Soldiers with PTSD see a world full of threat: MEG reveals enhanced tuning to combat-related cues

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Abstract

Background. Post-traumatic stress disorder (PTSD) is linked to elevated arousal and alterations in cognitive processes. Yet whether a traumatic experience is linked to neural and behavioural differences in selective attentional tuning to traumatic stimuli is not known. The present study examined selective awareness of threat stimuli and underlying temporal-spatial patterns of brain activation associated with PTSD.

Methods. Participants were 44 soldiers from the Canadian Armed Forces, 22 with PTSD and 22 without. All completed neuropsychological tests and clinical assessments. Magnetoencephalography (MEG) data were collected while participants identified two targets in a rapidly presented stream of words. The first target was a number and the second target (T2) was either a combat-related or neutral word. The difference in accuracy for combat-related vs. neutral words was used as a measure of attentional bias.

Results. All soldiers showed a bias for combat-related words. This bias was enhanced in the PTSD group, and behavioural differences were associated with distinct patterns of brain activity. At early latencies non-PTSD soldiers showed activation of midline frontal regions associated with fear regulation (90-340ms after T2 presentation), whereas those with PTSD showed greater visual cortex activation linked to enhanced visual processing of trauma stimuli (200-300ms).

Conclusions. These findings suggest that attentional biases in PTSD are linked to deficits in very rapid regulatory activation observed in healthy controls. Thus, sufferers with PTSD may literally see a world more populated by traumatic cues, contributing to a positive feedback loop that perpetuates the effects of trauma.

Introduction

Posttraumatic Stress Disorder (PTSD) is a trauma-related mental disorder with anxious and depressive features, resulting from exposure to one or more events involving actual or threatened death or serious injury. Although the clinical presentation varies, individuals suffering from this condition experience symptoms that include re-experiencing the traumatic event, avoidance of associated situations or stimuli, negative mood and appraisals, and elevated levels of arousal and reactivity (1). It is well documented that a traumatic experience can influence a wide range of cognitive processes [e.g., (2)]. Yet it is still not known whether a history of traumatic experience is associated with specific patterns of selective attention that may influence how an individual literally sees the world, and whether neural and behavioural indices of selective attention characterize PTSD. Here we examined these questions by investigating patterns of perceptual awareness for combat-related stimuli in Canadian soldiers with and without diagnoses of PTSD as well as in civilians, and used magnetoencephalography (MEG) to measure the temporal-spatial patterns of associated brain activation in the soldiers.

A body of evidence indicates there is preferential allocation of attention to trauma-related stimuli following a traumatic experience. Studies of trauma-related attentional biases indicate difficulty disengaging both spatial [for review see (3)] and temporal (4) attentional resources from trauma-related stimuli. Other studies have found enhanced perception of trauma-related stimuli as measured by an increased signal to noise ratio in perception for both visual (5) and auditory (6) information. However, some studies have failed to find such attentional biases (7). The specificity of attentional biases for trauma-related stimuli or threat in general has also been questioned (8, 9).

The attentional blink (AB) (10) is an experimental manipulation that effectively measures biases in rapid perceptual encoding and resulting awareness. The 'blink' itself is a phenomenon where participants are typically unable to report a target stimulus when it is presented within ~500ms of a previous target in a rapid stream of stimuli. There are a number of competing interpretations of the AB phenomenon, but one interpretation that has garnered empirical support is that it reflects a failure of attentional filters to consolidate the second target into working memory when it appears too quickly after the first, resulting in impaired perceptual awareness (11). When the second target (T2) is emotionally salient (e.g., 'RAPE' vs. 'ROPE'), there is a reduced blink, or an 'emotional sparing' (12-14). This emotional sparing can be seen as reflecting the relative robustness of selective attention for affective stimuli (15). Fear conditioning can also elicit AB sparing for conditioned stimuli, suggesting a link between emotional learning and enhanced perceptual awareness (16), and fMRI research has found sparing for conditioned stimuli in healthy controls to be mediated by co-activation between the amygdalae and visual cortices (16). Further, in healthy adults, an MEG investigation of the temporal-spatial patterns of sparing for emotionally salient words has found emotional sparing to be characterized by early activation in regions of the extended amygdalae followed by later activation in key frontal regions (17).

Individual differences in the degree of AB emotional sparing have been observed, and may be influenced by temperament, genotype, and experience. Greater emotional sparing for threatening faces has been linked to higher levels of trait anxiety (18). Moreover, carrying a deletion variant of the *ADRA2b* gene influencing norepinephrine levels has been linked to higher levels of overall emotional enhancement of memory, including intrusive memory following trauma (19). Notably, the *ADRA2b* deletion variant is also associated with greater sparing for negatively valenced words (20). Such links between common genetic variations associated with intrusive traumatic memory, enhanced limbic

activation linked to emotional sparing, and AB emotional sparing linked to threat provide convergent evidence suggesting PTSD may be associated with enhanced AB sparing for trauma-related cues.

Such enhanced AB sparing should also be related to distinct patterns of brain activity in PTSD. Although neuroimaging studies using different experimental tasks show mixed results, meta-analyses of fMRI data indicate that overall symptom provocation elicits greater activation in bilateral amygdalae, mid-cingulate cortex and precuneus, and reduced activation in ventromedial prefrontal cortex and fronto-parietal control networks in participants with PTSD relative to controls (21, 22). PTSD has also been linked to patterns of altered functional connectivity (23). Yet rapidly-occurring patterns of brain activity coupled to sorting salient from mundane stimuli in the AB, which may be crucially altered in PTSD, may not be captured by the slow time-courses of PET and fMRI.

The present study addressed the question of whether PTSD is linked to altered tuning of attentional filters to the visual environment under conditions of high visual competition. Here we used MEG to examine the connection between PTSD, behavioural indices of AB emotional sparing for trauma-specific stimuli, and patterns of brain activation at a high temporal resolution. Combat veterans currently in the Canadian Armed Forces performed an AB task in the MEG scanner using combat-related and neutral words as the second target (T2) stimuli. We predicted that AB performance would differentiate soldiers with and without PTSD, such that soldiers with PTSD would show greater AB sparing than soldiers without PTSD. For participants with no combat experience, the AB for combat-related words should not differ from that for neutral words. Based on evidence of altered structure and function of regulatory processes in PTSD, we predicted that control soldiers would show greater activation in regulatory regions of anterior cingulate cortex in the presence of combat-related stimuli. Based on convergent evidence of the role of valuation networks in AB sparing and greater excitability of valuation networks in PTSD, we predicted that those with PTSD would show

either enhanced activation in nodes of valuation networks (amygdalae, orbitofrontal cortex), or higher levels of visual cortex activity associated with emotional sparing, or both.

Materials and Methods

Participants for the MEG study were active-duty service members from the Canadian Armed Forces (CAF). The initial sample included 24 soldiers diagnosed with PTSD (all males; mean age = 37.7 years ± 6.8 SD; range 26-48 years) and 24 control soldiers (all males; mean age = 32.9 years ± 4.6 SD; range 27-42 years). All participants were veterans of combat who had served in Afghanistan. At the time of MEG testing 4 soldiers were excluded because of scanner incompatibility or unusable MEG data, leaving a final N of 22 soldiers with PTSD (mean age = 37.6 years; range 26-48 years) and 22 soldiers without PTSD (mean age = 32.4 years; range 27-40 years). We also collected behavioural data from an additional group of 18 age and education matched participants with no combat experience (all males; mean age = 28.05 years ± 5.84 SD; range 20-39 years) to serve as non-military controls. These civilians were actively recruited from the hospital and university community for a separate study on traumatic brain injury, and agreed to complete the behavioural version of the AB task.

Individuals with PTSD were diagnosed using a semi-structured clinical interview for DSM-IV Axis I Disorders (American Psychiatric Publishing Inc.), performed by a military psychiatrist according to Canadian Forces protocol. The diagnosis also included psychometric testing by a psychiatrist or psychologist at a Canadian Armed Forces Operational Trauma and Stress Support Centre (OTSSC) and identified through clinicians at one of the CAF OTSSCs (for details see supplemental information and for demographic information see Table 1). All testing was conducted in the MEG Lab at the Hospital for Sick Children and received institutional ethics approvals from both the Hospital for Sick Children and Defense Research and Development Canada. All participants gave informed written consent.

Neuropsychological and Clinical Assessments. All participants completed a short battery of neuropsychological tests as well as brief clinical assessments (see supplemental information). The tests, their means and standard deviations for each group are contained in Table 1.

Experimental tasks. Before entering the MEG scanner participants performed a practice version of the AB task using only neutral T2 words. Following the practice task participants entered the MEG scanner and MEG data were collected while participants performed the experimental version of the AB task. Both the practice and the experimental versions of the AB task were rapid serial visual presentation (RSVP) tasks with the following parameters: In each trial, following a fixation cross, 15 stimuli were presented sequentially for 100ms each in a rapid stream (see Figure 1). For each trial participants were required to report two targets that were presented amongst the series of distractors: the first (T1) was a string of numbers and the second (T2) was always a word, both presented in green font. Distractor words were neutral, presented in black font, and selected to be longer than target words to optimize masking effects. Following each trial, participants were asked to report both targets.

Practice task. The practice task was used for two purposes: To familiarize participants with the experimental task and to determine the lag at which each participant had approximately 60% accuracy for T2 words (see supplemental material for details)**.** All T2 words were emotionally neutral.

Experimental Task (MEG). In the MEG version of the task T2 words were either combat-related words, selected to be emotionally arousing for soldiers, or neutral words (a separate set of neutral words from those employed in the practice task). Combat-related words and neutral words were balanced for length, written frequency, and neighbourhood frequency (the frequency of words of the same length that could be created by changing a single letter) (27). Stimuli were presented

foveally and subtended a visual angle of 6°. After each trial there was a variable inter-stimulus interval between the final word in the stream and the fixation cross that marked the beginning of the next trial. During this interval participants observed a black screen and reported both targets verbally into a microphone. Responses were scored as hits (accurately reported numbers and words) or misses (either T1 or T2 inaccurately reported) by an experimenter during data acquisition (for trial counts see Supplemental Table S1). In total participants completed 172 trials, 86 in which T2 was combat-related and 86 in which it was neutral.

MEG data acquisition and preprocessing. MEG data were recorded continuously (600 Hz sampling rate, 100 Hz low-pass filter, third-order spatial gradient noise cancellation) on a 151 channel whole-head CTF system (MISL Ltd., Canada) in a magnetically-shielded room (for details and calculation of global field power see supplemental material).

As we were interested in measures related to accuracy for T2, all reported activations were time-locked to T2 onset. T2 trials were sorted by combat-related and neutral words. A vector beamformer source localization algorithm (24, 25) integrated over 50ms non-overlapping time windows from 90 – 590ms was applied with a spatial resolution of 5 mm over the whole brain. This resulted in images for 10 time windows (i.e., 90-140, 140-190, 190-240, 240-290, 290-340, 340-390, 390-440, 440-490, 490-540, 540-590ms). The beamforming algorithm was applied to each condition separately, so that the covariance matrix was appropriately computed for the number of trials and variability in the data.

Results

Behavioural results

Word Ratings. After completing the AB task participants rated all T2 words for both subjective levels of arousal and word familiarity. Full results are reported in the supplemental information, and arousal ratings for each group are illustrated in Figure 2.

Accuracy. Accuracy was calculated as the proportion of correctly reported words for T2 trials that followed correct T1 trials in the combat-related and neutral conditions (Supplemental Table S1). A repeated measures ANOVA was performed on accuracy with T2 category (combat-related vs. neutral) as the within-subject factor and PTSD group as the between-subject factor. All reported contrasts were Bonferroni corrected to control for multiple comparisons. There was no main effect of group, $F(1, 42) = 1.56$, $p > 0.20$, indicating that the groups did not differ in overall accuracy. There was a main effect of T2 category, $F(1, 42) = 113.24$, $p < 0.001$, $\eta_p^2 = .73$, with higher accuracy signifying a reduced attentional blink, or AB sparing, for combat-related words. Contrasts showed this effect to be significant in both groups separately, *p*s < 0.001. This was qualified by a PTSD group by T2 accuracy interaction, $F(1, 42) = 6.34$, $p = 0.01$, $\eta_p^2 = .13$, indicating a greater difference in accuracy between combat-related and neutral words for the soldiers with PTSD. Thus, whereas all soldiers showed an advantage in perceptual encoding of combat-related relative to neutral words, those with PTSD had a greater advantage than those without (Figure 2b).

To ensure that the overall AB sparing for combat-related words was due to combat experience and not such factors as greater semantic relatedness, we examined behavioural data from control participants with no combat experience. Analysis of accuracy results indicated no combat-related sparing for civilian controls. Familiarity and arousal ratings as well as AB accuracy results for all groups are reported in the supplemental materials and arousal ratings are illustrated in figure 3.

Because attentional biases are symptomatic of anxiety and depression (26-28), we further examined the relation between combat-word sparing and GAD-7 and PHQ9 scores, as well as the relationship between PTSD symptoms as measured by the PCL and combat-word sparing within the PTSD group alone. Results, reported in detail in the supplemental information and illustrated in Figure 2c, indicated that combat-word sparing was related to both anxiety and depression, and this difference was driven by the soldiers with PTSD. They also revealed a continuous relationship between PTSD symptoms and combat-word sparing.

MEG Results

Global Field Power (GFP) results. MEG analyses were conducted only on the two groups of soldiers. Whole-head GFP plots for the soldiers with and without PTSD for each category of stimuli were used to identify beamformer window widths that would encompass prominent peaks. GFPs for each subject were visually inspected prior to inclusion in source analysis to ensure adequate data quality. Three soldiers in the PTSD group and 3 in the no-PTSD group were excluded from MEG source analysis due to excessively high-amplitude signals and poor signal-to-noise ratios, leaving 19 participants in each group. GFP plots of the frontal sensors, between groups, show that both groups reveal the typically observed differences between hits and misses (collapsed across word category) at the time of the P3 (~400ms)(Figure 3).

Source Analyses. To assess activation across time in specific source regions, we focused on brain activity underlying the emotional sparing effect (the difference between correct combat-related and neutral words) in 50ms time windows using the following contrasts: In one analysis [(Combat hits – Neutral hits) – (Combat misses – Neutral misses)] in the PTSD group were subtracted from [(Combat hits – Neutral hits) – (Combat misses – Neutral misses)] in the military controls. In the other analysis

the same contrasts in military controls were subtracted from those in the PTSD group. To control for multiple comparisons, data were permuted (2946 permutations) across to-be-compared conditions, and the largest differences for any voxel in this surrogate data were used to obtain a threshold for each voxel. Locations with significant activations between groups ($p < 0.05$, corrected) are listed in Table 2 and all significant results are plotted on 3-dimensional brains for visualization (for 3D depictions of all regions showing contrasts related to differences in AB sparing between groups see Supplemental Figure 1).

Here we focus on the most robust results related to group differences in neural substrates of emotional sparing in hypothesized regions. First, there was greater activation associated with combat-word sparing for the control group over the PTSD group at an early latency (90-140ms) with a peak in the caudate nucleus and activation extending along the subgenual anterior cingulate cortex (ACC). This early ventral midline activity was followed directly by activation in the dorsal ACC at 140-190ms and by dorsal ACC again 100ms later at 290-340ms (Figure 4). Thus, soldiers without PTSD showed more rapid activation than the PTSD group in regions known to modulate amygdalae and autonomic activation. At a longer latency (540-590ms), military controls showed greater activation in the right inferior orbital gyrus, a prefrontal region previously found to discriminate between emotional and neutral T2 hits in healthy controls (17). In the opposite direction, there was a robust mid-latency activation (290 -340ms) that was greater for the PTSD than non-PTSD group in occipital visual cortex with peaks in the left posterior precuneus and left lingual gyrus (Figure 4).

Discussion

In this study we employed a novel experimental paradigm in PTSD research — an attentional blink (AB) task — to index selective awareness of trauma-related cues. We compared task

performance and temporal-spatial patterns of brain activation in Canadian combat veterans with and without diagnoses of PTSD. Results showed that whereas all combat veterans showed 'emotional sparing' of the attentional blink, with greater accuracy for combat-related over neutral words, this sparing was enhanced in the PTSD group.

Crucially, soldiers with PTSD also rated combat-related words as significantly more arousing relative to neutral words than soldiers without PTSD, indicating a greater subjective emotional response to the words. As Figure 2 (a & b) illustrates, these higher arousal patterns show a similar pattern to the AB accuracy results showing greater combat-word sparing for the PTSD group. This finding is consistent with a body of research in healthy adults finding that words rated as higher in arousal are subject to 'emotional sparing' of the attentional blink (12-14, 20). Thus, it is likely that the PTSD group showed higher levels of combat-word sparing because they found the combat-related words to be more arousing, consistent with patterns of elevated arousal and reactivity to trauma-related stimuli associated with PTSD (29, 30).

It should be noted that whereas there was greater sparing for combat-words, there was overall poorer performance for *neutral* words in the PTSD group relative to the military controls, and that the difference in performance was reduced by the combat-word sparing for combat-related words. This reduced performance for neutral words in the PTSD group may reflect a number of factors related to being in the scanner, including heightened stress/anxiety triggered by combat-related words, suppression of selective attention to neutral words in the presence of combat words, or greater deterioration of sustained attention to the task in the PTSD group.

Our MEG results revealed that the distinct patterns of brain activity for combat-related vs. neutral words further distinguished the two groups. Compared to those with PTSD, in soldiers without

PTSD combat-word sparing was characterized by early and strong activation of midline frontal regions associated with fear regulation and extinction (22, 31, 32). In contrast, at mid-latencies, PTSD soldiers showed extensive activation of visual cortex. These findings suggest that the differences in combat-word sparing observed in the two groups may be linked to reductions in rapid regulatory activity leading to enhanced processing of emotionally salient targets in the PTSD group.

Early-mid latency activation patterns. One influential model of PTSD proposes that symptoms reflect a failure of fear extinction processes following a traumatic event (33, 34). Consistent with this model, source localization results indicated that very early activation in prefrontal midline regions associated with amygdala/autonomic regulation differentiated control soldiers from those with PTSD. Between 90 and 140ms after T2 presentation, soldiers without PTSD showed greater activation in the caudate nucleus/subgenual ACC, regions consistently implicated in PTSD in both structural imaging and challenge studies (21, 29, 35, 36). It has been proposed that reduced caudate activity is linked to anhedonia characteristic of both depression and PTSD (35). Activity in subgenual ACC is implicated in modulation of amygdala activity in humans (37), and a large body of human and animal literature shows its key role in fear extinction [for review see (29, 38)]. Our pattern of activation suggests that, for control soldiers without PTSD, very rapid extinction-related processes are recruited immediately after encountering trauma-related stimuli. For controls, such processes were associated with greater successful perceptual encoding of combat-related stimuli.

The pattern of greater ventral midline activation associated with combat-word sparing for military controls was followed by greater dorsal ACC activation for controls in two subsequent early-to-mid latency time windows between 140 and 340ms. Interestingly, PTSD challenge studies using fMRI have typically revealed the opposite pattern, with enhanced relative activation in PTSD compared to controls (39, 40). Yet dorsal ACC activation has been consistently linked to both fear

acquisition/expression and its regulation/extinction (41), including modulation of amygdala activity via reappraisal (42), suggesting it may play a flexible role in these processes. Inconsistency with fMRI results may further reflect differences in measures (e.g., transient neuronal activity captured by MEG may not be detectable in the slower BOLD response) or differences in the AB task and emotional challenge paradigms typically used for PTSD. Overall, our data are consistent with a greater role for the dorsal ACC in regulation and appraisal for control participants. Here such regulatory activity occurred at latencies just prior to and during the time window when stimuli that reach awareness are discriminated from those that are subject to the attentional blink (17, 43).

Subsequently, we observed a period of greater activation in early visual cortex in the PTSD group than in military controls. AB sparing for fear-conditioned stimuli has been linked to greater connectivity between the amygdalae and visual cortex (16). PTSD challenge studies have also reported greater influence of the amygdalae and reduced influence of prefrontal regions on the visual cortex in PTSD (23), indicating that PTSD is associated with altered functional connectivity patterns that enhance visual processing of threat. Here the PTSD group showed visual cortex intensified activation patterns associated with enhanced emotional processing in the absence of regulatory activation observed in controls. Thus, our data suggest that, whereas combat-related cues are highly salient for all soldiers, at earlier latencies those *without* PTSD are able to rapidly down-regulate affective responses to stay on task. In contrast, PTSD is linked to intensified processing of emotional salience reflected in visual cortical processing.

Late activation patterns. At longer latencies, the beamforming results revealed that controls showed greater emotional-sparing-related activation than the PTSD group in right inferior orbital gyrus. This is consistent with a prefrontal region found to characterize emotional sparing at later latencies in healthy controls (17). The OFC plays a key role in the flexible evaluation of stimulus

salience in relation to context and has been implicated in learning and decision-making processes related to emotional or motivational salience (44-46). Here the non-PTSD group showed an activation pattern similar to that found to be associated with emotional sparing in civilian controls, with greater activation linked to context-sensitive valuation processes that appeared just prior to making a response. This finding is consistent with a pattern of reduced prefrontal activation in PTSD (29).

Although our analysis approach with the beamformer data did not permit examination of patterns correlated with individual differences in depression and anxiety, our behavioural findings suggest that the group differences in neural activation we observed reflect high frequency rates of comorbid depression and/or anxiety found in PTSD in an estimated 21-94% of PTSD sufferers [e.g., (47)]. Future research examining connectivity patterns could employ graph theory to correlate activation with individual behavioural scores. Another goal of future research is to examine patterns of phase synchrony at specific frequency bands to examine whether attentional tuning to trauma-related stimuli is characterized by altered patterns of functional connectivity between the amygdalae, anterior cingulate regions, and visual cortices. Other areas for future research include examining the relation between effects of medication and MEG activation to disembed potential medication effects. They can also include investigation of the relation between PTSD symptoms and neural and behavioural measures of combat-word sparing to ascertain whether the pattern of results we observed is independent of clinical levels of PTSD.

Conclusion: Heightened attentional tuning to combat-related words was observed for combat veterans with and without a diagnosis of PTSD; however those soldiers with PTSD showed higher levels of tuning to threat. Our results suggest that behavioural patterns that differ between groups only in degree reflect distinct patterns of neural activation. These differences are particularly distinct at early latencies, when emotionally significant stimuli may be pre-attentively sorted from the

mundane. Because of deficits in rapid regulatory activation, soldiers who suffer from PTSD may literally see a world more populated with reminders of trauma than those without.

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Figure Captions

Figure 1. Example of the attentional blink task with a combat-related word at T2.

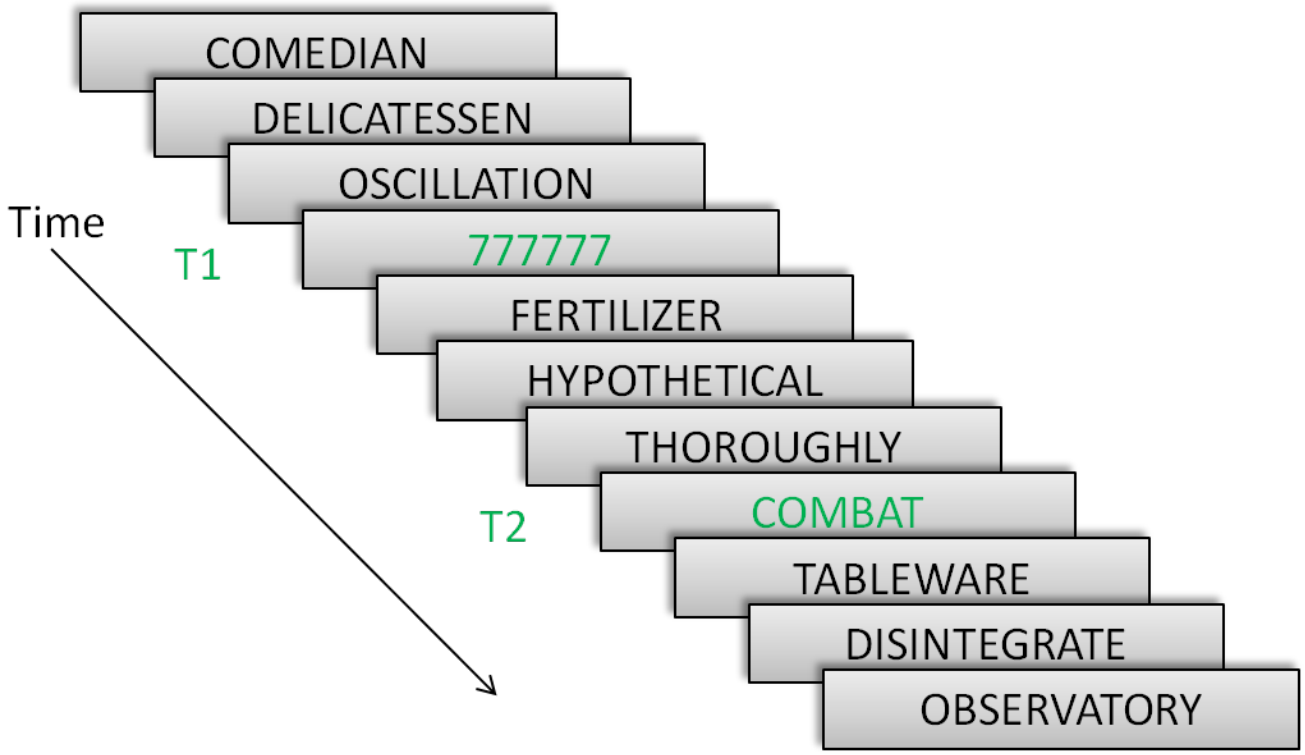


Figure 2. Behavioural results. (A) Arousal rating and (B) T2 accuracy for combat-related and neutral words for soldiers with PTSD, soldiers without PTSD and combat-naïve controls. (C) Correlations between T2 combat-word sparing (accuracy for combat words > neutral words) and: GAD-7 score as a measure of anxiety in the PTSD group and military controls (left); PHQ9 score as a measure of depression in the PTSD group and military controls (middle); PCL score in the PTSD group as a measure of PTSD symptoms (right).

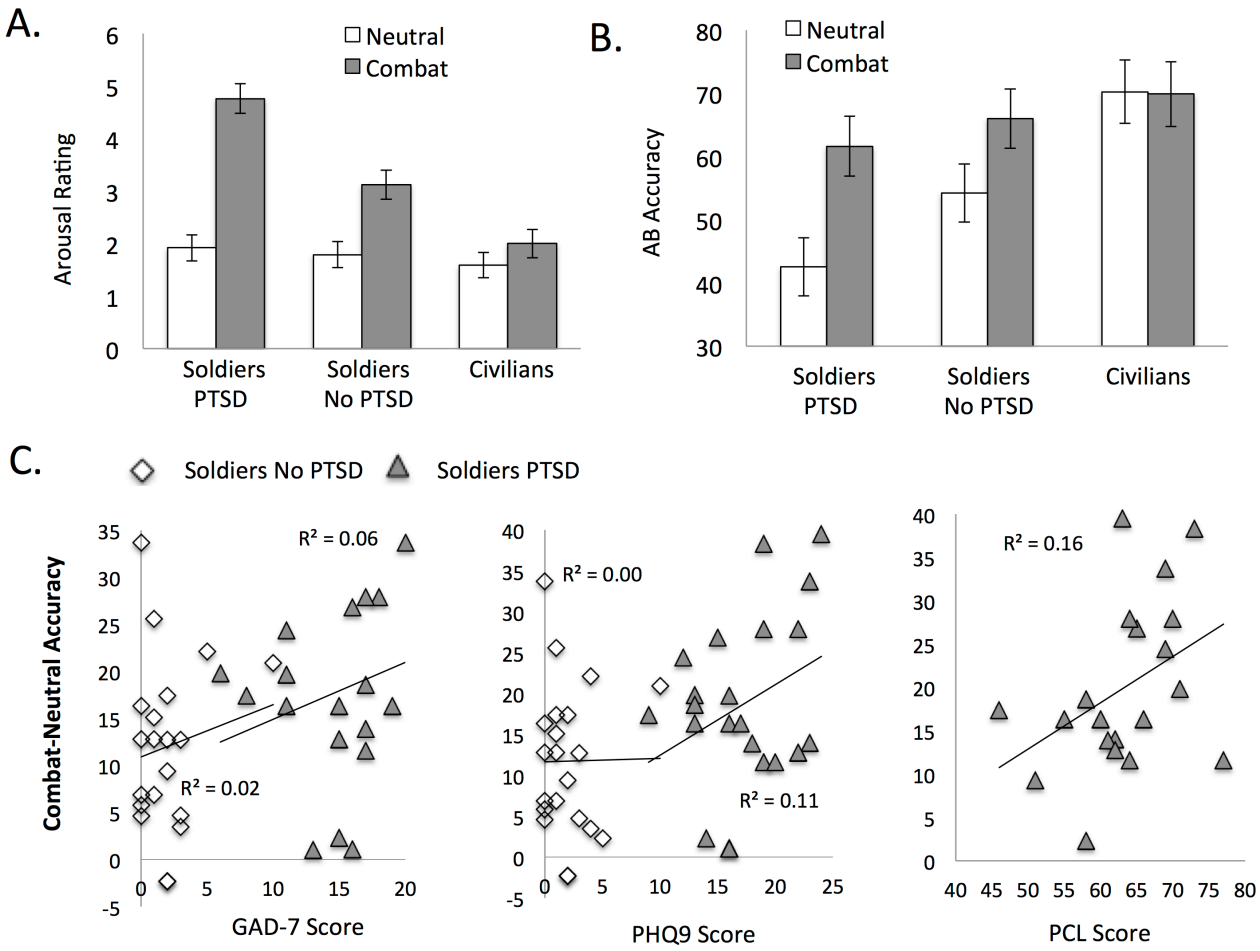


Figure 3. Global-field power (GFP, or the root mean square power over a set of sensors) plots from frontal sensors in a time window ranging from -200 to 600ms. The P3 component seen at around 400ms in both PTSD and non-PTSD groups to hits and not to misses, is larger in the PTSD group.

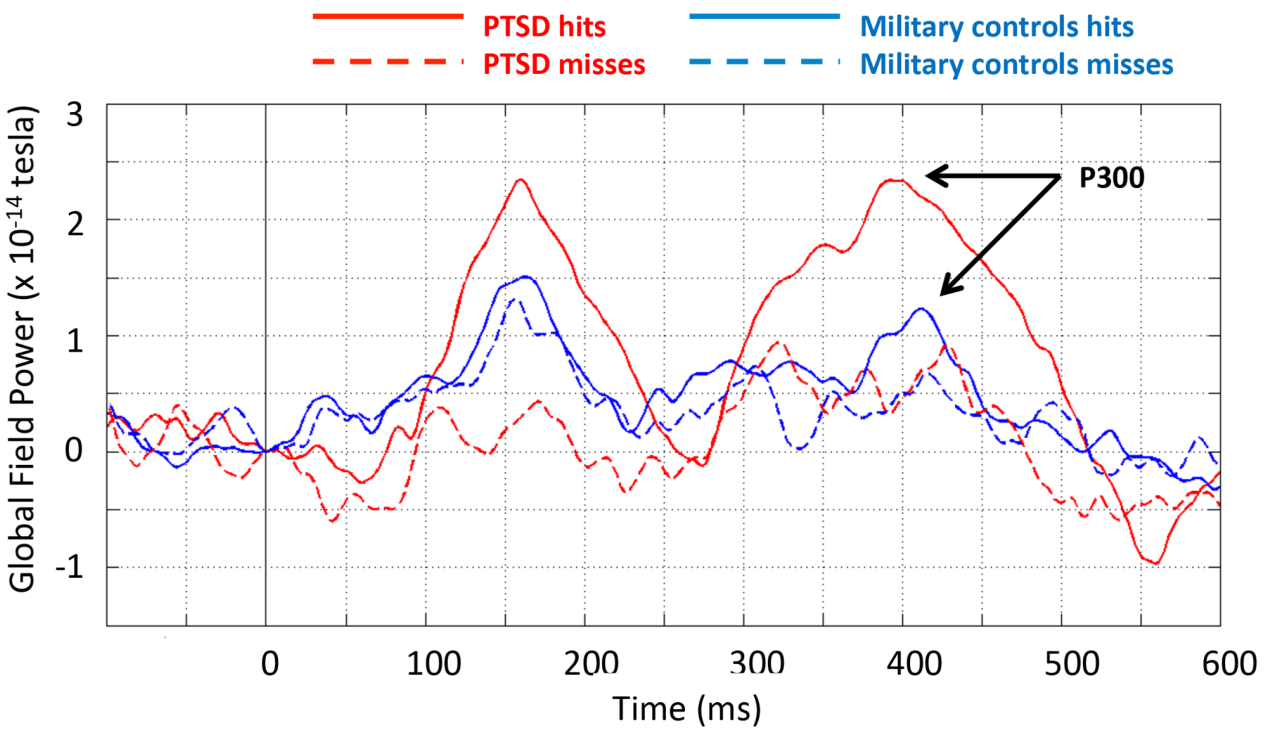
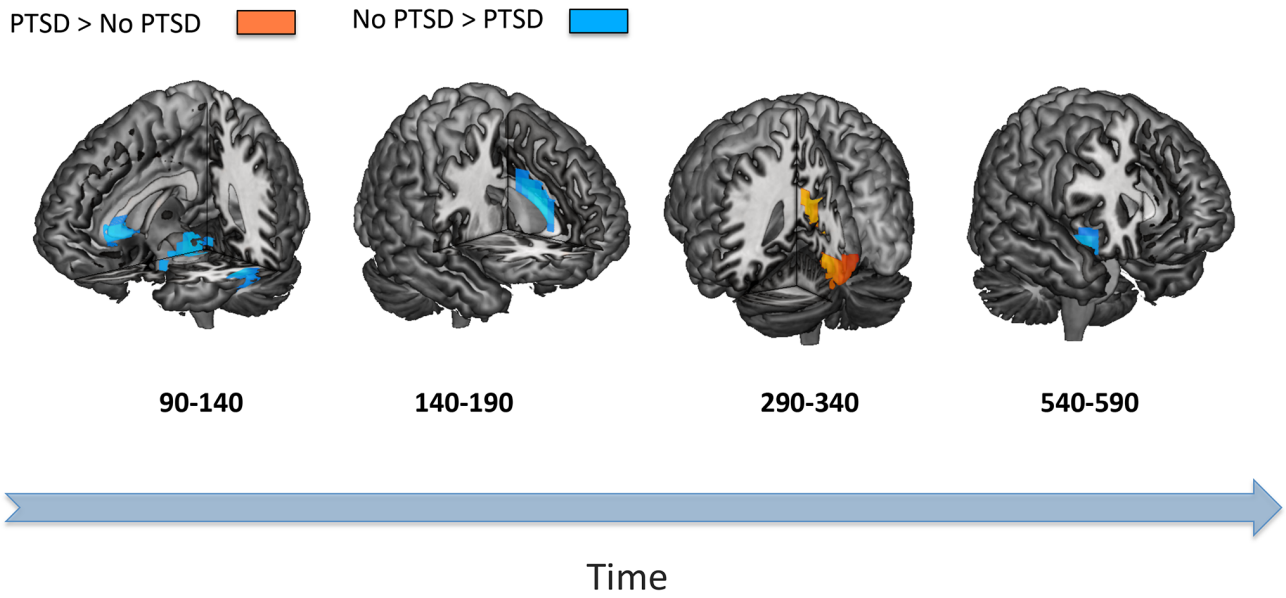


Figure 4. Locations where significantly greater activations were observed for emotional sparing of combat-related words in the PTSD compared to non-PTSD soldiers (red/orange) and when greater activations were observed for non-PTSD soldiers compared to those with PTSD (blue).



Tables

Table 1. Participant demographics

	PTSD	Military Controls	Non-military controls
n	22	22	24
age	37.6 ± 6.8 year*	32.4 ± 4.3 years	28.1 ± 5.8 years
handedness	17 right / 5 left	18 right / 3 left / 1 ambi	23 right / 1 left
WASI	108.8 ± 13.9^	117.1 ± 14.5	115.7 ± 7.9
AUDIT	8.2 ± 7.5	5.6 ± 3.6	5.6 ± 5.0
GAD-7	15.4 ± 4.1*	2.0 ± 1.9	2.9 ± 4.4
PHQ9	17.4 ± 4.5*	2.0 ± 2.3	2.4 ± 4.7

^p=0.057; *p<0.005 for t-test between PTSD and military control groups

Table 2. Brain regions associated with between-group differences in combat-word sparing in 50ms windows for soldiers with and without PTSD