were significant differences between TD and PTSD groups for the likeability of both novel and previously seen faces accounting for age and sex ($p < .001$; Results S1). However, only the novel faces regression model converged.

TABLE 1 Participant demographics

	Typically developing	Remit group	PTSD group	PTSD group comparisons
Basic demographic variables				
N	28	9	14	
Sex (female)	19	5	10	$c^2(1, N = 23) = 0.11$, $p = .74$
Age				
Baseline	14.28 (2.57)	13.56 (3.39)	14.46 (2.40)	$t(21) = -0.88$, $p = .39$
Tanner				
Baseline	3.25 (1.26)	2.79 (1.46)	3.18 (1.24)	$t(21) = -0.69$, $p = .50$
Follow-up	3.82 (1.22)	3.11 (1.26)	3.93 (1.17)	
IQ				
Baseline	109.57 (11.69)	100.00 (12.64)	98.36 (10.50)	$t(21) = 0.33$, $p = .74$
Follow-up	112.75 (11.97)	102.33 (15.72)	97.93 (8.49)	
Race				
White	22	7	12	$t(23) = 2.0$, $p = .18$
African American	0	2	1	
Asian	1	0	0	
Two or more	2	1	0	
Hispanic or Latino	1	1	2	
Not Hispanic Latino	24	9	11	
Not provided	2	0	1	
Parent education level				
Some high school	0	0	1	$t(22) = -0.88$, $p = .44$
High school degree	1	0	3	
Some college	5	6	6	
College degree	10	1	2	
Graduate degree	11	2	1	
Trauma variables				
Index trauma type				
Sexual abuse	–	2	9	$c^2(3, N = 21) = 4.09$, $p = .25$
Traumatic accident	–	1	2	
Traumatic news	–	2	2	
Witness deomestic violence	–	2	3	
No. of traumas from KSADS				
Baseline	–	3.11 (1.57)	4.07 (2.12)	$t(21) = -1.14$, $p = .27$
Follow-up	–	1.44 (2.23)	1.00 (2.18)	$t(21) = 0.46$, $p = .65$
Age of index trauma	–	8.58 (5.84)	7.46 (4.06)	$t(21) = 0.52$, $p = .61$
CTQ abuse				
Baseline	16.96 (2.56)	22.11 (7.66)	35.50 (11.61)	$t(21) = -2.98$, $p = .007$*
Follow-up	16.64 (1.57)	19.89 (5.41)	35.79 (16.39)	$t(21) = -2.74$, $p = .012$*
SLES				

(Continues)

TABLE 1 (Continued)

	Typically developing	Remit group	PTSD group	PTSD group comparisons
Baseline	20.46 (12.69)	70.67 (57.04)	83.93 (49.41)	$t(21) = -0.58$, $p = .57$
Follow-up	8.39 (8.13)	38.00 (36.01)	46.79 (40.60)	$t(21) = -0.52$, $p = .61$
CAPS				
Baseline	–	61.50 (22.69)	77.89 (16.95)	$t(19) = -1.82$, $p = .08$
Follow-up	–	30.39 (22.06)	67.75 (20.45)	$t(21) = -4.05$, $p < .01$*
PTSD-RI				
Baseline	–	44.89 (11.66)	52.88 (9.20)	$t(21) = -1.78$, $p = .09$
Follow-up	–	32.89 (12.20)	39.15 (17.56)	$t(20) = -0.90$, $p = .38$
MFQ				
Baseline	3.66 (2.77)	17.67 (11.73)	30.71 (17.39)	$t(21) = -1.93$, $p = .07$
Follow-up	3.79 (4.89)	13.9 (10.59)	30.36 (18.57)	$t(21) = -2.37$, $p = .03$*
SCARED				
Baseline	8.25 (5.28)	30.11 (13.99)	39.43 (17.26)	$t(21) = -1.33$, $p = .20$
Follow-up	8.79 (6.89)	22.00 (19.33)	37.07 (18.86)	$t(21) = -1.81$, $p = .08$
Presence of medication				
Baseline	–	0.56 (0.53)	0.43 (0.51)	$t(21) = 0.57$, $p = .57$
Follow-up	–	0.56 (0.53)	0.43 (0.51)	$t(21) = 0.57$, $p = .57$
History of therapy				
Baseline	–	0.22 (0.44)	0.36 (0.50)	$t(21) = -0.66$, $p = .52$
Follow-up	–	0.67 (0.50)	0.50 (0.52)	$t(21) = 0.76$, $p = .45$

Note: Full sample participant demographics. The Remit and PTSD groups did not differ significantly in sex, baseline age/Tanner/IQ, index trauma type, age at index trauma, number of trauma types, PTSD symptoms (PTSD-RI), or anxiety symptoms (SCARED). The PTSD group had significantly higher childhood maltreatment load (CTQ) at baseline and follow-up. Depression symptom severity (MFQ) differed only at follow-up. * Indicates significant differences between groups ($p < .05$).

Abbreviations: CAPS-CA, Clinician-Administered Child-Adolescent PTSD Scale; CTQ, Childhood Trauma Questionnaire; MFQ, Mood and Feelings Questionnaire; PTSD, posttraumatic stress disorder; PTSD-RI, PTSD-reaction index; SCARED, Screen for Child Anxiety-Related Mood Disorders; SLES, Stressful Life Events Screening.

TABLE 2 Functional brain analyses

Functional region	Model	Cluster size	Laterality	*F*	p_{FWE}
Activation analyses					
V4	Group × Time	117	Left	20.46	.02
Right fusiform	Group × Time	114	Right	14.75	.02
Right V3	Group × Time	107	Right	14.70	.03
Hippocampus	Group × Time × Valence	35	Right	12.93	.03
Connectivity analyses					
V4	Group ×Time × Valence	318	Left	14.07	<.001

3.3 | Primary activation analysis

Summary results from activation analyses are described in Table 2. Within the amygdala–hippocampal mask, we detected a significant Group by Time by Valence interaction in the right hippocampus ($k = 13$ voxels, $F[10,39] = 12.93$, $p_{FWE} = .04$; Figure 1). Here, we found significantly increased activation over time to threatening images ($b = 5.18$, $p = .026$, $F[9,40] = 5.34$) and decreased activation to neutral images ($b = -4.98$, $p = .018$, $F[9,40] = 6.06$) in PTSD compared to the TD group.

In whole-brain analyses, we detected three significant Group by Time interactions in left visual cortex (V4; $k = 117$, $F[10,39] = 20.46$,

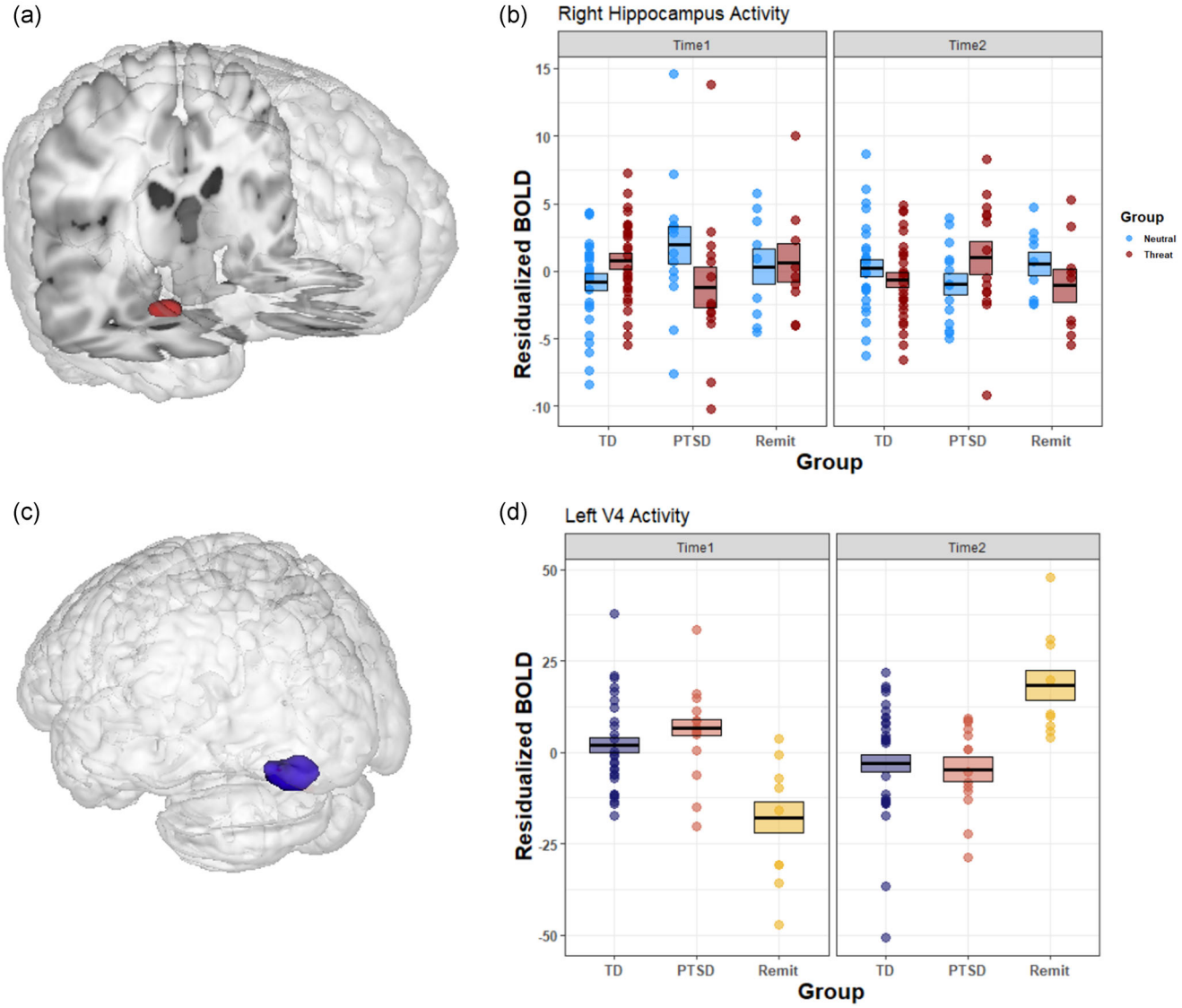

FIGURE 1 Activation analysis results. Youth with persistent posttraumatic stress disorder (PTSD; $n = 14$) and Remit ($n = 9$) youth exhibit differential visual and hippocampal brain activity over time compared to typically developing (TD, $n = 28$) youth. (a) Three-dimensional (3D) rendering of the right hippocampal cluster derived from the limbic mask activation analyses (13 voxels, $p_{FWE} = .04$). (b) We found significantly increased activation over time to threatening images (red) and decreased activation to neutral images (blue) in PTSD compared to the TD group. The plot depicts peak BOLD signal per group, timepoint, and valence, residualized for age and sex, overlayed on each participant's residualized BOLD signal. (c) 3D rendering of the left V4 cluster derived from the whole-brain activation analyses ($k = 117$; $p_{FWE} = .02$). (d) We observed an increase in left V4 activity over time in the Remit group as compared to the TD and PTSD groups and no differences in the TD and PTSD groups. The plot depicts peak BOLD signal per group and timepoint, residualized for age and sex, overlayed on each participant's residualized BOLD signal

$p_{FWE} = .02$; Figure 1), right fusiform gyrus ($k = 114$, $F[10,39] = 14.75$, $p_{FWE} = .02$), and right V3 ($k = 107$, $F[10,39] = 14.70$, $p_{FWE} = .03$; Supporting Information Results). Here, we observed an increase in left V4 activity over time in the Remit group as compared to the TD ($b = 40.75$, $p = 8.588e{-}08$, $F[9,40] = 32.96$) and PTSD ($b = 46.74$, $p = 9.30e{-}08$, $F[9,21] = 35.86$) groups. We also found significant increases in right fusiform activity in both the Remit ($b = 25.50$, $p = 1.58e{-}06$, $F[9,35] = 25.79$) and PTSD ($b = 10.12$, $p = .013$, $F[9,40] = 6.37$) groups compared to the TD group and the Remit group had increased activity over time compared to the PTSD group ($b = 15.38$, $p = .0023$, $F[9,21] = 25.79$). Lastly, in the right V3, we found significant increases over time in the Remit group compared to PTSD ($b = 27.76$, $p = .0005$, $F[9,21] = 13.37$) and TD groups ($b = 30.52$, $p = 4.203e{-}06$, $F[9,35] = 23.48$).

3.4 | Primary right hippocampus connectivity analysis

Results from the connectivity analyses are summarized in Table 2. We detected a significant Group by Time by Valence interaction to the left visual cortex (V4; $k = 318$, $F[10,39] = 14.07$, $p_{FWE} < .001$;

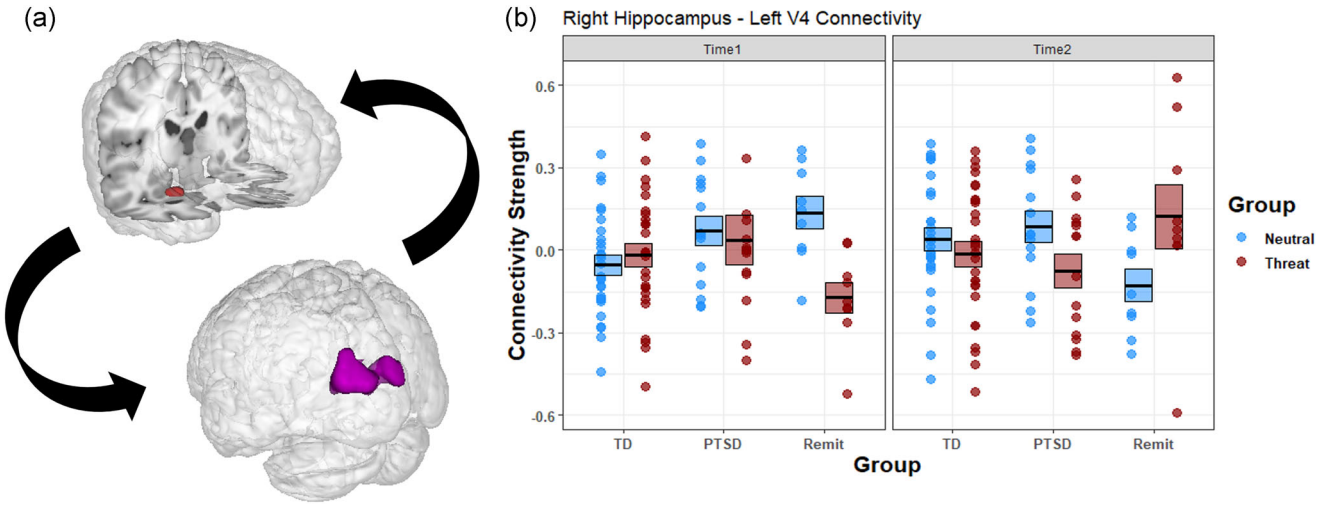

FIGURE 2 Connectivity analysis with hippocampal seed. Youth with posttraumatic stress disorder (PTSD; $n = 14$) showed decreased connectivity over time to threat images compared to Remit ($n = 9$) youth that showed increased connectivity between the hippocampus and visual area. (a) Three-dimensional rendering of the left V4 cluster derived from the right hippocampal seed connectivity analysis (318 voxels, $p_{FWE} < .001$). (b) The Remit group showed increasing connectivity over time between the right hippocampus and left V4 to negative images (red) compared to the PTSD group and the typically developing (TD) group, while showing the opposite pattern for neutral images (blue). The plot depicts peak connectivity strength per group, timepoint, and valence, residualized for age and sex, overlayed on each participant's residualized connectivity strength

Figure 2). Here, the Remit group showed increasing connectivity over time between the right hippocampus and left V4 to negative images compared to the PTSD group ($b = .44$, $p = .021$, $F[9,21] = 6.25$) and the TD group ($b = .32$, $p = .012$, $F[9,35] = 7.02$).

3.5 | Post hoc statistical analyses

First, we conducted an outlier analysis in R where individual data points were considered outliers if their z-score was > |3|. While one outlier was detected within the hippocampus activity cluster, sensitivity analyses revealed that exclusion of the outlier did not substantially change the significance and was therefore retained in the final analyses. For the connectivity analyses, outlier analyses revealed an outlier in the hippocampus to V4 cluster but exclusion of the outlier did not significantly change any corresponding effect and was therefore kept in final analyses.

Next, across both activation and connectivity analyses, all reported effects remained significant when adjusting for Tanner stage, IQ, age of index trauma, trauma load (CTQ abuse) therapy inclusion, and medication history ($p < .05$). Finally, no significant symptom–brain relationships or correlations between brain and memory or likeability ratings were detected (Results S1).

4 | DISCUSSION

To our knowledge, this preliminary study is one of the first to characterize functional biomarkers of persistence and remission of PTSD in a pediatric sample. Our evidence suggests that the neurodevelopmental mechanisms of threat processing, especially those related to hippocampal and visual processing of threat, may be disrupted in youth with PTSD. More specifically, longitudinal patterns of development in hippocampal and visual circuits may be a unique indicator of pPTSD remission. Here, the Remit group showed a return to TD patterns of hippocampus activation and hippocampus-V4 connectivity over time as compared to the PTSD group. Altogether, this suggests that reduced hippocampal reactivity to threat, along with increased hippocampal modulation of the visual pathway may be a potential marker of recovery in pPTSD. Notably, these biomarkers implicate potential changes in threat encoding that could be used to individualize therapeutic interventions for youth with PTSD.

While previous studies have implicated the medial PFC and other limbic regions, including the amygdala, in trauma-exposed youth, this study instead supports recent models suggesting that visual and memory systems may be indicative of remission from pPTSD over time (Calderon-Delgado et al., 2019; Cisler et al., 2018; Keding & Herringa, 2015; Wolf & Herringa, 2016). Our work is in contrast to adult studies that report hyperactivation of the amygdala potentially indicating that amygdala hyperactivation only manifests once in adulthood (Etkin & Wager, 2007; J. P. Hayes et al., 2012). One possible reason for this divergence from canonical frontolimbic involvement may be due to the nature of the emotion processing task itself. Our task did not require effortful emotion regulation and relied more on implicit processing of threat images. Top–down, explicit control of emotion responses generally implicates the amygdala and PFC connections; however, this may not be as true for passive emotion processing (Cisler & Herringa, 2020).

Despite the absence of prefrontal and amygdala correlates in pPTSD remission, findings from this study do implicate functional

changes in the hippocampus, which may uniquely modulate other emotion-related circuits to facilitate changes in threat processing. As compared to both TD and Remit groups, PTSD youth show increased hippocampal reactivity to threatening stimuli over time. The hippocampus itself has been implicated in numerous studies on adolescent PTSD as well as adult studies (Kuhn & Gallinat, 2013; Paquola et al., 2016). Briefly, studies have found that exposure to trauma is related to increased hippocampal activation and differences in connectivity between the hippocampus and the Salience Network (i.e., insula; Reda et al., 2021; van Rooij et al., 2020). Childhood maltreatment was also associated with decreased left hippocampal activity in adult veterans (Insana et al., 2015). The altered hippocampal function has also been related to deficits in emotion processing, memory encoding, and associative learning which are generally disrupted in affective disorders like PTSD (McEwen et al., 2016). The hippocampus is also notable for its high number of glucocorticoid receptors, which may make it particularly sensitive to the effects of severe stress during development (Hanson et al., 2015). Furthermore, trauma has been shown to affect the trajectory of hippocampal development which could lead to deficits in associative memory of emotional stimuli and in emotional processing including face processing (S. M. Hayes et al., 2009; Lambert et al., 2019). Due to its association with trauma, we theorize that differences in hippocampal activity and connectivity are markers of remission from PTSD. As our task utilizes threatening images, it is possible that being able to associate threat and safety in an environment is imperative to recovery from PTSD.

While the functional connection between the hippocampus to the visual streams is relatively understudied, there is emerging work, especially with regard to trauma (Lambert et al., 2019). One study found that child maltreatment was associated with differences in the left inferior longitudinal fasciculus (ILF) which connects the occipital cortex to anterior temporal lobes and is related to emotion processing and object recognition (Olson et al., 2019). The ILF has known connections to areas in the hippocampus indicating a possible direct connection between the two regions (Ramachandran et al., 2020). Further studies will be needed to understand how the hippocampus and visual pathways connect and modulate each other in emotional contexts and how these connections may be disrupted in trauma-related disorders.

Although not as commonly studied, the ventral and dorsal pathways of the visual system have been implicated in emotion processing, attention, and reactivity to emotional stimuli (Kravitz et al., 2013; Olson et al., 2019; Rosen et al., 2020). The occipitotemporal network, which incorporates these pathways, specifically is implicated in the processing of emotional stimuli in typically developing youth (Kravitz et al., 2013) and may be impacted by trauma exposure and/or PTSD. One study has implicated reduced gray matter volume and thickness in the bilateral primary visual cortex as well as the middle occipital area of adults who witnessed domestic violence in childhood (Tomoda et al., 2012), while another investigation of adult refugees with PTSD showed decreased activity in primary visual cortex to positive images compared to controls (Uldall et al., 2020). Emotional attention and stimuli have also been shown to modulate V4 activity indicating that modulation of this area is likely to occur from higher-order attention areas (Bi et al., 2019). Based on our data and previous work, we speculate that more effective modulation of the visual cortex by the hippocampus during threat imagery may reduce reactivity to or encoding of negative stimuli to facilitate recovery from PTSD. Here, further studies would be warranted to understand more precisely how changes in the hippocampus-visual circuit relate to reactivity and encoding of threat content.

Lending further support to a theory of visual system impairments in pPTSD, we also detected longitudinal group differences in the fusiform gyrus and V3. Both of these regions are utilized in the ventral visual processing stream and are used for object and face recognition (Sheth & Young, 2016). One study found that there was an increase in negative connectivity with the dorsal anterior cingulate cortex (dACC) and the fusiform gyrus in a maltreatment-resilient group compared to a nonresilient group. While these effects did not show a valence interaction, they further implicate changes in visual processing as a potential marker of remission and resilience for trauma-related disorders.

Though this study utilized a well-phenotyped sample of pPTSD across time to detect biomarkers of remission in neurodevelopment, it is not without limitations. First, our sample is modest, a frequent challenge in this difficult to recruit population. This study would thus benefit from replication in a larger sample. On the other hand, the three-group longitudinal design offers novel opportunities to explore potential neural substrates of recovery as compared to both persistent psychopathology and typical development. Second, due to the correlational nature of connectivity analyses, we are unable to definitively identify the directionality of hippocampus-V4 modulation. However, the hippocampus has previously been shown to modulate many other sensory systems (Bast & Feldon, 2003; Lambert et al., 2019) suggesting the potential for similar effects with the visual system. Future studies employing longitudinal designs with causal modeling (e.g., dynamic causal modeling) may be helpful in disentangling the directionality of these findings. Finally, our study did not include a trauma-exposed group without PTSD at baseline, precluding comparison of how the PTSD and Remit group patterns relate to neural patterns of PTSD resilience over time. However, post hoc analyses suggest that the longitudinal biomarkers of PTSD persistence and recovery were unrelated to trauma exposure variables per se.

5 | CONCLUSIONS

In summary, this study represents novel longitudinal neural correlates of remission versus persistence of pPTSD during emotional processing. Our findings support a mechanism of decreased hippocampal reactivity to threat, along with increased hippocampal modulation of visual processing streams as a potential biomarker of remission in youth with PTSD. These findings suggest that targeting of both memory and visual processing of threatening stimuli could prove

fruitful in expediting recovery from PTSD in youth. Future studies would be warranted to probe how current or novel therapies may help facilitate change in these nodes and lead to remission within this vulnerable population of youth.

ACKNOWLEDGMENTS

The authors would like to thank the Brave Research Lab with their help in recruitment and data collection for this study and their feedback on the results. The authors also want to extend our genuine gratitude to the families and youth who have participated in our study. Funding for this study was provided by the National Institute of Mental Health Career Development Award (K08 MH100267 to Ryan J. Herringa), American Academy of Child and Adolescent Psychiatry Junior Investigator Award (to Ryan J. Herringa), NARSAD Young Investigator Grant (to Ryan J. Herringa), University of Wisconsin Institute for Clinical and Translational Research Translational Pilot Grant Award (NIH/NCATS UL1TR000427 to Ryan J. Herringa), the National Institute of Mental Health (R01MH117141, R01MH115910 to Ryan J. Herringa), the National Institute of Mental Health Diversity Supplement (MSN217744 to Grace C. George), the National Science Foundation Graduate Research Fellowship Program (DGE 1747503 to Taylor J. Keding), and University of Wisconsin School of Medicine and Public Health. None of these funding sources had a direct effect on the design, analysis, or interpretation of the study results or in preparation of the manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: George, G. C., Keding, T. J., Heyn, S. A., & Herringa, R. J. (2022). Longitudinal hippocampal circuit change differentiates persistence and remission of pediatric posttraumatic stress disorder. *Depression and Anxiety*, 39, 8–18. https://doi.org/10.1002/da.23229