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Post-traumatic stress disorder is associated with altered modulation of prefrontal alpha band oscillations during working memory

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HIGHLIGHTS

- Post-traumatic stress disorder (PTSD) is associated with increased rates of false recognition in a working memory task.
- PTSD is also associated with reduced modulation of left prefrontal alpha band activity.
- Prefrontal alpha oscillations may have a role in filtering out irrelevant memory traces.

ABSTRACT

Objective: To investigate the relationship between the severity of PTSD symptoms, modulation of alpha band oscillations, and behavioral performance in a working memory task.
Methods: Magnetoencephalography data were recorded in 35 participants with combat exposure and various degrees of PTSD symptom severity while they performed a modified Sternberg working memory task: briefly presented sets of two or six letters had to be held in memory and participants indicated whether subsequent probe letters were present or absent from these sets.
Results: PTSD scores were positively correlated with the false positive rate in the high memory load condition. Higher rates of false recognition were associated with negative probes that were seen in recent previous trials (negative probe recency effect) or were physically similar with the list letters. The relative alpha band power in the left middle frontal gyrus was negatively correlated with both PTSD scores and false positive rates.
Conclusions: Reduced task specific modulation of alpha band oscillations in left middle frontal cortex may reflect alterations in the functions of pattern separation and suppression of memory traces for irrelevant or no longer relevant information in PTSD.
Significance: The lower amplitude of prefrontal alpha band oscillations may represent an important physiological basis for core PTSD symptoms and can provide a target for interventions to augment response to treatment.

1. Introduction

Patients with post-traumatic stress disorder (PTSD) present with characteristic symptoms, such as re-experiencing of the traumatic event through intrusive thoughts, nightmares and flashbacks, emotional distress and physical reactivity to reminders of the traumatic event, emotional numbing, irritability, and difficulty sleeping and concentrating (Diagnostic and Statistical Manual of Mental Disorders DSM-5, American Psychiatric Association, 2013). The prevalence of PTSD is particularly high among individuals exposed to military combat, with approximately 14% of veterans from Operation Enduring Freedom and Operation Iraqi Freedom being diagnosed with PTSD (Schell and Marshall, 2008), while among Vietnam War veterans estimates of lifetime prevalence of PTSD are of about 19% (Dohrenwend et al., 2006). Several studies have demonstrated that these symptoms are accompanied by lower cognitive performance on neuropsychological measures

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of attention, working memory and executive function (e.g. Vasterling et al., 1998; Bremner et al., 2004; Yehuda et al., 2005; Aupperle et al., 2012; Scott et al., 2015), but the physiological mechanisms responsible for this association are not well understood. Recent conceptualizations of the PTSD pathophysiology have implicated impairments in executive function, including working memory, as important physiological phenomena related to the expression of emotional and arousal symptoms, as opposed to simply being co-morbid deficits (Aupperle et al., 2012).

In a previous magnetoencephalography (MEG) study in service members with exposure to emotional combat-related experiences, we observed a reduction in the amplitude of resting-state prefrontal alpha band activity that was associated with the severity of their PTSD symptoms (Popescu et al., 2016). Our findings were consistent with results of other EEG studies that reported a lower alpha-band power in PTSD relative to controls (Jokić-Begić and Begić, 2003; Veltmeyer et al., 2006). One possible mechanism leading to alterations in alpha-band oscillatory activity in PTSD is the dysfunction of neurotransmitter systems that can occur in some individuals following psychological trauma. For example, studies of the cholinergic response elicited by a life-threatening event demonstrated that the transitory increase in acetylcholine release triggered by psychological trauma may be followed by compensatory changes in the expression of cholinergic genes (Friedman et al., 1996; Kaufer et al., 1998; Meshorer et al., 2002), which may result in a long-term reduction in cholinergic function. This may lead to alterations in the modulation of alpha band oscillations, since the cholinergic system is known to perform a regulatory role for cortical alpha activity (Kikuchi et al., 1999; Ebert et al., 2001; Brassen and Adler, 2003; Bosboom et al., 2009).

The relatively low levels of alpha band oscillatory activity may represent one neurophysiological substrate for cognitive deficits in patients with PTSD symptoms. Support for this theory comes from reports of positive correlations between the resting-state alpha band power and global cognitive level across normal aging and patients with mild cognitive impairment and Alzheimer disease (Claus et al., 2000; Babiloni et al., 2006; Luckhaus et al., 2008). The role of alpha band oscillations in cognitive function has also been demonstrated using cognitive tasks in healthy participants (Palva and Palva, 2007). For example, selective modulation of alpha band oscillatory activity has been shown in visual attention tasks (Worden et al., 2000; Thut et al., 2006), and an increase in power (Jensen et al., 2002; Busch and Herrmann, 2003; Sauseng et al., 2005) and synchrony (Palva et al., 2005) of alpha band oscillations has been observed during maintenance or manipulation of items in working memory. Altered modulation of alpha band oscillations during working memory tasks has also been reported by studies in psychiatric disorders, such as schizophrenia (Haenschel et al., 2009) and obsessive-compulsive disorder (Ciesielski et al., 2007), which are characterized by the presence of intrusive or obsessive thoughts.

An understanding of the neurophysiological substrates of working memory deficits in patients with PTSD is important because they are believed to contribute to or exacerbate the core emotional/anxiety symptoms of PTSD and also may reduce the effectiveness of cognitive-behavioral therapy for PTSD (Falconer et al., 2013). In this study, we aimed to investigate the relationship between PTSD symptoms severity, modulation of alpha band oscillations, and behavioral performance in a working memory task in service members with combat exposure and various degrees of PTSD symptom severity. We used a modified Sternberg paradigm (Jensen et al., 2002), in which participants were visually presented with lists of letters and were required to respond after a retention interval if a probe letter was present in the previous list. EEG studies in healthy participants (Jensen et al., 2002; Busch and Herrmann, 2003; Sauseng et al., 2005) have shown that alpha band power over the retention interval increases with memory load. In some studies, the increase was seen predominantly over centro-parietal and occipital electrodes (Jensen et al., 2002), while others reported such an increase over frontal sites (Sauseng et al., 2005), particularly when the maintained information had to be manipulated. While these observations have led to a consensus that alpha band oscillations play a role in the successful retention of information in memory, the exact nature of this contribution is under debate, with some investigators endorsing a role in the inhibition of task-irrelevant regions and others proposing a more direct function in the active maintenance of the neuronal representations of the target items (Palva and Palva, 2007; Roux and Uhlhaas, 2014). In light of a proposed underlying alteration in the *regulation* of alpha band oscillations, we hypothesized that patients with high PTSD symptom severity may show altered *modulation* of alpha-band oscillations during the retention of information in memory, which would depend on memory load and would affect their behavioral performance on the task. Using MEG recordings and source estimation methods, we aimed to localize those brain regions or networks that show patterns of altered modulation of alpha band oscillations. Demonstrating a potential association between PTSD symptom severity and task-related alpha modulation can provide direct support to the hypothesis that alterations of the neurophysiological mechanisms underlying the regulation of alpha band oscillations may explain some of the cognitive difficulties that are commonly present in PTSD. Furthermore, given the proposed role of alpha oscillations in the inhibition of task-irrelevant neuronal representations, such a finding will be consistent with a possible contribution of the alterations in alpha band oscillatory activity to core PTSD symptoms of re-experiencing of a traumatic event through intrusive thoughts or images that cannot be inhibited. Studying participants with propensity for altered alpha band oscillatory activity may also help to improve our understanding of the role of these oscillations in working memory.

2. Methods

2.1. Participants

Study participants (n = 47) were active-duty service members enrolled in a four-week interdisciplinary intensive outpatient program for patients with post-concussive and post-traumatic psychological health symptoms at the National Intrepid Center of Excellence (NICoE), Walter Reed National Military Medical Center. The study was approved by the Institutional Review Board of the Walter Reed National Military Medical Center in compliance with all applicable federal regulations governing the protection of human subjects. Informed consent was obtained from each subject before participation in the study.

Each participant completed the PTSD Check List-Military version (PCL-M), which is a 17-item questionnaire used for screening active-duty service members and veterans for PTSD (Kang et al., 2003; Bliese et al., 2008). Individual PCL-M items rate symptoms of re-experiencing, avoidance/numbing and hyperarousal elicited by stressful military experiences on a scale from 1 to 5 (the total score ranges from 17 to 85, with higher values indicating higher symptom severity). The participants in our study reported psychologically traumatic events that included highly emotional combat-related experiences, such as receiving incoming artillery, rocket, or mortar fire, witnessing the death of unit members and seeing seriously injured bodies. The exposure to such combat-related events occurred over an extended period of time, during which they have also experienced mild traumatic brain injuries (mTBI), defined according to the standard criteria (American Congress of Rehabilitation Medicine, 1993). Previous studies have reported an increased risk of PTSD in service members (Hoge et al., 2008; Schneiderman et al., 2008; Yurgil et al., 2014; Stein et al., 2015) and civilians (Bryant et al., 2009; 2010) with a history of mTBI.

Patients completed the Patient Health Questionnaire PHQ-9, which is a brief 9-item depression severity measure with total score range from 0 to 27 (Spitzer et al., 1999; Kroenke et al., 2001). They completed also the AUDIT-C alcohol consumption screening test (Bush et al., 1998), with total score between 0 and 12, and were administered the Wechsler Adult Intelligence Scale (WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition, 2008) by a clinical neuropsychologist as part of their clinical evaluation at the NICoE.

Several participants had to be excluded from the analysis for the following reasons: one participant had a diagnosis of bipolar disorder, one participant had a childhood diagnosis of attention deficit disorder, one participant had a diagnosis of meningitis, six participants had MEG data contaminated by large movement artifacts, and three participants experienced significant drowsiness/sleepiness during the recording. Across the remaining participants (n = 35, all males, age 42.4 ± 7.6 years), the mean PCL-M score was 42.8 ± 17.2, with individual scores ranging from 19 to 80. Fifteen participants met the DSM-IV criteria for PTSD, which requires ratings of moderate or above on at least one item in the re-experiencing cluster, at least three items in the avoidance/numbing cluster and at least two items in the hyperarousal cluster. Fifteen participants (43%) had PCL-M scores equal or higher than 45, eleven participants (31%) had PCL-M scores in a moderate range between 30 and 43, and nine participants (26%) had PCL-M scores lower than 30. Twelve participants had a history of mTBI injuries without loss of consciousness (LOC), thirteen participants had one mTBI with LOC, and ten participants had multiple mTBI with LOC. No participants in this study, who were all active-duty service members, had a history of use or abuse of recreational drugs.

No significant correlations were present between PCL-M scores and age, education, AUDIT-3 scores and full scale IQ (Table 1). The mean PCL-M scores showed an ascending trend for the three subgroups of patients with increasing mTBI severity, *i.e.* no injury with LOC (mean PCLM = 39.3 ± 16.9), one injury with LOC (mean PCL-M = 42.5 ± 14.4), and multiple injuries with LOC (mean PCL-M = 47.4 ± 20.3), but they were not significantly different between these groups (Kruskall-Wallis test: $H = 0.88$, $p = 0.6$). The PCL-M scores were correlated with the PHQ-9 scores, which is expected because depression and PTSD share a series of symptoms (anhedonia, sleep disturbances, difficulties concentrating) that are probed by both the PHQ-9 and PCL-M scales; because of this, severity of depressive symptoms was not used as an exclusion criterion for this study. Four participants (11%) had PHQ-9 scores in the range of severe depression (three of them met also the DSM-IV criteria for PTSD). A follow-up analysis conducted without these participants confirmed all the reported relationships (in terms of statistical significance) between PCL-M scores and the other variables reported in Table 1, as well as between the PCL-M scores and mTBI severity.

Table 1
Demographic, screening and neuropsychological data (mean values and standard deviations) and their correlation with PCL-M scores.

	Mean ± std	Correlation with PCLM scores	
		Spearman r	p
Age (years)	42.4 ± 7.6	$r = -0.005$	$p = 0.97$
Education (years)	15.4 ± 2.5	$r = -0.063$	$p = 0.72$
AUDIT-C	3.3 ± 1.9	$r = -0.081$	$p = 0.64$
Full scale IQ[a]	110.6 ± 12.8	$r = -0.027$	$p = 0.89$
PHQ-9	9.6 ± 6.3	$r = 0.72$	$p < 0.001$

[a] Full scale IQ information was available for 30 participants (86% of the total).

Participants were not excluded from the analysis based on their use of medications with central nervous system effects. Six patients were taking antidepressant medication (selective serotonin reuptake inhibitors, SSRI) at the time of the MEG recording (Sertraline-4, Fluoxetine-1, Citalopram-1). Additionally, ten patients were taking anticonvulsant medications for headache prophylaxis (Gabapentin). Five patients were taking Prazosin as a treatment for nightmares. Some patients were taking multiple medications (the total number of patients taking at least one type of medication from the categories described above was sixteen). No significant difference in the distribution of PCL-M scores was present between *non-medicated* versus *medicated* participants (Mann-Whitney test: $u = 194$, $z = -1.37$, $p = 0.17$). The same result was obtained if the four patients with severe depression were excluded from this analysis.

2.2. Radiological evaluation

T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR) and susceptibility-weighted MR images were acquired with a 3 T MRI scanner using a 32-channel head coil (General Electric, Milwaukee, WI). These images were reviewed by a neuroradiologist to identify possible brain parenchymal abnormalities due to the TBI and rule out other incidental findings which could potentially confound the results of this study. To investigate the relationship between PTSD and brain parenchymal abnormalities, we conducted an analysis using a median-split of the participant sample into two subgroups based on PCL-M scores: low PTSD symptom severity ($\text{PCLM} \leq 38$, n = 17) and high PTSD symptom severity ($\text{PCLM} \geq 41$, n = 18). Fisher's exact tests of proportions were used to investigate potential differences in the proportion of participants with brain parenchymal abnormalities between these two subgroups.

2.3. Experimental paradigm

MEG data were recorded while participants performed a variant of the Sternberg working memory task adapted from (Jensen et al., 2002). Each trial started with a fixation cross shown in the center of a screen (positioned at 95 cm in front of the participants) that was replaced 900 ms later by a set of two or six uppercase consonant letters that needed to be held in memory over a short retention interval. The letters in the set were simultaneously presented in one row at the center of the screen for 0.5 s using Arial fonts of white color on a black background. The very brief presentation of the letters increases task difficulty, particularly for six letter sets. The sets of two letters were flanked on each side by two filler symbols (">" and "<") so that the string had the same physical size as for the six letters sets, *i.e.* 15 cm on the horizontal dimension (corresponding to 9 degree visual angle) and 2 cm on the vertical dimension. The presentation of the letter sets was followed by a retention interval of 2.433 s. At the end of the retention interval, a probe letter was displayed in the center of the screen and the participants had to respond by button press to indicate as quickly and as accurately as possible if the probe letter was present (positive probe) or not (negative probe) in the previously presented set. Participants used the index and middle fingers of their dominant hand for button presses corresponding to positive and negative responses, respectively (all but one participant included in the analysis were right handed). Across the trials with positive probes (henceforth referred to as positive trials), probe letters were equally likely to match each serial position in the set of letters. Each response was followed by an inter-trial interval of 2.0 s. Trials with two and six letter sets were intermixed and presented in the same sequence for all participants. There were 32 positive trials (with probe present in the list) and 28 negative trials (with probe absent from the list) for each set size, making a total of 120 trials for the whole recording session. The recording sessions were split into four blocks of approximately 4 minutes duration each, with short breaks between blocks. The sequence of stimuli was presented using the Neuroscan Stim2 software (Compumedics Neuroscan, El Paso, TX, USA). Throughout the results and subsequent figures, all latencies will be reported with respect to the onset of the letter sets (set as time axis origin), unless otherwise mentioned.

2.4. MEG data acquisition and pre-processing

MEG recordings were performed using the Elekta VectorView™ whole-head MEG system (Elekta-Neuromag Oy, Helsinki, Finland) equipped with 102 triplet-sensors (each made of one magnetometer and two orthogonal planar gradiometers) with the participant sitting in a chair inside a magnetically-shielded room. To co-register the MEG and MRI data, a 3D Fastrak digitizer (Polhemus, Colchester, VT, USA) was used to digitize the location of three fiduciary points (nasion, and left and right auricular points) defining the head-frame coordinate system, the location of four localization coils placed on the head, and a set of head surface points. The head position relative to the sensor array was determined at the beginning of the recording using the localization coils. Data were acquired with a sampling rate of 1 kHz.

Data were band-pass filtered off-line between 1 Hz and 100 Hz, with a powerline filter at 60 Hz, and then down sampled at 500 Hz. Independent Component Analysis using an Infomax algorithm (EEGLAB, Delorme and Makeig, 2004) was used to filter out independent components corresponding to cardiac and eye movement interferences, as well as other sources of external artifacts (if any). The filtered MEG data were subsequently divided into epochs from −1000 ms to 7000 ms relative to the onset of the fixation cross marking the beginning of each trial. Only epochs with correct responses were included in the analysis. The selected trials were bandpass filtered in the alpha band defined from 7 to 14 Hz.

2.5. Source reconstruction

The cortical surface was determined from the T1-weighted MR images of each participant using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu). The Brainstorm software package (Tadel et al., 2011) was used to estimate the sources of the magnetic fields at 10,000 cortical locations with a minimum norm estimator (Hämäläinen and Ilmoniemi, 1994), using a depth weighting parameter of 0.5 and a multiple sphere model of the volume conductor. The inverse projection operator incorporated a diagonal noise-covariance matrix derived from 1 minute long empty-room noise recordings filtered in the alpha band. The estimated cortical currents with unconstrained orientation were subsequently projected on the averaged FreeSurfer template brain. The power of the reconstructed currents was spatially integrated in each of the 84 regions of a modified Desikan-Killiany anatomical atlas (Desikan et al., 2006). The original atlas with 68 regions was refined by dividing regions of large area into smaller, functionally more specific sub-regions (Popescu et al., 2017). The regional power was estimated at every time sample in each trial and then used to determine the averaged power across trials for each condition. The averaged power was subsequently transformed into percent change relative to a baseline interval defined from −800 ms to −300 ms relative to the onset of the fixation cross shown at the beginning of each trial.

2.6. Statistical analysis of the behavioral performance data

Behavioral performance (response accuracy and median reaction time) was compared between conditions using Wilcoxon signed-rank tests. The correlation between PCL-M scores and behavioral performance was investigated separately in each condition of the experiment using Spearman rank correlation tests.

Since a main finding from the analysis of the behavioral data was a correlation between PCL-M scores and false recognition rate for six-letter sets (described in the Results section), we conducted analyses to investigate two potential factors that may have influenced the rate of false positive responses for this condition. First, we investigated the potential effect of *negative probe recency,* which consists of an increase in the error rate for negative probes recently seen as list items in preceding trials compared with negative probes that are novel or were not seen in the sequence of stimuli for a longer period of time (Monsell, 1978). The six-letter trials with negative probes were split into two categories: one category included trials with negative probes that were recently seen in the target list of the first or second trials preceding the current trial irrespective of their letter string size (recent negative probes), whereas a second category included trials with either novel negative probes or negative probes that were last seen at least three trials before (novel or old negative probes). No special treatment was necessary at the start of each block, since negative trials with six-letter sets were not presented within the first two trials of each block. This categorization resulted in a balanced number of trials, *i.e.* 14 trials per category. The mean error rates for recent versus novel/old negative probes were compared across participants using a Wilcoxon signed-rank test. A similar analysis investigating the potential effect of *positive probe recency* was not carried out because recent positive probes were present in only 5 of the 32 trials with positive probes, which would prevent the robust estimation of the rates of correct responses in this condition.

A second analysis of the behavioral data investigated the potential effect of visual similarity between list letters and negative probes on the rate of false positive responses. Using previously reported similarity data for letter pairs (Simpson et al., 2013), we computed a similarity index for each negative trial as the mean similarity between the negative probe and each letter in the corresponding six-letters list. A median split of the similarity indices was subsequently used to categorize the trials with negative probes into trials with high or low target letters-probe similarity. Half of the trials with recent negative probes and half of the trials with novel or old negative probes were characterized by a high target-probe similarity, *i.e.* the negative probe *recency* and *similarity* factors were orthogonal (uncorrelated) across trials. As for the previous analysis, the mean error rates for trials with high versus low similarity between the target letters and the negative probe were compared across participants using a Wilcoxon signed-rank test.

2.7. Statistical analysis of the MEG data

A preliminary statistical analysis was conducted to ascertain if a memory load dependent increase in alpha power during the retention interval is present in our sample of participants, as has been reported by previous studies in healthy participants (Jensen et al., 2002). First, we investigated the regional temporal course of the alpha band power during a temporal interval spanning the encoding, maintenance and retrieval from memory for each condition (low and high memory load) separately. The relative change in power in each brain region was determined on time intervals of 250 ms. Then, one-sample *t*-tests were used to determine if the relative change in power is significantly different than zero at time samples separated by 125 ms (half of the duration of the temporal interval used for power integration), starting from 125 ms and ending at 3375 ms after the onset of the letter strings to be memorized (corresponding to 442 ms after the probe letter was shown). Significance thresholds were corrected to control the false discovery rate (FDR) at 0.05, to account for the multiple comparisons performed across 84 regions of the brain and 27 temporal intervals. In a second analysis, we used paired *t*-tests to identify the temporal intervals and brain regions for which the alpha band power was sensitive to memory load by contrasting the two conditions (six vs. two letter sets).

The correlation between PCL-M scores and regional relative changes in alpha band power was investigated using Spearman rank correlation tests.

2.8. Follow-up analyses

Because some previous studies reported also significant increases in theta band activity with memory load (*e.g.* Gevins et al., 1997; Jensen and Tesche, 2002), we conducted a follow-up analysis to examine the power spectral density (PSD) of the estimated sources in brain regions that showed significant correlations between relative alpha band power and behavioral performance. This analysis was conducted to rule out the possibility that the spectral components in alpha band which made the focus of our analysis are present on a descending part of a dominant spectral peak in theta band. For this purpose, the cortical sources of the wideband MEG signals were estimated using a similar procedure like the one described before. The mean PSD across sources from a brain region was estimated in each trial over the retention interval and then averaged across trials of each condition.

The main analyses of the MEG data focused on the trials with correct responses. Since a main finding from the analysis of the behavioral data was a correlation between PCL-M scores and false recognition rate for six-letter sets, another follow-up analysis (described in detail in Supplementary Material) was conducted to ascertain if the distribution of alpha band power across trials with false positive responses was different than the one across trials with correct responses.

3. Results

3.1. Behavioral performance

Participants responded correctly in 96.6% ± 3.9% of the trials with low memory load, and in 78.2% ± 6.3% of the trials with high memory load. Accuracy was significantly lower for six-letter sets compared to two-letter sets for both positive (70.4% ± 11% vs. 95.6% ± 5.5%, $W = -630$, $z = -5.6$, $p < 0.001$) and negative probes (86.9% ± 7.4% vs. 97.9% ± 3.3%, $W = -553$, $z = -4.9$, $p < 0.001$). The difference in reaction time for positive vs. negative probes was statistically significant for two-letter sets (732 ± 138 ms vs. 782 ± 151 ms, $W = -376$, $z = -3.08$, $p = 0.002$), but it was not significant for six-letter sets (945 ± 174 ms vs. 965 ± 208 ms, $W = -67$, $z = -0.54$, $p = 0.59$). Differences in reaction times for two- vs. six-letter sets were significant for both positive ($W = -618$, $z = -5.1$, $p < 0.001$) and negative ($W = -558$, $z = -4.6$, $p < 0.001$) probes.

In the six-letter condition, PCL-M scores were negatively correlated with the response accuracy in negative trials (Spearman $r = -0.383$, $p = 0.023$), indicating that patients with higher PTSD symptom severity are more likely to mistakenly report that some lures (negative probes) were presented in the item list, *i.e.* they are more prone to *false recognition*. No other significant correlations were found between PCL-M scores and response accuracy or between PCL-M scores and reaction time.

The mean error rates across participants were 17.9% ± 10.1% for trials with recent negative probes and 7.1% ± 9.2% for trials with novel/old negative probes. The error rates for these two categories of trials were significantly different (Wilcoxon signed-rank test: $W = 414$, $z = 4.05$, $p < 0.001$), indicating that one potential source of false positive responses is the persistence of some memory traces across trials: when the negative probe letter in the current trial matches a letter that was recently seen in a previous trial and induced a temporally decaying memory trace, the source of that memory trace could be mistakenly attributed to the most recent list of items, leading to a false positive response.

The mean error rates were 18.6% ± 10.4% for trials with high similarity between the target letters and the negative probe and 6.5% ± 9.4% for trials with low similarity between the target letters and the negative probe. These rates were also significantly different across participants ($W = 481$, $z = 4.11$, $p < 0.001$), indicating that a second source of false positive responses for six letter sets is the visual similarity between target letters and negative probes.

3.2. Neuromagnetic alpha band power

Brief transient increases in alpha band power observed during the early components of the visual response elicited by the letter sets are followed by a relative decrease in alpha band power in many cortical regions for the remaining duration of the stimulus and for the interval immediately following the offset of the letter sets (Fig. 1 and Supplementary Material, Video 1). The alpha band power suppression lasts longer in the six-letter condition compared to the two-letter condition (see the average time courses of alpha band power in Fig. 2a), resulting in a significantly lower alpha band power over many cortical regions in the high compared to the low memory load condition over an approximately 750 ms interval that starts after the stimulus offset.

A transition from negative to positive change in alpha band power is seen over many cortical regions starting from 1000 ms for two-letter sets and 1250 ms for six-letter sets. Consistent with observations from previous studies (Jensen et al, 2002), we found that some of these regions show higher relative change in alpha band power in the high versus low memory load condition over the middle and late retention interval (Fig. 2b and Supplementary Material, Video 1). Such an increase in alpha band power with memory load is present around the middle of the retention interval (1750 to 2000 ms) over medial frontal, parietal and occipital regions and over regions of the right temporal lobe. Generally, prefrontal regions show less modulation of the alpha band power compared to occipital, parietal and temporal regions, which is reflected by the different values on the vertical axes in Fig. 2a, b.

During the second half of the retention interval, starting from 1750 ms, a relative alpha band power *decrease* is seen in the two-letter condition in the primary motor cortex, and in the caudal (premotor cortex) and rostral regions of the dorsal middle frontal cortex of the left hemisphere. Alpha band power suppression is also observed in the six-letter condition toward the end of the retention interval (starting from 2750 ms) in the rostral middle frontal region, supramarginal gyrus and posterior part of the superior temporal sulcus of the left hemisphere (Supplementary Material, Video 1).

Finally, the presentation of the probe letter induces a decrease in alpha band power, which is seen first in regions of the left hemisphere and spreading soon after over virtually the whole cortical surface.

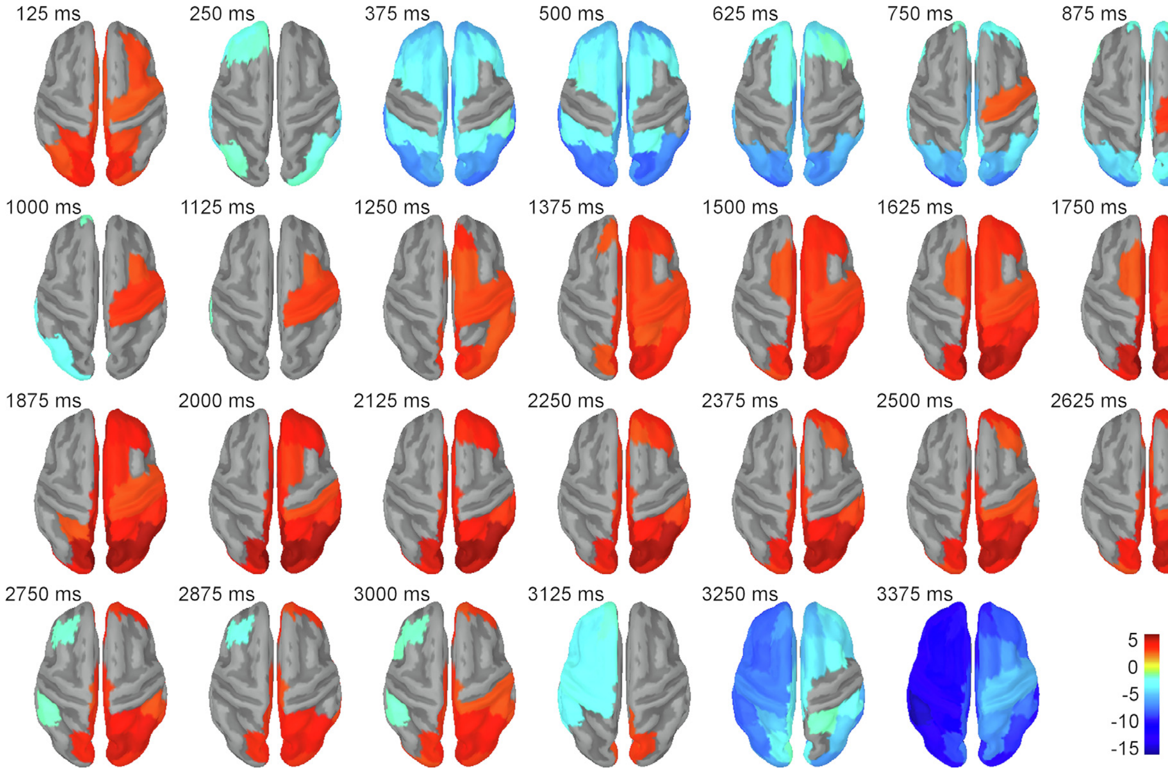

Fig. 1. Results of the spatio-temporal statistical analysis of the relative change in alpha band power using *t*-tests against the baseline are shown for the six-letters condition. Statistical maps (t-values) are thresholded to show only regions with $p < 0.05$ corrected to control the FDR. Latencies are representative for mid-points of 250 ms intervals. The letter sets are shown on the screen at time zero for 500 ms and the probe letter is shown at 2933 ms. Statistical results are shown in top-views of the brain; statistical results are also shown in lateral and interior views of the two hemispheres in Supplementary Material, Video 1.

3.3. Correlation between alpha power, PCL-M scores and behavioral performance

The previous analysis showed that the expected increase in alpha band power is not present from the beginning of the retention interval (marked by the letter set offset), but it starts with a delay of approximately 500 ms to 750 ms after stimulus offset in the two conditions of the experiment. To minimize the risk of mixing the effects of an increase in alpha power during maintenance in memory with those of the alpha power suppression that is still present for some time after the stimulus offset, we investigated the correlation between relative alpha band power during retention in memory, PCL-M scores and behavioral performance over a temporal interval defined from 1200 ms to 2600 ms with respect to the letter set onset. The end of this interval has been selected before the onset of the probe letters to minimize the risk of including components from the transient response elicited by the probe letters due to temporal smearing associated with band-pass filtering.

In a first correlation analysis, we sought to determine if the increase in alpha band power over this interval is related to the severity of the PTSD symptoms measured by PCL-M scores. The correlation analysis performed over the 84 regions of the cortical surface showed that in the high memory load condition, the PCL-M scores were negatively correlated with the relative change in alpha band power in the left *rostral middle frontal* cortex (Spearman $r = -0.6$, $p = 0.0001$) and left *pars opercularis* (Spearman $r = -80.55$, $p = 0.0006$). This result indicates that during the retention interval patients with higher PTSD symptom severity have less relative change in alpha band power in these regions, which correspond approximately to Brodmann areas 46 and 45, respectively (Fig. 3a). No significant correlations were found for the two-letter condition.

A follow-up analysis showed that the relative change in alpha power in the left rostral middle frontal region was positively correlated with response accuracy in the negative trials with high-memory load (Pearson $r = 0.22$, $p = 0.04$, one-tailed test, Fig. 3b). No correlation was found for the left pars opercularis (Pearson $r = 0.09$, $p = 0.23$). This result indicates that patients with less relative change in alpha band power in the left rostral middle frontal cortex during the retention interval are more likely to give false positive responses.

The significant correlation between the change in alpha band power during retention in memory and PTSD symptom severity was observed for six-letter sets in prefrontal regions that did not show a significant increase in relative alpha band power (Fig. 1) when the comparison against baseline was done for the whole sample of participants. On the contrary, the rostral middle frontal cortex was one of the few regions showing *negative* levels of relative change in alpha band power during the later part of the retention interval. To further investigate the relationship between PTSD and alpha band power in this region, we compared the mean temporal variation of the relative change in alpha band power between the subgroups of participants with low PTSD symptom severity (PCLM $\leq$ 38, n = 17) and high PTSD symptom severity (PCLM $\geq$ 41, n = 18) (Fig. 3b). For patients with low PTSD symptom severity, the mean relative change in alpha band power has positive values during the retention interval, whereas for patients with high PTSD symptom severity it remains negative during the whole retention interval. *t*-tests comparing the relative power values (integrated on temporal intervals of 250 ms) at time samples separated by 125 ms, starting from −875 ms (immediately after presentation of the fixation cross) and ending at 3375 ms after the letter set onset, showed significant differences between the two subgroups from 1 sec after the letter set onset and lasting until the end of

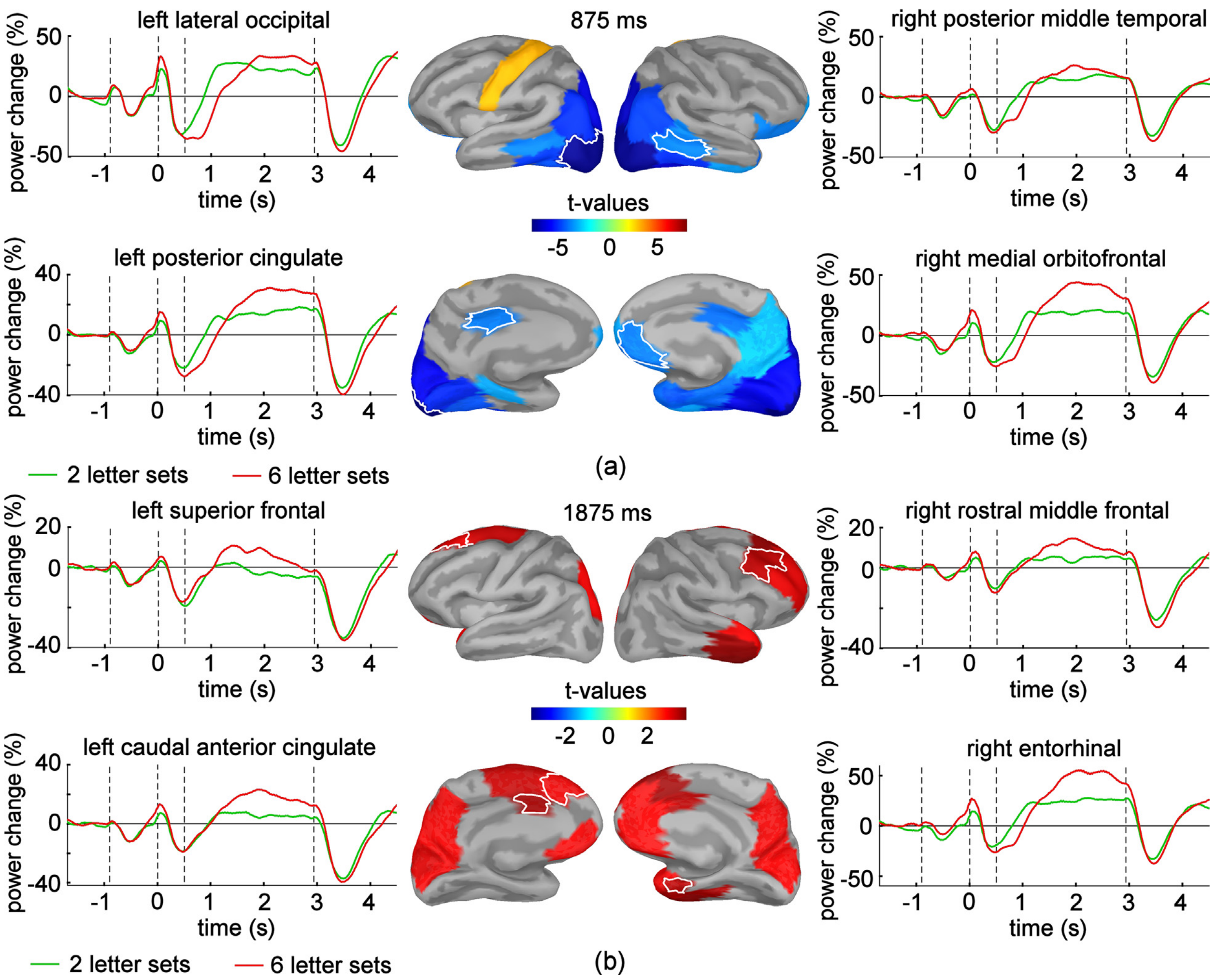

Fig. 2. Contrast between the change in alpha band power elicited by six-letter versus two-letter sets. Results of the regional paired *t*-tests are exemplified for the early retention interval (latency 875 ms) in (a) and for the late retention interval (latency 1875 ms) in (b). For each latency, the cortical maps of *t*-values are shown in the middle in external and internal views of the two hemispheres. Statistical maps are thresholded to show only regions with *p*-values smaller than 0.05 after correction for multiple comparisons. Blue colors over many of the brain regions in (a) indicate that power is lower for the six-letter compared to the two-letter sets at 875 ms for those regions. Red colors in (b) indicate a higher alpha band power in the six-letter compared to the two-letter condition at 1875 ms. The time course of the mean alpha band power (% change relative to baseline) across subjects is exemplified in (a) and (b) for subsets of brain regions that are delineated with white borders. Time 0 corresponds to the onset of the letter sets, which are shown on the screen for 500 ms. The four vertical lines shown mark the time of the trial onset (*i.e.* onset of the fixation cross), the onset and offset of the letter sets, and the onset of the probe letter, respectively. The alpha band power signals were smoothed using a 250 ms moving average. The differences between the six- and two-letter conditions are shown at other latencies in Supplementary Material, Video 1.

the retention interval (Fig. 3c). Significant differences were also found for two intervals centered at −875 ms and −750 ms, *i.e.* after the presentation of the fixation cross and before the onset of the letter sets. The p-values for these tests were corrected to control the FDR to account for multiple comparisons performed at 35 time samples.

The relative change in alpha power in the left rostral middle frontal region was not significantly different for *medicated* (n = 16) versus *non-medicated* (n = 19) participants ($t = 0.93$, $p = 0.36$), and its correlation with the AUDIT-C scores was not significant (Spearman $r = -0.08$, $p = 0.62$). These results indicate that medication status and alcohol consumption did not play a significant role in altering the modulation of the alpha oscillations during working memory. The mean relative changes in alpha power in the rostral middle frontal region showed a descending trend across the three subgroups of patients with increasing mTBI severity based on presence and number of injuries with LOC (no injury with LOC, single injury with LOC, multiple injuries with LOC, respectively), but differences between these subgroups were not statistically significant (one-way ANOVA: $F = 0.5$, $p = 0.6$). A subsequent analysis using multiple linear regression with change in alpha power in the rostral middle frontal region as dependent variable and PCL-M scores, medication status, mTBI severity and AUDIT-C scores as predictor variables showed also that only the PCL-M scores were a significant predictor for the change in alpha power ($t = -2.9$, $p = 0.007$), while the other three predictors were not (all $ps > 0.64$). When repeated without the four participants with PHQ-9 scores in the range of severe depression, these analyses confirmed the previous results in terms of statistical significance.

3.4. Radiologic findings

Small foci of T2 hyper-intensities were identified in the white matter for 19 participants (54% of the total number of participants). Areas of white matter gliosis were present in three subjects, and a microhemorrhage was identified in one subject. The Fisher's exact tests of proportions showed no significant differences in the proportion of participants with brain parenchymal abnormalities

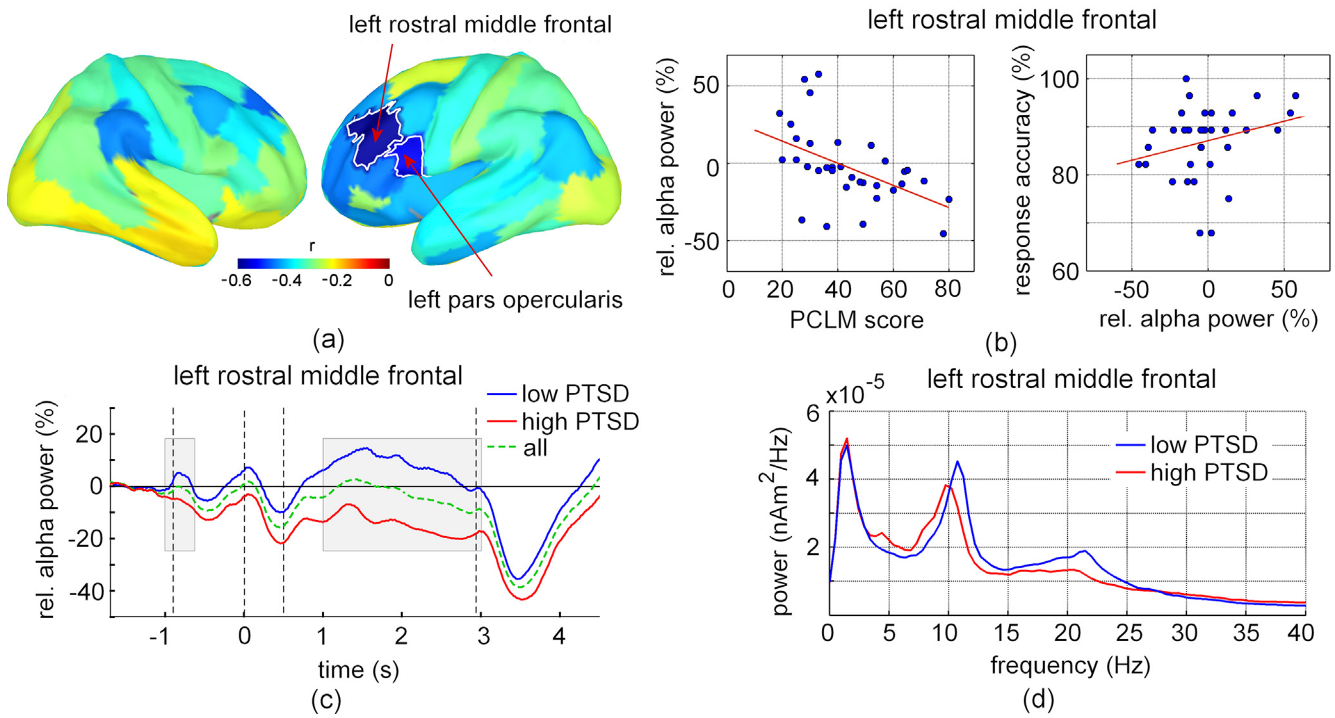

Fig. 3. (a) Maps of correlation coefficients between PCL-M scores and the relative change in alpha band power during retention in memory are shown in right and left lateral views of the brain (the maps of correlation coefficients are shown in other views of the two hemispheres in Supplementary Fig. 1). The thin white lines mark the borders of the two brain regions (left rostral middle frontal and left pars opercularis) with correlations that were significant after adjusting to control the FDR. (b) Scatter plots with regression lines showing the PCL-M scores and response accuracy for negative probes, respectively, versus the relative change in alpha band power in left rostral middle frontal region during the retention interval of the six-letter condition. (c) Time course of the mean relative change in alpha band power (% change relative to baseline) in the six-letter condition for the left rostral middle frontal region for subgroups of participants with low and high PTSD symptom severity. The four vertical lines mark the time of the trial onset (*i.e.* onset of the fixation cross), the onset and offset of the letter sets, and the onset of the probe letter, respectively. The gray rectangles mark the temporal intervals with statistically significant differences in relative alpha band power between the two subgroups. (d) Averaged power spectral density for reconstructed sources in left rostral middle frontal region during the retention interval (1.2–2.6 s) is shown separately for the subgroups of participants with *low* and *high* PTSD symptom severity. The power spectra show clear peaks in alpha band for both subgroups.

between the subgroups of participants with low versus high PTSD symptom severity.

3.5. Follow-up analyses

Fig. 3d shows the mean PSD in the left middle frontal region computed separately in the six-letter condition for participants with low and high PTSD symptom severity. Both spectra show clearly defined peaks in the alpha band, demonstrating that alpha oscillations dominate the signal during the retention interval. The mean peak alpha band frequency (defined as the frequency of the maximum power in the alpha band) for the subgroups of participants with high and low PTSD symptom severity was 9.5 ± 1.4 Hz and 10.7 ± 1.2 Hz, respectively. The difference in peak alpha band frequencies between the two subgroups was significant (Mann-Whitney test, $U = 222.5$, $z = -2.28$, $p = 0.023$).

The correlation between the relative change in alpha band power in left rostral middle frontal region and response accuracy in the high memory load condition suggests that a lower modulation of alpha band power during retention in memory may be associated with higher propensity for false recognition. The observed correlation was found using exclusively trials with correct responses in the analysis, which leaves open the possibility that for trials with incorrect responses the alpha band power might have been significantly different than for the trials with correct responses. The result of a follow-up analysis (described in Supplementary Material), showed that this was not the case and the power values in negative trials with incorrect responses were not systematically higher or lower than the power values from trials with correct responses.

Lastly, an analysis was conducted to determine if specific clusters of PTSD symptoms may be primarily associated with the relative change in alpha band power in left rostral middle frontal cortex, *i.e.* the region that showed significant correlation of relative change in alpha band power with response accuracy in the negative trials of the high memory load condition. This analysis showed significant correlations between the relative change in alpha band power in this region and subscores derived from the following clusters of PCL-M items: re-experiencing (questions B1-B5, Spearman $r = -0.5$, $p = 0.002$), avoidance of remainders (questions C1–C3, $r = -0.45$, $p = 0.007$), emotional numbing (questions C4–C7, $r = -0.69$, $p < 0.0001$), and hyperarousal (questions D1–D5, $r = -0.55$, $p = 0.0006$).

4. Discussion

Using a modified Sternberg working memory paradigm, we observed a significant increase in the power of alpha band oscillations over multiple brain regions during the retention period for both low and high memory load conditions. The relative increase in alpha band power was sensitive to memory load in several brain regions (including regions of the default mode network), consistent with observations from previous studies in healthy individuals (Jensen et al., 2002). In the high memory load condition, a higher PTSD symptom severity was associated with a higher false positive rate and with lower relative changes in alpha band power in regions of the left middle and inferior frontal cortex. Furthermore, the relative change in alpha power in the left rostral middle frontal cortex was negatively correlated with the propensity to report that lures (negative probe letters) were present in the six-letter sets. The correlation between an impairment in the ability to modulate alpha band power during the retention interval and an impairment in behavioral performance on the task, in this case a propensity for false recognition, is a distinctive result of our study compared to previous studies of working memory in other patient populations (*e.g.* Haenschel et al., 2009; Ciesielski et al., 2007). In the following, we will discuss the general role of the dorsolateral prefrontal cortex in maintenance of information in memory, the potential mechanisms through which lower alpha band activity may lead to increased rate of false recognition, and how the observed associations between severity of the PTSD symptoms, modulation of prefrontal alpha oscillations and performance on the task may be related to some core symptoms of PTSD.

The dorsolateral prefrontal cortex (DLPFC) may contribute to the processing of stimulus features (Desimone and Duncan, 1995), maintenance of mnemonic patterns of neuronal activity, and generation of (flexible) mappings between probe letters and motor responses required for the task (Miller and Cohen, 2001). Recurrent collateral connections from neuronal ensembles in DLPFC may help to preserve memory representations or learned associative relations (such as stimulus-response mappings) by maintaining certain states in auto-association (attractor) networks (Rolls, 2016, p. 86), which can also facilitate the maintenance or reinstatement of attractor states in other regions of a processing hierarchy. The recurrent activity within DLPFC may play a particularly important role in the maintenance of multiple mnemonic representations and for their flexible processing when it is necessary to coordinate complex behavior (Miller and Cohen, 2001). This processing flexibility may come at the cost of an increased likelihood of destructive interference in the presence of multiple mnemonic representations for same-category items, a risk that may increase with higher cognitive demand or when the mnemonic representations are weakly activated (*i.e.* shallow memories). For example, in the low memory load condition when two letters had to be memorized, the stimulus duration (0.5 sec) allowed sufficient time for the conscious perception of the stimuli and activation of relatively strong mnemonic representations through efficiently biased competition and recurrent activation. As a result, a robust representation of the mapping between the incoming probe letter and required motor response is made available, as reflected by the high percentage of correct responses and relatively short reaction times. On the other hand, the same brief stimulus presentation entails increased cognitive demand for six-letter sets due to higher memory load and shorter time available for the encoding of individual list items, with one or more items possibly not reaching a level of conscious recognition of the specific letter. Rather, only a subset of visual features of these letters may be explicitly processed or alternatively, exclusively implicit processing of those letters or some of their visual features may take place. Reliance on weakly activated visual features could make the activity patterns in DLPFC vulnerable to interference from (1) neuronal representations of competing items which share similar visual features with the list items, and (2) weak residual activations from visual presentation of some items in previous trials. In the end, the weaker (less stable) memories for target items and the greater competition between memory representations of target and interfering items may lead to decreased response accuracy, including higher rates of false recognition and longer reaction times. The vulnerability to false recognition when letter stimuli are presented in suboptimal conditions (brief, small, peripheral, noisy or low contrast) has been demonstrated in previous studies (Mueller and Weidemann, 2012).

The negative correlation between the relative change in alpha band power and the rate of false positive responses indicates that a reduced amplitude modulation of the alpha band oscillatory activity in the left DLPFC could be one factor leading to a higher propensity for false recognition in patients with more severe PTSD symptoms. Notably, the lateralization of the region exhibiting altered modulation of alpha band oscillations may be related to the linguistic nature of the stimuli used in our study (letters). The right prefrontal cortex would also theoretically be characterized by a similar alteration in alpha band modulation that is associated with impaired behavioral performance using a working memory task with abstract pictorial stimuli not susceptible to memorization strategies based on narratives or verbal associations. However, although our paradigm utilized letters as stimuli, it should be emphasized that during the presentation of the high load working memory stimuli, six letters were presented simultaneously for a time interval that is too short to make appropriate orthographic transformations of all the perceived letter shapes, much less to make orthographic to phonological letter transformations on all six letters. The retention of the stimuli in working memory in our task therefore likely relies on components of visual working memory (shapes and shape fragments of letters), orthographic working memory (with visual and linguistic memory components) and phonological working memory.

Previous studies have proposed a role of alpha band oscillations in preventing some neuronal activity (*e.g.* elicited by external stimuli irrelevant to the task or associated with selective features of a stimulus that need to be ignored) from interfering with processing or retention of relevant information in memory (Snyder and Foxe, 2010; Haegens et al., 2011; 2012; Bonnefond and Jensen, 2012; Payne and Sekuler, 2014). Our results suggest that an increase in alpha band oscillations may be necessary to filter out another type of interference as well, *i.e.* that arising from recently activated neuronal representations of same-category items that can act as competitors for the list items to be memorized. Three mechanisms may contribute to the inappropriate activation level of the representations of competing items in each trial of the experiment in the setting of reduced alpha frequency activity: (1) enhanced spreading activation in visual association cortex under the control of prefrontal regions, (2) failure to suppress the activation of representations of stimuli from previous trials, and (3) an impaired pattern separation function. We elaborate on these proposed mechanisms in the following paragraphs.

First, due to spreading activation in neuronal networks, cortical activity representing associative relations to physically similar items that are not present in the current list can be automatically triggered in the initial stages of stimulus encoding at multiple levels in the sensory processing hierarchy. These activations are normally suppressed with time after stimulus onset through recurrent activity that leads to strengthening of the neuronal representation of list items and weakening of the neuronal representations of competing items. Rhythmic increases in mean local inhibition level (reflected in the amplitude of alpha band oscillations) can increase the firing thresholds of excitatory neurons, leading to more sparse representations of the stored (mnemonic) patterns. Computational models of recurrently connected networks (Rolls, 2016) have shown that the sparseness of neuronal representations can have positive effects, such as reducing interference (or increasing separability) between stored patterns or increasing the number of patterns that can be stored in associative memories.

Second, some active neuronal representations may be residually activated representations of *no-longer-relevant* items that were presented in previous trials of the experiment and of their previously learned mapping to motor responses. The persistence of such memory traces across several trials was demonstrated by the effect of negative probe recency on the rate of false positive responses, which consists of an increase in the error rates for negative probes that have been recently seen as list items in other preceding trials of the experiment. When the negative probe matched a letter that was seen in a past trial of the experiment and induced a lasting memory trace, the source (origin) of the residual memory trace could be erroneously attributed to the most recent list leading to a false positive response. Alpha oscillations may promote filtering out or *forgetting* of irrelevant or no-longer-relevant neuronal representations that can induce such memory traces lasting over temporal scales in the range of seconds to tens of seconds (across multiple trials of the experiment). Typically, these competing residual neuronal representations are weaker compared with those of the most recently presented list items. During the retention interval, an increase in alpha oscillations may further suppress these shallow competing memories, increasing the signal-to-interferer ratio for the neuronal representations of the most recent (target) list items. Previous studies using intracranial recordings in DLPFC in monkeys provide support to this hypothesis, by showing that alpha oscillations may contribute to deselect neuronal ensembles encoding no-longer-relevant rules in a rule-switching task (Buschman et al, 2012). The lower amplitude modulation of alpha band oscillations observed during the retention interval in patients with significant PTSD symptoms may therefore be associated with inefficient suppression of the weakly activated neuronal representations representing irrelevant or no-longer-relevant information.

Finally, false positive responses may also arise from representations of stimuli that may be erroneously activated or matched to negative probe stimuli due to an alteration in the function of pattern separation, which is impaired in PTSD patients and forms a theoretical basis for the pathological generalization of fear responses in this patient population (Lange et al, 2017). When processing a stimulus or an array of stimuli (a scene), the hippocampus, in conjunction with the left DLPFC (Pidgeon and Morcom, 2016), must perform either a pattern completion operation, to match the stimulus representation to that of a previously experienced episodic event, or alternatively, this system must perform a pattern separation operation, to distinguish the current stimulus or event from previously experienced stimuli despite overlap in stimulus features (Rolls, 2013). The greater the overlap in features between a current and previous stimulus, the greater is the likelihood for pattern completion to predominate over pattern separation. Within the hippocampus, the pattern separation function is attributed primarily to the dentate gyrus (Bakker et al, 2008; Schmidt et al, 2012), which exhibits a reduced volume in PTSD patients compared to healthy controls (Hayes et al, 2017). When considering the results of this study, we suggest that a pathological bias towards pattern completion occurred during exposure to the larger (six letter) stimulus set, particularly when the list letters share similar physical features with other letters recently seen in the preceding trials, contributing to the maintenance of neuronal representations for no longer relevant items and sometimes leading to the occurrence of false positive responses. An enhanced tendency for pattern completion over pattern separation has been implicated in the impaired discrimination of stimuli in the PTSD population. By facilitating a sustained activation level for neuronal representations of previously experienced stimuli, the inability to appropriately enhance alpha frequency power in DLPFC may contribute to an ineffective pattern separation process.

The mean alpha band power across patients with high PTSD symptom severity (Fig. 3c) shows a decreasing trend in the left middle frontal cortex starting immediately after the onset of the fixation cross (*i.e.* before presentation of the letter sets). This observation suggests that factors related to the state of the participants with elevated PTSD symptom severity could have played a contribution in lowering the alpha band power during the retention interval. The characteristic PTSD symptoms include, for example, heightened arousal and reactivity to salient stimuli. Some studies have found that heightened arousal induced before memory encoding can increase the frequency of false memories (Corson and Verrier, 2007). In our study, an exaggerated autonomic or alerting/orienting response triggered by the warning signal (onset of the fixation cross) in each trial, followed by an exaggerated motor response preparation, possibly associated with a state of anxiety and hypervigilance that are characteristic in PTSD, could have contributed to the decrease in the amplitude of alpha band oscillations, enabling the persistence of mnemonic representations for irrelevant or no-longer-relevant information. The evidence supporting this hypothesis is somewhat limited by the fact that significant differences in alpha band power between the two subgroups of patients (with high and low PTSD symptom severity) did not persist over the whole interval that included the time immediately before and after the presentation of the letter sets. Nevertheless, this hypothesis deserves further investigation in future studies given the fact that a low amplitude of prefrontal alpha band oscillations that is influenced by the state of the participants could represent a potential neurophysiological mechanism linking the seemingly unrelated PTSD symptoms of anxiety/hypervigilance, intrusive memories, and lower cognitive performance. The significant negative correlations observed in our study between the increase in alpha band power in the left rostral middle frontal cortex and the PTSD symptoms of re-experiencing, avoidance and hyperarousal could stem *from* (and provide support *to*) this possible causality relationship.

The possible relationship between a reduced ability to modulate alpha band activity and the re-experiencing symptoms in PTSD can be addressed within the framework of the global workspace theory of conscious information processing (Baars, 1988; 2005). According to this model, most cortical information processing takes place below the level of consciousness and only when a particular level of activation of a representation is exceeded, then an “ignition” or amplification of activity occurs that leads to reverberation of that information throughout a widely distributed cortical network which makes this information globally available to cortical processing systems (Dehaene and Changeux, 2011). DLPFC is a crucial component of this ignition process and its involvement is mandatory for conscious perception and thought. An inability to appropriately enhance alpha band power may allow for the amplification of unwanted intrusive memories or at least specific memory features that activate more complex episodic memories and allow these memories to enter conscious thought. Such memory representations may maintain an elevated baseline activation level due to their highly emotional and salient nature. An increase in alpha power in prefrontal cortex has been implicated in the successful suppression of memories in a healthy control population (Depue et al, 2013), whereas the failure to suppress memories has been correlated with reduced prefrontal alpha activity (Gaillard et al., 2009). It is therefore possible that in patients with PTSD symptoms, an impairment in extinction of fear conditioning will lead to a higher baseline and episodic level of activation of traumatic memories, but a preserved ability to modulate prefrontal alpha band power may allow the patient to minimize the experience of intrusive memories entering conscious thought, by inhibiting the activation level of these memories or specific memory features. In this regard, given the prominence of visual imagery in the re-experiencing phenomena of intrusive memories in PTSD, it would be valuable to replicate our findings, derived with the use of letters as stimuli, with a similar task using visual stimuli that are less susceptible to memorization strategies based on verbal associations.

Decision making in conditions of uncertainty or increased cognitive demand (such as those of the high memory load condition) may be influenced by factors like guessing biases (general shifts in the decision criterion) and difficulties with inhibition of prepotent or dominant motor responses. For example, PTSD is known to be associated with higher rates of commission errors in Go/NoGo experiments (Falconer et al., 2008; Swick et al., 2012), which require participants to inhibit prepotent motor responses. In our implementation of the modified Sternberg paradigm, the number of positive trials was only slightly higher than the number of negative trials in each condition (32 positive versus 28 negative trials), which makes it unlikely for responses to positive trials to become prepotent. Furthermore, potential difficulties with the inhibition of prepotent responses, as well as the presence of guessing biases, would have likely been accompanied by a higher rate of true positives and shorter reaction times, which was not observed in our data. Nevertheless, if impulsivity is associated with a propensity for executing prepotent motor responses, then the observed negative correlation between alpha band power in the left rostral middle frontal cortex and the rate of false positives suggests that the level of alpha oscillations during the delay interval may also be related to a threshold for movement initiation, with higher alpha band oscillations leading to better inhibition of dominant motor responses. This hypothesis can be tested in patients with PTSD in future studies using Go/NoGo paradigms.

Some participants in our study were taking medications with central nervous system effects, specifically SSRI antidepressants, Gabapentin and Prazosin. The effect of these medications on the EEG spectrum has been investigated by previous studies using *resting-state* recordings. Some studies have reported changes in alpha band power after administration of antidepressant medications to healthy subjects, mostly consisting in a dose-dependent decrease in alpha band power (Dumont et al., 2005). However, a study investigating the effect of long-term treatment with antidepressants in depressed patients did not find changes in alpha band power (Bruder et al., 2008), suggesting a decrease in alpha power due to SSRI administration may be limited to an acute effect which is not relevant to our study participants. Thus, a direct comparison between patients with PTSD who were receiving antidepressants versus non-medicated patients with PTSD revealed no significant difference in resting-state alpha band power, although differences were present at higher frequencies (Veltmeyer et al., 2006). Administration of Gabapentin to healthy volunteers resulted in a decrease in alpha band power in one study (Saletu et al., 1986) and to a decrease in peak alpha frequency but no alteration in alpha band power in another study assessing the effect of long-term treatment (Salinsky et al., 2002). To our knowledge, the effect of Prazosin on the EEG spectrum in humans has not been characterized; one study in rodents demonstrated an acute effect consisting of an increase in EEG power over a frequency range that included the alpha band (Sebban et al., 1999). The medication status did not have a significant effect on measures of alpha band activity assessed in our study. This finding suggests that although some of these medications may have an effect on the *resting-state* alpha band power, they do not appear to significantly influence the task-related *modulation* (relative change) of alpha band power during the retention period of working memory.

One limitation of our study arises from the fact that all participants had a history of mTBI, a factor that may contribute to alterations in brain oscillatory activity through various mechanisms (Popescu et al., 2016). Some studies reported differences in resting-state EEG spectra for patients with a history of mTBI compared to healthy controls, including differences in alpha band power (a review is available in Nuwer et al., 2005). Across our sample of participants, there was no evidence that the *modulation* of alpha band oscillations during the retention interval in this working memory task is sensitive to injury severity (characterized by the presence and number of mTBI events with LOC). Nevertheless, a future study correlating PTSD symptom severity with altered modulation of alpha band power in PTSD patients without a history of TBI would be helpful in determining whether or not our findings are limited to patients with PTSD in the setting of a history of mTBI. Studying participants who all had previous combat exposure served the main objective of our study, *i.e.* to determine if the severity of present PTSD symptoms is associated with distinct patterns of brain electrophysiology. Future studies using healthy control participants with no combat exposure may also help to elucidate if a certain degree of alteration in alpha band oscillations is present in all participants with combat exposure (*i.e.* who experienced psychologically traumatic events), irrespective of the severity of their PTSD symptoms. Finally, our study demonstrated the association between PTSD symptom severity and task-related alpha modulation but could not determine causality between the altered modulation of alpha band oscillations, cognitive performance and development of PTSD symptoms due to its cross-sectional design. Our findings do not exclude the possibility that genetic or developmental factors, for example, may lead to a preexisting alteration in the modulation of prefrontal alpha band oscillations that may or may not be exacerbated by exposure to psychological trauma or by the presence of post-traumatic stress symptoms (PTSS). Such factors may also predispose some individuals to experience more severe PTSS following psychological trauma. Furthermore, they may lead to a potential association between altered modulation of prefrontal alpha band oscillations and propensity to false recognition on this task in healthy individuals (due to a normal variability in alpha modulation) or in other patient populations (due to either such a normal variability or due to a pathologically enhanced variability).

To conclude, our main finding is that the severity of PTSD symptoms negatively correlates with a load related increase in alpha band power during retention of information in working memory and is associated with a higher rate of false positive responses. This indicates that an increase in amplitude of alpha band oscillations during the retention period could be one mechanism that contributes to filtering out or "forgetting" of (weakly activated) irrelevant or no-longer-relevant information and to ensure appropriate pattern separation. The lower alpha activity in the left middle frontal gyrus that we observed in patients with higher PTSD symptoms during the retention period may have facilitated the persistence of memory traces for irrelevant information including previously learned stimulus-response associations. The inability to effectively enhance alpha activity in appropriate cortical regions as required by behavioral demands may be related to specific components of PTSD symptomology, including impaired pattern separation leading to fear generalization and the re-experiencing of intrusive memories. Pharmacological and nonpharmacological strategies to enhance alpha power modulation may be sought as PTSD therapies, either independently or in combination with cognitive therapies (Kozel et al., 2018). Previous studies have shown that a substantial proportion of patients with PTSD do not demonstrate a significant therapeutic benefit from cognitive-behavioral therapy (CBT) and investigators have suggested that an impairment in working memory may prevent an effective engagement of those patients in CBT, lowering their treatment response (Bradley et al., 2005; Falconer et al., 2013). Neurofeedback or transcranial magnetic stimulation, which have been previously shown to be effective at enhancing prefrontal alpha-band oscillation power in patients with PTSD (Kluetsch et al., 2014; Taghva et al., 2015), may also be effective in increasing task-specific alpha power modulation and may be assessed as independent PTSD therapies or as "add-on" interventions that can potentially improve the effectiveness of CBT.

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Disclaimers

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.

The identification of specific products, scientific instrumentation or organizations is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author, Department of Defense, or any component agency.

The study protocol was approved by the Walter Reed National Military Medical Center in compliance with all applicable Federal regulations governing the protection of human subjects.

Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.06.227.

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