Episodic memory after trauma exposure: Medial temporal lobe function is positively related to re-experiencing and inversely related to negative affect symptoms

Jennifer S. Stevens[a,*], Renuka Reddy[a], Ye Ji Kim[a], Sanne J.H. van Rooij[a], Timothy D. Ely[a], Stephan Hamann[b], Kerry J. Ressler[a,c,d], Tanja Jovanovic[a]

[a] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA
[b] Department of Psychology, Emory University, Atlanta, GA, USA
[c] Harvard Medical School, Boston, MA, USA
[d] McLean Hospital, Belmont, MA, USA

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ABSTRACT

Hippocampal structure is particularly sensitive to trauma and other stressors. However, previous findings linking hippocampal function with trauma-related psychopathology have been mixed. Heterogeneity in psychological responses to trauma has not been considered with respect to hippocampal function and may contribute to mixed findings. To address these issues, we examined associations between data-driven symptom dimensions and episodic memory formation, a key function of the hippocampus, in a trauma-exposed sample. Symptom dimensions were defined using principal components analysis (PCA) in 3881 trauma-exposed African-American women recruited from primary care waiting rooms of a large urban hospital. Hippocampal and amygdala function were subsequently investigated in an fMRI study of episodic memory formation in a subset of 54 women. Participants viewed scenes with neutral, negative, and positive content during fMRI, and completed a delayed cued recall task. PCA analysis produced five symptom dimensions interpreted as reflecting negative affect, somatic symptoms, re-experiencing, hyper-arousal, and numbing. *Re*-experiencing was the only symptom type associated with hippocampal function, predicting increased memory encoding-related activation in the hippocampus as well as the amygdala. In contrast, the negative affect component predicted lower amygdala activation for subsequently recalled scenes, and lower functional coupling with other important memory-related regions including the precuneus, inferior frontal gyrus, and occipital cortex. Symptom dimensions were not related to hippocampal volume. The fMRI findings for re-experiencing versus negative affect parallel differences in behavioral memory phenomena in PTSD versus MDD, and highlight a need for more complex models of trauma-related pathology.

1. Introduction

Although numerous studies have shown a relationship between traumatic stress and hippocampal structure (O'Doherty et al., 2015; Riem et al., 2015), the role of hippocampal function in trauma-related psychopathology is less clear. The hippocampus is critically involved in the formation of episodic memories (Eichenbaum, 2004; Squire and Zola-Morgan, 1991; Tulving and Markowitsch, 1998), defined as consciously-accessible memories of specific personal experiences (Tulving, 2002). However, relatively few studies have investigated how prior trauma exposure influences episodic memory function in the hippocampus or the amygdala (typically involved in the formation of episodic

memories for emotional stimuli), and the existing findings have been mixed (Brohawn et al., 2010; Dickie et al., 2008, 2011; Hayes et al., 2011; Thomaes et al., 2013; Thomaes et al., 2009). Disagreements may be related, in part, to the large heterogeneity in post-traumatic stress disorder (PTSD) symptoms across individuals, and the fact that co-morbid depression symptoms are often ignored. In the aftermath of trauma, similar rates of major depressive disorder (MDD) and PTSD diagnoses are observed (Shalev et al., 1998), and the two are highly co-morbid (Breslau et al., 2000; Shalev et al., 1998). To address some of these outstanding issues, here we conducted an fMRI study of episodic memory encoding, examining links with continuous symptom dimensions related to PTSD and depression in a trauma-exposed sample.

Relative to other brain regions, the hippocampus is particularly sensitive to trauma and other forms of stress. Studies of human hippocampal structure indicate reduced volume related to trauma, PTSD, and MDD (Logue et al., 2017; O'Doherty et al., 2015; Riem et al., 2015; Schmaal et al., 2015), particularly in CA3 and the dentate gyrus (Hayes et al., 2017; Teicher et al., 2012), regions of the hippocampus that perform central roles in episodic memory function (Eichenbaum, 2004). Despite similar decreases in hippocampal volume in both PTSD and MDD, these disorders are associated with very different memory-related symptoms. In PTSD, intrusive conscious recollections of the initial trauma are a central feature, consistent with the possibility of an overactive episodic memory system. In contrast, individuals with MDD show less detailed autobiographical memory than healthy individuals (Brittlebank et al., 1993; Williams and Scott, 1988), and impaired episodic memory performance (Bearden et al., 2006; Burt et al., 1995). Such findings suggest that neural processes supporting episodic memory function may differ in trauma-exposed individuals with intrusive PTSD symptoms versus depressive symptoms.

Consistent with this possibility, studies linking hippocampal function with trauma-related pathology have produced mixed results. Among previous studies of episodic memory encoding in PTSD, two found increased encoding-related hippocampal activation (Brohawn et al., 2010; Thomaes et al., 2009), one found decreased hippocampal activation (Hayes et al., 2011), and three found no association (Dickie et al., 2008, 2011; Thomaes et al., 2013). For negative stimuli, PTSD-related differences in encoding were also observed in the amygdala (Brohawn et al., 2010; Dickie et al., 2008; Hayes et al., 2011), a region that coordinates emotional responses and whose activity has been shown to enhance hippocampal encoding-related processes (Cahill and McGaugh, 1998; McGaugh, 2002). These findings have been interpreted as providing a possible neural correlate of PTSD vulnerability, such that vulnerable individuals might more strongly engage the amygdala in memory encoding of negative or threatening experiences, facilitating hippocampal encoding or post-encoding processes, and resulting in longer-lasting or more detailed trauma memories.

Depressive symptoms following trauma have not been examined with respect to memory encoding in the hippocampus and amygdala. However, trauma-related depression is likely to share some of the neural abnormalities observed in MDD. Patients with MDD show lower involvement of the hippocampus in memory for positive stimuli (van Tol et al., 2012), and greater involvement of the amygdala for negative stimuli (Ai et al., 2015; van Tol et al., 2012). There is a great need for approaches that consider both PTSD and depression symptoms together. For example, a study of symptom dimensions across several diagnostic categories (PTSD, MDD, healthy controls) showed that depression symptoms predicted impaired resting-state connectivity between the amygdala and dorsolateral prefrontal cortex, dorsal anterior cingulate cortex (ACC), and anterior insula, whereas anxiety symptoms predicted hyperconnectivity between the amygdala and subgenual ACC (Satterthwaite et al., 2016). These associations were observed irrespective of the primary diagnosis. Similar research efforts identifying heterogeneous symptom presentation in the trauma literature have focused on hyper-arousal versus dissociative symptom profiles (Lanius et al., 2010). In complex PTSD, which often involves dissociation, depressive symptoms were found to predict greater hippocampal activation to negative stimuli (Thomaes et al., 2013). Studies of this type can identify cross-cutting risk factors underlying multiple diagnoses, and instances in which abnormalities in brain function do not map cleanly onto diagnostic categories.

Many previous efforts have been made to define trauma-related symptom dimensions. For example, in PTSD, a recent longstanding conceptualization in the DSM-IV-TR outlined three symptom dimensions: re-experiencing, hyper-arousal, and avoidance/numbing symptoms (Association, 2000a). However, studies clustering symptoms in a data-driven manner supported the separation of avoidance versus numbing symptoms (King et al., 1998; Simms et al., 2002) leading to

new symptom clusters for PTSD in the DSM-5 (Association, 2013). In depression, a two-factor solution has been observed, separating negative affect from somatic symptoms (Whisman et al., 2000). However, no widely accepted model has yet emerged which considers both PTSD and depression symptoms in a single model of psychological responses to trauma.

Here we constructed symptom dimensions using principal components analysis (PCA) of the individual items on the PTSD Symptom Scale (PSS) and Beck Depression Inventory (BDI). PCA analysis facilitated a parsimonious combined analysis of PTSD and depression symptoms because it: 1) defined symptom dimensions in a hypothesis-neutral manner, 2) allowed for the possibility that similar symptoms from both PSS and BDI might cluster together, and 3) addressed potential confounding effects of score range for scales with different numbers of items (17 items on PSS, 21 items on BDI). Principal components were then used to examine associations with hippocampus and amygdala volume, and function in episodic memory function. Participants completed an episodic memory encoding task during functional magnetic resonance imaging (fMRI), viewing neutral, negative, and positive emotional scenes. Thirty minutes following encoding, participants completed a cued recall task. We hypothesized that PTSD and depression symptom severity would be associated with reduced hippocampal and amygdala volumes. We also predicted that encoding-related hippocampal activity would be positively associated with re-experiencing symptoms, and negatively associated with depressive symptoms. Finally, we predicted that the amygdala's contribution to memory encoding, particularly for negative stimuli, would be positively associated with hyper-arousal, re-experiencing, and depressive symptoms.

2. Materials and methods

2.1. Participants

Participants were drawn from a larger study of risk factors for PTSD conducted in a low-socioeconomic status, urban cohort recruited in the general medical clinics of a large public hospital in Atlanta, GA. This study focused on women because of their higher risk for PTSD relative to men (Kessler et al., 2005). To minimize heterogeneity, we included only African-American women. Additional inclusion and exclusion criteria are listed in the Supplementary Methods. $N = 64$ trauma-exposed women completed the MRI study. MRI data were excluded from two participants for falx calcification leading to EPI signal dropout, two for technical problems with the scanner or stimulus presentation, one who fell asleep during scanning, and five participants due to excessive head motion (> 2 mm/volume). The final sample for fMRI analysis included 54 women; demographics and clinical characteristics are shown in Table 1. 21 participants met for current PTSD, and 33 did not and were considered trauma-exposed controls (TC). Study procedures were approved by the Institutional Review Board of Emory University and the Research Oversight Committee of Grady Memorial Hospital, and all participants provided written informed consent prior to participating.

2.2. Psychological assessment

PTSD symptoms were measured using the PSS (Foa and Tolin, 2000), a 17-item self-report measure of PTSD symptom severity over the last two weeks assessing DSM-IV-TR criteria for PTSD (Association, 2000b). Participants who met for current PTSD endorsed at least 1 re-experiencing symptom, 3 avoidance/numbing symptoms, and 2 hyper-arousal symptoms, following DSM-IV-TR. Depression symptoms were measured using the BDI, a 21-item self-report measure of symptom severity (Beck et al., 1988). Adult trauma exposure was quantified as the number of different types of traumas reported as occurring after the age of 18 on the Traumatic Events Inventory (TEI, Gillespie et al.,

Table 1
MRI study sample characteristics (N = 54)

Characteristic			Pearson's r				
	M	SD	PC1 Neg affect	PC2 Somatic	PC3 *Re*-exp	PC4 Hyper-arousal	PC5 Numb
Age	36.9	10.6	− 0.20	− 0.06	0.03	− 0.05	− 0.13
Adult trauma load (TEI)	4.6	2.7	0.13	0.04	0.05	0.32*	0.28*
Childhood trauma load (CTQ)	43.8	18.9	0.42**	0.23	− 0.05	0.30*	0.25
Depression severity (BDI)	13.8	12.8	0.68**	0.30*	0.01	0.21	0.12
PTSD symptom severity (PSS)	14.0	12.0	0.44**	0.18	0.39**	0.42**	0.23
Intrusive	3.3	3.7	0.37**	0.09	0.55**	0.28*	0.12
Avoidance/numbing	5.0	5.4	0.42**	0.14	0.29*	0.41**	0.39**
Hyperarousal	5.6	4.4	0.34*	0.32*	0.31*	0.42**	0.06
Left hippocampus volume (μL)	3681.5	402.7	0.04	− 0.10	− 0.18	0.15	0.18
Right hippocampus volume (μL)	3730.6	403.3	0.05	− 0.06	− 0.14	0.13	0.19
Left amygdala volume (μL)	1603.1	198.5	0.11	− 0.09	0.14	− 0.02	− 0.00
Right amygdala volume (μL)	1614.4	234.5	0.16	− 0.26	− 0.05	0.12	0.05

* $p < 0.05$.
** $p < 0.01$.

2009), an 11-item questionnaire probing traumas including natural disaster, accidental injury, military combat, and interpersonal violence. Childhood trauma exposure was quantified as the total score on the Childhood Trauma Questionnaire (CTQ, Bernstein et al., 1994), a 25-item scale probing dimensions of childhood abuse and neglect.

2.3. PTSD and depression symptom dimension reduction

A principal components analysis (PCA) with Varimax rotation was conducted in IBM SPSS 24.0, with the inputs including the 17 items from the PSS and 21 items from the BDI. Components with eigenvalue > 1 survived. To improve estimation of the PCA component values, PCA was conducted on a larger sample drawn from the parent study. All African-American women who reported at least one lifetime trauma exposure were included (N = 3881, additional sample characteristics outlined in Table S1). The N = 64 women in the MRI study represented a subset of this sample. PCA scores (PCs) were estimated based on the sample of N = 3881, and the PCs for the women in the MRI study were exported and used as predictors in the neuroimaging analyses.

2.4. MRI study procedure

In the fMRI memory encoding task, participants viewed static scenes from the International Affective Picture System (Lang et al., 2008), and made a valence rating of each item (like/neutral/dislike) using a button box. Memory encoding was incidental; participants were not informed of the later memory test or otherwise instructed to remember or attend to the viewed scenes. Trial structure is outlined in Supplementary Methods.

Thirty minutes following the encoding task, participants completed cued recall (2004) and emotion rating tasks outside the scanner. The experimenter gave a verbal cue for each item, reading out loud a 1–3 word phrase that described an item from the encoding task, and the participant indicated recall by describing additional details about the item, which were recorded by the experimenter for later scoring (detailed in Supplementary Methods). Cued recall performance was summarized using the proportion of items recalled out of the total number of items presented during encoding. In the rating task, the 108 items from the encoding task were presented on a laptop, and participants reported subjective emotional arousal responses to the scenes (1 - very little or no arousal, 5 - high arousal). Item order in the encoding, recall, and rating tasks was counterbalanced across participants. Stimulus presentation in the encoding and ratings tasks took place in EPrime 2.0.8 (Psychology Software Tools, Pittsburgh, PA).

2.5. MRI acquisition and analysis

Scanning took place on a 3.0 T Siemens Trio with echo-planar imaging (Siemens, Malvern, PA). High-resolution T1-weighted anatomical scans were collected using a 3D MP-RAGE sequence, with 176 contiguous 1 mm sagittal slices (TR/TE/TI = 2000/3.02/900 ms, 1 mm³ voxel size). Functional images were gathered using 37 3 mm axial slices in an ascending interleaved sequence, with no gap between slices (TR/TE = 2000/30 ms, FA = 90°, 3 mm³ voxel size).

2.5.1. Volumetric analysis

T1 images were processed in Freesurfer version 5.3 (https://surfer.nmr.mgh.harvard.edu). Gray matter volume from subcortical structures was extracted through automated segmentation, and data quality checks were performed following the ENIGMA 2 protocol (http://enigma.ini.usc.edu/protocols/imaging-protocols/), a method designed to standardize quality control procedures across laboratories to facilitate replication. Briefly, segmented T1 images were visually examined for errors, and summary statistics and a summary of outliers ± 3 *SD* from the mean were generated from the segmentation of the left and right amygdala and hippocampus. Regional volumes that were visually confirmed to contain a segmentation error were discarded: 1 participant had the left hippocampal volume discarded; all other volumes were retained.

2.5.2. Analysis of fMRI regional activation

Preprocessing details for the fMRI data are included in the Supplementary Methods. BOLD responses to the scene stimuli were modeled in SPM8, using 6 task conditions: positive recalled, positive not recalled, negative recalled, negative not recalled, neutral recalled, and neutral not recalled. Task-related activity was modeled by convolving 1.5-s scene presentation events in the six conditions with a canonical hemodynamic response function. Six rigid-body motion regressors from re-alignment were also included in first-level models. To examine memory encoding-related activation, activation for scenes that were later recalled was compared with activation to scenes that were not recalled.

Group-level analyses examined the effects of the symptom PCs on encoding-related activation in anatomically-defined regions of interest (ROIs) for the amygdala and hippocampus (Amunts et al., 2005), as well as in exploratory whole-brain analyses. For whole-brain analyses, all symptom PCs were included together in a single regression model. Effects of PTSD diagnosis were modeled as a two-sample *t*-test. SPM's cluster-based statistical correction was implemented with an initial threshold of $p < 0.005$, corrected to a family-wise error (FWE) rate of

$p < 0.05$.

2.5.3. Functional connectivity analysis

Task-based functional connectivity analyses were conducted using the CONN toolbox v.17.a (https://www.nitrc.org/projects/conn). The bilateral hippocampus and amygdala ROIs were used as seed regions. Generalized psychophysiological interaction (gPPI) analyses were performed, to model voxels whose covariance with the hippocampus and amygdala was influenced by recall status (subsequently recalled, not recalled) and emotion condition (neutral, negative, positive). Timecourses extracted from each voxel of the normalized, smoothed fMRI volumes were high-pass filtered at .01 Hz. Individual participants' motion parameters and main effects of task condition were modeled as nuisance covariates. To test for effects of symptom PCs on amygdala-hippocampal connectivity, the bilateral amygdala and hippocampus ROIs were used as target regions (amygdala seed paired with hippocampal target; hippocampus seed paired with amygdala target), using a voxel-wise family-wise error (FWE) rate of $p < 0.05$. For exploratory whole-brain analyses, all symptom PCs (or PTSD diagnosis group in comparison analyses) were included in a single model, and cluster-based statistical correction was established with an initial threshold of $p < 0.005$, FWE-corrected to $p < 0.05$.

2.6. Statistical analyses

For the analysis of regional volume, mixed measures ANOVAs included hemisphere as a within-subjects variable, all symptom PCs included together as between-subjects variables, and covariates to control for lifetime history of trauma exposure: age, CTQ total, and TEI total.

For the memory encoding task, mixed measures ANOVAs were used to model recall, arousal ratings, and activation of the hippocampus and amygdala ROIs. These models included emotion condition (positive, negative, neutral scene stimuli) and hemisphere (left, right; used in ROI analyses only) as within-subjects variables, all symptom PCs, and covariates for age, CTQ total, and TEI total. Significant interactions were investigated using partial correlation analyses that controlled for the covariates of age, CTQ total, and TEI total. Exploratory whole-brain models of fMRI activation and gPPI connectivity were conducted as described in the previous MRI analysis sections

For comparison with previous studies that employed a case-control design, all models were run using PTSD diagnosis (PTSD +, trauma-exposed controls) as a between-subjects variable, instead of the symptom PCs, but retaining all other components of the model.

3. Results

3.1. PCA analysis of PTSD and depression symptoms

Inter-item correlations for items from the PSS and BDI ranged from 0.15–0.59. The PCA produced 5 principal components (PCs) that explained 52.2% of the total variance in symptom measures. Item loadings and the variance accounted for by each component are shown in Table 2. The five components were interpreted as reflecting 1) negative affect, 2) somatic symptoms, 3) re-experiencing, 4) hyper-arousal and reminder avoidance, and 5) numbing.

3.2. Volumes of the hippocampus and amygdala

Descriptive statistics are shown in Table 1. For hippocampal volume, there was no effect of any symptom PC, nor any interaction between symptom PCs and hemisphere. For amygdala volume, there were interactions between the somatic PC and hemisphere ($F(1,44) = 5.82$, $p = 0.02$), and the re-experiencing PC and hemisphere ($F(1,44) = 4.92$, $p = 0.03$), but no significant association with symptom PC in either individual hemisphere (somatic PC: right: $r = -0.25$, $p = 0.08$, left: $r = -0.08$, $p = 0.57$; re-experiencing PC: left: $r = -0.18$, $p = 0.20$,

right: $r = -0.03$, $p = 0.81$). No PC showed a significant main effect on amygdala volume.

3.3. Cued recall performance and emotion ratings

There was an enhancing effect of emotion on memory ($F(2,96) = 63.92$, $p < 0.001$), such that participants showed greater recall for negative and positive scenes than neutral scenes (Fig. 1a). There was also an effect of emotion condition on arousal ratings ($F(2,96) = 33.97$, $p < 0.001$), such that negative and positive scenes were rated as more emotionally arousing than neutral scenes (Fig. 1b). There were no main effects of the symptom PCs on recall or arousal ratings, nor interactions between the PCs and emotion condition, ps > 0.05.

3.4. Memory encoding-related fMRI activation

For the hippocampus, the re-experiencing PC was positively associated with activation to images that were later recalled vs. not recalled (Fig. 2; $F(1,45) = 5.86$, $p = 0.02$). In addition, there was a significant interaction between the re-experiencing PC and emotion condition, $F(2,90) = 6.35$, $p = 0.003$. Follow up analysis showed that the re-experiencing PC was positively correlated with activation to recalled > not recalled items for neutral ($r(49) = 0.44$, $p = 0.001$) and negative stimuli ($r(49) = 0.28$, $p = 0.05$), but not positive stimuli ($r(49) = -0.20$, $p = 0.16$). There were no main effects of any of the other symptom PCs, nor interactions between the other PCs and emotion condition or hemisphere, and no main effect of emotion or hemisphere.

Similarly, for the amygdala, the re-experiencing PC was positively associated with activation to images that were later recalled vs. not recalled (Fig. 2; $F(1,45) = 13.16$, $p = 0.001$). Again, there was an interaction between the re-experiencing PC and emotion condition, $F(2,90) = 5.52$, $p = 0.005$, such that the re-experiencing PC was positively correlated with activation to neutral stimuli ($r(49) = 0.51$, $p < 0.001$), but not negative or positive stimuli, ps > 0.10. In addition, the negative affect PC was inversely associated with amygdala activation (Fig. 2; $F(1,45) = 5.04$, $p = 0.03$), and there was no interaction with emotion condition, $p = 0.54$. There were no main effects of the other symptom PCs, nor interactions between the other PCs and emotion condition or hemisphere, and no main effect of emotion or hemisphere, ps > 0.05.

Whole-brain analyses of the recalled > not recalled contrast are summarized in the Supplementary Results. *Re*-experiencing was positively correlated with encoding-related activation in the bilateral amygdala, left hippocampus, dorsomedial prefrontal cortex (dmPFC), and bilateral inferior frontal gyrus and middle frontal gyrus, and lateral temporal cortex. For the other PCs, there were no significant clusters in which symptoms predicted encoding-related activation.

3.5. Encoding-related connectivity of the hippocampus and amygdala

To better understand how symptom dimensions might influence networks of regions contributing to memory formation, we conducted task-related functional connectivity analyses using the hippocampus and amygdala as seed regions.

3.5.1. Hippocampus seed

For the recalled > not recalled comparison, there was no significant effect of any symptom PC on hippocampal connectivity with the amygdala target region, nor in exploratory analyses of the whole brain.

3.5.2. Amygdala seed

For the recalled > not recalled comparison, there was no effect of the symptom PCs, nor PTSD diagnosis, on amygdala connectivity with the hippocampus target region. In the whole-brain analysis, the negative affect PC predicted less connectivity between the amygdala and

Table 2
Rotated component matrix for symptoms of PTSD and depression, and percent variance accounted for by rotated components

Symptom type	Measure/item #	Symptom	PC1 16.5%	PC2 11.3%	PC3 9.6%	PC4 8.4%	PC5 6.6%
Negative affect	BDI 8	Self-criticalness	**0.71**	0.16	0.15	0.15	0.03
	BDI 14	Worthlessness	**0.71**	0.17	0.07	0.13	0.17
	BDI 3	Past failure	**0.69**	0.13	0.11	0.11	0.16
	BDI 7	Self-dislike	**0.68**	0.20	0.11	0.16	0.19
	BDI 6	Punishment feelings	**0.66**	0.13	0.16	0.14	0.09
	BDI 2	Pessimism	**0.65**	0.19	0.13	0.05	0.24
	BDI 5	Guilty feelings	**0.64**	0.18	0.21	0.15	0.07
	BDI 13	Indecisiveness	**0.60**	0.32	0.09	0.14	0.18
	BDI 1	Sadness	**0.52**	0.31	0.28	0.14	0.20
	BDI 12	Loss of interest	**0.51**	0.40	0.08	0.12	0.37
	BDI 4	Loss of pleasure	**0.50**	0.32	0.11	0.06	0.40
	BDI 9	Suicidal thoughts, wishes	**0.50**	0.12	0.14	0.11	0.05
	BDI 10	Crying	0.40	0.33	0.11	0.23	− 0.02
Somatic symptoms	BDI 16	Changes in sleeping patterns	0.12	**0.70**	0.17	0.13	0.06
	PSS 12	Difficulty sleeping	0.08	**0.53**	0.30	0.25	0.22
	BDI 20	Tiredness, fatigue	0.29	**0.68**	0.09	0.02	0.20
	BDI 15	Loss of energy	0.33	**0.63**	0.08	0.01	0.24
	BDI 18	Changes in appetite	0.19	**0.61**	0.12	0.11	0.04
	BDI 17	Irritability	0.41	**0.54**	0.10	0.22	0.05
	BDI 11	Agitation	0.37	**0.50**	0.15	0.29	− 0.07
	BDI 19	Concentration difficulty	0.46	0.48	0.11	0.19	0.21
	PSS 14	Concentration difficulty	0.31	0.37	0.28	0.37	0.30
Re-experiencing	PSS 1	Intrusive distressing thoughts	0.19	0.13	**0.76**	0.09	0.23
	PSS 3	Flashbacks	0.17	0.13	**0.74**	0.16	0.07
	PSS 4	Intense emotion to reminder	0.21	0.15	**0.69**	0.25	0.17
	PSS 2	Recurrent nightmares	0.14	0.15	**0.65**	0.18	0.09
	PSS 5	Avoid thoughts, feelings	0.14	0.10	0.49	0.47	0.12
	PSS 17	Intense phys rxns at reminder	0.20	0.21	0.46	0.41	0.19
Hyper-arousal, reminder avoidance	PSS 15	Overly alert	0.10	0.17	0.15	**0.70**	− 0.02
	PSS 16	Jumpier, easily startled	0.20	0.21	0.27	**0.61**	0.16
	PSS 6	Avoid activities, places	0.12	0.06	0.35	**0.57**	0.19
	PSS 7	Can't recall import aspects	0.17	0.03	0.05	0.48	0.20
	PSS 13	Irritable, anger outbursts	0.25	0.35	0.27	0.41	0.19
Numbing	PSS 8	Loss interest in activities	0.21	0.20	0.31	0.24	**0.63**
	PSS 9	Detached, cut-off from others	0.26	0.17	0.30	0.34	**0.59**
	PSS 11	Changed future plans, hopes	0.21	0.08	0.32	0.25	**0.55**
	PSS 10	Impaired range of emotions	0.25	0.15	0.15	0.43	0.45
	BDI 21	Loss of interest in sex	0.24	0.40	0.04	− 0.01	0.41

To highlight relationships with individual items, component loadings > 0.50 are highlighted in bold font.

precuneus (xyz = 3, − 79,10, Z = 4.08, k = 114), as well as several additional clusters in occipital cortex (left middle occipital gyrus: xyz = 39, − 72,4, Z = 4.48, k = 109; right lingual gyrus: xyz = 18, − 73, − 11, Z = 4.20, k = 317). Follow-up analyses separated the recalled > not-recalled comparison by emotion condition. For neutral items (Fig. 3), the negative affect PC predicted reduced amygdala connectivity with bilateral occipital cortex, rostral anterior cingulate cortex, and bilateral inferior frontal gyrus. There was no association between the negative affect PC and amygdala connectivity for positive and negative item encoding. There was no effect of any other PC on whole-brain amygdala connectivity for the recalled > not recalled comparison. There were also no differences between the PTSD and control groups.

3.6. Comparison case-control analysis

For the volumes of the hippocampus and amygdala, there was no effect of PTSD diagnosis (PTSD group, control group) and no interactions with hemisphere, ps > 0.60.

For cued recall performance, there was no main effect of PTSD diagnosis, and no interaction between diagnosis and emotion condition, ps > 0.20. For subjective arousal ratings of the scene stimuli, the PTSD group gave lower overall ratings, $F(1,42) = 4.29$, $p = 0.04$, PTSD = 2.40(1.05), TC = 3.08(0.89), but there was no interaction with emotion condition, $p = 0.88$.

For the ROI analyses of the memory encoding task, there were no main effects of PTSD diagnosis, nor interactions between PTSD

diagnosis and either emotion condition or hemisphere, for either the hippocampus or amygdala ROIs, ps > 0.50. Whole brain analyses showed no differences between the PTSD and control groups using the FWE-corrected threshold of $p < 0.05$. Relaxing the initial threshold to a liberal $p < 0.01$, FWE-corrected to $p < 0.05$, showed greater activation in the PTSD group relative to controls in several clusters. These included a cluster overlapping the right superior temporal gyrus and hippocampus (Z = 3.74, xyz = 42, − 31,4, k = 43), as well as the right precentral gyrus (Z = 3.55, xyz = 48,2,40, k = 98), right supplementary motor area (Z = 3.49, xyz = 3, − 10,52, k = 69), and right lingual gyrus (Z = 3.09, xyz = 12,-52,1, k = 43).

The gPPI analyses showed no differences between the PTSD and control groups for either the hippocampus or amygdala seed regions.

4. Discussion

This study examined the effect of trauma-related symptom severity on fMRI activation associated with episodic memory encoding. Dimensionality reduction of symptoms in the larger sample produced principal components corresponding to negative affect, somatic symptoms, re-experiencing, hyper-arousal, and numbing. These components were, for the most part, consistent with previous models of the symptom structure of depression and PTSD (King et al., 1998; Simms et al., 2002; Whisman et al., 2000); only the somatic symptoms PC captured similar symptoms from both the PSS and BDI, including sleep loss and concentration difficulty. The fMRI results supported the hypothesis that re-experiencing symptoms would be associated with
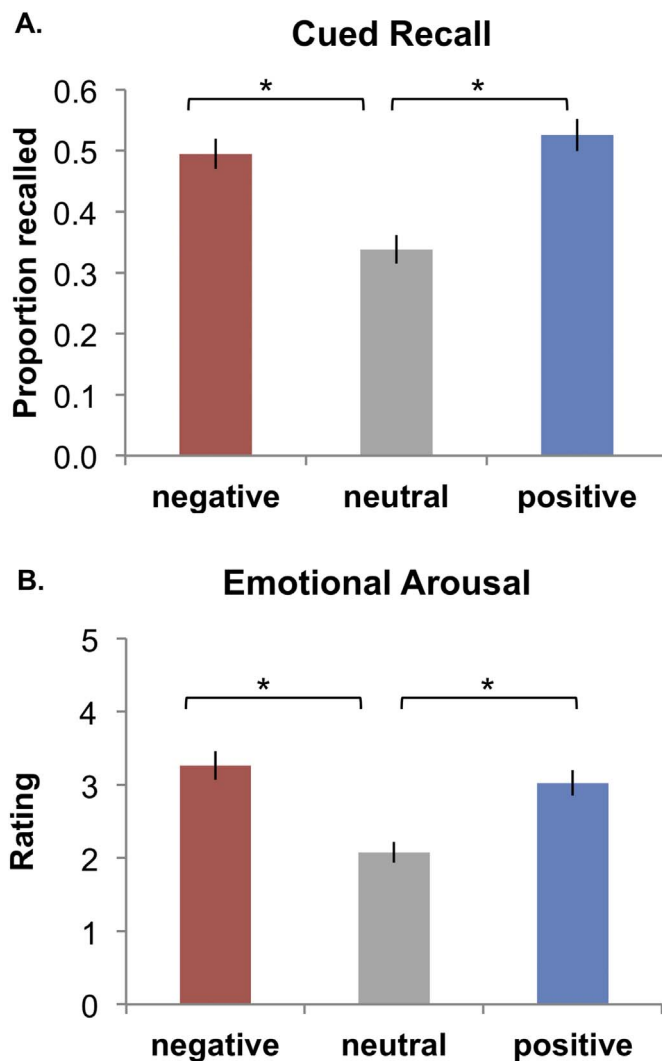
A.

Cued Recall

B.

Emotional Arousal

Fig. 1. Effects of emotion condition on recall and subjective rating of emotion. A: Negative and positive items were better recalled than neutral items (negative: $t = 8.81$, $p < 0.001$; positive: $t = 12.76$, $p < 0.001$). B: Negative and positive items were rated as more emotionally arousing than neutral items (negative: $t = 7.06$, $p < 0.001$; positive: $t = 10.33$, $p < 0.001$). Error bars show $\pm$ 1 SEM.

greater encoding-related activation in the hippocampus and amygdala. The re-experiencing component also positively predicted activation in bilateral inferior and middle frontal gyri, areas associated with semantic elaboration and working memory processes during emotional encoding (Murty et al., 2010). Interestingly, the negative affect component showed the opposite effect in the amygdala, such that greater symptoms predicted less encoding-related activation. This is the largest study to examine the effect of trauma-related symptoms on the neural correlates of episodic memory function, and the first to use data-driven symptom factors. This approach allowed us to capture neural phenotypes associated with different subsets of trauma-related symptoms (e.g., re-experiencing versus negative affect), which would not otherwise be observed in more traditional case-control analyses.

Among the five symptom types captured in the current study, the only symptom dimension that was associated with hippocampal episodic memory processes was re-experiencing. Symptom severity on the re-experiencing PC predicted greater encoding-related activation in the hippocampus, as well as the amygdala. In both regions, this effect was qualified by an interaction with emotion condition, where re-experiencing had the strongest influence on encoding-related activation to neutral stimuli. This was an unexpected finding, as we originally hypothesized that the encoding of negative stimuli would be most strongly

related to re-experiencing symptoms, based on the idea that individuals who more deeply encode negative arousing material may form maladaptive memories of traumatic events. However, the findings were consistent with a previous study of episodic encoding in PTSD, in which trauma-exposed controls engaged the amygdala and hippocampus more when encoding negative than neutral stimuli, whereas individuals with PTSD engaged the amygdala and hippocampus more for neutral than negative stimuli (Hayes et al., 2011).

One possible interpretation of the relationship with neutral scenes is that there may have been a ceiling effect for emotional scenes. Consistent with previous studies in healthy samples (Dolcos et al., 2004; Hamann et al., 1999), we observed an enhancing effect of emotion on cued recall performance, such that participants recalled more negative and positive than neutral items. This effect is thought to be mediated by the amygdala, and its facilitation of hippocampal encoding-related processes (Dolcos et al., 2004; Hamann et al., 1999). It is possible that the amygdala and hippocampus were strongly engaged by all participants during the encoding of negative and positive scenes, and this ceiling-like effect masked relationships with symptom severity.

A more interesting possibility is that individuals with high re-experiencing symptoms devoted additional resources to encoding neutral scenes because they did not down-regulate activation of threat neurocircuitry to neutral or "safe" stimuli. This is consistent with previous studies in PTSD showing heightened hippocampal activation and physiological responses to a safe stimulus or context during fear conditioning and extinction, even when subjective reports indicated that patients were aware that the stimulus or context did not present a threat (Garfinkel et al., 2014; Jovanovic et al., 2010; Kaczkurkin et al., 2017). Prevailing theories of memory hypothesize that an adaptive function of the enhancing effect of emotion on memory is to prioritize the storage of goal-relevant information (Levine and Edelstein, 2009; Mather and Sutherland, 2011). Individuals with high re-experiencing symptoms may prioritize the information contained in the neutral scenes as goal-relevant. The current study cannot distinguish whether high levels of encoding-related activation in the amygdala and hippocampus represent a trait-like risk factor that pre-dates trauma exposure, or whether this arises after trauma. It may be that a stress-related increase in episodic memory function following trauma (a potentially adaptive response to a dangerous environment) may over time result in maladaptive prolonged maintenance of re-experiencing symptoms.

It was notable that there was no relationship between the re-experiencing PC (or any other symptom dimension) and cued recall performance. On one hand, the absence of any effect of symptoms on behavior aids with interpretation of the neuroimaging findings, as effects of the symptom PCs on fMRI activation were not confounded by the number of trials included in the recalled versus not recalled conditions. It is often the case in neuroimaging studies that individual differences in neural function are not reflected in behavior, and this has been highlighted as one of the primary advantages of studying neurobiological phenotypes in addition to self-report and behavior (Gottesman and Gould, 2003; Hariri et al., 2002). On the other hand, however, it is not clear whether greater hippocampus and amygdala activation reflects an augmentation of episodic memory processes, or inefficient/compensatory processes that do not enhance memory encoding.

Such changes in function may occur even in the absence of impacts on hippocampal volume. Here we observed no association between hippocampal volume and re-experiencing, or any other symptom PC. This was somewhat unexpected given that both PTSD and depression symptoms have previously been linked with smaller hippocampal volumes in trauma-exposed samples (Lindauer et al., 2004; Villarreal et al., 2002). We also did not observe differences in volume in case-control analyses. The fact that we did not replicate such findings may be related to our dimensional approach in which we recruited broadly from a general civilian population at high risk for trauma, who had a broad range of symptoms and a sub-syndromal mean, whereas most previous studies focused specifically on groups that met diagnostic
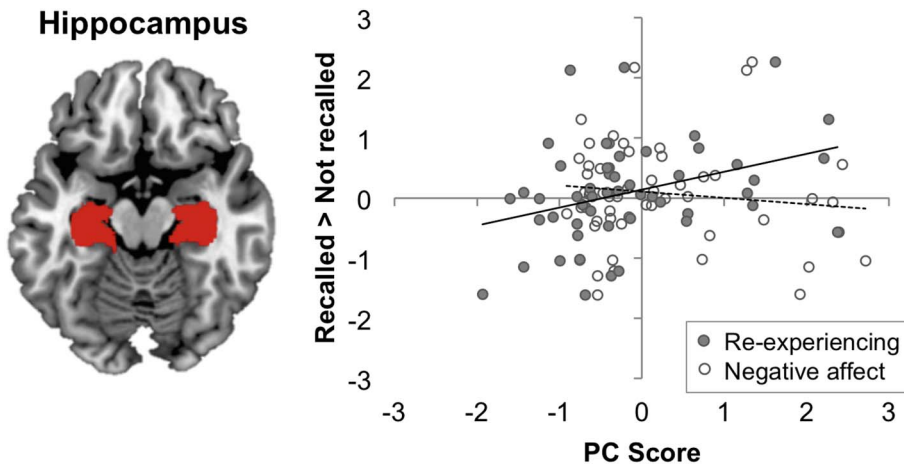
Fig. 2. Effects of re-experiencing and negative affect symptoms on encoding-related activation in the hippocampus and amygdala. Contrast estimates for the recalled > not recalled contrast are plotted for the hippocampus (red) and amygdala (green) ROIs, shown on axial brain slices. Solid regression lines indicate re-experiencing symptoms, and dotted lines indicate negative affect symptoms. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
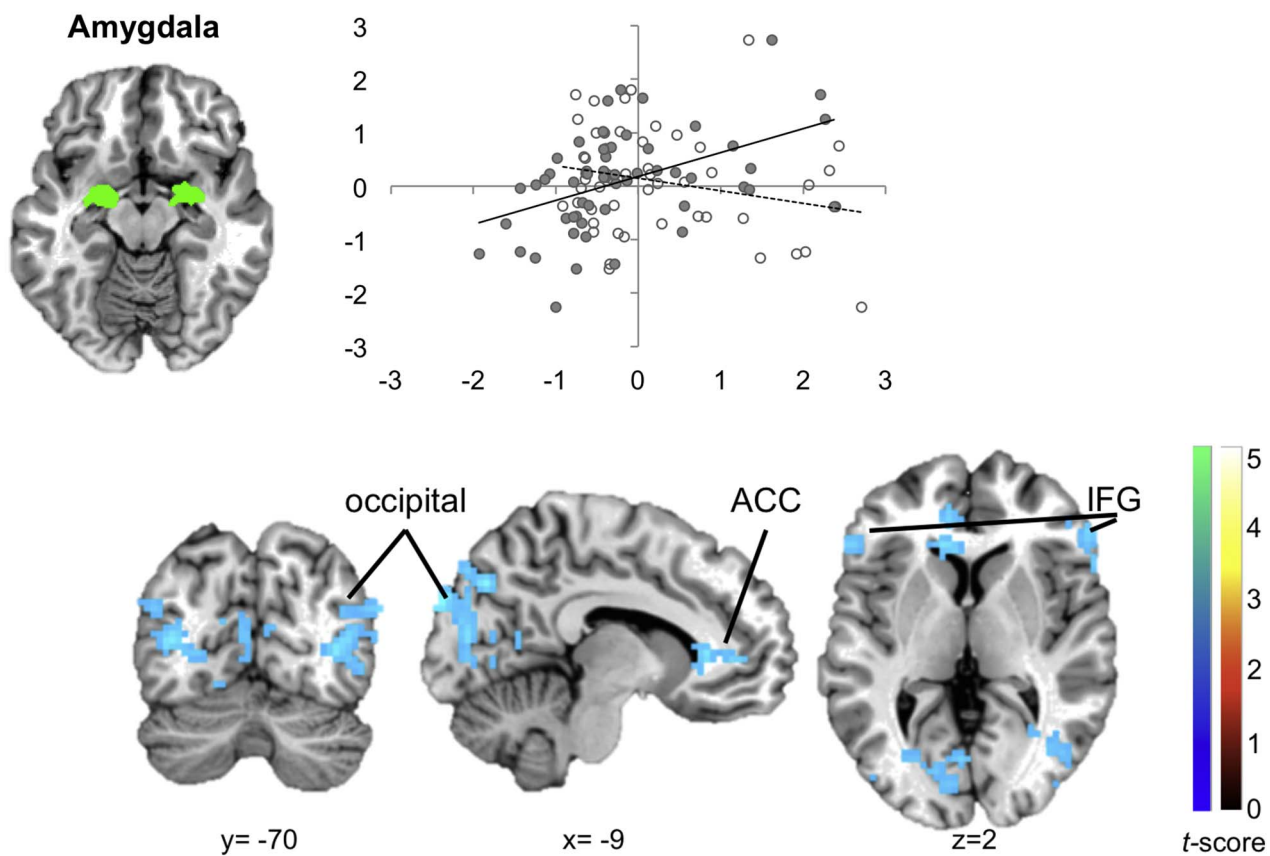
Fig. 3. Task-related functional connectivity analyses for the bilateral amygdala seed region. For the encoding of neutral items (neutral recalled > neutral not recalled), the negative affect PC predicted lesser connectivity between the amygdala and several cortical clusters including bilateral occipital cortex (left: xyz = − 39, − 70,10, Z = 4.21, k = 739; right: xyz = 18, − 55, 10, Z = 3.75, k = 288; xyz = 18, − 76, − 14, Z = 3.61, k = 84), rostral anterior cingulate cortex (ACC; xyz = − 3, 41,4, Z = 3.72, k = 74), and bilateral inferior frontal gyrus (IFG; left: xyz = − 57,32,13, Z = 4.03, k = 111; right: xyz = 60,17, − 2, Z = 4.25, k = 85; xyz = 27,29,25, Z = 4.51, k = 103).

criteria for PTSD. Although not significant, the trend was for a negative association between re-experiencing symptoms and hippocampal volume; dimensional models may require larger sample sizes to observe relationships that are apparent in extreme-phenotypes models.

A very different pattern of findings emerged for the negative affect PC. We observed a negative correlation with encoding-related amygdala activation, even when controlling for trauma history, and no interaction with stimulus emotion condition. These findings contradicted our prediction that depressive symptoms would predict greater encoding-related amygdala activation, motivated by previous studies of MDD (Ai et al., 2015; van Tol et al., 2012). In contrast with studies of

MDD, here we focused on a specific aspect of depressive symptoms—those reflecting negative affect—in a cohort of participants who had all experienced moderate to high levels of trauma. A lesser involvement of the amygdala in memory encoding in individuals with high levels of negative affect may reflect an overall disengagement of amygdala-mediated emotional or goal-related processes from the processes involved in episodic memory formation. The gPPI findings supported this idea, showing that the negative affect PC predicted reduced encoding-related connectivity between the amygdala and precuneus, as well as visual occipital regions and the inferior frontal gyrus. Reduced connectivity with the precuneus was notable because this region has

been implicated in memory-related visual imagery (Fletcher et al., 1995), and a similar impairment in resting state connectivity of the hippocampus and precuneus/posterior cingulate has previously been associated with PTSD numbing symptoms (Miller et al., 2017). Relatedly, connectivity between the amygdala and visual cortical regions has been interpreted to reflect perceptual processing of salient aspects of scene stimuli (e.g., Vuilleumier and Driver, 2007). Additionally, the left inferior frontal gyrus has been implicated in semantic elaboration processes during encoding that facilitate later memory (Murty et al., 2010). Taken together, the findings suggest impairment in amygdala-mediated facilitation of sensory and elaborative processing during memory formation in individuals with high negative affect following trauma.

The different profiles of findings for re-experiencing versus negative affect were consistent with the behavioral literatures on episodic memory showing impairing increases in episodic memory in PTSD, and deficits in MDD. These differences may explain why previous fMRI studies observed mixed results when studying episodic memory in PTSD, a disagreement that has contributed to a lack of emphasis on the study of hippocampus-dependent function post-trauma, relative to the emphasis on amygdala-centric fear systems. Previous studies primarily employed a case-control design (Brohawn et al., 2010; Dickie et al., 2008, 2011; Hayes et al., 2011; Thomaes et al., 2013; Thomaes et al., 2009), possibly weighting toward re-experiencing symptoms on the one hand, or negative affect symptoms on the other. Studies that observed greater hippocampal and amygdala contributions to memory encoding were similar to the current study in that participants had high levels of PTSD and depression symptoms, with trauma exposure primarily in adulthood, and most female (Brohawn et al., 2010; Dickie et al., 2008; Thomaes et al., 2009). In our case-control analyses, our findings were directionally consistent with these studies, showing greater hippocampal activation in the PTSD versus control group in whole-brain analysis, but only when relaxing the statistical threshold. In contrast, the effects of the re-experiencing PC were large, for example explaining 19% of the variance in hippocampal encoding-related activation for neutral stimuli, above and beyond effects of age, childhood trauma, and adult trauma load. These findings illustrate the power of dimensional analyses to detect symptom-related abnormalities that would not be clear in comparisons based on diagnostic group, and may be particularly relevant to understanding the neurobiology of individuals who have impairing symptoms following trauma but do not meet diagnostic criteria across all DSM-based symptom clusters.

Several limitations must be noted. First, the fMRI study was conducted in African-American women. The sample was selected because of increased risk for trauma-related psychopathology in women, and particularly minority women living in an urban environment with high levels of community violence. However, much of the previous research on hippocampal and amygdala structure and function has been conducted in male veteran samples, and further research is needed to investigate the extent to which these findings might generalize. Second, this was a cross-sectional study sampling current symptom levels, and it cannot directly address questions about vulnerability for trauma-related psychopathology. Third, we investigated memory using a cued recall task, which limits our ability to make direct comparisons with previous studies that used recognition tasks.

4.1. Conclusions

The findings indicated that, in trauma-exposed individuals, re-experiencing symptoms predicted greater involvement of the hippocampus and amygdala in episodic memory encoding, whereas negative affect symptoms predicted reduced involvement of the amygdala in encoding, and reduced connectivity with a network of regions involved in visual imagery and elaboration. These findings highlight the need for additional consideration of heterogeneity in psychological responses to trauma, while also pointing to neural targets for interventions in

treating those responses.

Declaration of interest

The authors declare no conflict of interest, financial or otherwise.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2017.11.016.

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