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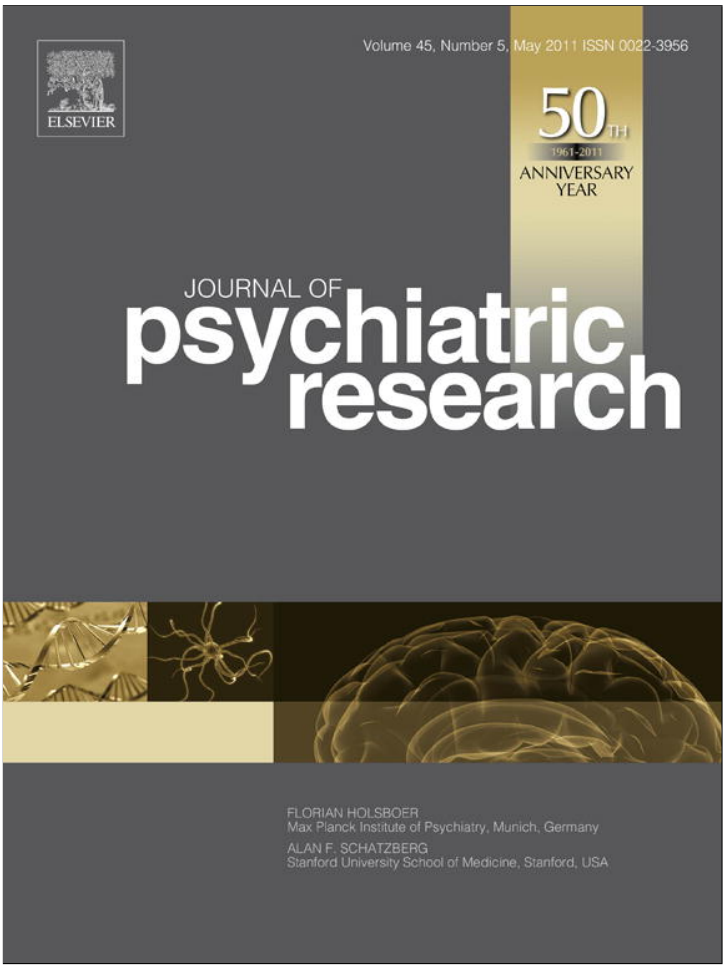

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Functional neuroimaging of emotionally intense autobiographical memories in post-traumatic stress disorder

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ABSTRACT

Post-traumatic stress disorder (PTSD) affects regions that support autobiographical memory (AM) retrieval, such as the hippocampus, amygdala and ventral medial prefrontal cortex (PFC). However, it is not well understood how PTSD may impact the neural mechanisms of memory retrieval for the personal past. We used a generic cue method combined with parametric modulation analysis and functional MRI (fMRI) to investigate the neural mechanisms affected by PTSD symptoms during the retrieval of a large sample of emotionally intense AMs. There were three main results. First, the PTSD group showed greater recruitment of the amygdala/hippocampus during the construction of negative versus positive emotionally intense AMs, when compared to controls. Second, across both the construction and elaboration phases of retrieval the PTSD group showed greater recruitment of the ventral medial PFC for negatively intense memories, but less recruitment for positively intense memories. Third, the PTSD group showed greater functional coupling between the ventral medial PFC and the amygdala for negatively intense memories, but less coupling for positively intense memories. In sum, the fMRI data suggest that there was greater recruitment and coupling of emotional brain regions during the retrieval of negatively intense AMs in the PTSD group when compared to controls.

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1. Introduction

Neuroimaging studies of traumatic experiences in post-traumatic stress disorder (PTSD) and other disorders (e.g., Driessen et al., 2004; Lanius et al., 2001; Lanius et al., 2004) have observed consistent differences in regions that are frequently recruited during autobiographical memory (AM) retrieval (Cabeza & St. Jacques, 2007), such as the hippocampus, amygdala, and medial prefrontal cortex (PFC). Reduced volume of the hippocampus, a region critical for memory, is frequently observed in PTSD but it is less clear whether there are also functional changes here (Shin et al., 2006). The amygdala, a region critical in the detection of emotion and the generation of physiological response, is hyperactive during negative emotional tasks in PTSD patients and the level of activity here is associated with the severity of symptoms (Etkin and Wager, 2007; Shin et al., 2006). In contrast, the medial PFC, a region associated with controlled emotional processes, is often hypoactive in PTSD patients (Etkin and Wager, 2007; Shin et al., 2006). Moreover, changes in the coupling between the amygdala and medial PFC may underlie emotional dysregulation symptoms in PTSD (Etkin and Wager, 2007; Frewen and Lanius, 2006; Milad and Rauch, 2007; Shin et al., 2006). Confirming the critical role of the amygdala and medial PFC in the pathogenesis of PTSD, a patient study by Koenigs and colleagues (Koenigs et al., 2008) found that isolated lesions to these brain regions were related to reduced occurrence of PTSD in Vietnam War veterans.

The effect of PTSD on brain regions involved in AM suggests that a broader examination of personal memory beyond traumatic experiences is warranted (Lanius et al., 2003). Moreover, in participants with PTSD or high levels of symptom severity, the effects of emotional reactions extend beyond traumatic memories to word-cued, important but non-trauma related, and positive autobiographical memories (Rubin et al., 2008b). Thus, although PTSD diagnosis relies on a single traumatic event the impact of PTSD is more widespread across AM. Little, however, is known about the neural basis of these effects.

In the present study, we investigate the neural mechanisms affected by PTSD symptoms during retrieval of a large sample of emotionally intense AMs. We employed a generic cue method that

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used emotional words to elicit AMs in order to distinguish early construction and later elaboration phases of retrieval. Further, we acquired online ratings of emotional experience for parametric analysis of functional activations associated with emotionally intense memories. We explored the hypothesis that PTSD would involve reduced recruitment of the hippocampus, increased recruitment of the amygdala and reduced recruitment of the medial PFC when recalling emotionally intense AMs.

2. Methods

2.1. Participants

Young adult participants were recruited from Duke University (18–35 years of age). Participants in the control group were recruited from a database of healthy young adults, who had participated in previous fMRI research studies. Inclusion criteria for the control group followed procedures that we have routinely used in behavioral studies in the Durham Veteran's Association Medical Clinic (VAMC), which do not include having had a previous trauma. This allowed us to examine the effect of PTSD versus a control group that was a random sample rather than one that was resilient to PTSD. Participants in the PTSD group were recruited from advertisements seeking volunteers who had experienced a traumatic memory and from a pre-screen test administered during a large group screening. The Clinician Administered PTSD Scale (CAPs) was used to determine PTSD diagnostic status in this group (Blake et al., 1995; Weathers et al., 2001). All participants in the PTSD group met the DSM-IV-TR criterion as measured by highly trained master's level clinicians who were experienced in giving the CAPS in a research setting at the Durham VAMC. There were nineteen participants in each group. All participants reported that they were not taking medication known to affect cognitive function (e.g., antidepressants, benzodiazepines, or any other psychiatric medication). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board. Five controls and four participants in the PTSD group were excluded from the analyses because of technical issues (e.g., no key responses recorded) or problems with completing the task as instructed (e.g., falling asleep, not following instructions). Thus, the reported results are based on data from fourteen controls (7 females; mean Age = 24.43, *SD* = 3.73) and fifteen PTSD (11 females; mean Age = 22.21, *SD* = 4.23) participants, except where noted.

Demographic and psychometric data (see Table 1) were obtained in a separate session within one week of the scanning session. As expected, the PTSD group had higher scores on the PTSD Check List (PCL; Weathers et al., 1994) when compared to the control group. The PTSD group also had higher scores on the Beck Depression Index (BDI-II; Beck et al., 1996). There were no group differences in the age, number of years of education, the Weschler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), verbal fluency (FAS), or categorical fluency (animal names and supermarket items).

Table 1
Participant variables by group.

	M		SD		t (27)
	Controls	PTSD	Controls	PTSD	
Age (years)	24.43	22.21	3.73	4.23	1.47
Education (years)	16.50	14.70	2.28	2.56	1.95
PCL[†]	27.93	49.00	7.99	12.94	−5.19*
BDI	3.93	16.86	3.29	11.00	−4.22*
WASI-full IQ	122.36	121.50	7.66	10.14	0.25
WASI-verbal IQ	120.93	123.93	7.87	11.44	−0.81
WASI-performance IQ	118.14	114.72	7.49	10.17	1.01
Verbal fluency	47.43	51.36	10.87	10.49	−0.97
Categorical fluency	23.57	27.50	6.69	6.00	−1.63

*$p < .001$.
† df = 26.

2.2. Materials

Memory cues consisted of 60 emotionally arousing words selected from the affective norms for English words (ANEW) database (Bradley and Lang, 1999), such that there were 30 positive (Valence mean = 7.93, *SD* = 0.45; Arousal Mean = 5.96; *SD* = 0.83) and 30 negative (Valence Mean = 2.17, *SD* = 0.52; Arousal Mean = 6.00; *SD* = 1.03) words that were equally arousing. In order to create auditory cues the words were recorded in a female voice and constrained to an equal duration of 1 s.

2.3. Procedure

The procedure was similar to Daselaar et al. (2008); (also see Greenberg et al., 2005). During scanning participants were asked to search for AMs triggered by the auditory cue words. Participants were instructed to retrieve an AM with specific spatiotemporal coordinates. They indicated when a specific AM was found by making a response on the button-box and then continued to elaborate on the retrieved event in as much detail as possible for the rest of the trial. Thirty seconds following the onset of the auditory cue participants were given auditory instructions to rate the amount of emotion (negatively arousing to positively arousing) and reliving (low to high) associated with the memory on an 8-point scale. Rating responses were self-paced (up to 6 s) and separated by at least 0.5 s, and the order was counterbalanced between participants. There were 6 functional runs, with 10 memory cues in each run (5 positive words and 5 negative word), and an inter-trial interval at least 1.5–7.5 s. Participants were instructed to keep their eyes closed for the duration of each run so that any potential effects of visual imagery were not confounded by external attention to the stimulus.

Immediately following the scanning session participants were asked to provide a short title for the memory retrieved during scanning and to answer additional questions on a subset of the AM questionnaire (e.g., Rubin et al., 2003). Participants were asked to *date* when the event had occurred (e.g., last day to > 10 years ago), to indicate the amount of *vividness* or how clearly the event was remembered, the *perspective* or whether the memory was seen through their own eyes or through the eyes of an outside observer, the *significance* of the memory, and the *physiological* response during retrieval (e.g., heart pounding, etc.). Also, given that AM comprises different types of events (Brewer, 1986) we asked participants to indicate whether the type of memory retrieved was a unique event (referring to a particular time and place), repeated event (memory for an event with multiple occurrences), extended event (occurring longer than one day), or semantic information (long-standing facts about one's own life) (Williams, 1995).

Within two days of the scanning session, participants returned for an additional session in which they were cued by the title they had provided following the scanning session and asked to verbally recall the memories retrieved during scanning. A coder rated the narrative descriptions to determine whether they referred to the event the participant identified as a stressful experience on the PCL. A narrative was rated as referring to a PCL event if it specifically described the event (e.g., "the car flipped three times" if the given event was "car accident") or if it made reference to the event (e.g., "that happened right after the accident"). PCL-related memories

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were recorded as a percentage of the total number of memories. Data were missing from two participants in the PTSD group due to experimenter error. Thus the reported results for this analysis are based on 13 participants in the PTSD group and 14 participants in the controls.

2.4. fMRI methods

2.4.1. Image acquisition

Scanning was conducted using a 4T GE magnet. Auditory stimuli were presented using headphones and behavioral responses were recorded using an eight-button fiber optic response box (Resonance Technology, Northridge, CA). Head motion was minimized using foam pads and a headband. Anatomical scanning started with a T1-weighted sagittal localizer series, and then 3D fast spoiled gradient echo recalled (SPGR) structural images were acquired in the coronal plane (256^2 matrix, TR = 12.3 ms, TE = 5.4 ms, flip angle = 20°, FOV = 240, 68 slices, 1.9 mm slice thickness). Coplanar functional images were subsequently acquired using an inverse spiral sequence (64^2 image matrix, TR = 2000 ms, TE = 6 ms, FOV = 240, flip angle = 60°, 34 slices, 3.8 mm slice thickness).

2.4.2. Image processing

Image processing and analyses were performed using Statistical Parameter Mapping software in Matlab (SPM5; Wellcome Department of Imaging Neuroscience). Functional images were corrected for slice acquisition order, realigned to correct for motion artifacts, and then spatially normalized to a standard stereotactic space, using the template implemented in SPM5. Subsequently, the functional images were spatially smoothed using an 8 mm isotropic Gaussian kernel.

2.4.3. fMRI Analyses

To account for the fact that we used a self-paced paradigm in which participants indicated when they recalled a specific event, we implemented a flexible fMRI design in the context of the general linear model (GLM). The design distinguished six components in each trial: four transient and two sustained regressors. Transient regressors included the memory cue (immediately at onset of the trial), response-related decision processes (750 ms before the response indicating a memory was recalled), and the two ratings (second and third response). Sustained regressors included the memory construction period (from trial onset to response) and the elaboration period (from response to the first rating). Both transient and sustained regressors were modeled by convolving a canonical hemodynamic response function with a vector representing period onsets, but the sustained regressors included a non-zero duration that varied on each trial based on the button press. In order to account for differences in the timing of activations due to the self-paced design, the response indicating that a memory was accessed determined the duration of the memory construction period as well as the onsets of the response and elaboration periods.

2.4.4. Parametric modulation by online ratings

To examine the neural correlates modulated by emotion we employed a parametric approach, which allowed us to examine how deviations from the average effect during the construction and elaboration phases were modulated by discrete changes in emotional intensity on each trial. To identify increases in activity as a function of increasing emotional intensity (i.e., absolute emotion ratings from 1 = low to 4 = high), we created a GLM in which construction and elaboration phases were modulated by the intensity associated with each memory using the first-order parametric modulation option integrated in SPM5. Subsequently, random-effects analyses were performed on the parameter estimate of the parametric regressor for emotional intensity. We assessed group differences in activity modulated by emotional intensity during retrieval of negative (emotion ratings: −1 to −4) and positive (emotion ratings: +1 to +4) AMs by employing a 2 (Group: PTSD, controls) × 2 (Retrieval Phase: Construction, Elaboration) × 2 (Valence: Positive, Negative) ANOVA. A threshold of $p = .005$ and a cluster size >= 5 voxels was chosen to provide a good balance between controlling for both Type I and II error rates for whole-brain analysis (Lieberman and Cunningham, 2009). Given the *a priori* role of the hippocampus and amygdala in AM retrieval and our hypothesis regarding their differential recruitment in PTSD (Etkin and Wager, 2007; Shin et al., 2006), we also conducted an additional region of interest analysis ($p = .01$) on the results of the ANOVA using the Talaraich Daemon Atlas (Lancaster et al., 1997; Lancaster et al., 2000) implemented with PickAtlas software (Maldjian et al., 2003). A similar ANOVA approach examining activity modulated by online ratings of reliving did not reveal any significant finding at the specified threshold; thus, the effects of reliving were not analyzed further.

2.4.5. Task-related functional connectivity analysis

A seed voxel in the medial PFC, in which a Group × Valence interaction was identified by our previous parametric analysis, was further interrogated to examine the functional network of brain regions supporting this valence effect. To find these functional connectivity maps, we employed a second analysis based on individual trial activity (Rissman et al., 2004). Specifically, we first created a GLM in which each individual trial was modeled by a separate covariate, thus yielding different parameter estimates for each individual trial and for each individual subject. The resulting correlation maps were Fisher transformed to allow for statistical comparison. Then, to examine differences in task-related functional connectivity of the medial PFC associated with the valence effect observed in this region we conducted a Group × Valence interaction on emotionally intense AMs in SPM5 ($p = .005$, with a cluster size >=5 voxels).

3. Results

3.1. Behavioral results

Participants were able to recall an event matching the cue on more than 97% of trials (see Table 2 for mean behavioral scores, standard deviations, *t*-scores, *p*-values, and effect sizes). There were no group differences in reaction time to retrieve an AM or in the online ratings of reliving or emotional intensity. Post-scan ratings of vividness, significance, physiological response, date of the memory, and type of memory did not differ between the groups. However, as expected (Rubin et al., 2008a), the perspective from which memories retrieved differed between the two groups. Compared to the control group, memories retrieved by the PTSD group were recalled less from the perspective of one's own eyes and more from an observer's perspective.

We also examined potential group differences in the behavioral data on retrieval of negative versus positive AMs (see Table 2 for means, SD and group comparisons). These results revealed that the PTSD group reported a greater sense of reliving for negative versus positive AMs, $t\,(14) = 2.13$, $p <= 0.05$, and there was a trend for greater reliving in negative AMs when compared to controls, $p = .09$. Further, the PTSD group also reported that negative AMs were more personally significant when compared both to positive AMs, $t\,(14) = 2.68$, $p < .05$, and to controls. No other group effects on valence were observed.

Coding of the narrative descriptions revealed that there were also group differences in the proportion of AMs that were

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Table 2
Mean behavioral responses by group.

	M		SD		t (27)
	Controls	PTSD	Controls	PTSD	
Scanning					
AMs	0.98	0.97	0.04	0.05	1.26
Negative AMs	0.48	0.49	0.06	0.11	−0.54
Reaction time (s)					
AM retrieval	6.51	6.53	2.16	1.83	−0.02
Reliving	2.49	2.39	0.60	0.55	0.46
Emotion	2.14	2.13	0.69	0.53	−0.02
Online ratings					
Reliving	5.03	5.35	1.06	0.68	−0.97
Negative	4.96	5.54	1.07	0.64	−1.87
Positive	5.06	5.24	1.12	0.82	−0.48
Intensity	2.50	2.54	0.08	0.10	−0.33
Negative	2.54	2.50	0.32	0.41	0.32
Positive	2.46	2.55	0.38	0.44	0.65
Post-scanning ratings					
Vividness	4.67	4.68	0.78	0.71	0.06
Significance	3.00	3.40	0.81	0.53	−1.57
Negative	3.04	3.72	0.80	0.71	−2.44*
Positive	2.95	3.05	0.94	0.73	−0.32
Physiological response	2.30	2.61	0.98	0.78	−0.92
Perspective					
Own eyes	5.75	4.86	0.84	1.22	2.29*
Observer	2.39	3.23	0.92	1.18	−2.13*
Date of memory					
Day	0.05	0.03	0.04	0.03	1.60
Week	0.09	0.07	0.06	0.06	0.74
Month	0.12	0.11	0.08	0.08	0.35
Year	0.25	0.28	0.01	0.01	−0.83
5 years	0.26	0.23	0.11	0.15	0.64
10 years	0.14	0.13	0.08	0.08	0.39
> 10 years	0.09	0.15	0.06	0.18	−1.20
Memory type					
Unique	0.81	0.77	0.15	0.16	0.71
Repeated	0.14	0.14	0.09	0.09	0.03
Extended	0.05	0.09	0.07	0.1	−0.94
Coding of narrative descriptions					
PCL-related AMs†	0.04	0.11	0.03	0.11	−2.35*

*$p < .05$.
† df = 25.

associated with the stressful event identified on the PCL. The PTSD group recalled a greater proportion of AMs that referred to the stressful event identified in the PCL when compared to controls. The increase in the number of stressful events retrieved by the PTSD group, however, did not result in group differences in emotional intensity or the overall proportion of negative events - although it may have contributed to some of the valence effects noted above.

3.2. fMRI results

3.2.1. Influence of emotion

The 3-way ANOVA examining the influence of emotional intensity on group (PTSD, control), retrieval phase (construction, elaboration), and valence (positive, negative) revealed several interactions and main effects (see Table 3). There was a significant 3-way interaction in the recruitment of the right amygdala/hippocampus (see Fig. 1), dorsolateral PFC (DLPFC) and middle temporal cortex. The 3-way interaction reflected a pattern whereby the PTSD group elicited greater activity in these regions for negatively intense AMs during construction greater than elaboration, but where the control group elicited the greater activity during construction of positively intense AMs.

There were several significant effects when examining the 2-way interaction terms (see Table 3). First, there was a significant Group × Valence interaction, which revealed a valence reversal in the role of the medial PFC. Across the AM retrieval phases, the PTSD group elicited greater activity in the ventral medial PFC (see Fig. 2) and orbitofrontal cortex for emotionally intense negative AMs, whereas the control group elicited greater activity in these same regions for emotionally intense positive AMs. Second, there was a significant Group × Retrieval Phase interaction, which revealed that the PTSD group elicited greater activity in the left retrosplenial cortex and thalamus during construction vs. elaboration of emotionally intense AMs, when compared to the control group. The Retrieval Phase × Valence interaction did not reveal any significant effects at the specified threshold.

There were several significant main effects, which are qualified by the significant interactions indicated above. First, there was a significant main effect of group which revealed less recruitment of the left temporal cortices and left occipital cortex in the PTSD group. Second, there was a significant main effect of retrieval phase, which revealed greater recruitment of primarily left-lateralized regions during construction compared to elaboration. In particular, construction recruited greater left DLPFC, frontopolar, middle temporal cortex, posterior cingulate, and retrosplenial cortices. There were no significant main effects of valence.

3.2.2. Task-related functional connectivity analysis

Both groups recruited the ventral medial PFC during retrieval of emotionally intense AMs, but the function of this region differed according to emotional valence. In order to better understand these valence reversal effects in the ventral medial PFC, we examined group differences in the functional connectivity of this region for emotionally intense positive vs. negative AMs. For examining functional connectivity we used the peak voxel identified by the Group × Valence interaction in the medial PFC as a seed voxel in individual trial-based analyses. These results revealed that the PTSD group had greater coactivation of the ventral mPFC with the right amygdala, retrosplenial and bilateral occipital cortices for negative emotionally intense AMs, but less coactivation among this network for positive emotionally intense AMs (see Table 4 and Fig. 3).

3.2.3. Brain–behavior correlations

Given our *a priori* interest in the amygdala, hippocampus and medial PFC and the importance of these regions to PTSD we conducted an ancillary analysis to determine whether the parametric response of these regions was correlated with PCL scores. These results revealed brain–behavior correlations in the parametric response of the amygdala/hippocampus, but not in the ventral medial PFC. Specifically, there was a correlation between the total PCL score and the parametric response of the amygdala/hippocampus during the construction of negatively intense memories, $r = 0.43$, $p < .05$, but there was no correlation for positively intense memories, $r = -0.06$, $p = .78$. Although in the correct direction, there was no correlation in the medial PFC during the retrieval of negatively intense memories, $r = 0.21$, $p = .29$, or positively intense memories, $r = -0.13$, $p = 51$. Thus, participants who had a higher total PCL score recruited the amygdala/hippocampus to a greater extent during the construction of negatively intense memories.

4. Discussion

The current study presents a novel investigation to examine the neural mechanisms underlying retrieval of a sample of emotionally intense AMs in PTSD. Previous functional neuroimaging studies examining the impact of PTSD on personal memory have primarily focused on the neural mechanisms supporting traumatic

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Table 3
Parametric modulation by emotional intensity: group × retrieval phase × valence.

Region	BA	H	X	Y	Z	F	Z	Voxels
Group × retrieval phase × valence								
PTSD: negative (elaboration > construction) vs. positive (construction > elaboration) and Controls: negative (construction > elaboration) vs. positive (elaboration > construction								
No significant voxels								
PTSD: negative (construction > elaboration) vs. positive (elaboration > construction) and Controls: negative (elaboration > construction) vs. positive (construction > elaboration)								
Dorsolateral PFC	9	R	33	23	27	13.86	3.42	28
Middle temporal cortex	21	R	48	−15	−18	9.80	2.84	8
Amygdala/Hippocampus	–	R	22	−8	−22	9.09	2.64	5
Group × retrieval phase								
PTSD: construction > elaboration and Controls: elaboration > construction								
Premotor cortex	8	R	19	24	37	9.73	2.83	8
Retrosplenial cortex	30	L	−7	−40	5	11.17	3.05	10
Thalamus	–	L	–	−3	11	9.32	2.76	7
PTSD: elaboration > construction and Controls: construction > elaboration								
No significant voxels								
Group × valence								
PTSD: negative > positive and Controls: positive > negative								
Ventral medial PFC	10	L	−11	58	1	13.29	3.35	5
Orbitofrontal cortex	47/11	L	−19	32	−8	9.57	2.8	6
PTSD: positive > negative and Controls: negative > positive								
No significant voxels								
Retrieval phase × valence								
No significant voxels								
Main effect of group								
PTSD > controls	No significant voxels							
Controls > PTSD								
Middle temporal cortex	21	L	−59	−22	−12	18.39	3.95	28
Superior temporal cortex	42	L	−63	−29	12	9.6	2.87	6
Occipital cortex	18	L	−19	−97	19	13.02	3.31	7
Main effect of retrieval phase								
Construction > elaboration								
Dorsolateral PFC	9	L	−48	24	34	11.84	3.15	24
Dorsal Medial PFC	9	L	−11	46	47	14.99	3.56	20
Frontopolar cortex	10	L	−22	59	8	12.8	3.28	20
Suplemental motor area	6	C	0	−26	64	10.35	2.93	10
Precuneus	7	C	0	−78	39	11.67	3.12	36
Posterior cingulate	31	L	−7	−72	18	14.48	3.5	211
Elaboration > construction								
No significant voxels								
Main effect of valence								
No significant voxels								

Talaraich coordinates reported. BA, Brodmann's area; H, Hemisphere.
ANOVA = Analysis of variance, PFC = Prefrontal cortex, PTSD = Post-traumatic stress disorder.

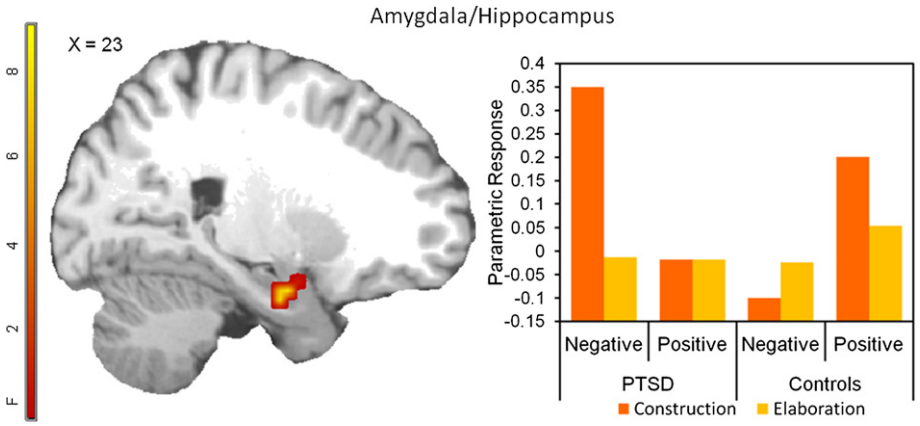

Fig. 1. Group × valence × phase interaction. There was differential sensitivity of the right amygdala/hippocampus to emotional intensity in PTSD vs. controls according to valence and retrieval phase. The PTSD group showed greater recruitment of this region during the construction of emotionally intense negative autobiographical memories, whereas the control group showed greater recruitment here during construction of emotionally intense positive memories.

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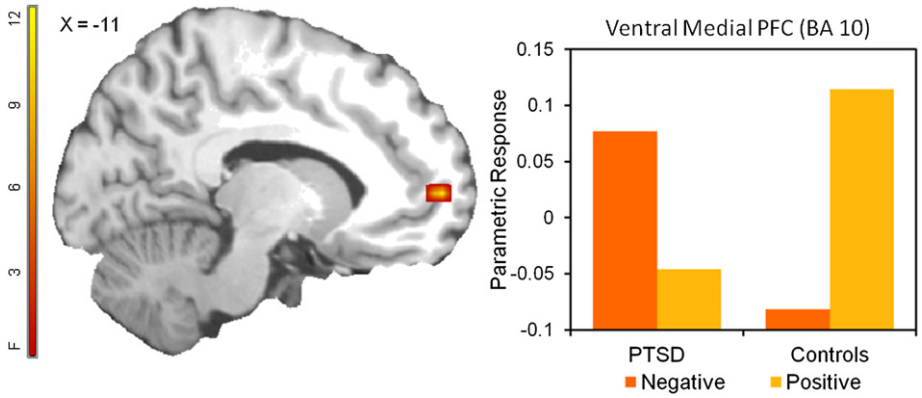

Fig. 2. Group × valence interaction. There was differential sensitivity in the ventral medial prefrontal cortex (PFC) in PTSD vs. controls to valence across both construction and elaboration phases of autobiographical memory retrieval. The PTSD group showed greater recruitment of the ventral medial PFC for negatively intense autobiographical memories, whereas the control group showed greater recruitment of this region for positively intense memories.

memories, often using scripts of traumatic events (although see Driessen et al., 2004; for a review see Francati et al., 2007). Here, we used a generic cue method to elicit spontaneously generated memories during scanning, combined with online ratings of emotional experience to examine brain activity during construction and elaboration that parametrically varied with the emotional intensity associated with retrieved memories on each trial. The fMRI data suggests greater reactivity in emotional brain regions during the initial construction of negatively intense AMs in PTSD when compared to controls. There were three main findings supporting this idea. First, we found that the PTSD group showed greater recruitment of the amygdala/hippocampus during the construction of negatively intense AMs, but less recruitment in this region for positively intense memories during construction, whereas controls showed the reverse pattern. Second, across both the construction and elaboration phases of retrieval the PTSD group showed greater recruitment of the ventral medial PFC for negatively intense memories, but less recruitment for positively intense memories. Third, the PTSD group showed greater functional coupling between the ventral medial PFC and the amygdala for negatively intense memories, but less coupling for positively intense memories. We discuss these results in detail below.

The amygdala modulated the extent of emotional intensity during AM retrieval, with group differences emerging with respect to both valence and retrieval phase (i.e., 3-way interaction). The PTSD group recruited the right amygdala/hippocampus to a greater extent during construction versus elaboration of negative versus positive AMs, whereas controls showed the reverse pattern such that they recruited this region more during the construction of positive AMs. Further, participants with higher PCL scores recruited this region to a greater extent during the construction of their negatively intense memories, but not for positively intense memories. The current results extend previous accounts of the hyperactive response of the amygdala to traumatic events in PTSD (Etkin and Wager, 2007; Shin et al., 2006) by showing that exaggerated activity in this region may be associated with negative valence rather than the overall intensity of the stimulus. Further, they are in line with some behavioral studies of PTSD suggesting a reduced response to positive stimuli such as those that signal reward (e.g., Elman et al., 2005). The cluster of activation in the right amygdala/hippocampus found here overlaps with a recent meta-analysis that observed hyperactivation in the response of the ventral amygdala during fear conditioning in PTSD and other patients with anxiety disorders (Etkin and Wager, 2007). Etkin and Wager (Etkin and Wager, 2007) speculated that hyperactivation of

Table 4
Functional connectivity of ventral medial PFC: group × valence.

Region	BA	H	X	Y	Z	F	Voxels
Premotor cortex	6	R	22	7	66	17.43	9
Supplementary motor area	6	L	−4	−1	53	10.31	5
Somatosensory cortex	5	L	−37	−48	62	14.65	7
Superior temporal cortex	41	R	−52	−18	4	10.06	6
Amygdala	–	R	30	−4	−16	13.91	5
Retrosplenial cortex	29	R	7	−47	16	16.55	5
Fusiform	37	R	37	−55	−13	11.27	6
Occipital cortex	18	L	−19	−94	5	12.94	7
	18	L	26	−90	25	10.93	8
	18	R	33	−95	2	16.78	55
	18	R	15	−80	1	11.22	6

Talaraich coordinates reported. BA, Brodmann's area; H, Hemisphere.
PFC = Prefrontal Cortex.

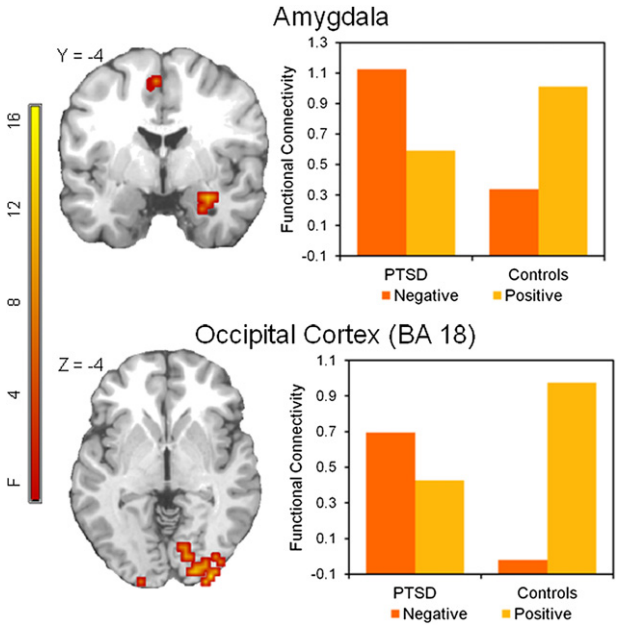

Fig. 3. Task-related functional connectivity with the ventral medial prefrontal cortex (PFC). There was a valence reversal in the functional connectivity of the ventral medial PFC with the right amygdala and bilateral occipital cortices in PTSD vs. controls. The PTSD group showed greater coactivation with the ventral medial PFC in the amygdala and occipital cortices during retrieval of emotionally intense negative autobiographical memories, whereas the control group showed greater coactivation here for emotionally intense positive memories.

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the ventral amygdala in PTSD is linked to the role of the basolateral portion of the amygdala in emotional memory (LeDoux, 2000). The greater sensitivity of the amygdala/hippocampus to negative emotional experiences during AM retrieval in PTSD could lead to potential differences in the quality of memory retrieval as has been found in some behavioral studies (Rubin et al., 2008b). Although we did not find behavioral differences in subjective ratings of emotional intensity, the PTSD group retrieved a larger proportion of AMs that referred to the stressful event identified in the PCL, which potentially could contribute to the greater reactivity of the amygdala/hippocampus to intense negative AMs.

Emotions signal appropriate actions that may function as early warnings (Leventhal and Scherer, 1987), and tend to come online earlier during AM retrieval (Daselaar et al., 2008). This should be especially true in PTSD because symptoms include avoiding external stimuli and thoughts that cue traumatic events and general hypervigilance, as indicated by being especially alert or watchful even when it is not necessary. To produce these symptoms negative events would have to affect processing early during retrieval, and do so even for situations not directly related to the trauma. Here we show that the PTSD group elicited greater activity in the amygdala/hippocampus during construction compared to elaboration of negative versus positive intense AMs when compared to controls. Additionally, during construction we found other regions in the AM retrieval network (Cabeza & St. Jacques, 2007; Svoboda et al., 2006), such as the retrosplenial cortex and the thalamus, that were sensitive to emotional intensity for both negative and positive memories in PTSD versus controls. The fMRI results suggest that not only did the PTSD group show greater reactivity in the recruitment of emotional brain regions during the retrieval of negatively intense AMs, but that overall their emotionally intense memories come with earlier activation within the memory system. The greater initial recruitment of the memory retrieval network in the PTSD group may contribute to the greater sense of re-experience associated with negative AMs. In sum, one potential interpretation of the current findings, which warrants further investigation, is that symptoms of hypervigilance in PTSD may involve greater reactivity or a boost in the initial recruitment of the memory network to emotionally intense stimuli- particularly for negative valence.

Across the construction and elaboration phases of AM retrieval, the PTSD group showed greater sensitivity of the ventral medial PFC to emotionally intense negative memories but less sensitivity for positive memories. The medial PFC is one of the most frequent regions observed during emotional tasks (Phan et al., 2002) and is associated with both the regulation and experience of emotion, with ventral portions important for processing emotional valence (Anderson et al., 2003; Dolcos et al., 2004; Small et al., 2003). However, the medial PFC is also frequently recruited during tasks that rely on internally directed or self-referential processes (Buckner and Carroll, 2007; Mitchell, 2009; Spreng et al., 2009) such as AM retrieval (Cabeza & St. Jacques, 2007; Svoboda et al., 2006), and ventral portions of the medial PFC may support the ability to re-experience the personal past (Levine et al., 2004; Maguire and Mummery, 1999; St. Jacques et al., 2010). Previous functional neuroimaging studies of PTSD have observed a hypoactive response of the medial PFC, which is a finding mainly attributed to emotional dysregulation (Etkin and Wager, 2007; Frewen and Lanius, 2006; Shin et al., 2006). A recent lesion study (Koenigs et al., 2008), however, indicates that the role of ventral medial PFC in PTSD may be much more complex than previously thought. Koenigs and colleagues examined the prevalence of PTSD symptoms in combat veterans with combined brain injury and exposure to traumatic experiences. They found that, rather than exacerbating symptoms- as predicted by dysregulation accounts- damage to the ventral medial PFC protected against PTSD symptoms implying that this region actively contributes to the up-regulation of emotional re-experience in PTSD (also see Koenigs and Grafman, 2009). The valence reversal in the ventral medial PFC found here is consistent with this implication and may reflect group differences in the re-experience or personal significance associated with negative and positive memories.

A similar valence reversal was observed in the functional connectivity of the ventral medial PFC, with the PTSD group showing greater coactivation here with the right amygdala for negative versus positive intense AMs when compared to controls. Ventral medial PFC has reciprocal anatomical connections with the amygdala (Price, 2003), thus, supporting empirical evidence of its involvement in emotional regulation (Ochsner and Gross, 2005). Previous functional neuroimaging studies of PTSD have observed changes in amygdalar-medial PFC coupling during the retrieval of negative experiences (for a review see Shin et al., 2006). The synchrony between ventral medial PFC and the amygdala observed here potentially suggests greater up-regulation of emotional experience during retrieval of negative versus positive intense AMs in the PTSD group, which could account for the behavioral differences in re-experience and personal significance. Supporting this interpretation, we also observed greater coactivation of the ventral medial PFC with retrosplenial and occipital cortices, which are regions that contribute to recollection and vividness during AM retrieval (Cabeza & St. Jacques, 2007). In sum, the valence reversal observed in the recruitment of the ventral medial PFC combined with the functional connectivity of this region suggests that the re-experience of negative AMs is up-regulated to a greater extent in PTSD versus controls.

There were some limitations to the current investigation which should be considered when interpreting the results. In particular, the current study compared functional activations underlying the retrieval of emotional AMs in PTSD versus a random control group, and thus, we did not control for trauma exposure or comorbidity with depression. Future research should consider whether similar results are obtained when comparing PTSD to a trauma-exposed control group in order to investigate potential influences of resiliency and to a depression control group in order to understand the specificity of these effects to PTSD. Additionally, a quantitative CAPs was not acquired, and thus, there may be potential differences in symptom severity between this and previous studies that could have influenced the reported findings.

Conclusions

Increased emotional intensity in AM is a central factor in PTSD (Berntsen et al., 2008; Rubin et al., 2008a; Rubin et al., 2008b). Here, we found that compared to controls PTSD participants showed differential recruitment and coupling between brain regions supporting AM retrieval for a sample of emotionally intense events. Moreover, our fMRI findings suggest that PTSD affects the initial reactivity of brain regions supporting emotion and memory- particularly for negatively intense memories, which may contribute to the observed behavioral differences in re-experience and personal significance. In sum, the results suggest that emotional re-experience associated with the retrieval of the personal past is altered in PTSD.

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Contributors

PLS and DCR designed the study and wrote the protocol. PLS, AM and AB recruited participants conducted the scanning sessions. PLS undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

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