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Archival Report

The Role of the Hippocampus in Predicting Future Posttraumatic Stress Disorder Symptoms in Recently Traumatized Civilians

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ABSTRACT

BACKGROUND: Understanding the neurobiological mechanisms that predict posttraumatic stress disorder (PTSD) in recent trauma survivors is important for early interventions. Impaired inhibition of fear or behavioral responses is thought to be central to PTSD symptomatology, but its role in predicting PTSD is unknown. Here we examine whether brain function during response inhibition early after a civilian trauma can predict future PTSD symptoms.

METHODS: Participants (original sample, n = 27; replication sample, n = 31) were recruited in the emergency department within 24 hours of trauma exposure. PTSD symptoms were assessed in the emergency department and 1, 3, and 6 months posttrauma. A Go/NoGo procedure in a 3T magnetic resonance imaging scanner was used to measure neural correlates of response inhibition 1 to 2 months posttrauma. Elastic net regression was used to define the most optimal model to predict PTSD symptoms at 3 and 6 months among demographic, clinical, and imaging measures.

RESULTS: Less hippocampal activation was a significant predictor in the model predicting PTSD symptoms at 3 months ($F_{11,22}$ = 4.33, p = .01) and 6 months ($F_{9,19}$ = 4.96, p = .01). Other significant predictors in the model were race and pain level in the emergency department (3 months), and race and baseline depression symptoms (6 months). Using these predictors in a linear regression in the replication sample again resulted in significant models (3 months [$F_{3,23}$ = 3.03, p = .05], 6 months [$F_{3,20}$ = 5.74, p = .007]) with hippocampal activation predicting PTSD symptoms at 3 and 6 months.

CONCLUSIONS: Decreased inhibition-related hippocampal activation soon after trauma predicted future PTSD symptom severity. This finding may contribute to early identification of at-risk individuals and reveals potential targets for intervention or symptom prevention in the aftermath of trauma.

Keywords: Emergency department, fMRI, Functional magnetic resonance imaging, Hippocampus, Longitudinal study, Posttraumatic stress disorder, Predictive biomarkers, Prospective study, PTSD, Response inhibition

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Up to 90% of the general population in the United States is exposed to a traumatic event at some point in their life (1). Traumatic events can include combat exposure, natural disasters, or terrorist attacks, and life-threatening accidents or assaults, many of which result in a need for emergency hospitalization. About 5% to 10% of trauma-exposed individuals develop posttraumatic stress disorder (PTSD) (2); therefore, one of the main goals of trauma research is to understand why some individuals develop PTSD whereas others do not. Prospective studies are critical for improving our understanding of the neurobiological mechanisms that are associated with the development of PTSD in trauma survivors.

A specific and key impairment in PTSD is the inability to suppress a fear response in a safe environment (3). Although learning to associate a neutral cue with true danger is beneficial for survival, the ability to regulate behavioral and emotional responses in a safe environment is critical for ongoing health and well-being (4). The core symptoms of PTSD include excessive fear responses to trauma reminders, intrusive thoughts, and re-experiencing of the traumatic event despite being in another environment (4). Impaired fear inhibition has been demonstrated in both psychophysiological studies (5–7) and imaging studies (8,9) of PTSD. Individuals with PTSD show reduced ventromedial prefrontal cortex (vmPFC) (9) and hippocampal recruitment during fear inhibition (8,10), and these areas are activated together during extinction recall (11). The vmPFC regulates or inhibits the fear response (12,13), whereas the hippocampus provides contextual information

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required for regulation of responses (12,14,15). Importantly, previous studies demonstrated that PTSD patients also showed reduced inhibition (16–18) and impaired processing of contextual cues (18,19) during nonemotional response inhibition paradigms, indicating a more general inhibition and context-processing deficit in PTSD. When using a simple Go/NoGo task with a red rectangle in the background as NoGo cue, brain regions associated with impaired fear inhibition and context processing in PTSD are hypoactive during response inhibition: in one study PTSD participants showed less vmPFC activation than trauma control subjects (17), and in a group of highly traumatized women decreased hippocampal activation correlated with more PTSD symptoms and less trait resilience (20). Moreover, hippocampal activation mediated the relationship between childhood trauma and PTSD symptoms versus resilience (20). Another study showed that inhibition of the startle response during early extinction was correlated with increased functional coupling of the hippocampus and vmPFC during NoGo relative to Go trials, as well as structural connectivity of white matter tracts connecting the hippocampus and the vmPFC (21). The hippocampus is important for modulation of behavior based on new sensory information or contextual cues (22), and previous findings suggest that increased hippocampal recruitment may be an important mechanism for coping with traumatic stress (20).

Previous studies have demonstrated that impaired inhibition in PTSD is not limited to fear regulation and may therefore represent a more general deficit in PTSD (18,23). Furthermore, impaired inhibition-related brain functioning in PTSD, particularly in the right inferior frontal gyrus (rIFG), did not improve with successful treatment (19). It was therefore suggested that impaired inhibition-related brain functioning may be a vulnerability factor for PTSD. This underscores the relevance of investigating neural correlates of response inhibition as potential biomarkers for PTSD development in the first months after trauma exposure. In a prospective functional magnetic resonance imaging (fMRI) study, prefrontal responses to threat stimuli were not predictive of later PTSD symptoms (24); however, no explicit response inhibition task was used. Another prospective study showed that decreased hippocampal activation during active downregulation of negative emotional stimuli was related to increased PTSD symptoms (25). In the current study we aimed to probe brain regions associated with PTSD and previously shown to be impaired in PTSD with this response inhibition task, i.e., the hippocampus and vmPFC. Furthermore, we included the rIFG as a region of interest (ROI), as it has often been implicated in response inhibition (26), and whose function has been associated with PTSD (19).

The current prospective, longitudinal fMRI study recruited participants who were brought to a large Level I emergency department (ED) trauma center within 24 hours of experiencing a traumatic event. fMRI scans using a Go/NoGo response inhibition task were collected before PTSD diagnosis, 1 to 2 months posttrauma. Clinical data were collected in the ED at enrollment and 1, 3, and 6 months following trauma exposure. The data were used to investigate the hypothesis that response inhibition–related brain activation after trauma exposure predicts future PTSD symptoms. More specifically, we hypothesized that greater hippocampal, vmPFC, and rIFG activation would predict fewer PTSD symptoms at 3 and 6 months posttrauma.

METHODS AND MATERIALS

Participants

Participants were recruited as part of a large prospective study conducted in the ED at Grady Memorial Hospital, the largest Level I Trauma Center in Georgia (USA). Participants were eligible for the study if they had suffered a DSM-IV-TR Criterion A trauma (27) in the past 24 hours. Exclusion criteria were a history of mania, schizophrenia, or other psychosis; current suicidal ideation; suicide attempt in the last 3 months; current intoxication; or experiencing loss of consciousness (>5 minutes) as a result of the trauma. Participants were excluded if they showed any impairment on the Glasgow Coma Scale (28) to exclude for traumatic brain injury. During their 1-month visit, MRI-eligible participants were invited for a scan, which took place within 2 to 3 weeks of the 1-month visit, on average 54 ± 14 days (range = 26 to 93 days) after trauma exposure. Because the study moved to another scan facility and updated scan parameters in midst of recruitment, the study resulted in two samples that were analyzed separately: an original sample (n = 38) and a replication sample (n = 39). After complete written and verbal description of the study, all participants provided written informed consent. The Institutional Review Boards of Emory University, Georgia Institute of Technology, and the Research Oversight Committee of Grady Memorial Hospital approved the study procedures.

Clinical Assessment

Baseline assessment in the ED included the Standardized Trauma Interview, a 41-item interview on demographics, characteristics of the trauma, patient-rated severity, and social support (29). The Posttraumatic Diagnostic Scale, a 49-item self-report measure, was used to measure lifetime trauma history and current PTSD symptoms related to trauma occurring before the current index event (30). Current depression symptoms were assessed using the 21-item self-report Beck Depression Inventory (31). Trauma exposure during childhood was assessed using the Childhood Trauma Questionnaire (CTQ) (32), a 25-item questionnaire on trauma experienced before age 18 years. Follow-up assessments of PTSD symptoms were performed at 1, 3, and 6 months posttrauma using the PTSD Symptom Scale (PSS) (33). The number of symptoms as measured with the PSS was used as the outcome variable in the analyses.

Functional Magnetic Resonance Imaging

Response Inhibition Task. A Go/NoGo task was used to measure response inhibition (34). Participants were asked to respond to the Go trials (white X or O on black screen), but to withhold their response to the NoGo trials (red rectangle in the background of the X or O). All participants responded correctly to at least 75% of the Go and NoGo trials, and most participants had an accuracy score of 100% (Table 1). Only correct Go and NoGo trials were included in the analyses, and correct NoGo > correct Go was used as the contrast of interest in all analyses. The task is described in more detail in Figure 1.

Table 1. Participant Demographic and Clinical Data

	Original Sample (n = 27)	Replication Sample (n = 31)	Statistic	p Value
Age, Years	31.5 ± 10.3	36.9 ± 12.5	$t = -1.79$	.08
Female	13/27 (48)	11/31 (35)	$\chi^2 = 0.95$	.33
Race			$\chi^2 = 3.63$	.31
Black	17/27 (63)	26/31 (84)		
White	6/27 (22)	3/31 (10)		
Mixed	3/27 (11)	1/31 (3)		
Other	1/27 (4)	1/31 (3)		
Education Level			$\chi^2 = 3.26$	.52
Master's degree	1/27 (4)	2/31 (6)		
Bachelor's degree	2/27 (7)	4/31 (13)		
Associate's degree, some college	15/27 (56)	10/31 (32)		
High school degree	7/27 (26)	12/31 (39)		
Some high school	2/27 (7)	3/31 (10)		
Type of Trauma			$\chi^2 = 5.56$	.59
Nonsexual assault	1/27 (4)	1/31 (3)		
Motor vehicle collision	19/27 (70)	19/31 (61)		
Motor cycle collision	0/27 (0)	1/31 (3)		
Pedestrian vs. auto	3/27 (11)	4/31 (13)		
Gunshot wound	0/27 (0)	1/31 (3)		
Industrial/home accident	0/27 (0)	3/31 (10)		
Bicycle accident	2/27 (7)	1/31 (3)		
Sexual assault	2/27 (7)	1/31 (3)		
Pain After Trauma (range 0–10)	5.12 ± 2.8	6.00 ± 2.5	$t = -1.23$	.23
Patient-Rated Trauma Severity (range 0–5)	3.8 ± 1.1	4.2 ± 0.9	$t = -1.53$	.13
Clinician-Rated Trauma Severity (range 0–5)	2.5 ± 0.8	2.6 ± 0.7	$t = -0.85$	.40
Social Support	2.8 ± 0.6	2.7 ± 0.6	$t = 0.46$	.65
Childhood Trauma [CTQ (32)]	37.8 ± 12.7	37.0 ± 14.3	$t = 0.20$	.84
Received Treatment	7/27 (26)	4/31 (13)	$\chi^2 = 1.59$	.21
Days Between Trauma and Scan	54.0 ± 14.3	53.9 ± 13.8	$t = 0.04$	.97
Depression Symptoms [BDI (31)] in the ED	8.6 ± 9.3	11.6 ± 11.6	$t = -1.07$	.29
PTSD Symptoms [PDS (30)] in the ED	4.6 ± 7.7	7.3 ± 7.4	$t = -1.29$	.20
Meet DSM-IV criteria	2/27 (7)	3/31 (10)	$\chi^2 = 0.09$	.76
PTSD Symptoms [PSS (33)] at 1 Month	16.9 ± 12.8	15.0 ± 11.0	$t = 0.61$	.55
Meet DSM-IV criteria	11/27 (41)	11/31 (35)	$\chi^2 = 0.17$	.68
PTSD Symptoms [PSS (33)] at 3 Months	12.7 ± 11.8	9.1 ± 8.5	$t = 1.18$	.24
Meet DSM-IV criteria	6/23 (26)	6/24 (25)	$\chi^2 = 0.01$	.93
PTSD Symptoms [PSS (33)] at 6 Months	10.0 ± 12.2	8.5 ± 8.3	$t = 0.46$	.65
Meet DSM-IV criteria	5/20 (25)	4/21 (19)	$\chi^2 = 0.21$	.65
Percentage Correct Go Trials	97.4 ± 4.8	98.2 ± 4.2	$t = 0.49$	.50
Percentage Correct NoGo Trials	97.4 ± 4.8	99.4 ± 1.4	$t = -2.06$	.05

Values are mean ± SD or n/n (%). Statistical tests were performed to compare the 2 samples; independent-samples t tests were conducted to compare means, and chi-square tests were performed to compare proportions.

BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire; ED, emergency department; PDS, Posttraumatic Stress Diagnostic Scale; PSS, PTSD Symptom Scale; PTSD, posttraumatic stress disorder.

Brain Imaging Acquisition and Analyses. MRI scans for the 2 samples were collected at different scanners, using dissimilar scanner parameters, but both were Siemens 3.0T Magnetom Trio total imaging matrix whole-body MR scanners (Siemens Healthcare, Malvern, PA) using a 12-channel head coil. Functional data were preprocessed and analyzed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Further information on data acquisition and analyses is described in the Supplement.

Group Analyses. The fMRI analyses were performed for the hippocampus, vmPFC, and rlFG as ROIs. Functional, anatomically constrained ROIs were created for each sample individually (35,36). We used a $p < .05$ threshold within the anatomically defined (Automated Anatomical Labeling atlas) bilateral hippocampus, vmPFC, and rlFG to identify task-responsive voxels within this larger anatomical ROI. Mean contrast estimates for the NoGo > Go contrast were extracted from the resulting maps using SPM8 and were exported to

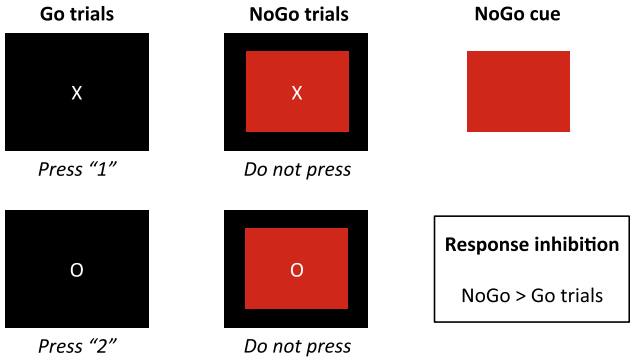

Figure 1. Response inhibition was measured using the Go/NoGo task that followed previous work by Leibenluft *et al.* (34). On Go trials, a white X or O appeared on a black background for 1000 ms. Participants were instructed to respond as fast as possible to this Go trial by pressing a 1 for X and 2 for O. However, one third of the trials were NoGo trials (indicated by a red rectangle behind X or O), and participants were instructed to withhold their response. The stimulus event was followed by a jittered intertrial interval ranging from 1250 to 2500 ms, and a 500-ms white fixation cross. The task consisted of 4 runs separated by three 30-second rest periods. Each run comprised 26 Go trials, 13 NoGo trials, and 14 blank trials distributed randomly. Response inhibition was measured by subtracting correct Go trials from correct NoGo trials.

SPSS 24.0 (IBM Corp., Armonk, NY). Missing data (only for CTQ and pain level) were imputed using mode.

First, correlation analyses were performed to investigate the relationship between hippocampal, vmPFC, and rIFG contrast estimates and PTSD symptoms at 3 and 6 months. Second, elastic net regression was used to define the most optimal model to predict PTSD symptoms in the original sample. Group analyses were conducted using elastic net regularization procedures with SPSS default settings (37). For the predictors in the model, elastic net regression minimizes overfitting by penalizing coefficient estimates, thereby reducing the variance of estimates so that they are more stable and more generalizable to the larger population. Elastic net is particularly well suited to models in which the predictors are highly correlated (38). PTSD symptoms at 3 and 6 months were used as continuous outcome measures in two different models. In addition to hippocampal, vmPFC, or rIFG activation, models incorporated simultaneous estimation of numerous additional predictors that may influence the development of PTSD including demographics (age, gender, race, education), baseline symptoms (PTSD and depression in the ED), and childhood trauma (CTQ); patient- and clinician-rated severity; type of trauma, pain level in the ED; and days between enrollment and scan, treatment, and social support (Table 1). The expected prediction error for each model was estimated with the .632 bootstrap (39). In accordance with the 1-SE rule, the most parsimonious model within 1 SE of the model with minimum expected prediction error was selected. Next, significant predictors resulting from this analysis were used in a linear regression model to predict PTSD symptoms at 3 and 6 months in the replication sample. Finally, correlation analyses and elastic net regression were performed to assess the relationship between PTSD symptoms at 1 month and hippocampal, vmPFC, or rIFG activation.

Task-based whole-brain activation for each group is presented in Supplemental Table S1. Additionally, to investigate the correlation between PTSD symptoms at 3 and 6 months and response inhibition–related activation outside the ROIs, we performed whole-brain multiple regression analyses using PSS as a covariate. The resulting maps were tested for significance at a cluster-defining threshold of $p < .001$ [as recommended by Woo *et al.* (40)], and a $p < .05$ familywise error–corrected critical cluster size of k = 41 was determined using SPM8 and a script (CorrClusTh.m; www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm).

RESULTS

Participants

Demographic and clinical information is presented in Table 1.

Original Sample. Thirty-eight participants were scanned, but after excluding for head motion (>1 mm per repetition time, $n = 5$), falx calcification ($n = 3$), and technical issues during data collection ($n = 3$), 27 participants (13 women) were included in the analyses. Twenty-three participants returned for their 3-month follow-up assessments, and 20 returned for their 6-month follow-up. At 6 months, 25% of participants met criteria for PTSD. Seven participants sought treatment from a psychologist, psychiatrist, or mental health counselor between their index trauma and the 6-month follow-up. Use of treatment services was included in the statistical model.

Replication Sample. Thirty-nine participants were scanned, of which 31 (11 women) were included in the analyses. Participants were excluded for head motion ($n = 5$), falx calcification ($n = 1$), technical issues ($n = 2$), or no behavioral response ($n = 1$). At 3 months, 24 participants returned for their follow-up assessments, and 21 returned for their 6-month assessments. At 6 months, 19% met criteria for PTSD, and 4 participants sought treatment during the course of the study.

fMRI Results

Original Sample. The functional hippocampal ROIs are presented in Figure 2A. The correlation analyses with PTSD symptoms at 3 and 6 months are shown in Figure 2B. Response inhibition–related hippocampal activation correlated significantly with PTSD symptoms at 3 months ($r = -.56$, $p = .006$) and 6 months ($r = -.66$, $p = .002$).[1] No significant correlations with the vmPFC or rIFG were observed.

Lasso regression with elastic net was used to define the most optimal model to predict PTSD symptoms at 3 and 6 months using imaging measures and the demographic and clinical variables in Table 1. Table 2 displays the regression coefficients separately for all variables included in the most parsimonious models predicting PTSD symptoms at

[1] There are different approaches to define the hippocampus, and we therefore reanalyzed the data using the Hammers atlas as recommended by Rodionov *et al.* (68). Again, a significant correlation was demonstrated between bilateral hippocampal activation and PTSD symptoms in the original sample at 3 months ($r = -.48$, $p = .020$) and 6 months ($r = -.58$, $p = .008$), and in the replication sample at 3 months ($r = -.46$, $p = .024$) and 6 months ($r = -.44$, $p = .045$).

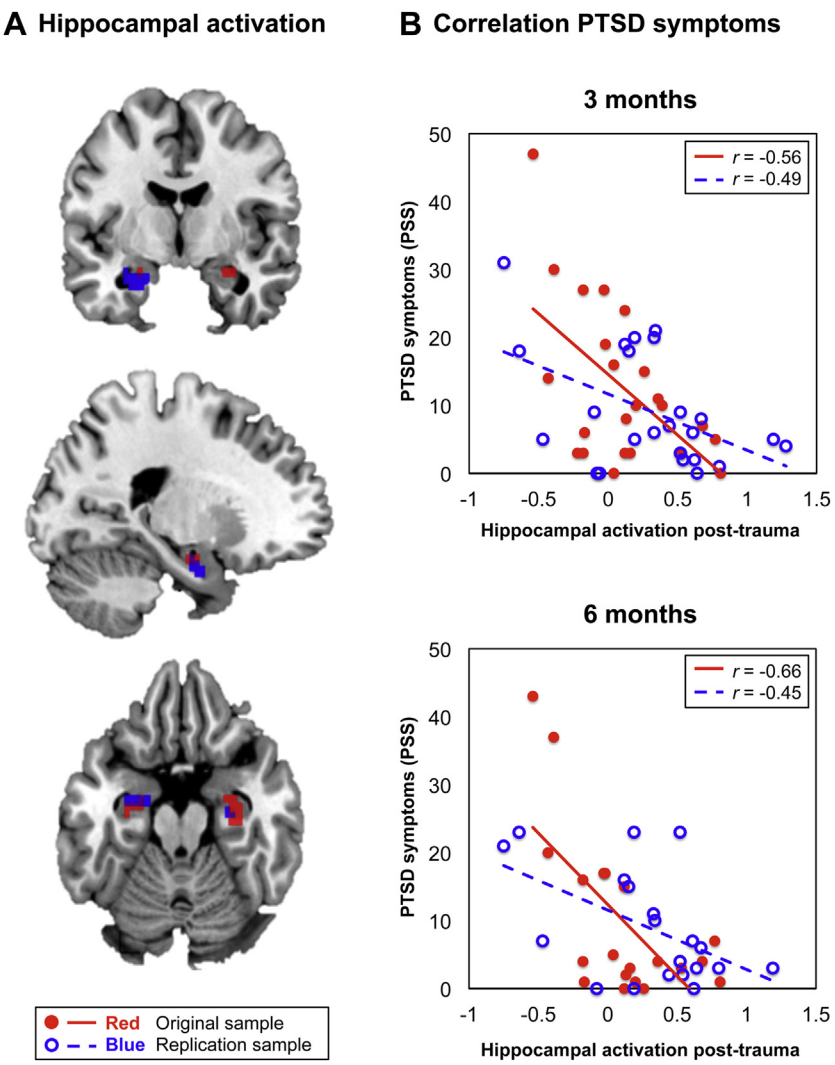

Figure 2. Hippocampal activation predicts posttraumatic stress disorder (PTSD) symptoms. **(A)** Activated voxels for the NoGo > Go inhibition contrast within the Automated Anatomical Labeling atlas–defined bilateral hippocampus. The activated voxels for the original sample (n = 27, k = 16; in red) and the replication sample (n = 31, k = 45; in blue) were extracted for functional region-of-interest analyses. **(B)** Correlation between the contrast estimate in this functional hippocampal region of interest (x axis) and PTSD symptom score (y axis) measured with the PTSD Symptom Scale (PSS) (33). Hippocampal activation significantly correlated with PTSD symptoms at 3 months (original sample, p = .006; replication sample, p = .02) and 6 months (original sample, p = .002; replication sample, p = .04).

3 months and 6 months. For the selected model predicting PTSD symptoms at 3 months, the apparent proportion of explained variance was 0.81 ($F_{11,22}$ = 4.33, p = .01). Hippocampal activation, race, and pain level in the ED were significant predictors, with less hippocampal activation, black/mixed race, and more pain in the ED predicting more PTSD symptoms at 3 months. At 6 months, the apparent proportion of explained variance for the selected model was 0.82 ($F_{9,19}$ = 4.96, p = .01). Less hippocampal activation, black/mixed race, and more depression symptoms in the ED predicted more PTSD symptoms at 6 months.

Replication Sample. Response inhibition–related hippocampal activation in the replication sample also significantly correlated with PTSD symptoms at 3 months (r = −.49, p = .02) and 6 months (r = −.45, p = .04; Figure 2).[1] No significant correlations with the vmPFC or rIFG were observed.

Including all significant predictors defined in the original sample (Table 2) resulted in a significant model to predict PTSD symptoms at 3 months ($F_{3,23}$ = 3.03, p = .05, R^2 = .31, adjusted R^2 = .21) and 6 months ($F_{3,20}$ = 5.74, p = .007, R^2 = .50, adjusted R^2 = .42), with the hippocampus significantly predicting PTSD symptoms at 3 and 6 months.

PSS Before Scan. A significant correlation between PTSD symptoms at 1 month and hippocampal activation was observed in the original sample (r = −.41, p = .04), but not in the replication sample (r = −.11, p = .54). Using elastic net regression in the original sample revealed that hippocampal activation was not associated with PSS at 1 month; moreover, the overall model was not significant. No correlations were observed with the vmPFC or rIFG.

Whole-Brain Analyses. Figure 3 displays the results from the whole-brain analyses (p < .001, and a p < .05 familywise error–corrected cluster threshold of k = 41) showing the negative correlation between PSS at 6 months and the middle cingulate cortex in the original sample, and the positive correlation between PSS at 6 months and the right middle frontal gyrus in the replication sample.

Table 2. Regression Coefficients for Predicting PTSD Symptoms

	Beta	SE	*df*	*F*	*p* Value
Original Sample: Selected Models Using Lasso Regression With Elastic Net					
PTSD symptoms at 3 months					
Hippocampal activation	−0.26	0.10	1	6.18	.03[a]
Race	0.23	0.12	3	3.78	.04[a]
Pain level in ED	0.32	0.11	4	8.44	.002[a]
Depression symptoms in ED [BDI (31)]	0.18	0.08	1	4.57	.06
PTSD Symptoms in ED [PDS (30)]	0.10	0.14	1	0.51	.49
Treatment	0.11	0.09	1	1.33	.27
PTSD symptoms at 6 months					
Hippocampal activation	−0.36	0.10	1	13.19	.005[a]
Race	0.25	0.13	3	3.80	.05[a]
Pain level in the ED	0.13	0.13	2	1.01	.40
Depression symptoms in ED [BDI (31)]	0.31	0.11	1	7.51	.02[a]
PTSD symptoms in ED [PDS (30)]	0.13	0.15	1	0.75	.41
Days between enrollment and scan	−0.01	0.07	1	0.01	.94
	Beta	**SE**	***t***		***p* Value**
Replication Sample: Using the Selected Significant Predictors					
PTSD symptoms at 3 months					
Hippocampal activation	−0.52	3.25	−2.71		.01[a]
Race	−0.25	1.03	−1.32		.20
Pain level in ED	−0.09	0.83	−0.44		.66
PTSD symptoms at 6 months					
Hippocampal activation	−0.42	2.98	−2.47		.02[a]
Race	−0.24	0.89	−1.33		.20
Depression symptoms in ED [BDI (31)]	0.44	0.12	2.50		.02[a]

Lasso regression with elastic net was performed in the original sample. Imaging measures and the demographic and clinical variables in Table 1 were included in the analyses. Regression coefficients for all variables included in the most optimal models to predict posttraumatic stress disorder (PTSD) symptoms at 3 and 6 months are presented. Significant factors were included in linear regression models to predict PTSD symptoms at 3 and 6 months in the replication sample.

BDI, Beck Depression Inventory; ED, emergency department; PDS, Posttraumatic Stress Diagnostic Scale.

[a]$p = .05$.

DISCUSSION

The current prospective, longitudinal fMRI study aimed to identify neurobiological predictors for the development of PTSD by recruiting participants in the ED after a Criterion A trauma, scanning them 1 to 2 months later and assessing PTSD symptoms at 3 and 6 months posttrauma. We are the first to show that less anterior hippocampal activation predicted greater PTSD symptoms at 3 and 6 months posttrauma. Black/mixed race and more pain in the ED predicted more PTSD symptoms at 3 months, and black/mixed race and more baseline depression symptoms predicted more symptoms at 6 months. An out-of-sample test of these predictors in a replication sample showed again that reduced hippocampal activation significantly predicted PTSD symptoms at 3 and 6 months. These data show that increased response inhibition–related activation in the hippocampus predicts decreased risk for developing PTSD symptoms after trauma exposure. The implications of the study are that hippocampal function

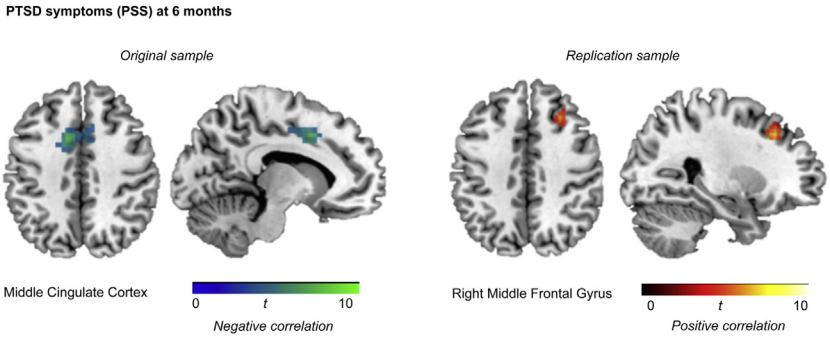

Figure 3. Whole-brain correlations with posttraumatic stress disorder (PTSD) symptoms. Whole-brain analyses ($p < .001$, and familywise error–corrected cluster threshold of k = 41) for the correlation between response inhibition–related activation and PTSD symptoms are displayed for the original sample (left) and replication sample (right). PSS, PTSD Symptom Scale.

could serve as a target for early intervention in traumatized individuals.

The hippocampus is a particularly plastic and vulnerable region of the brain (41). Smaller hippocampal volume has been repeatedly associated with development (42) and persistence (43) of PTSD. This is the first study showing a role for hippocampal activation in the development of PTSD. Although the hippocampus is not typically linked to response inhibition and its role has mainly been demonstrated during contextual fear inhibition (8,9,11), we have previously demonstrated a relationship between hippocampal activation during response inhibition and PTSD symptoms (20,21). Hippocampal functioning in Go/NoGo tasks has also been demonstrated in other studies: less hippocampal activation was shown in heavy drinkers compared with light drinkers (44), in violent adolescents (45), and in cannabis-using attention-deficit/hyperactivity disorder patients (46) relative to control subjects. Similarly, hippocampal activation during Go/NoGo tasks was found to increase posttreatment in adolescents with bipolar disorder (47). Taken together, these findings suggest that lower levels of hippocampal involvement in response inhibition may contribute to transdiagnostic risk for psychiatric dysfunction, particularly for disorders with an impulsive motivational component. Additional basic research is needed to better define the specific cognitive functions performed by the hippocampus during response inhibition.

The hippocampus plays a key role in many aspects of cognition that are relevant to PTSD risk. The hippocampus is essential for the formation and retrieval of new memories, especially episodic memories consisting of autobiographical events and contextual information (48,49). Impaired episodic memory of traumatic events is thought to contribute to the development of PTSD (50) and is related to hippocampal structure (51,52) and function (53). Furthermore, the hippocampus plays a crucial role in contextual modulation of behavior by comparing new sensory inputs to existing representations (22). While we did not directly manipulate contextual cues, we likely tapped into the role of the hippocampus in processing information related to the NoGo trials (i.e., presence of a red background). As evident from animal research, the hippocampus is involved in occasion setting, where a contextual cue modulates discrimination between different stimuli (54,55). Holland *et al.* (56) suggested that hippocampal lesions hinder inhibitory learning about contextual and explicit cues, whereas dorsal hippocampal lesions in another study specifically impacted the processing of contextual cues (57). These studies emphasize the importance of the hippocampus in context processing and stimulus discrimination.

A recent perspective article suggested that dysregulation within the context-processing circuitry, consisting of the hippocampus and vmPFC, is a potentially key deficit in PTSD (23), and our findings support this growing literature. Another potential mechanism by which the hippocampus may participate in response inhibition is pattern separation, i.e., the conversion of comparable experiences or events into separate, nonoverlapping representations (22). This hippocampus-dependent mechanism is fundamental to successful context processing, and impairment results in the inability to discriminate two similar yet different situations. Several studies have demonstrated that PTSD patients show impaired memory for specific patterns (58), poor processing of spatial cues (59), and impaired safety discrimination (3). The hippocampus is critical for the regulation of impulsivity. Hippocampal lesions in rats resulted in impulsive choice, reflected in a preference for an immediate small reward over a delayed, larger reward (60). Impulsive choice may explain reduced inhibition-related hippocampal activation seen in heavy drinkers (44), violent adolescents (45), and attention-deficit/hyperactivity disorder patients (46). Impulsivity has also been associated with the development of PTSD in both military (61) and civilian (62) populations. There is clear evidence for the role of the hippocampus in PTSD risk, suggesting that better episodic memory and the ability to use and integrate contextual information may help an individual successfully regulate behavioral and emotional responses. Many previous studies have linked hippocampal structure to PTSD [e.g., (42,43,52)], and some have shown altered hippocampal activation (10,20,63). This is, however, the first study to examine hippocampus function prospectively in the early aftermath of trauma and show its critical role in the development of PTSD symptoms.

vmPFC functioning during the Go/NoGo task has previously been shown to be impaired in PTSD (17); however, here we did not show its involvement in predicting the development of PTSD. As demonstrated by Stevens *et al.* (64), vmPFC activation in PTSD may be specifically related to childhood trauma exposure. Also, the rIFG was not related to current or future PTSD symptoms. An explanation for this may be that in previous studies (18,19) the rIFG was associated with PTSD during proactive inhibition, i.e., the anticipation of a stop signal, whereas the simpler task we used here did not include an anticipation component. Alternatively, the differences in study sample, type of trauma, and duration of symptoms may explain the absence of rIFG findings in this study.

In the whole-brain analyses, we observed a positive correlation with the right middle frontal gyrus, and a negative correlation between PTSD symptoms and inhibition-related activation in the middle cingulate cortex. The right middle frontal gyrus is activated during Go/NoGo tasks, particularly during more complex stimulus identification (65). The middle cingulate cortex is typically activated during motor tasks and is highly connected with the precentral gyrus (66), a motor area involved in the planning and execution of movements. Previous studies have observed a relationship between inhibition-related motor and frontal activation in PTSD patients (16–18), and here we show that reduced activation in motor control regions is also related to the development of PTSD. Furthermore, our results support the hypothesis from a pre-/posttreatment study that showed reduced inhibition despite clinical improvement, and therefore postulated that it may represent a vulnerability factor for development of PTSD (19). However, the observed whole-brain correlations were not the same across samples and should therefore be interpreted with caution.

An important strength of this study is the inclusion of a replication sample. The hippocampus finding was replicated, even though MRI scans of the second sample were collected at a different scanner site, using different scan parameters, and despite the fact that the range of PTSD symptoms was smaller in the replication sample (6 months, range = 0 to 23) than in the original dataset (range = 0 to 43). This demonstrates that the correlation was not dependent on more severe PTSD cases in

the original sample. Hippocampal activation also predicted the development of mild PTSD symptoms, underscoring the robustness of inhibition-related hippocampal activation as a predictor, and the potential generalizability of this finding.

One of the limitations of this study was the sample size of each individual sample. There was a relatively high number of dropouts due to head motion, falx calcification, and technical issues during data collection. However, as the numbers were comparable for the two samples and the final groups did not differ on demographic or clinical measures, we believe that the impact of this dropout on the results is negligible. A bigger sample is needed to appropriately power exploratory voxelwise analyses of the whole brain. The majority of our population consisted of survivors of severe accidents; therefore, replication in military samples or individuals with high levels of interpersonal trauma is of interest. However, type of trauma did not influence PTSD outcome in our analyses. Another limitation of the current study is the timing of the MRI scan. The scan was collected on average 54 days after trauma, rather than immediately posttrauma. It is likely that some individuals have developed PTSD symptoms at this time, and PTSD severity may therefore correlate with hippocampal activation. Indeed, we observed a correlation between hippocampal activation and PTSD symptoms at 1 month in the original sample; however, this correlation was less strong than the correlations with PTSD symptoms at 3 and 6 months. Furthermore, this correlation was not observed in the replication sample, and was not associated with PTSD symptoms at 1 month in the elastic net regression. There are logistical and medical barriers to conducting scans immediately after trauma, especially if there was any injury to the head or body. On the other hand, the current approach has the benefit of capturing any trauma-related neural changes, i.e., direct mechanical action, systemic effects, or neurocognitive influences. Future studies collecting data prior to trauma exposure are of high interest to determine pretrauma vulnerability factors (67). However, scanning prior to trauma exposure, particularly in a civilian sample, is challenging and requires a very large sample. Finally, a more complex task with manipulation of contextual cues could possibly provide more insight in underlying processes, and moreover, may show a relationship with hippocampal functioning or PTSD symptoms. This is of high interest as it is not always feasible to scan recently traumatized individuals to assess risk for PTSD.

In conclusion, we showed that decreased hippocampal activation during response inhibition in the first months posttrauma significantly predicts an increased risk for the development of PTSD. Conversely, increased recruitment of the hippocampus may help an individual to successfully regulate behavioral and emotional responses, beneficial for coping with a traumatic experience. This finding may contribute to an early identification of trauma survivors at risk for PTSD. Furthermore, the identification of specific mechanisms that affect risk for PTSD in the period after trauma exposure generates opportunities for the development of more specific targets for intervention and treatment, such as psychotherapy or pharmacological interventions aiming to increase hippocampal activation. Because of its inherent neural plasticity, the hippocampus may respond well to these interventions. Future studies targeting hippocampal-dependent functioning in the immediate aftermath of trauma are of high interest.

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