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Focal and aberrant prefrontal engagement during emotion regulation in veterans with posttraumatic stress disorder

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Abstract

Background—Collectively, functional neuroimaging studies implicate frontal-limbic dysfunction in the pathophysiology of posttraumatic stress disorder (PTSD), as reflected by altered amygdala reactivity and deficient prefrontal responses. These neural patterns are often elicited by social signals of threat (fearful/angry faces) and traumatic reminders (combat sounds, script-driven imagery). Although PTSD can be conceptualized as a disorder of emotion dysregulation, few studies to-date have directly investigated the neural correlates of volitional attempts at regulating negative affect in PTSD.

Methods—Using functional magnetic resonance imaging and a well-validated task involving cognitive regulation of negative affect via reappraisal and known to engage prefrontal cortical regions, the authors compared brain activation in veterans with PTSD (n=21) and without PTSD (n=21, combat-exposed controls/CEC), following military combat trauma experience during deployments in Afghanistan or Iraq. The primary outcome measure was brain activation during cognitive reappraisal (i.e., decrease negative affect) as compared to passive viewing (i.e., maintain negative affect) of emotionally-evocative aversive images.

Results—The subjects in both groups reported similar successful reduction in negative affect following reappraisal. The PTSD group engaged the dorsolateral prefrontal cortex during cognitive reappraisal, albeit to a lesser extent than the CEC group. Although the amygdala was engaged in both groups during passive viewing of aversive images, neither group exhibited attenuation of amygdala activation during cognitive reappraisal.

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Conclusions—Veterans with combat-related PTSD showed less recruitment of the dorsolateral prefrontal cortex involved in cognitive reappraisal, suggesting focal and aberrant neural activation during volitional, self-regulation of negative affective states.

Keywords

PTSD; emotion regulation; fMRI; combat; prefrontal cortex; reappraisal

INTRODUCTION

In the past decade, over 2.2 million U.S. soldiers have been deployed to Afghanistan and Iraq in Operations Enduring Freedom (OEF), Iraqi Freedom (OIF), and New Dawn (OND)[1], with many of them exposed to traumatic stress[2]. Approximately 14–16% of these individuals have developed posttraumatic stress disorder (PTSD)[3], making it one of the most prevalent injuries suffered among military men and women[3]. PTSD is a debilitating disorder characterized by a heterogeneous and diverse array of symptoms, including intrusive memories, avoidance of reminders, affect dysregulation (e.g., irritability), and emotional numbing[4].

Emerging evidence from functional neuroimaging implicates aberrant prefrontal-limbic brain function in the pathophysiology of PTSD. For instance, individuals with PTSD have been shown to exhibit reduced activation in the ventromedial prefrontal cortex[5], lateral prefrontal cortex[6] and other frontal areas[7] during the provocation of anxious states and negative affect. These prefrontal areas are thought to be critical for cognitive control and affect regulation[8] which may underlie the emotion dysregulation difficulties observed in PTSD[9]. However, the majority of these findings[9–11] have come from passive social-emotion processing or symptom provocation tasks in which individuals are asked to view and/or experience unpleasant (e.g., angry/fearful faces, unpleasant pictures) or trauma-related (e.g., combat sounds, scripted imagery) stimuli. That is, very few studies to-date have used tasks designed to directly probe prefrontal function in the context of volitional emotion regulation in PTSD.

According to cognitive models of PTSD, affect dysregulation may underlie the development and maintenance of the disorder[12] and individuals with combat-related PTSD in particular, have been shown to exhibit significant difficulty in the ability to control emotional responses[13]. In neuroimaging of healthy individuals, the willful down-regulation of negative affect via cognitive reappraisal (i.e., reframing) of aversive images has been found to be associated with reduced self-report ratings of emotionality[14], as well as reduced amygdala activity[15], (but see[16–20]). Cognitive reappraisal has also been found to increase activity in prefrontal regions involved in cognitive control[21], including the dorsolateral prefrontal cortex (dlPFC)[14,22], the ventrolateral PFC (vlPFC)[15,23], the dorsomedial PFC (dmPFC)[14,24], anterior cingulate cortex (ACC)[25–27], and the ventromedial PFC (vmPFC)[28] (for a recent meta-analysis, see Buhle et al [29])[21]. Activity in the PFC has also been found to be inversely related to activity in emotion-processing regions of the brain [i.e., the amygdala[29]] suggesting that successful down-regulation of negative affect may rely upon top-down control from the PFC[8].

Despite evidence of both prefrontal abnormalities and affect dysregulation in PTSD, only one study has consolidated these lines of work by examining the neural basis of emotion dysregulation in PTSD[30]. New and colleagues[30] assessed female survivors of sexual assault, and found that compared to healthy controls, women with PTSD showed an impaired ability to down-regulate their negative emotional responses to aversive images, as evidenced by self-report ratings (though this effect was absent when controlling for levels of trauma burden). Of note, reappraisal reduced activity in the amygdala; however this effect did not differ between groups. In addition, compared to non-traumatized controls, traumatized women (both with and without PTSD) showed reduced activation of lateral and medial regions of the PFC, with a trend observed for less PFC engagement in the PTSD group compared to the traumatized control group. However, whether these PFC deficits are also evident in PTSD from combat trauma remains unknown.

The present study examined the neural correlates of cognitive regulation (e.g., reappraisal) of negative affect in a group of returning OEF/OIF veterans with and without combat-related PTSD. Participants performed a version of the Emotion Regulation Task (ERT), which has been validated in our laboratory[14,24] and others[29] as an effective probe of PFC function during volitional attempts to cognitively regulate negative affect. Based on extant literature on the engagement of dlPFC, dmPFC, ACC, vmPFC and vlPFC in healthy individuals[21,29,31,32] and deficient dlPFC and dmPFC engagement in PTSD related to sexual assault, we had an *a priori* hypothesis that PTSD participants would activate these regions less than combat-exposed controls without PTSD when they were instructed to reappraise (i.e., reduce negative affect) versus passively view (i.e., maintain negative affect) the emotionally-evocative content of aversive images. Based on the centrality of the amygdala to theories of PTSD[33,34], we also expected to observe group differences in the extent of amygdala regulation during reappraisal in the PTSD group.

METHODS AND MATERIALS

Participants

Forty-two right-handed, male OEF/OIF veterans participated in this study. Twenty-one participants met criteria for PTSD (Caucasian = 19; African American = 1; Hispanic or Latino = 1) and 21 participants matched on levels of combat-exposure, but who did not have a diagnosis of PTSD (Combat Exposed Control [CEC] group; Caucasian = 19; African American = 1; Asian = 1). Psychiatric diagnoses were established via the Structured Clinical Interview for DSM-IV[35]. Additional assessment measures included the Clinician Administered PTSD Scale (CAPS)[36], the PTSD Checklist: Military (PCL-M)[37], the Combat Exposure Scale (CES)[38], the Hamilton Anxiety Scale (HAM-A)[39], the Hamilton Depression Inventory (HAM-D)[40], the Beck Depression Inventory (BDI-II)[41] and the Emotion Regulation Questionnaire (ERQ)[42] (Table 1).

Some of the PTSD patients had psychiatric co-morbidity at the time of scanning (n = 2 major depressive disorder; n = 1 alcohol abuse). In addition, some PTSD patients had a history of psychotropic medication usage (n = 7), however, all participants were free of psychoactive medications for at least 4 weeks prior to scanning. None of the participants had a history of head trauma, loss of consciousness, traumatic brain injury (of any severity),

clinically significant medical or neurologic conditions, or a positive urine toxicology screen at the time of scanning. All participants gave written informed consent, as approved by the VA Ann Arbor Healthcare System and University of Michigan Institutional Review Boards.

Emotion Regulation Task

The ERT[14,24] is a block-design variant of the reappraisal-based emotion regulation task developed in our laboratory based on paradigms previously validated by Ochsner and colleagues[15] and Davidson and colleagues[28]. Stimuli consisted of 64 unpleasant and 32 neutral images from the International Affective Picture System [IAPS][43]. The task involved three conditions. In the “Look” condition, participants simply looked at neutral images. In the “Maintain” condition, participants were instructed to passively process (e.g., experience naturally) unpleasant images. During the “Reappraise” condition, participants were instructed to use the cognitive strategy of reappraisal to decrease negative affect evoked by unpleasant images.

Prior to scanning, participants were instructed to use two validated strategies of reappraisal[14,15]: 1) conceptualizing the depicted scenario in a less negative way (e.g., women crying outside of a church could be attending a wedding not a funeral); and 2) objectifying the content of the pictures (e.g., a woman with facial bruises could be an actor in a movie). Participants were instructed not to look away from pictorial stimuli and understanding of the task was confirmed prior to scanning by reviewing examples of reappraisal strategies generated by subjects with sample IAPS images not used in the ERT during scanning.

Participants viewed two 20-second blocks of each condition interspersed with 20-second baseline blocks consisting of an image of a white fixation cross on a black background. During the baseline blocks, participants were asked to “relax and clear your mind.” Each experimental block consisted of four images, presented for 5 seconds each without an interstimulus interval. Prior to each block, the instruction to “Look”, “Maintain” or “Reappraise” appeared in white text on a black screen for 5 seconds. Immediately following each task block, participants were asked to rate “How negative do you feel?” on a 5-point scale (1 = not at all, 5 = extremely) via button response. The order of blocks was pseudo-randomized over 4 separate runs of 5 minutes each.

Following the scanning session, participants viewed each of the 96 previously seen pictures and rated these images on Valence (1 = most unpleasant; 5 = neutral; 9 = most pleasant) and Arousal (1 = not at all arousing; 5 = somewhat arousing; 9 = extremely arousing).

Functional imaging acquisition

FMRI scanning was performed on a 3T GE Signa System (General Electric; Milwaukee, WI) using a standard radiofrequency coil at the University of Michigan Functional MRI Laboratory. Whole-brain functional images (i.e., blood oxygen level-dependent [BOLD]) were collected from 43 axial, 3-mm-thick slices using a T_2*-sensitive gradient echo reverse spiral acquisition sequence (repetition time, 2000 ms; echo time, 30 ms; 64 × 64 matrix; 220 mm field of view; flip angle, 90), optimized to minimize susceptibility artifacts (signal loss) at the medial temporal lobe (including the amygdala)[44]. A T_1-weighted anatomical image

was collected in the same planes as the functional data, but with higher in-plane resolution ($1mm^2$, T_1-overlay) to aid in later co-registration. A high-resolution, T_1-weighted volumetric anatomical scan (T_1-SPGR; three-dimensional spoiled gradient echo) was also acquired for precise anatomical localization and normalization.

Functional imaging analysis

Functional imaging data were processed using conventional methods and analyzed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Center for Neuroimaging, University College, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Images were temporally corrected to account for slice time acquisition differences and spatially realigned to correct for head movement. Each participant's T_1-overlay was co-registered to the time-series data and the T_1-SPGR was then co-registered to the co-registered T_1-overlay image. The co-registered T_1-SPGR was then segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using the VBM8 toolbox of SPM8 and normalized Montreal Neurological Institute (MNI) space using DARTEL[45] and the resulting deformation field was applied to the time-series data. These normalized time-series data were subsequently re-sampled to 2 mm^3 voxels and smoothed with a 6 mm Gaussian kernel to minimize noise and effects due to residual differences in functional and gyral anatomy during inter-subject averaging.

The general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Condition effects during the 20-second block of images were modeled with box-car regressors representing the occurrence of each block type, and effects were estimated at each voxel and for each subject. In addition, the six movement parameters obtained during realignment were included in the model as regressors to account for motion-related effects in BOLD. Of note, the preceding instruction screen and the following affect rating period were modeled separately and collapsed across conditions. The individual SPMs were then analyzed at the second level in a random-effects statistical model. We conducted an ROI analysis using a 10-mm radius sphere centered on peaks independently defined based on a recent meta-analysis of 48 neuroimaging studies of reappraisal, most of which involve down-regulation of negative affect[46] (see Table 2 for a list of coordinates); however this meta-analysis did not observe any clusters in the vmPFC; therefore we used coordinates identified from a separate meta-analysis[31] for the vmPFC in our ROI analysis (see Table 2). We identified significant activations that survived small-volume correction ($P < 0.05$, family-wise error-corrected, FWE) for our *a priori* regions of interest for our main contrasts of interest (Reappraise > Maintain; Maintain > Look) for within-group and between-group (PTSD > CEC; CEC > PTSD) comparisons which balances the risk of Type I and II errors in the context of strong *a priori* regionally-based hypotheses[47] and is comparable to thresholds used in prior fMRI studies of cognitive regulation of emotion[29] and of PTSD[9–11].

To clarify the direction of differences in activation between the CEC and PTSD groups during the Reappraise > Maintain contrast, we extracted BOLD signal responses (parameter estimates, β-weights in arbitrary units [a.u.] of activation in terms of mean ± SD) averaged across all voxels within a 10 mm sphere surrounding the peak activation. Of note, we did not conduct between-group statistical tests on these measures as they were already defined as

significant from between-group independent samples *t*-tests analyses. In the PTSD group, activation in areas exhibiting group differences was correlated with PTSD symptom severity. In both groups, the extent of activation (Reappraise > Maintain) was correlated with the reduction in negative affect (Maintain > Reappraise) as well as ERQ scores. For completeness, to obviate bias and to generate hypotheses in future studies, we show all additional significant activations at a whole-brain voxel-wise threshold of $P < 0.001$ with a minimum cluster extent of > 133 contiguous voxels (1064 mm^3), to correct for multiple comparisons at a corrected $P < 0.05$ calculated using Monte-Carlo simulations (AFNI 3dClustSim, http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) (Table 4).

Subjective ratings analysis

Subjective ratings were assessed using a 2 (group: CEC, PTSD) X 3 (condition: Look, Maintain, Reappraise) mixed measures analysis of variance (ANOVA). Follow-up tests were performed using paired or independent sample *t*-tests, as appropriate.

RESULTS

Subjective ratings

There was a main effect of group ($F_{(1,40)} = 4.86$, $P = 0.03$), a main effect of instruction ($F_{(2,80)} = 105.74$, $P < 0.001$) and a group by instruction interaction ($F_{(2,80)} = 3.64$, $P = 0.03$) on the “online” subjective ratings. Participants reported less negative affect following the Reappraise compared to the Maintain condition (Maintain > Reappraise mean ± SD: CEC, $t_{(20)} = 3.70$, $P = 0.001$; PTSD, $t_{(20)} = 3.66$, $P = 0.002$; Table 3) and the magnitude of reappraisal-related reductions in negative affect did not differ between groups ($t_{(40)} = 0.26$, $P = 0.80$; Table 3). Both groups reported greater negative affect following the Maintain compared to the Look blocks (Maintain > Look: CEC, $t_{(20)} = 10.35$, $P < 0.001$; PTSD, $t_{(20)} = 7.81$, $P < 0.001$; Table 3); however, there was a trend for the CEC group to report greater negative affect following Maintain blocks (Maintain > Look; ($t_{(40)} = 2.01$, $P = 0.05$; Table 3).

Data from post-scan ratings (Table 3) were missing from one PTSD participant. For valence ratings, there was a main effect of image type ($F_{(1, 39)} = 72.65$, $P < 0.001$), indicating that unpleasant images were rated as less pleasant than neutral images; there was no main effect of group ($F_{(1, 39)} = 2.89$, $P = 0.10$) and no group by image type interaction ($F_{(1, 39)} = 2.82$, $P = 0.10$). For the arousal ratings, there was a main effect of group ($F_{(1, 39)} = 7.84$, $P = 0.008$), a main effect of image type ($F_{(1, 39)} = 36.31$, $P < 0.001$) and a group by image type interaction ($F_{(1, 39)} = 7.76$, $P = 0.02$). Both groups rated unpleasant images as more arousing than neutral images (CEC, $t_{(20)} = 6.66$, $P < 0.001$; PTSD, $t_{(19)} = 2.34$, $P = 0.03$; Table 3), however participants in the PTSD group reported less arousal for unpleasant minus neutral images ($t_{(39)} = -2.36$, $P = 0.02$; Table 3).

Functional MRI results

Within our *a priori* regions, the between-group analysis revealed that the CEC group showed significantly greater activation in the left dlPFC (peak MNI coordinate [−44, 16, 26];

volume = 752 mm^3; Z = 3.17, p = 0.05, corrected, Fig. 1) compared to the PTSD group during Reappraise (> Maintain)[1]. Follow-up inspection of ROI-extracted BOLD signal (β weights) from the left dlPFC clarified the direction of increased left dlPFC activation in the CEC group during Reappraise, which was attenuated in the PTSD group (mean $\beta \pm$ SD: CEC, 0.35 ± 0.34 vs. PTSD, 0.15 ± 0.32; Cohen's $d = 0.61$). The magnitude of dlPFC activation did not correlate with PTSD symptom severity within the PTSD group (CAPS overall: $r_{(19)} = -0.13$, $P = 0.57$; CAPS sub-scales: Re-experiencing: $r_{(19)} = 0.41$, $P = 0.07$; Avoidance and Numbing: $r_{(19)} = 0.01$, $P = 0.71$; Hyperarousal: $r_{(19)} = -0.18$ $P = 0.43$; PCL-M: $r_{(19)} = -0.12$, $P = 0.62$), reduction in negative affect ratings across all subjects (Maintain > Reappraise: $r_{(40)} = -0.163$, $P = 0.30$) or with ERQ scores across all subjects (overall and subscales: all $r_{(40)}$s < .16; all Ps > .30). There were no areas in which the PTSD group showed increased activation compared to the CEC group during Reappraise (> Maintain). No group differences were observed in dmPFC, ACC, vmPFC, vlPFC, or amygdala (Table 4). Additional significant within- and between-group activations outside *a priori* regions during Reappraise (> Maintain) are reported in Table 4. Of note, both PTSD and CEC groups activated dlPFC, dmPFC, and vlPFC during Reappraise (> Maintain) as reflected in within-group analyses (see Table 4).

Post-hoc generalized psycho-physiological interaction (gPPI) analysis[48] was performed using a dlPFC seed defined as a 10 mm radius sphere placed at the peak coordinate (MNI [−44, 16, 26]) from the between-group contrast during Reappraise (> Maintain). The dlPFC exhibited increased context-dependent coupling with the dmPFC ([6, −8, 70]; volume = 1048 mm^3; Z = 3.39, $P = 0.05$, corrected) during Reappraise (> Maintain) in the CEC group. There were no areas in which the PTSD group showed increased functional coupling with the dlPFC during Reappraise (> Maintain) and no group differences were observed.

In a secondary analysis, we examined the Maintain (> Look) condition to determine whether unpleasant images effectively evoked amygdala activation. Localization of these activations within the amygdala were defined by anatomical landmarks using MARINA software[49] based on masks from the atlas of Tzourio-Mazoyer and colleagues[50]. As expected, both groups exhibited increased left amygdala (CEC: [−20, −8, −16]; volume = 1024 mm^3; Z = 3.65, $P = 0.05$, corrected; PTSD: [−24, −8, −16]; volume = 848 mm^3; Z = 3.23, $P = 0.05$, corrected) and right amygdala (CEC: [24, −4, −14]; volume = 1312 mm^3; Z = 3.37, $P = 0.05$, corrected; PTSD: [26, −2, −20]; volume = 1440 mm^3; Z = 4.60, $P = 0.05$, corrected) activation during Maintain (>Look); the extent of amygdala activation during Maintain (>Look) did not differ between the CEC and PTSD groups (see Table 5; Fig. 2). Follow-up inspection of ROI-extracted BOLD signal (β weights) from the left and right amygdala confirmed increased activation in both groups during Maintain (> Look; Fig. 2) (mean $\beta \pm$ SD: left amygdala: CEC, 0.16 ± 0.29; PTSD, 0.27 ± 0.39; right amygdala: CEC, 0.25 ± 0.31; PTSD, 0.29 ± 0.29). Additional significant within and between-group activations outside our *a priori* regions during Maintain (> Look) are reported in Table 5. Next, we

[1]In a separate model we included BDI-II scores and education in years for all participants in order to control for elevated depressive symptoms reported by the PTSD group and the between-group difference in education level. We found that the results were unchanged (i.e., the CEC group still showed significantly greater activation in the dlPFC compared to the PTSD group during Reappraise > Maintain).

compared amygdala activation between Maintain and Reappraise to see if cognitive reappraisal attenuated amygdala activation; significant differences were not observed in either the CEC or PTSD group (see Table 4; Fig. 2).

DISCUSSION

It has been suggested that returning veterans with military combat trauma struggle with emotion regulation difficulties that may contribute to the development and maintenance of PTSD and comorbid conditions such as depression and alcohol/substance abuse[13,51]. However, no study to-date has examined the neural bases of volitional affect regulation in combat-related PTSD. The present study showed that veterans with and without PTSD similarly reported successful down-regulation of negative affect using cognitive reappraisal. However, at the neural level, veterans with PTSD showed less recruitment of the dlPFC during cognitive regulation of affect, compared to veterans exposed to similar levels of combat stress without PTSD.

Cognitive reappraisal is a complex process that is likely comprised of a number of subprocesses[8,23]. At its core, reappraisal involves the generation and subsequent maintenance of alternative interpretations of stimulus content. Along with other prefrontal brain regions, the dlPFC likely facilitates these processes via the selection of stimulus features suitable to reinterpretation and the maintenance of reappraisal goals and content in working memory[8]; left-lateralized activation of the dlPFC (observed here) may reflect the verbal nature of reappraisal[8]. In the present study, we found that combat-exposed veterans with and without PTSD activated prefrontal regions, including the dlPFC, during reappraisal, consistent with findings from healthy, non-traumatized participants[8,23].

However, the current findings show that veterans with PTSD engaged the dlPFC less than those without PTSD during the cognitive reappraisal of unpleasant images, suggesting reduced involvement of prefrontal resources in the down-regulation of negative affect. The results are broadly in line with prior work[30], which found evidence of prefrontal deficits in traumatized individuals (both with and without PTSD) during an emotion regulation task. Moreover, the results may have implications for cognitive theories of PTSD[12], which suggest aberrant prefrontal engagement during cognitive reappraisal may contribute to the development and maintenance of PTSD. Interestingly, unlike in other emotion-based studies of PTSD [e.g., 52,53–64] we did not observe group differences in the dmPFC, ACC, vlPFC or vmPFC. Differences in results may be due to small sample size or task variations. For example, whereas the current study used an emotion regulation task, prior work used symptom provocation tasks in which individuals were asked to view and/or experience unpleasant [52–55,65–67]) or trauma-related[58–64,68] stimuli, or used Pavlovian fear conditioning-extinction paradigms [56,57].

The PTSD-related dlPFC anomalies observed here may indicate broader cognitive deficits in PTSD. For example, in prior work that used a verbal working memory task, individuals with PTSD were found to exhibit less activation of the left dlPFC, even though stimuli were non-threatening[69,see also 70]. Nevertheless, dlPFC deficits – which may indicate reduced neural support for the verbal manipulation and organization of information – could underlie

affective symptomatology in PTSD[5,71]. For instance, reduced verbal representation of working memory content might play a role in the intrusive nature of traumatic memories in PTSD [5].

However, because PTSD-related neural abnormalities observed here did not co-occur with reduced subjective success at the reappraisal task (i.e., affect ratings) in the Reappraisal condition, our results come with some caveats. Despite group differences in the extent of dlPFC activation during reappraisal, both PTSD and non-PTSD groups reported similar success at reducing negative affect using cognitive reappraisal (see also [30]). One possibility is that demand characteristics may have motivated *all* participants to report reduced negative affect following the Reappraisal blocks. Another possibility is that unpleasant pictures were perceived less negatively or less arousing by the PTSD group as shown by subjective ratings of negative affect during scanning and of arousal rating post-scanning, and that consequently, PTSD subjects engaged the dlPFC to a lesser extent during reappraisal because there was *less* of a need to recruit additional prefrontal resources to implement affect regulation. Alternatively, given the subjective ratings, diminished reappraisal-related prefrontal brain activity in the PTSD group might also have been related to dissociation[72], numbing or blunted emotional responses reported by some patients with PTSD[73,74]. Of note, these subjective rating differences occurred in the context of similar levels of amygdala activation (Maintain > Look) in the PTSD and non-PTSD groups.

We predicted an attenuation effect of reappraisal on the amygdala reactivity in PTSD. Instead, we found no effect of reappraisal on the amygdala in either group and no group differences in modulation of amygdala activation. While some prior work has found a down-regulatory effect of reappraisal on amygdala activity[22,75,76], other studies have not[14,28,77]; moreover, several studies have failed to find evidence of increased amygdala activity in PTSD[78,79]. Notably, in the only other reappraisal study published on PTSD to date, reappraisal reduced activity in the amygdala, however this effect did not differ between groups[30]. It is also possible that the ERT which employs cognitive reappraisal may not be sensitive to group differences in amygdala modulation, and that future studies may test if tasks that employ alternative cognitive strategies (e.g., distancing, attention re-direction) are better suited to delineate PTSD from non-PTSD in this regard.

Other limitations are noteworthy and prompt further investigation. Future work could help explain the discrepancies between subjective and neural measures of affect regulation in PTSD by incorporating additional behavioral or psychophysiological measures of emotional arousal (e.g., skin conductance) as well as emotional awareness[72], which were not probed in the current study. Additionally, the inclusion of a non-traumatized control group would help isolate the effects of traumatic experience itself. Of note, however, the pattern of increased dorsal prefrontal activation observed here for the combat-traumatized control group is in line with prior findings from cognitive reappraisal studies of non-traumatized healthy individuals[29].

In conclusion, the results suggest that combat-related PTSD is associated with less recruitment of the dlPFC during the cognitive regulation of negative affect via reappraisal strategies. Similar results have been observed in other fear-based disorders, such as

generalized anxiety and panic disorders[80] (see also [81]), and mood disorders, like major depression[82–84], suggesting that perhaps alterations of prefrontal reactivity during emotion regulation may be a shared feature underlying several disorders. Importantly, these findings suggest that future studies investigating mechanisms underlying the pathophysiology of anxiety and mood disorders may be more appropriately approached from a dimensional or trans-diagnostic rather than a categorical or single diagnostic perspective [85]. In addition, it remains for future work to determine how findings from explicit and implicit emotion regulation paradigms in PTSD can be integrated into existing neurocircuity models of PTSD[33], which to-date have been derived largely from studies of threat- and trauma-related cue processing.

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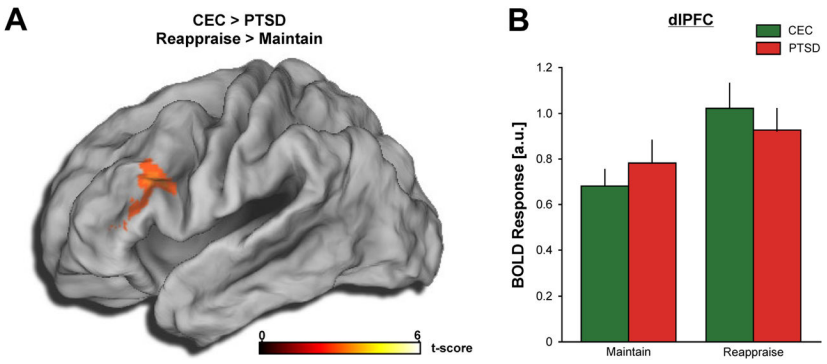

Fig. 1. Between-group differences in dorsolateral prefrontal cortex activation during Reappraise (> Maintain)

A, Between-group voxel-wise statistical *t* map overlaid on a canonical brain rendering (MNI sagittal) showing increased dorsolateral prefrontal cortex (dlPFC) reactivity during Reappraise (> Maintain) in the CEC group compared to the PTSD group. Threshold for displaying the image is set at $P = 0.05$ and masked; color bars represent statistical *t* scores. *B,* Mean BOLD response (β weights, arbitrary units [a.u.]) from the left dlPFC [−44, 16, 26] from each condition showing greater activation during Reappraise than during Maintain in the CEC group, compared to the PTSD group. CEC, combat-exposed controls (green bars); PTSD, posttraumatic stress disorder (red bars). Error bars indicate standard error of the mean.

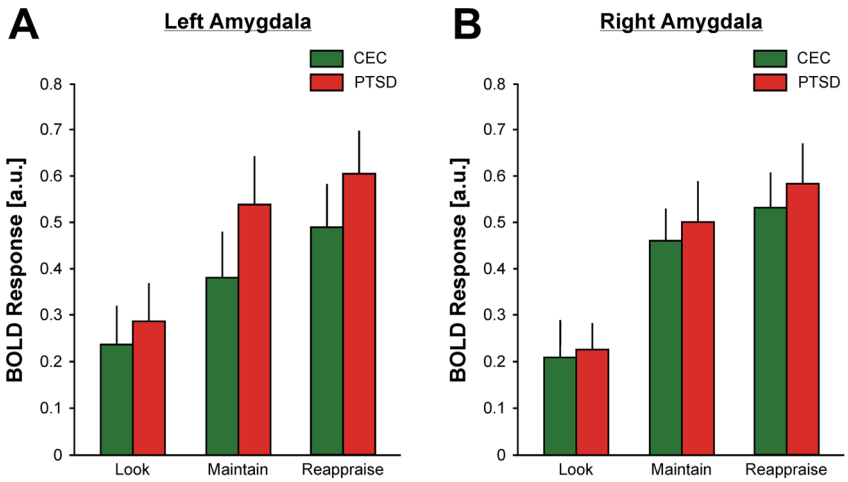

Fig. 2. Mean BOLD Response from the amygdala from each condition within groups

A, Mean BOLD response (β weights, arbitrary units [a.u.]) from the left amygdala ***(A)*** and from the right amygdala ***(B)*** [defined by anatomical landmarks using MARINA software[49] based on masks from the atlas of Tzourio-Mazoyer and colleagues[50]] from each condition showing greater activation during Maintain compared to Look, no difference between Reappraise and Maintain and no between-group differences. CEC, combat-exposed controls (green bars); PTSD, posttraumatic stress disorder (red bars). Error bars indicate standard error of the mean.

Table 1

Demographic and clinical characteristics of PTSD and CEC groups.

	PTSD (*n*=21)		**CEC (*n*=21)**		**Group comparison**	
	Mean	***SD***	***Mean***	***SD***	***t***	***P***
Age (years)	30.24	7.29	34.81	9.54	−1.74	*ns*
Education (years)	13.38	1.46	15.48	1.72	−4.25	< 0.001
Combat Exposure Scale	23.90	6.07	20.76	5.16	1.81	*ns*
Clinician-Administered PTSD Scale	66.62	13.06	4.95	5.52	19.93	< 0.001
Intrusive	16.81	6.46	0.38	0.97	11.25	< 0.001
Avoidance	24.00	7.18	1.67	2.31	13.58	< 0.001
Hyperarousal	25.81	4.51	2.90	3.66	18.07	< 0.001
PTSD Checklist – Military version	53.57	8.31	25.76	10.91	9.29	< 0.001
Hamilton Depression Scale	10.00	4.00	2.05	2.44	7.78	< 0.001
Hamilton Anxiety Scale	12.33	4.33	2.24	2.39	9.36	< 0.001
Beck Depression Inventory	21.43	6.89	5.43	6.52	7.73	< 0.001
Emotion Regulation Questionnaire						
– Reappraisal	27.33	7.35	29.29	7.27	−0.86	*ns*
– Suppression	18.71	4.95	15.57	5.57	1.93	*ns*

PTSD, posttraumatic stress disorder; CEC, combat-exposed controls, ns, non-significant (p > 0.05).

Table 2

Coordinates used in ROI analysis from Buhle et al[46].

	MNI Coordinates		
Brain Region	**x**	**y**	**z**
Dorsomedial Prefrontal Cortex	9	30	39
	0	15	63
	0	6	63
	0	−9	63
	0	18	42
	−9	12	69
Anterior Cingulate Cortex	−3	24	30
Dorsolateral Prefrontal Cortex	51	15	48
	51	6	48
	42	21	45
	42	30	39
	−33	3	54
	−36	22	−2
	−42	18	9
	−51	12	21
	−51	21	9
Ventrolateral Prefrontal Cortex	60	24	3
	48	24	9
	48	16	6
	−42	45	−6
Ventromedial Prefrontal Cortex*	6	40	−22
	0	38	−18

*vmPFC coordinate from Diekhof et al[31]. ROI analyses were conducted by creating a 10 mm radius sphere around the peak coordinate and identifying significant activations that survived small volume correction ($P < 0.05$, corrected). MNI, Montreal Neurological Institute

Table 3

Subjective ratings of negative affect and post-scanning valence and arousal ratings.

	PTSD		CEC	
"Online" (during scanning)				
Negative Affect Rating	***Mean***	***SD***	***Mean***	***SD***
Look	1.12	0.18	1.10	0.23
Maintain	2.40	0.82	2.86	0.71
Reappraise	1.90	0.66	2.40	0.74
Maintain-Reappraise	0.50	0.63	0.46	0.57
Maintain-Look	1.28	0.75	1.76	0.78
Post-scanning				
Valence Rating				
Neutral	5.41	0.66	5.52	1.34
Unpleasant	3.74	0.88	3.03	0.79
Arousal Rating				
Neutral	2.01	1.39	2.67	1.72
Unpleasant	2.97	1.39	4.86	2.10
Unpleasant-Neutral	0.96	1.83	2.19	1.51

PTSD, posttraumatic stress disorder; CEC, combat-exposed controls

Table 4

Whole-brain within- and between-group activation comparison during Reappraise (> Maintain)

				MNI Coordinates		
Brain Region	**Laterality**	**Volume (mm^3)**	**Z-score**	**x**	**y**	**z**
CEC						
Middle Temporal Gyrus	R	10512	5.66	40	−58	8
	L	10456	4.99	−48	−60	10
	L	1120	4.23	−48	2	−28
Ventrolateral Prefrontal Cortex	***R***	***2152***	***4.22***	***50***	***26***	***8***
	L	***80***	***3.46***	***−42***	***36***	***−6***
Dorsolateral Prefrontal Cortex	***L***	***87***	***4.04***	***−44***	***16***	***26***
	R	***1120***	***3.97***	***40***	***18***	***46***
	L	***97***	***3.95***	***−40***	***22***	***12***
	R	***144***	***3.65***	***50***	***14***	***42***
	R	***312***	***3.58***	***40***	***22***	***44***
	L	***384***	***3.58***	***−44***	***22***	***14***
	L	***376***	***3.51***	***−34***	***26***	***2***
	L	***120***	***3.35***	***−44***	***12***	***12***
	L	***104***	***3.21***	***−38***	***2***	***46***
Dorsomedial Prefrontal Cortex	***R***	***136***	***3.78***	***8***	***38***	***36***
	L	***160***	***3.47***	***−6***	***22***	***42***
PTSD						
Middle Temporal Gyrus	R	7928	5.16	48	−60	12
Middle Occipital Gyrus	L	4224	5.02	−36	−72	16
Dorsolateral Prefrontal Cortex	***R***	***1336***	***4.73***	***46***	***16***	***40***
	R	***1856***	***3.64***	***46***	***22***	***18***
Calcarine Fissure	R	1224	4.51	14	−72	6
Dorsomedial Prefrontal Cortex	***R***	***2896***	***3.70***	***10***	***32***	***40***
	L	***2072***	***3.29***	***−8***	***16***	***42***
Ventrolateral Prefrontal Cortex	***R***	***224***	***2.98***	***52***	***26***	***8***

CEC > PTSD

Brain Region	Laterality	Volume (mm^3)	Z-score	MNI Coordinates x	y	z
Dorsolateral Prefrontal Cortex	***L***	***752***	***3.17***	***−44***	***16***	***26***
PTSD > CEC						
No significant activations						

A priori ROIs shown in bold and italics. *A priori* ROI activation are significant ($P < 0.05$, corrected) and all other activations are significant at a whole-brain voxel-wise threshold of $P < 0.05$, corrected, based on 3dClustSim. MNI, Montreal Neurological Institute; CEC, combat-exposed controls; PTSD, posttraumatic stress disorder.

Table 5

Whole-brain within- and between-group activation during Maintain (> Look)

				MNI Coordinates		
Brain Region	**Laterality**	**Volume (mm^3)**	**Z-score**	**x**	**y**	**z**
CEC						
Fusiform Gyrus	R	78592	6.54	38	−54	−18
Ventrolateral Prefrontal Cortex	***R***	***3432***	***5.48***	***46***	***22***	***18***
	R	***816***	***4.17***	***52***	***24***	***0***
	L	***768***	***3.16***	***−46***	***38***	***−2***
Dorsomedial Prefrontal Cortex	***R***	***1928***	***5.28***	***6***	***22***	***60***
	L	***2504***	***4.41***	***−6***	***10***	***62***
	M	***2120***	***4.06***	***0***	***18***	***52***
	M	***1760***	***3.96***	***0***	***34***	***44***
	L	888	3.57	−6	0	64
Midbrain	R	8544	5.10	4	−30	−4
Dorsolateral Prefrontal Cortex	***R***	***1856***	***4.98***	***44***	***4***	***54***
	L	***2792***	***4.89***	***−48***	***28***	***10***
	L	***2800***	***4.88***	***−40***	***−2***	***54***
	L	***3576***	***4.79***	***−40***	***28***	***−8***
	L	***1744***	***4.55***	***−48***	***20***	***20***
	L	***824***	***3.99***	***−40***	***8***	***54***
Ventromedial Prefrontal Cortex	***M***	***1720***	***4.89***	***0***	***48***	***−18***
Posterior Cingulate Cortex	L	3512	4.61	−4	−52	22
Middle Temporal Gyrus	L	2760	4.47	−52	0	−22
	R	1872	4.43	50	−14	−14
Amygdala	***L***	***1024***	***3.65***	***−20***	***−8***	***−16***
	R	***1312***	***3.37***	***24***	***−4***	***−14***
PTSD						
Midbrain	L	5120	6.05	−6	−26	−8
Middle Occipital Gyrus	L	85520	5.97	−42	−80	2
Dorsolateral Prefrontal Cortex	***L***	***944***	***4.63***	***−40***	***12***	***50***

				MNI Coordinates		
Brain Region	**Laterality**	**Volume (mm^3)**	**Z-score**	**x**	**y**	**z**
	L	***2128***	***4.47***	***−52***	***18***	***22***
	R	***1224***	***4.16***	***46***	***4***	***40***
	L	***2028***	***3.49***	***−50***	***28***	***16***
	L	***2456***	***3.41***	***−48***	***18***	***2***
Amygdala	***R***	***1440***	***4.60***	***26***	***−2***	***−20***
	L	***848***	***3.23***	***−24***	***−8***	***−16***
Ventrolateral Prefrontal Cortex	***R***	***2048***	***4.41***	***52***	***30***	***4***
	R	***1056***	***3.38***	***48***	***26***	***6***
Dorsomedial Prefrontal Cortex	***R***	***1192***	***4.38***	***2***	***18***	***56***
	R	***2400***	***3.97***	***12***	***34***	***48***
	L	***160***	***3.81***	***−10***	***16***	***62***
	R	***1292***	***3.66***	***4***	***14***	***60***
Ventromedial Prefrontal Cortex	***M***	***1168***	***4.08***	***0***	***44***	***−18***
Caudate	R	2848	3.98	12	4	14
CEC > PTSD						
No significant activations						
PTSD > CEC						
No significant activations						

A priori ROIs shown in bold and italics. *A priori* ROI activation are significant ($P < 0.05$, corrected) and all other activations are significant at a whole-brain voxel-wise threshold of $P < 0.05$, corrected, based on 3dClustSim. MNI, Montreal Neurological Institute; CEC, combat-exposed controls; PTSD, posttraumatic stress disorder.