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Neurobiological Basis of Failure to Recall Extinction Memory in Posttraumatic Stress Disorder

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Abstract

Background: A clinical characteristic of posttraumatic stress disorder (PTSD) is persistently elevated fear responses to stimuli associated with the traumatic event. The objective herein is to determine whether extinction of fear responses is impaired in PTSD and whether such impairment is related to dysfunctional activation of brain regions known to be involved in fear extinction, viz., amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), and dorsal anterior cingulate cortex (dACC).

Methods: Sixteen individuals diagnosed with PTSD and 15 trauma-exposed non-PTSD controls (TENCs) underwent a two-day fear conditioning and extinction protocol in a 3T fMRI scanner. Conditioning and extinction training were conducted on day 1. Extinction recall (or extinction memory) test was conducted on day 2 (extinguished conditioned stimuli presented in the absence of shock). Skin conductance response (SCR) was scored throughout the experiment as an index of the conditioned response.

Results: SCR data revealed no significant differences between groups during acquisition and extinction of conditioned fear on day 1. On day 2, however, PTSD subjects showed impaired recall of extinction memory. Analysis of fMRI data showed greater amygdala activation in the PTSD group during day 1 extinction learning. During extinction recall, lesser activation in hippocampus and vmPFC, and greater activation in dACC, was observed in the PTSD group. The magnitude of extinction memory across all subjects was correlated with activation of hippocampus and vmPFC during extinction recall testing.

Conclusions: These findings support the hypothesis that fear extinction is impaired in PTSD. They further suggest that dysfunctional activation in brain structures that mediate fear extinction learning, and especially its recall, underlie this impairment.

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Keywords

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Introduction

The pathophysiology of posttraumatic stress disorder (PTSD) has been extensively studied over the past several years using neuroimaging and probes such as script-driven imagery and visual emotional stimuli (reviewed in 1,2,3,4). Studies have identified a network of dysfunctional brain regions, including amygdala, hippocampus, and subregions of the medial prefrontal cortex, including ventromedial prefrontal cortex (vmPFC) and dorsal anterior cingulate cortex (dACC). Individuals with PTSD typically show exaggerated amygdala and diminished hippocampal activation relative to controls (5-10). The dACC has emerged as another brain region that appears hyperactive in PTSD (11-13). Most studies have shown that vmPFC is hypoactive in this disorder (12,14-21), but a few have reported hyperactivity (10,13,22-24). Although findings from these studies provide insight into the pathophysiology of PTSD, the function of these brain regions within the context of fear extinction learning and its recall (or retention) has not been directly examined. Extinction learning refers to the gradual, within-session decrements of conditioned fear responses, whereas extinction recall refers to the retrieval and expression of the learned extinction memory after a delay (25). Understanding the basis of these processes is important given that one of the main clinical characteristics of PTSD is exaggerated and persistent fear responses to reminders of the traumatic event. It is also important in that the current behavioral treatment of choice, exposure therapy, relies on extinction-based mechanisms (26,27).

Pavlovian fear conditioning is commonly employed to probe the neurobiology of fear acquisition and its inhibition in rodents (28-31), and it has also been used in psychophysiological (32-34) and neuroimaging studies of humans (35-37). In this procedure, conditioned responses (CRs) are formed when a conditioned stimulus (CS) is paired with an aversive unconditioned stimulus (US), such as a mild electric shock. These CRs can then be diminished, or extinguished, by the repeated presentation of the CS in the absence of the US. Pavlovian fear conditioning and extinction are relevant to the neurobiology of PTSD, given that this disorder involves learned fear (27) that may persist for decades after the trauma exposure (38). Studying them may elucidate mechanisms by which perseverant fear responses occur. The hypothesis that extinction of conditioned fear is deficient in PTSD (3,39) is supported by de novo fear conditioning and extinction studies that have demonstrated deficient extinction learning (40). Moreover, we recently reported psychophysiological data indicating that Vietnam veterans diagnosed with PTSD have an acquired impairment in the retention of extinction memory (41).

Neurobiological research has advanced our understanding of the mechanisms underlying extinction learning and recall. Numerous studies conducted in rodents with various pharmacological and molecular manipulations and electrophysiological and micro-stimulation tools have indicated that extinction learning and recall involve different cellular mechanisms and possibly different brain regions (for review, see 42). For example, studies suggest that in addition to its role in fear acquisition, the amygdala appears to be implicated in extinction learning, whereas the vmPFC (corresponding to the infralimbic cortex in rodents) and hippocampus appear to be involved in extinction recall (29,31,42-44). In contrast, a region dorsal to the vmPFC in rats, viz., the prelimbic cortex, has been found to promote conditioned fear expression (45,46).

Neuroimaging studies have recently examined extinction circuitry in healthy humans. In a study using functional magnetic resonance imaging (fMRI) (47), amygdala was activated during extinction learning, whereas vmPFC was activated during extinction recall. More recently, we reported that vmPFC and hippocampus are co-activated during extinction recall and that the degree of such activation is positively correlated with psychophysiologically measured extinction retention (48), as is vmPFC thickness (49). In contrast, thickness and functional activation of the dACC, homologous to rat prelimbic cortex, are correlated with expression of conditioned fear in humans (37). Thus, there is converging evidence in rodents and humans implicating the vmPFC and hippocampus in extinction recall and the dACC in fear expression. Finally, the amygdala appears to be involved both in fear expression and extinction learning, which may lead to ambiguous predictions.

The objective of the present study was to examine the neurobiological basis of deficient extinction recall in PTSD with a focus on the above-mentioned brain regions. While in a 3T fMRI scanner, PTSD and trauma-exposed, non-PTSD control (TENC) subjects underwent a two-day Pavlovian fear conditioning and extinction procedure that we have previously used in healthy (39،50،51) and PTSD subjects (41). Skin conductance response (SCR), a commonly used measure in human fear studies (47،52) served as the dependent measure of conditioned responding. On day 1, subjects underwent fear conditioning to two pictures of differently colored lamps, followed by extinction for one of them. Day 2 tested recall of the extinction that had been learned the previous day by contrasting responses to the previously extinguished and unextinguished stimuli.

Several hypotheses were tested. First, we predicted impaired extinction recall as measured by SCR in PTSD. Not only would this represent a replication of our previous report (41); it would also extend this finding to PTSD caused by civilian trauma. Second, we predicted lesser vmPFC activation during extinction learning in the PTSD group. However, no directional predictions were made for amygdala activation during extinction learning because of its ambiguous role described above. Third, we predicted lesser vmPFC and hippocampal activations and greater amygdala and dACC activations during (impaired) extinction recall in the PTSD group. Fourth, we predicted that the magnitude of extinction recall, indexed by diminished SCR, would be positively correlated with vmPFC and hippocampal activations and inversely correlated with amygdala and dACC activations across all subjects.

Methods and Materials

Subjects

A total of 19 PTSD patients and 20 trauma-exposed non-PTSD control (TENC) subjects were recruited from the community. After a full explanation of the study's procedures, written informed consent was obtained in accordance with the requirements of the Partners Healthcare System Human Research Committee. All subjects completed participation in the two-day fear conditioning and extinction paradigm. Three PTSD and 5 TENC subjects were excluded from the data analysis because of excessive motion in the scanner. There remained 16 PTSD (6 females, 10 males) and 15 TENC subjects (8 females, 7 males, Fisher's exact test p=0.48).

Psychodiagnostics, Demographics, and Psychometrics

The Clinician-Administered PTSD Scale (CAPS) conferred PTSD diagnostic status. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) determined the presence of other mental disorders. TENC subjects with any current mental disorder were excluded. PTSD subjects with current substance dependence were excluded, as were subjects who had

used any psychotropic medication within 4 weeks prior to participation (1 year for neuroleptics). Type of trauma and current comorbid disorders appear in Table 1, as do group mean age, education, total CAPS scores, and age at first trauma exposure.

Fear Conditioning, Extinction, and Testing Procedures

The previously described (37,48) two-day experimental protocol is summarized in figure 1. All subjects selected a level of shock they regarded as highly annoying but not painful, to be used in the experiment. On day 1, during the *Habituation* phase, the to-be extinguished CS+ (CS+E), unextinguished CS+ (CS+U), and the CS that is never to be paired with the shock (CS−) (4 of each) were presented in a counterbalanced manner within either the to-be conditioning or the to-be extinction context. During the *Conditioning* phase, two CS+s (e.g., red and blue lights) were depicted within a photograph of a distinct room (conditioning context), and each was paired with the US at a partial reinforcement rate of 60%. A third CS (e.g., a yellow light) was also depicted within the conditioning context but never paired with the US (CS−). There were 8 CS+Es, 8 CS+Us, and 16 CS− trials. When the shock US occurred, it followed the CS+ offset without delay. The shock electrodes remained attached to the subject's fingers during all subsequent phases, and subjects were instructed throughout the experiment (except during the Habituation phase) that they “may or may not receive the electric shock.” However, shocks were *only* delivered during the Conditioning phase. After an approximate 1-minute break, the *Extinction Learning* phase began. During this phase, the CS+E was depicted within a photograph of another distinct room (extinction context) and presented in the absence of the US, whereas the CS+U was not presented. There were 16 CS +E and 16 CS− trials. On day 2, during the *Extinction Recall* phase, 8 CS+E, 8 CS+U, and 16 CS− trials were again presented depicted within the extinction context. For each trial during the experiment, the context picture was presented for 9 seconds: 3 seconds alone followed by 6 seconds in combination with the CS+E, CS+U, or CS−. The mean inter-trial interval was 15 seconds (range: 12-18 seconds). All experimental phases were conducted while blood-oxygen-level dependent (BOLD) signal data were being acquired via fMRI.

Psychophysiological Measures

As previously described, (40,50,53) an SCR for each CS trial was calculated by subtracting the mean skin conductance level during the 2 seconds prior to CS onset (during which the context alone was being presented) from the highest skin conductance level during the 6-second CS duration. Thus, SCRs to the CS+E, CS+U, and CS− reflected changes in skin conductance level beyond any change in SC level produced by the context. The magnitude of extinction retention (recall) was quantified as follows: each subject's SCR to the first four CS+ trials of the extinction Recall phase was divided by their largest SCR to a CS+ trial during the Conditioning phase and then multiplied by 100, yielding a percentage of maximal conditioned responding. This in turn was subtracted from 100% to yield an “extinction retention index.” The purpose of calculating the extinction retention index was to normalize each subject's SCR during extinction recall to that exhibited during the conditioning phase. This index is important because it adjusts the SCR during extinction recall for differences in CR magnitude during acquisition. Unless otherwise specified, all data are presented as means ± standard error. Analysis of variance (ANOVA) and Student's t-tests were performed to test for statistically significant differences between means, with appropriate Bonferroni corrections when required.

Image Acquisition

The image acquisition parameters were identical to those previously used in our laboratory (48). Briefly, a Trio 3.0 Tesla whole body high-speed imaging device equipped for echo planer imaging (EPI) (Siemens Medical Systems, Iselin NJ) with an 8-channel gradient head coil was used. Head movement was restricted using foam cushions. After an automated

scout image was obtained and shimming procedures performed, high-resolution 3D MPRAGE sequences (TR/TE/Flip angle=7.25ms/3ms/7°; 1×1mm in plane × 1.3mm) were collected for spatial normalization and positioning the subsequent scans. Scans using T1 (TR/TE/Flip angle=8sec/39ms/90°) and T2 (TR/TE/Flip angle=10sec/48ms/120°) sequences were used for registration of individual functional data. Functional MRI images (i.e. blood oxygenation level dependent, BOLD) were acquired using gradient echo T2*-weighted sequence (TR/TE/Flip angle=3 sec/30ms/90°)(54). The T1, T2, and gradient-echo functional images were collected in the same plane (45 coronal oblique slices parallel to the anterior-posterior commissure line, tilted 30 degrees anterior) with the same slice thickness (3 mm × 3 mm × 3mm). The same scanning procedure was conducted on Day 2.

Functional MRI Data Analysis

Functional MRI data were analyzed using the Freesurfer Functional Analysis Stream (FS-FAST) (http://surfer.nmr.mgh.harvard.edu). All functional runs were motion-corrected using the AFNI (Analysis of Functional Images) motion correction tool, spatially smoothed (FWHM=5mm) using a 3D Gaussian filter, and intensity-normalized to the low level baseline. Images were manually inspected for motion artifact, and subjects with greater than 2mm total vector motion were excluded. Subjects' functional runs were then individually registered to their anatomical volumes using FLIRT (FMRIB's Linear Image Registration Tool), and the registrations were visually inspected for accuracy. Estimates of the stimulus effects at each voxel were made using an event-related design and by convolving the functional signal for each event with a canonical hemodynamic response function (HRF). The analysis included a linear correction to account for low-frequency drift.

Statistical parametric maps were calculated according to a general linear model for the contrasts of interest across the time window (55). The contrast used for the Stimulus factor during the Extinction Learning phase was the last 12 CS+E vs. the last 12 CS− trials in the Extinction Learning phase. Note that no US was delivered during this phase. The contrast used for the Stimulus factor during Extinction Recall phase was the first four CS+E vs. the first four CS+U trials. These specific trials were selected for three reasons. First, their use minimizes the confound introduced by additional extinction learning that may take place during this phase and be especially reflected in responses to the latter trials. Second, electrophysiological data from rodents indicate that the vmPFC signals extinction recall only during the early portion of extinction recall. Third, we found that this contrast revealed the most robust activation of the vmPFC in our previous studies in healthy humans.

Group × Stimulus interactions (i.e., PTSD vs. TENC contrasts on the Stimulus contrast maps) were analyzed separately for the Extinction Learning and Recall phases. Functional regions of interest (ROIs) were empirically defined as clusters of contiguous voxels exceeding the *a priori* statistical threshold below. BOLD signal values were extracted from these ROIs to calculate percent signal change. These values were then used for regression analyses with the extinction retention index. Coordinates for the peak voxels in each region were specified in terms of the Talairach atlas (56) to allow comparison to results of previous studies. We focused our fMRI data analysis *a priori* on the vmPFC, amygdala, hippocampus, and dACC, within which areas we employed a threshold of uncorrected, one-tailed $p < 0.001$. We used a more stringent threshold of $p < 0.0001$ for activations and deactivations in remaining brain regions.

Results

Psychophysiological responses during fear conditioning (acquisition)

ANOVA revealed a significant Stimulus main effect (F=19.6, *p<0.001*), with greater responses to the CS+ (combined across the first four to-be CS+E and to-be CS+U trials) than to the CS− (combined across the first four trials) in the PTSD (0.28 μS ± 0.07 vs. 0.07μS ± 0.05) and in TENC (0.15 μS ± 0.04 vs. −0.08 μS ± 0.05) groups. Importantly, there were no group differences in conditioning, as evidenced by the absence of a significant Group main effect (F=2.8, *p=0.10*) or Group × Stimulus interaction (F=0.13, *p=0.72*). Functional MRI analysis was not conducted for this phase.

Psychophysiological and fMRI responses during extinction learning

ANOVA for the late extinction SCR data (last 12 CS+E vs. last 12 CS− trials) revealed no significant main effect of Stimulus (F=1.06, *p=0.31*) or Group (F=1.62, *p=0.21*), and no significant Group × Stimulus interaction (F=2.13, *p=0.16*), suggesting that comparable extinction learning had been achieved in both groups (figure 2a). Regarding the fMRI data, there was a significant Group × Stimulus interaction in right amygdala, which was more reactive to the CS+E relative to the CS− in PTSD relative to TENC subjects (t = 3.71, *p= 0.00025*, figure 2b). The Group × Stimulus interaction in vmPFC was marginally significant, showing deactivation to the CS+E relative to the CS− in PTSD relative to TENC subjects (t = −3.28, *p= 0.0015*, figure 2b). Extracted % BOLD signal changes from the amygdala and vmPFC functional ROIs are shown in Figure 2c. These data indicate that during extinction learning, amygdala activation (to CS+ relative to CS−) was observed in PTSD subjects, and amygdala deactivation was observed in TENC subjects. The opposite pattern was observed in the vmPFC, i.e., deactivation in PTSD and activation in TENC.

Psychophysiological and fMRI responses during extinction Recall

ANOVA for the early extinction recall SCR data (first 4 CS+E vs. first 4 CS+U trials) revealed a significant Group × Stimulus interaction (F=4.99, *p=0.03*). Whereas the TENC group exhibited smaller SCRs to the stimulus that had been extinguished during the previous extinction learning phase compared to the stimulus that had not been extinguished (0.12 μS ± 0.07 for CS+E vs. 0.30μS ± 0.1 for CS+U, F=5.14, *p=0.03*), the PTSD group did not (0.40 μS ± 0.11 for CS+E vs. 0.37μS ± 0.10 for CS+U, F=1.1, *p=0.3*), suggesting impaired recall of extinction memory in the PTSD group (see figure 3a). Consistent with this, the extinction retention index was significantly smaller in the PTSD than the TENC group (46% vs. 85%, t=2.9, *p<0.01*). Moreover, within the PTSD group, total CAPS score was negatively correlated with extinction retention index (r= −0.71, *p= 0.01*). With respect to the fMRI data during extinction recall, the same contrast was used (first 4 CS+E vs. first 4 CS+U trials). There were significant Group by Stimulus interactions in right hippocampus (t= 4.27, p=0.0001); right vmPFC (t=3.54, *p=0.0007*); left vmPFC (t= 3.41, *p< 0.001*) and left dACC (t= 3.41, *p<0.001*) (figure 3b). Extracted % BOLD signal changes from these functional regions of interest are shown in Figure 3c. TENC subjects showed activation in left and right vmPFC and hippocampus, and deactivation in dACC, in response to the CS+E relative to the CS+U. PTSD subjects showed the opposite patterns.

To test for relationships between activations or deactivations in these brain regions during extinction recall and extinction memory, we conducted analyses correlating percent BOLD signal changes with extinction retention index across all subjects (figure 4). These analyses revealed significant positive correlations between activation in vmPFC (bilaterally) and hippocampus and extinction retention, as well as a trend toward a negative correlation between dACC activation and extinction retention.

Activations/deactivations outside the *a priori* hypothesized brain regions are shown in Table 2.

Subanalyses using comorbidity-free PTSD subjects

The key results were subjected to re-analysis excluding 6 PTSD subjects with current co-morbid Axis I disorders. This analysis revealed that the Group × Stimulus interaction remained significant for the SCR data during extinction recall (F=5.39, *p=0.02*). Moreover, the % extinction retention between the two groups remained statistically significant (52% for PTSD vs. 85% for TENC, t=2.18, *p=0.037*). Regarding the fMRI data, re-analysis of the main contrast during extinction recall (CS+E vs. CS+U) revealed that the deactivation in the bilateral vmPFC in the PTSD relative to TENC group is now marginally significant (t=3.25, *p=0.0015* for both right and left vmPFC), whereas the hippocampal difference between groups remained significant (t=4.05, *p=0.00025*). The increased activation in the dACC in the PTSD relative to the TENC group became more significant (t=4.20, *p=0.00015*). The reduced significance level regarding the vmPFC activation is most likely due to reduced power. Thus, this sub-analysis revealed that comorbidity in the PTSD sample analyzed in this study is unlikely to have accounted for the differences observed between groups with regard to either the psychophysiological or the fMRI data.

Discussion

The psychophysiological and fMRI data obtained in the TENC group show intact fear extinction memory (or recall), manifest in lower SCRs to a previously extinguished compared to a previously unextinguished CS that is associated with vmPFC and hippocampal activation during extinction recall, thereby replicating our previous report (48). In contrast, the psychophysiological data obtained in the PTSD group show impaired extinction retention, manifest in no difference between SCRs to the extinguished and unextinguished CSs, replicating another of our previous reports (41). In addition, the present data suggest that this deficient extinction retention in PTSD may be the result of dysfunctional responding in brain regions previously reported to be implicated in the recall of fear extinction in healthy subjects. Specifically, we found less activation in hippocampus and bilateral vmPFC, but more activation in dACC, during extinction recall in PTSD compared to TENC subjects. The amount of extinction retention across all subjects was positively correlated with activation in both vmPFC and hippocampus, and nearly significantly negatively correlated with activation in dACC, thereby replicating prior fMRI results in an independent sample of healthy subjects and extending them to PTSD (47،48،57).

The greater activation in the amygdala in PTSD patients during extinction learning replicates a recent report (16). However, despite their greater amygdala activation, and their lesser vmPFC activation, the PTSD group displayed extinction learning that was comparable to the TENC group. Normal extinction learning in the PTSD group in the absence of vmPFC activation is consistent with animal studies. For example, it has been previously shown that lesions or pharmacological manipulations of the vmPFC do not interfere with extinction learning per se (28). Rather, single neurons recorded from this brain region increase their neural activity to the extinguished CS+ only during extinction recall (58). Thus, the data gathered from the current study provide a translational link between rodent and human data indicating that vmPFC function is not necessary for initial extinction learning but is critical for extinction recall. In other words, the present data suggest that dysfunctional brain activation in the PTSD group (i.e., greater activity in amygdala, and lesser activity in vmPFC compared to the TENC group) during extinction learning may contribute to PTSD patients' failure to consolidate extinction memory. The present data further suggest that failure to activate vmPFC and hippocampus during recall contribute to deficient expression

of extinction memory in PTSD. As noted in the introduction, PTSD patients' failure to activate these brain regions has also been found in other neuroimaging tasks.

The dACC has traditionally been implicated in conflict monitoring, attention, and pain (59-61). One caveat when comparing the results of those studies and the data presented in the present study is that the term “dACC” has been used to refer to a broad area of the anterior cingulate. In a recent meta-analysis, Vogt and colleagues (59,60) identified a sub-region of the dACC (termed the anterior midcingulate, aMCC) that was specifically activated by fear-inducing stimuli. Importantly, the dACC region that showed activation during extinction recall in our PTSD subjects appears to overlap with aMCC. Moreover, we have previously shown that dACC thickness and function are positively correlated with conditioned responding during fear acquisition in healthy controls, suggesting that this brain region may be involved in promoting the fear response (37). A recent neuroimaging study reported increased activation of the dACC region in PTSD patients (11). All of these findings support a role for the dACC in the pathological expression of conditioned fear in PTSD.

In addition to the *a priori* regions of interest, we observed increased cerebellar activation in PTSD patients relative to controls during extinction recall (see table 1). The meaning of this finding is unclear, given that we previously observed cerebellar activation during extinction recall in a healthy cohort (48). In addition to the well-documented role of this brain region in movement and motor coordination, the cerebellum has been reported to be involved in the processing of fear memories (62,63) and in extinction of eye-blink conditioning (64). Further studies are needed to clarify its role in emotional learning and memory, including fear extinction, in general, and in PTSD.

It has been hypothesized that fear extinction and its retention are deficient in PTSD due to failure to activate brain extinction circuitry, including hippocampus and vmPFC (31,42). Using PET, Bremner and colleagues (16) were the first to examine fear conditioning and extinction learning in PTSD. The authors reported increased amygdala and decreased vmPFC activity in PTSD relative to controls, which is consistent with this hypothesis. In the current study, the link here between deficient, psychophysiologically measured extinction recall in PTSD and failure to activate vmPFC and hippocampus during extinction recall provide direct data in support of this model. The present results also provide neurobiological evidence that the pathologically elevated and persistent conditioned fear clinically observed in PTSD is at least in part due to failure to activate vmPFC and hippocampus, as well as to hyperactivation of dACC and amygdala.

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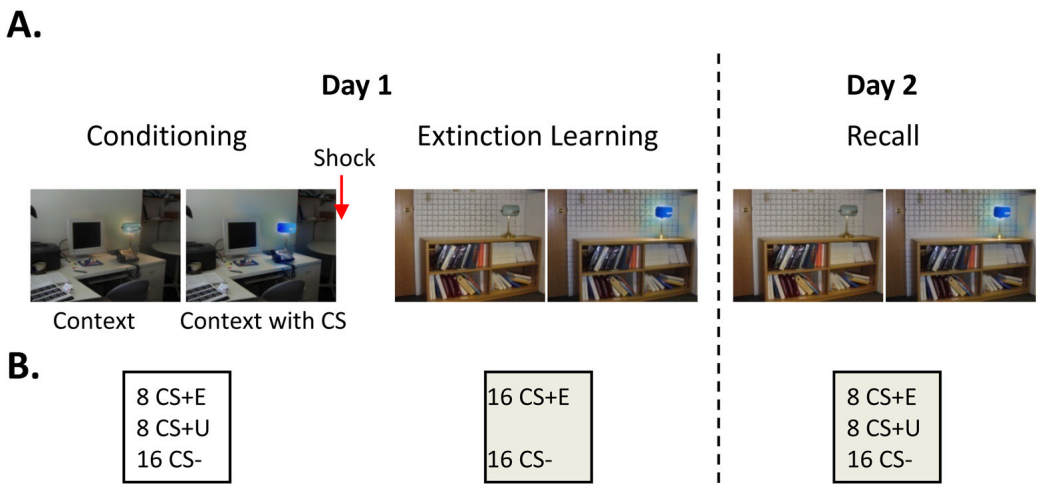

Figure 1.

Schematic of experimental protocol. A. Pictures showing the visual contexts used in the experiment, within which conditioned stimuli were presented. In this example, pictures of an office and a conference room represent conditioning and extinction contexts respectively, whereas the blue light represents the CS+ that was paired with the shock and later extinguished. Extinction recall was conducted on day 2. B. Schematic representation of the different phases of the experiment. The numbers of each stimulus type presented during the conditioning, extinction learning, and extinction recall are indicated. Gray shading represents the extinction context. Habituation phase is not shown.

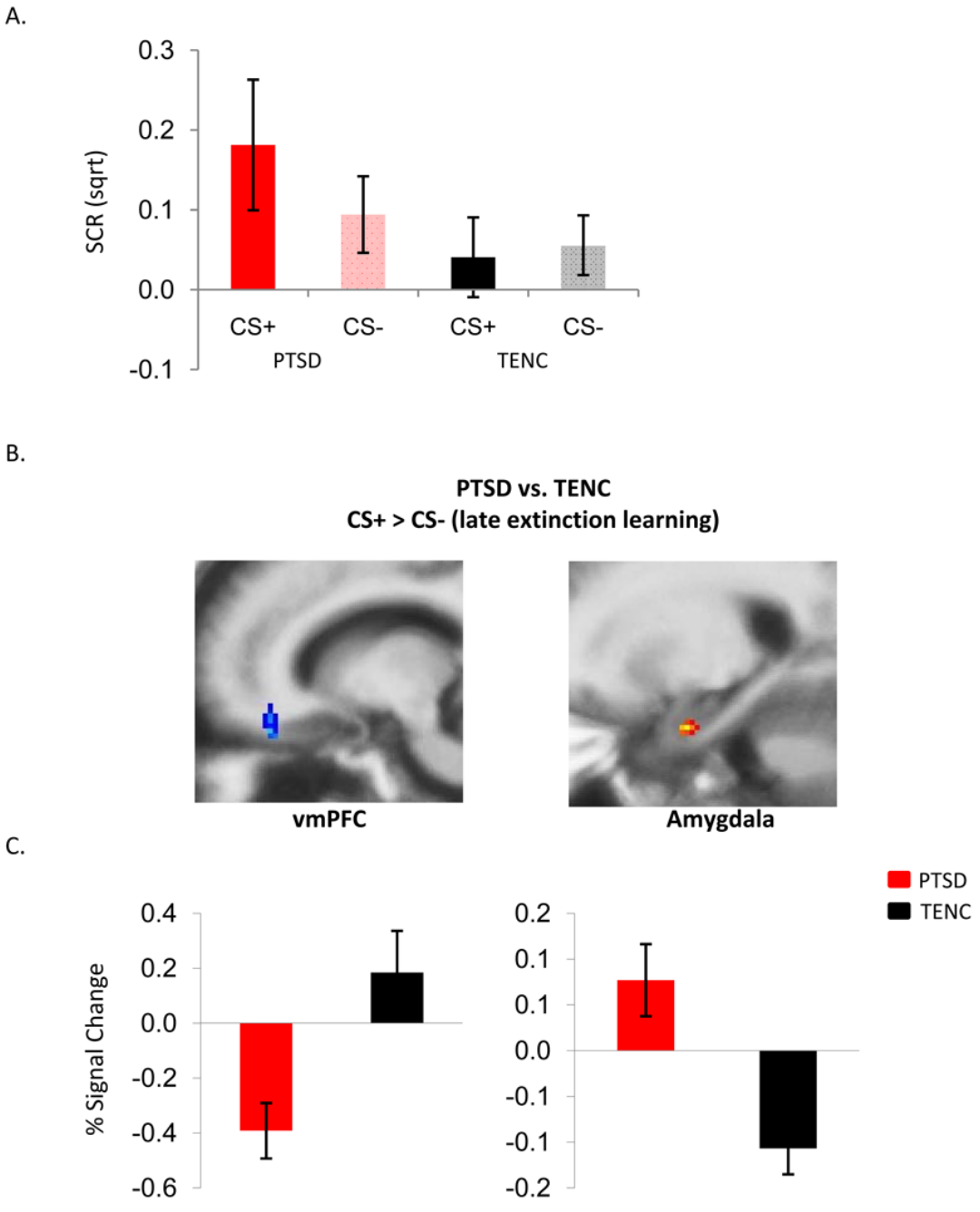

Figure 2.

Responses during late extinction learning (last 12 of 16 trials). A. SCRs to the conditioned stimulus that was previously paired with shock (CS+, dark shading) vs. the conditioned stimulus that was never paired with shock (CS-, light shading) in PTSD (red) vs. TENC (black) subjects. B. Group × Stimulus interaction in vmPFC and amygdala, Talairach coordinates: x= −15, y=34, z= −21 for vmPFC and x= 25, y= −6, z= −24 for amygdala. Image is masked to show only the activation in this hypothesized brain region. Threshold for displaying the images is set at p = 0.01. C. Percent signal change extracted from the amygdala and vmPFC functional region of interest shown in B.

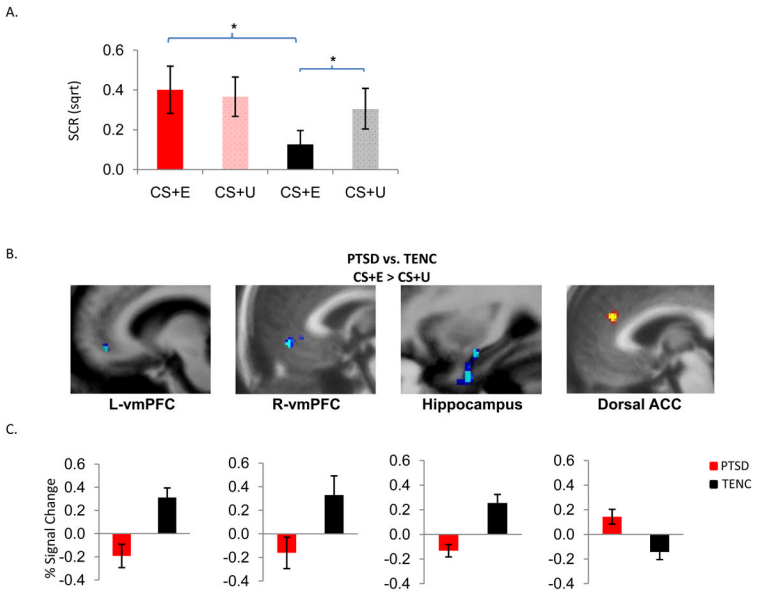

Figure 3.

Responses during early extinction recall (first four trials). A. SCRs to the stimulus that was previously extinguished on day 1 (CS+E, dark shading) vs. the CS that was not extinguished on day 1 (CS+U, light shading) in PTSD (red) vs. TENC (black) subjects. * $p < 0.05$. B. Group × Stimulus interactions. Talairach coordinates: L-vmPFC: x= −10, y= 43, z= −11; R-vmPFC: x= 2, y= 45, z= −12; hippocampus, x= 32, y= −9, z= −27; dACC: x= −2, y= 37, z= 18. All images were masked to only show activations/deactivations in hypothesized brain regions. Threshold for displaying the images is set at $p = 0.01$. C. Percent signal change extracted from the functional regions of interest shown in B.

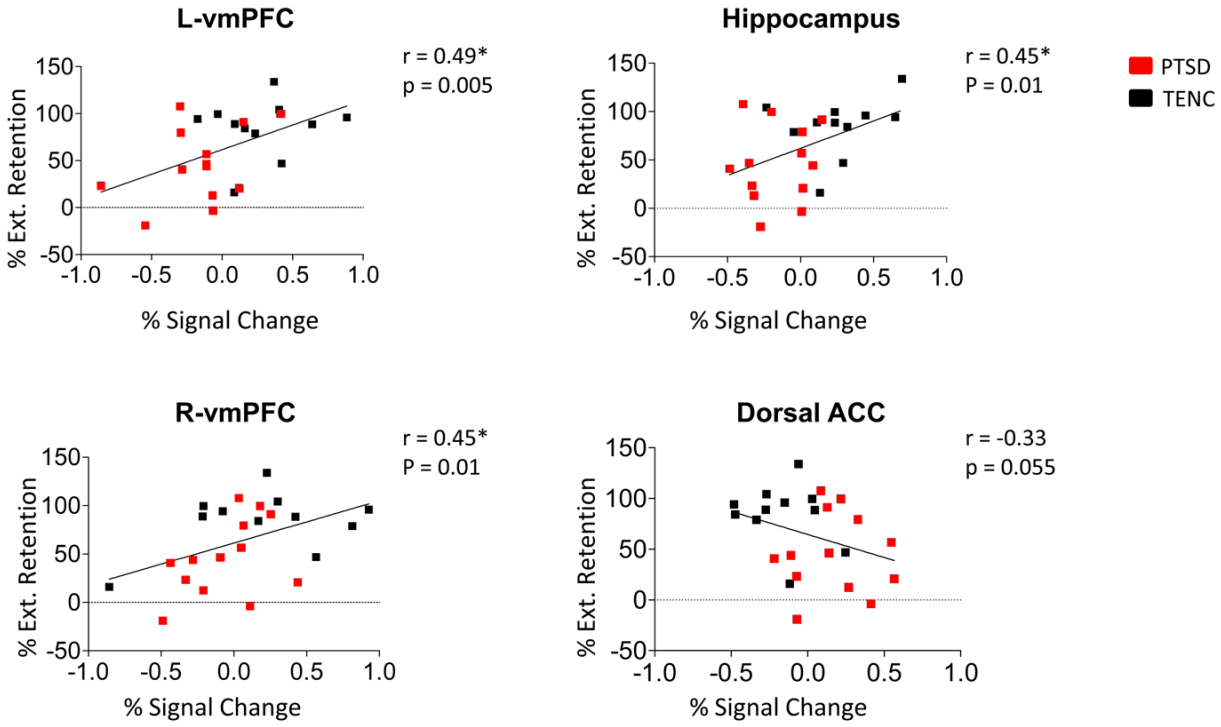

Figure 4.

Regression plots between % extinction retention and % BOLD signal change during extinction recall extracted from the functional regions of interest shown in Figure 2, collapsed across groups. All p values listed in the figures are below the Bonferroni correction threshold.

Table 1

Description of demographics, co-morbidities, and types of trauma exposure in cohort studied. The number of co-morbid disorders and types of trauma shown may exceed the number of subjects, because a subject may have had more than one co-morbid disorder or type of traumatic event.

Demographics			
	PTSD	**TENC**	
Age	33.6 (±3.1)	30.4(±3.4)	p = 0.8
Education	15 (± 0.53)	15.9 (± 0.74)	p = 0.43
Mean age at trauma exposure	17 (± 3.5)	22.4 (± 3.86)	p = 0.30
CAPS Score	66 (± 6.04)	10.5 (± 2.66)	p < 0.0001
Current co-morbidities (numbers of subjects)			
	PTSD	TENC	
Major depression	5	0	
Panic disorder	2	0	
Alcohol abuse	1	0	
Other substance abuse	2	0	
Eating disorder	2	0	
Type of trauma exposure (numbers of subjects)			
	PTSD	TENC	
Motor vehicle accidents	2	2	
Sexual assaults	8	2	
Physical assaults	4	6	
Childhood abuse	6	1	
Combat	3	0	
Witness to traumatic events	3	4	

Note: ± designates standard error of the mean (S.E.M).

Table 2

Significant activations in regions outside the *a priori* regions of interest (threshold for peak voxel $p < 10^{-4}$, two-tailed, uncorrected).

Late Extinction Learning	**Contrast: PTSD > TENC, late CS+E vs. CS−**	
Area of activation	**Talairach Coordinates**	**P values**
Regions outside the a priori *areas*		
Superior Temporal Cortex (R)	61, −11, −4	3.1×10^{-5}
Superior Temporal Cortex (R)	64, −9, 0	4.3×10^{-5}
Superior Temporal Cortex (L)	−51, 5, −8	7.9×10^{-5}
Extinction Recall	Contrast: PTSD > TENC, early CS+E vs. CS+U	
Area of activation	Talairach Coordinates	P values
Regions outside the a priori *areas*		
Cerebellar Cortex (R)	22, −46, −14	4.0×10^{-6}
Cerebellar Cortex (R)	9, −59, −40	1.2×10^{-5}
Cerebellar Cortex (R)	40, −67, −34	2.8×10^{-5}
Medial Prietal Cortex (R)	−4, −17, 61	3.0×10^{-5}
Occipital Cortex (L)	−48, −69, −1	4.7×10^{-5}