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Post-traumatic stress disorder is associated with alterations in evoked cortical activation during visual recognition of scenes

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ABSTRACT

We recorded magnetoencephalography data during a visual recognition task in participants with combat exposure (n = 40, age: 41.2 ± 7.2 years) to investigate the relationship between the evoked brain activity, behavioral performance, and the severity of their post-traumatic stress symptoms assessed using the PTSD Check List for DSM V version (PCL-5). In an initial study session, participants were presented with a series of images of outdoor scenes and were instructed to study the images for an upcoming recognition test. In a subsequent session, the original images were shown intermixed with novel images while participants performed the recognition task. PCL-5 scores were negatively correlated with discrimination performance and with the recognition accuracy for original images. During the recognition session, higher PCL-5 scores were associated with reduced relative power of the evoked response to original images from 100 ms to 300 ms following the image onset over a distributed brain network including the bilateral inferior frontal gyri, left middle frontal gyrus, left supramarginal gyrus, right precuneus and the bilateral superior temporal gyri. These findings indicate that the lower recognition performance in participants with higher PTSD symptom severity is associated with altered cortical activity in brain regions that are known to play a role in the elaboration on visual cues that supports recollection.

1. Introduction

Exposure to psychological trauma may lead to a range of symptoms including re-experiencing of the traumatic event through intrusive memories and flashbacks, emotional numbing, and difficulty sleeping and concentrating that typically resolve within weeks after the event. However, for a significant proportion of individuals (Kessler et al. 1995) such symptoms may persist over longer periods of time leading to post-traumatic stress disorder (PTSD). Military combat, for example, is a common cause of PTSD among men, and combat-related PTSD has been reported in 14% to 19% of war veterans (Dohrenwend et al., 2006; Schell and Marshall, 2008). Research studies have demonstrated that PTSD is accompanied by lower performance on neuropsychological tests of attention, 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). The cognitive impairments in PTSD are a topic of intense research interest because regardless of their etiology, *i.e.* either pre-existing or due to neurobiological alterations resulting from exposure to the traumatic event (acute stress) or from experiencing long-term PTSD symptoms, they may contribute to hallmark symptoms of PTSD (Vasterling et al., 1998; Vasterling and Brailey, 2005; Lambert and McLaughlin, 2019), including emotional and arousal symptoms (Aupperle et al., 2012).

The presence of intrusive memories of the traumatic event and the inability to recall important aspects of the trauma are part of the diagnostic criteria for PTSD (Diagnostic and Statistical Manual of Mental Disorders DSM-5, American Psychiatric Association, 2013). Intrusive memories are involuntary, can occur spontaneously in the absence of an obvious environmental reminder of the traumatic experience, are commonly of a visual nature (often comprising only a fragmentary element of a complex visual event, such as a single object), and are believed to be triggered by sensory stimuli that share some similarities with stimuli that were perceived in conjunction with the traumatic event, though such similarities need not be consciously appreciated by the patient (Ehlers et al., 2002; Ehlers, 2010). A strong perceptual priming effect for a small subset of sensory stimuli that were present around the time of the traumatic event and a difficulty in processing of discriminative sensory features and associative contextual information

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are considered factors with potential contribution to an over-generalization of trauma reminders and an increased frequency of intrusive memories in PTSD (Ehlers, 2010; Brewin et al., 2010; Maren et al., 2013; Kaczkurkin et al., 2017). Perceptual priming entails a facilitated perception of some stimulus features as a result of previous exposure to that stimulus, a form of *implicit* memory. Difficulties with the processing of contextual or discriminative information may prevent a rapid assessment of whether a stimulus that shares some perceptual similarities with stimuli experienced around the time of the traumatic event is threatening or not (Maren et al., 2013; Kaczkurkin et al., 2017). Several studies have indeed reported an association between PTSD and enhanced perceptual priming, but have suggested that this association might be specific only to trauma-related information (Michael et al., 2005, Ehring and Ehlers, 2011). On the other hand, there is evidence supporting a more general deficit in processing of contextual associative information in PTSD, which extends to trauma-unrelated and emotionally neutral information (Guez et al., 2011). Support to this hypothesis has also been provided by the negative correlation between performance in learning of spatial configurations and the frequency of intrusive memories, suggesting that individuals who excel in visual associative information processing may be better able to discriminate trauma-related stimuli from other similar stimuli in the environment (Meyer et al., 2013).

Previous studies that have investigated the brain activity underlying memory for previously experienced stimuli or events have characterized the important role of three brain structures: the hippocampus, the medial temporal lobe cortex (MTLC), most notably perirhinal cortex, and the prefrontal cortex. When activation induced by a sensory experience reaches the hippocampus, if the degree of overlap with representations of similar past experiences exceeds a certain threshold, it may trigger the process of hippocampal *pattern completion*, which consists of a reinstatement of the hippocampal representation of associative contextual information that was activated during past sensory experiences or episodes (Yonelinas et al., 2002; Norman and O'Reilly, 2003). The degree of match/mismatch between the representation of a current stimulus and the representation of past stimuli and contextual details re-activated in the hippocampus can also inform the decision of whether a stimulus is recognized. The neuronal activity in MTLC, including perirhinal cortex (for representations of most objects) and an adjacent region of parahippocampal cortex (for representations of buildings and scenes), appears to contribute to a feeling of prior occurrence of a stimulus based only on an appraisal of its familiarity or recency (Brown and Xiang, 1998), in the absence of the re-activation of neuronal representations of associative information (contextual details) available with retrieval of an episodic memory. The sensation of prior occurrence of a stimulus may be due at least in part to repetition priming effects in these MTLC regions, which have been suggested to emerge from intrinsic properties of competitive learning networks (Norman and O'Reilly, 2003), leading to *sharpening* of the neuronal representation of a repeated item and to shorter *settle-times* (the time needed for recurrent activity to settle through a network). Whether these mechanisms represent discreet memory processes with distinct neuroanatomical underpinnings or rather represent memory phenomena along a spectrum of memory function from recognition (which require a weaker form of memory elaboration with respect to a stimulus, sometimes simply a feeling of familiarity, possibly due to poor encoding of contextual details during the initial experience) to full recall of an episodic memory (which require greater memory elaboration, including the reactivation of the neuronal representation of contextual components of the memory) is currently a matter of debate. Lastly, the prefrontal cortex has been proposed to contribute to encoding and retrieval (*i.e.* re-activation of previous neuronal representations) through mechanisms of attention, reflected in the selection and monitoring of relevant features or contextual information associated with a stimulus or episode (Simons and Spiers, 2003). For example, the prefrontal cortex can control attention to contextual or discriminative details, which facilitates their initial encoding and the reinstatement of their neuronal representation during subsequent presentations of a stimulus. Other regions of the attention network (*e.g.* cortical parietal regions) are likely recruited in this process. Importantly, attention to discriminative details may also help to distinguish (perceive as novel) a stimulus that shares some features with other previously experienced items, by increasing the mismatch between stored representations of previously seen items and the representation of the current stimulus. Additionally, regions of prefrontal cortex have been implicated in an *attribution* process which may lead to a conscious awareness of the rapidity of stimulus processing (Chua et al., 2014; Bastin et al., 2019), with previously encountered stimuli processed more rapidly, giving rise to a feeling of familiarity via a phenomenon referred to as the fluency heuristic (Hertwig et al., 2008).

One approach to investigate the neural basis of implicit and explicit memory processes and of the process of discriminating novel versus previously encountered visual stimuli is based on the comparison of brain activity evoked by previously seen (*old*) items versus *new* items (*e.g.* images of objects or scenes) with varying degrees of similarity or overlap of visual elements (Wagner et al., 2005; Rugg and Curran, 2007 for reviews). Electrophysiological studies using this approach in healthy individuals have suggested the existence of a dual process underlying recognition memory, corresponding to a feeling of familiarity versus a recollection of the episodic event associated with previous encounters with the stimulus (Rugg and Curran, 2007). An early difference in evoked responses to items correctly categorized as old versus new (old/new effect) observed over frontal sites was interpreted as indicative of brain activity underlying a subjective feeling of familiarity, based on the fast, automatic reactivation of neuronal representations for previously visualized items. Familiarity with an object or scene has been attributed to facilitated processing of previously visualized items in MTLC (Norman and O'Reilly, 2003), which may be utilized in making a decision regarding past experience with a stimulus based on the fluency heuristic assessed in prefrontal cortex and conveying a conscious sense of familiarity. The timing of this early old/new effect varied depending on the stimulus category: for example, the effect was present from 100 ms after the onset of visual images of objects in background contextual scenes (Tsivilis et al., 2001), whereas for visually presented words it was observed from about 300 ms after the word onset (Rugg and Curran, 2007). The early old/new effect was followed by a subsequent old/new effect present over the posterior scalp and lateralized to the left hemisphere. The magnitude of this later effect was modulated by parameters (*i.e.* confidence level) used to characterize a process of explicit memory retrieval of contextual associative information (often referred to as "recollection") as opposed to isolated familiarity and was considered to be the result of a slower and more effortful process of elaboration on visual cues that would enhance the activation of neuronal representations for discriminative information encoded during the prior occurrence of an (old) item. In experiments using the old/new paradigm with separate *study* and *test* sessions, discriminative information for old items is bound (during encoding in the first session) to episodic contextual information associated with the experimental study session (Diana et al., 2006). The event-related potentials studies could not provide information about the exact location of the brain generators of this subsequent old/new effect, but fMRI studies in healthy participants (reviewed in Wagner et al., 2005) have consistently identified a distributed network of regions that included the medial parietal cortex (precuneus, extending into posterior cingulate and retrosplenial cortices), left lateral parietal cortex, and prefrontal cortex, that are activated during effective recollection (these findings generalized across word and picture stimuli). Under the control of the prefrontal cortex, this cortical network likely interacts with the hippocampus and influences the recognition process through mechanisms of attention, selection and monitoring of relevant attributes or contextual information (Simons and Spiers, 2003; Wagner et al., 2005).

The pathophysiological basis for intrusive sensory memories in PTSD remains unclear. One prominent theory of memory dysfunction in PTSD,

the dual representation theory (Brewin et al, 1996; Brewin et al., 2010), suggests that intrusive memories are a manifestation of a functional disconnection between two separate anatomical systems for representing sensory information that may be re-experienced at a later time. One involves medial temporal lobe structures including perirhinal cortex and the hippocampal formation, in conjunction with regions of the fronto-parietal attention network. This system represents flexible gist-like memories in a neutral allocentric form that can be voluntarily retrieved and manipulated. The second system involves predominantly primary and unimodal sensory association cortex as well as the amygdala and insular cortex. This system typically transiently represents detailed but isolated components of the sensory experience in memories from an egocentric viewpoint with an associated emotional tag. Under normal sensory processing circumstances, components of the latter detailed representation are rapidly integrated in the former MTL mediated flexible explicit memory, allowing physiological decay of the sensory cortical representation. In the setting of a severe psychological trauma, however, these systems become relatively physiologically isolated, with reduced allocation of normally broad attentional resources to forming a complete flexible explicit memory of the experience mediated by the hippocampus, whose function is also impaired. This impoverished explicit memory encoding occurs in association with enhanced functioning of the sensory cortex/amygdala system, leading to exceptionally strongly represented individual components of the sensory experience that were the focal point of attentional processing at the time of the traumatic event. These fragmented sensory phenomena have been hypothesized to exhibit enhanced perceptual priming and can be easily reactivated in cortex by sensory cues in the environment, and due to the phenomenon of overgeneralization can be reactivated even by cues that may have only vague sensory similarities to the original stimulus. When reactivated involuntarily by cues that may not be consciously perceived, these sensory phenomena are experienced vividly and as happening in the present due to the absence of a temporal contextualization normally mediated by the hippocampal system. It is not specified in this theory whether the functioning of these two mnemonic systems return fully to baseline in the aftermath of the traumatic event, or if ongoing PTSD symptoms will maintain some degree of functional disconnection of the two systems with a bias toward formation of strong sensory cortical representations characterized by enhanced perceptual priming and weak representations of contextual components of explicit memory for an event due to ongoing dysfunction of the hippocampal system.

If PTSD is associated with residual alterations in perceptual priming and/or processing of discriminative contextual information, it is therefore conceivable that such an association may be reflected in the spatio-temporal patterns of evoked brain responses during recognition of visual stimuli. To test this hypothesis, we use magnetoencephalographic (MEG) recordings and source estimation methods to investigate the relationship between electrophysiological features of visual recognition, behavioral performance, and severity of PTSD symptoms in service members with combat exposure. The participants in our study had PTSD symptom severity scores spanning a wide range, from very low scores which would not be consistent with a diagnosis of PTSD to very high scores which would fulfill the criteria for a PTSD diagnosis; the inclusion of participants with low PTSD symptom severity serves to control for trauma exposure in our analysis. We used a subsequent memory paradigm (Sanquist et al., 1980) with outdoor scene images that were presented serially in an initial study session, which was followed by a subsequent recognition test when participants were asked to recognize the original (old) scene images among other (new) scene images. The encoding and recognition of scenes involve processing of discriminative features that include contextual associative information about the configuration of scene components (Aminoff and Tarr, 2015). Images were selected from several categories such that scenes from each category shared similar elements (prototypical high-frequency features) but in different settings/configurations that were scene specific. This selection ensured some degree of overlap between neuronal representations of old and new images from the same category. Data from the encoding session of our study, which was the subject of an earlier report (Popescu et al., 2020), demonstrated alterations in oscillatory brain activity in bilateral ventral and medial temporal regions and left orbitofrontal cortex for the participants with high PTSD symptom severity that were indicative of ineffective encoding in memory. This may have a detrimental effect on the encoding of discriminative features and may influence brain activity during subsequent recognition, particularly the activity associated with re-activation of neuronal representations in those regions (Norman and O'Reilly, 2003). In the current study, we sought to determine if PTSD is also associated with distinct spatio-temporal patterns of brain activity during the recognition session, and whether these patterns could be indicative of alterations in specific processes proposed by previous studies to be involved in recognition memory.

2. Methods

2.1. Participants

Study participants (n = 40, age 41.2 ± 7.2 years, all males) were active-duty service members enrolled in an 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, who completed all sessions of this study. Patients were not included in this study if they had a history of moderate or severe traumatic brain injury or other neurological, developmental or psychiatric disorders. 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 participant before participation in the study. The participant sample has been described in detail in one of our previous reports (Popescu et al., 2020).

All participants completed the PTSD Check List for DSM V version (PCL-5, Bovin et al, 2015; Blevins et al, 2015). The individual PCL-5 scores ranged from 2 to 71. Participants had combat-related experiences that generally occurred over an extended period of time. The participants with low PCL-5 scores (which would not lead to a diagnosis of PTSD) served to control for trauma exposure in our analysis. PCL-5 scores were not significantly correlated with age, education, alcohol consumption scores, and full scale IQ (Popescu et al., 2020). None of the participants had a history of use or abuse of recreational drugs.

2.2. Experimental paradigm

The experimental paradigm consisted of two sessions of MEG recordings (Popescu et al., 2020). In the first session, participants were shown a series of 86 color images of outdoor scenes (list 1) and were instructed to study each image for a subsequent recognition test. Each image was shown for 3 sec and the inter-trial interval from the offset of one image to the onset of the next image was 1.5 s. Images were selected from different categories included in the urban and natural scene image database developed at the Computational Visual Cognition Laboratory, MIT (Oliva and Torralba, 2001). These categories were: *mountain* (10 images), *forest* (11), *coast* (11), *open country* (12), *inside city* (17), *highway* (4), *street* (10) and *tall buildings* (11).

In the second (recognition) session, which followed approximately 5 min after the encoding session, the images from list 1 were presented randomly intermixed with a set of 86 *novel* images. The number of novel images in each category matched the number of original images in that category. Using original and novel images from the same categories ensured a degree of overlap between their neuronal representations and increased the task difficulty. For each image, participants were asked to indicate whether they recognized it as an image from the first session or not. In each trial, images were shown on the screen until the participants

gave the button-press response. The inter-trial interval measured from the time of the response in one trial to the onset of the image in the next trial was of 1.5 s.

2.3. MEG data acquisition and pre-processing

MEG signals were recorded during both study sessions inside a magnetically-shielded room using the Elekta VectorView™ whole-head MEG system (Elekta- Neuromag, Helsinki, Finland) with 102 triplet-sensors (each made of one magnetometer and two orthogonal planar gradiometers). MEG data were acquired with 1 kHz sampling rate. The head position relative to the MEG sensors was determined with four localization coils attached to the participant's head. The locations of three fiduciary points (nasion, and left and right auricular points) defining the head-frame coordinate system, together with the location of the four localization coils and of a set of head surface points were digitized with a 3D Fastrak digitizer (Polhemus, Colchester, VT, USA) to allow co-registration of the MEG data with the corresponding T1-weighted MRI. Each individual T1-weighted MRI was acquired in a separate session with a 3 T MRI scanner (General Electric, Milwaukee, WI).

The current report focuses on the data recorded in the second (recognition) session. Data were band-pass filtered off-line between 1 Hz and 100 Hz, with a powerline filter at 60 Hz, and then processed using the Independent Component Analysis (ICA) Infomax algorithm (EEGLAB, Delorme and Makeig, 2004). Independent components corresponding to cardiac and eye movement interferences, as well as other sources of external artifacts (if any) were removed. The reconstructed data were split into epochs from −1200 ms to 2000 ms relative to the onset of the images. The epochs were averaged for each condition and the averaged datasets were subsequently used to estimate the cortical generators of the evoked responses.

2.4. Source reconstruction

The cortical surface was segmented using the FreeSurfer software (Fischl, 2012) from the T1-weighted MR images of each participant acquired with a 3 T MRI scanner using a 32-channel head coil (General Electric, Milwaukee, WI). The source reconstruction was done using the Brainstorm software (Tadel et al., 2011). Current sources were estimated for the averaged responses in each condition at 10,000 cortical locations using a minimum norm estimator (Hämäläinen and Ilmoniemi, 1994) with a multiple sphere model of the volume conductor and a depth weighting parameter of 0.5. Cortical currents with unconstrained orientation were estimated and subsequently projected on the averaged FreeSurfer template brain. The inverse projection operator incorporated a diagonal noise-covariance matrix derived from a 60 s time interval of empty room noise recordings. The power of the reconstructed currents was spatially integrated in each of the 84 cortical regions of a modified Desikan-Killiany anatomical atlas (Desikan et al., 2006). The original Desikan-Killiany atlas with 68 regions was refined by dividing several regions of relatively large area into smaller, functionally more specific sub-regions. All latencies reported herein were corrected for a delay of 18 ms (measured using a photodiode), which was introduced by the stimulus presentation system.

2.5. Statistical analysis

The correlation between PCL-5 scores and behavioral performance (accuracy and reaction time) was evaluated using Spearman rank correlation tests. The difference in accuracy and reaction time between the two conditions of the recognition session (old versus new images) was evaluated using Wilcoxon signed-rank tests.

In a first analysis of the MEG data, we investigated the old/new effect on the evoked responses by comparing the regional power of the averaged signal evoked by original and novel images using Wilcoxon signed-rank tests carried out across all subjects. This analysis was performed on separate temporal intervals, by integrating the regional signal power over five 100 ms long intervals with 50% overlap, starting at 50 ms after the image onset. The analysis was focused on the components of the evoked response with latencies of up to 350 ms, as this segment was unaffected by the presence of motor responses (the fastest reaction time across subjects and conditions was 406 ms). Only trials with correct responses were included in this analysis. Since the number of trials with correct responses were different between *old* vs. *new* conditions (as described in the Results section), the regional power in each condition was corrected by the corresponding power on a baseline interval from −0.8 s to −0.3 s relative to the image onset. This correction assumes that the signal present on the baseline interval is quasi-stationary and uncorrelated with the evoked signal. Significance thresholds were determined by controlling the false discovery rate (FDR) at $q = 0.1$ to account for the multiple comparisons across 84 brain regions and 5 temporal intervals.

A second analysis of the MEG data was conducted to determine if the PTSD symptom severity is associated with distinct patterns of evoked brain activity during visual scene recognition. To this end, we evaluated the Spearman correlations between the PCL-5 scores and the regional change in power of the signal evoked by original (old) images. All trials with old images were included in the averaging for this analysis, which was also performed over five 100 ms long intervals with 50% overlap, starting at 50 ms after the image onset. The signal power relative to the baseline interval defined from −0.8 s to −0.3 s with respect to the image onset was used in this analysis to mitigate the potential effects due to inter-subject variability in absolute signal power that may be due to factors unrelated to brain electrophysiology. Similarly to the first analysis, significance thresholds were determined by controlling the FDR at $q = 0.1$ to account for the multiple comparisons across 84 brain regions and 5 temporal intervals.

A third analysis of the MEG data was conducted to determine if the difference between the relative power of the evoked response in the *old* and *new* conditions is associated with the PTSD symptom severity. All trials with old and new images, respectively, were included in the averaging for this analysis, which was conducted on the same temporal intervals and using the same correction for multiple comparisons like the previous analyses.

3. Results

3.1. Behavioral performance

Participants recognized on average 76.0%±12.1% of the original images (range between 46.5% and 95.3%) and correctly categorized as novel 89.9%±7.0% of the novel images (range between 69.8% and 100%). PCL-5 scores were negatively correlated with the discrimination performance characterized by the cumulative correct responses to original and novel images (rs = -0.38, $p = 0.016$), and with the number of correct responses to original images (rs = -0.37, $p = 0.02$). The correlation between PCL-5 scores and the number of correct responses to novel images was not statistically significant (rs = -0.23, $p = 0.16$). Overall the participants were more accurate in their responses to novel images compared to original images (Wilcoxon signed-rank tests: $z = 4.98$, $p < 0.0001$).

The mean RT for correct responses to novel images (1230 ms ± 333 ms) were not significantly different than those to original images (1145 ms ± 297 ms), (Wilcoxon signed-rank tests: $z = 1.85$, $p = 0.064$). PCL-5 scores were not correlated with the mean reaction times to original (rs = -0.10, $p = 0.52$) or novel images ($rs = 0.04$, $p = 0.79$).

3.2. Old/new effects on averaged evoked responses

The results of Wilcoxon signed-rank tests comparing the regional signal power evoked by original and novel images are shown in Fig. 1 for

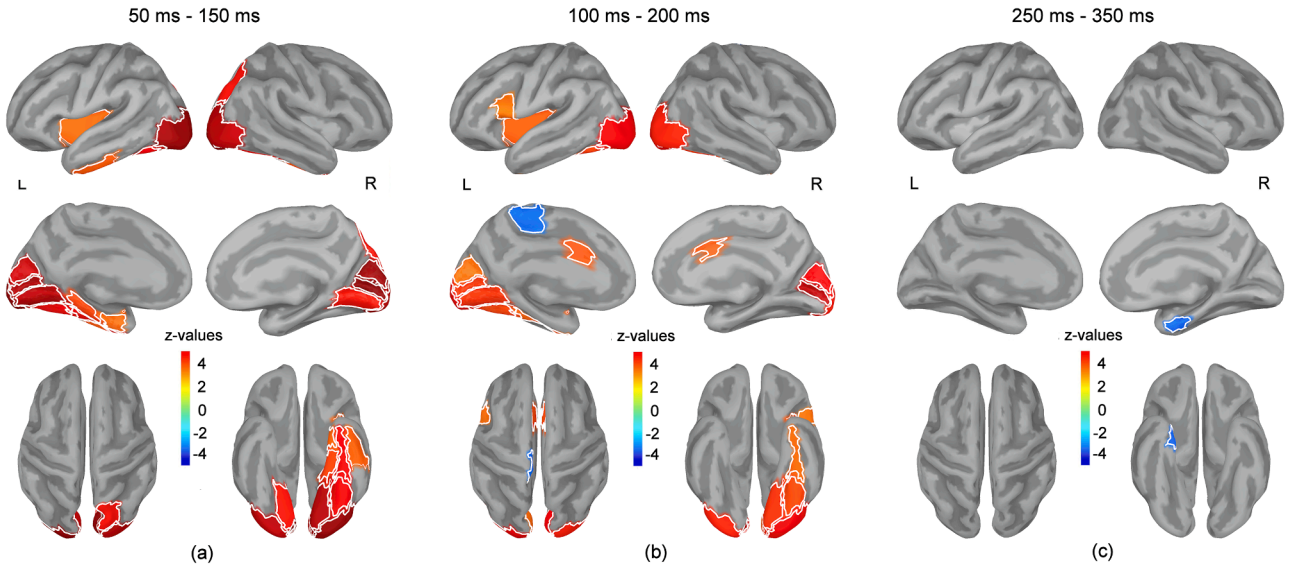

Fig. 1. Results of Wilcoxon signed-rank tests comparing the regional signal power evoked by original and novel images. Statistical maps of *z*-values show only regions that were significant after adjusting the *p*-values to control the FDR. Positive *z*-values (red colors) indicate a higher power of the signal evoked by original images. For each temporal interval, maps are shown in lateral (upper row) and medial views (middle row) of the two hemispheres, and in top and bottom views of the brain (lower row). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

temporal intervals with significant differences between these conditions. Original images evoked responses with higher regional power over bilateral occipital cortical regions (*lateral occipital*, *pericalcarine*, *cuneus*, *lingual*), right *superior parietal* cortex, left ventral temporal (*fusiform* and *inferior temporal* gyri) and medial temporal regions (*parahippocampal* gyrus and *entorhinal* cortex), left insular cortex, left inferior frontal gyrus (*pars opercularis*) and bilateral *caudal anterior cingulate*. These differences were seen during the earliest temporal intervals (50–150 ms and/or 100–200 ms). Novel images evoked responses with higher regional power in the left *paracentral lobule* (100–200 ms) and right *entorhinal* cortex (250–350 ms). The regional activation curves (exemplified in Fig. 2) show that ventral visual regions exhibit a dominant peak of activity at latencies that vary between ~100 ms and ~150 ms (slightly earlier in posterior than in anterior regions).

Compared to the ventral visual regions, the frontal regions (*e.g.* left *pars opercularis* exemplified in Fig. 2), exhibit a dominant peak of activity at a later latency, around 200 ms. This dominant signal component is also broader in time, possibly indicating (1) a sustained change in spiking rate of the neuronal population over an extended temporal interval, which may be due in part to convergence of inputs from multiple levels of processing that takes place in visual regions with neuronal populations that reach their peak spiking rate at slightly different latencies, and/or (2) a higher inter-subject and inter-trial variability in signal morphology compared to the early dominant components from ventral visual regions. The mean peak latency of this dominant response component is consistent with the reported timing of the peak rate of

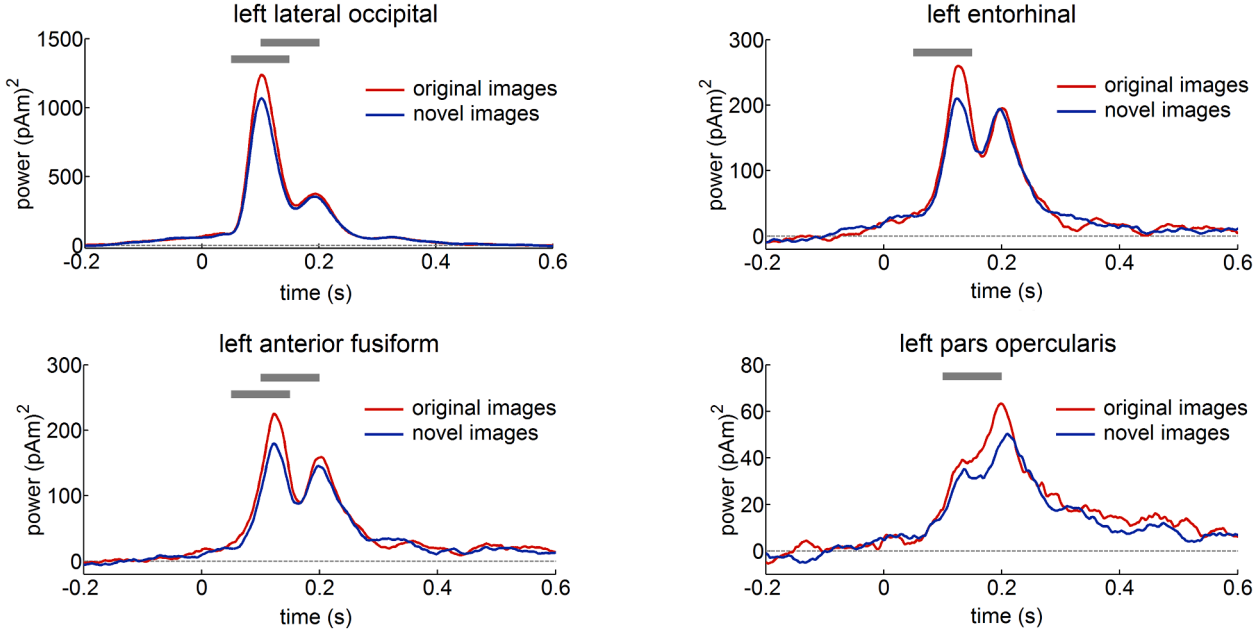

Fig. 2. The mean power of the responses evoked by original and novel images is exemplified for four brain regions. The top gray horizontal bars mark the 100 ms long temporal intervals with significant differences between the two conditions.

spiking activity in downstream prefrontal neuronal populations (targets of ventral and inferior parietal visual processing regions) that "readout" information encoded in the neuronal activity from visual processing regions to support higher level, goal-oriented or task-relevant cognitive functions, such as *e.g.* perceptual categorization (Freedman et al., 2001).

3.3. Correlations between evoked responses, PTSD symptom severity and subsequent recognition accuracy

Significant negative correlations were found between PCL-5 scores and regional relative power of the evoked responses to old images (*i.e.* higher PCL-5 scores were associated with lower relative power of the evoked response) bilaterally in the posterior part of the *superior temporal* gyrus and *prefrontal* cortex, as well as in the left *supramarginal* gyrus and right *precuneus* (Fig. 3). The prefrontal regions exhibiting significant negative correlations included the *pars opercularis*, *pars triangularis*, *pars orbitalis* and *rostral middle frontal* gyrus in the left hemisphere, and the *pars triangularis* in the right hemisphere. Fig. 4 exemplifies the relative power of the evoked signal in four of these cortical regions for the subgroups of patients with low and high PCL-5 scores. The brain regions with significant correlations on at least one temporal interval are summarized in Table 1 along with the corresponding statistical results.

A follow-up analysis was conducted to determine if the evoked brain activity in these regions is also associated with the recognition performance. For this purpose, we evaluated the Spearman correlations between the recognition accuracy for original images and the regional change in power of the signal evoked by original images. Several of the brain regions that showed significant correlations with PCL-5 scores also showed correlations with the behavioral performance that were significant after controlling the FDR at $q = 0.1$ to account for multiple comparisons across 84 brain regions and 5 temporal intervals: left *supramarginal* gyrus (on the temporal interval 100–200 ms, $r_s = 0.445$, $p = 0.004$), left *pars triangularis* (on the temporal interval 150–250 ms, $r_s = 0.5$, $p = 0.0009$), and the right *pars triangularis* (on the temporal interval 200–300 ms, $r_s = 0.45$, $p = 0.0033$). Other regions that showed significant correlations for some of the temporal intervals included in the analysis were the bilateral *superior parietal* and *somato-motor* cortex, and the right *supramarginal* and anterior *middle temporal* gyrus.

The correlation between PCL-5 scores and the difference in relative power of the evoked response in the *old* and *new* conditions did not show any significant result after correction for multiple comparisons. Additional scrutiny of the results revealed that only two of the regions that showed significant correlations between the PCL-5 scores and the power of the response evoked by old images in the previous analysis, showed also a mentionable correlation in this analysis (uncorrected $p < 0.05$) for the temporal interval between 150 ms and 250 ms: the left *pars opercularis* ($r_s = -0.4$, $p = 0.01$), and the left *pars triangularis* (rs = -0.386, p = 0.014). Both regions showed a smaller difference between the power of the evoked responses to *old* versus *new* images for participants with high PCL-5 scores.

4. Discussion

Our study characterized the evoked brain activity during visual recognition of scenes and its relationship with PTSD symptom severity in participants with previous exposure to combat experiences. We used a subsequent memory paradigm with scene images that were presented serially in an initial study session followed by a recognition test that asked the participants to recognize the original images among other novel images. During the visual recognition session, we observed an increase in the power of the early response components (from 50 ms to 200 ms) evoked by original images compared to novel images (old/new effect) over a distributed brain network including bilateral occipital cortical regions, right parietal cortex, left ventral and medial temporal regions, left insular cortex, left inferior frontal gyrus, and bilateral caudal anterior cingulate. We also found a negative correlation between PCL-5 scores and the power of the evoked responses bilaterally in the posterior part of the *superior temporal* gyrus and prefrontal cortex, left *supramarginal* gyrus and right *precuneus*. These effects were observed from 100 ms to 300 ms following the onset of the images. In the following, we will discuss the general role of the brain regions showing patterns of evoked responses that were associated with old/new effects and with the severity of the PTSD symptoms in our sample of participants, and how our findings may be related to symptoms of PTSD.

The spatio-temporal characteristics of the old/new effects that we identified primarily within visual processing regions and between 50 ms and 200 ms after image onset suggest an early modulation of the neuronal population activity in response to repeated (old) images, which

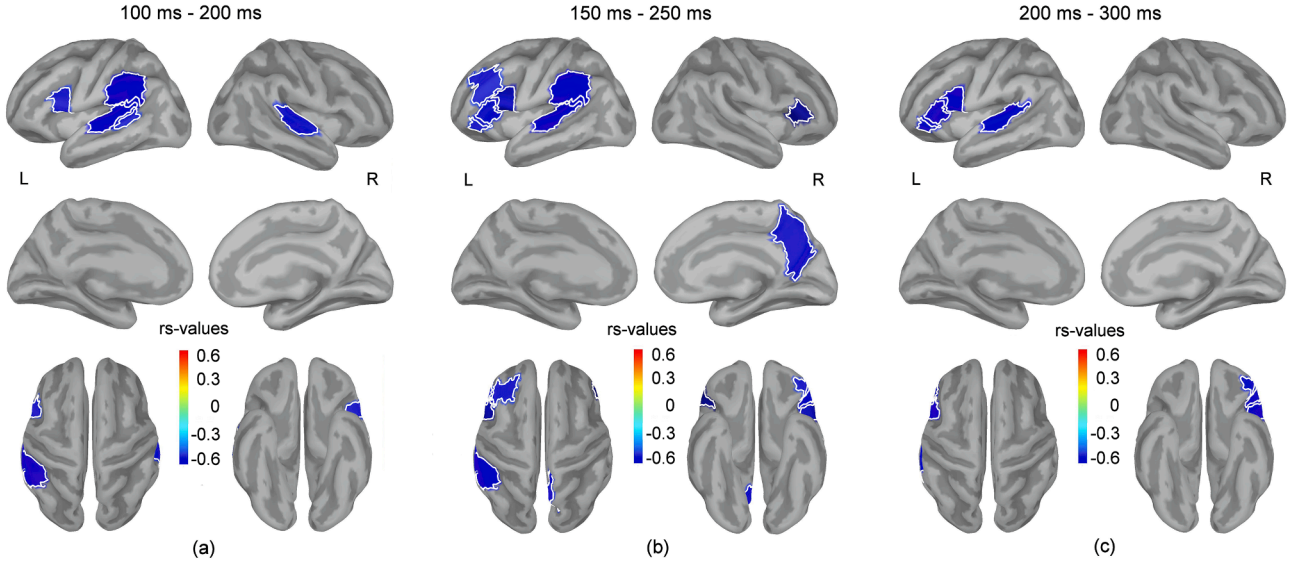

Fig. 3. Maps of correlation coefficients (r_s-values) between the relative signal power evoked by original images and PCL-5 scores. Maps show the regions with significant correlations after adjusting the *p*-values to control the FDR. Negative correlations (blue colors) indicate a lower regional power for participants with higher PCL-5 scores. For each temporal interval, maps are shown in lateral (upper row) and medial views (middle row) of the two hemispheres, and in top and bottom views of the brain (lower row). The brain regions with significant correlations on at least one temporal interval are summarized in Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

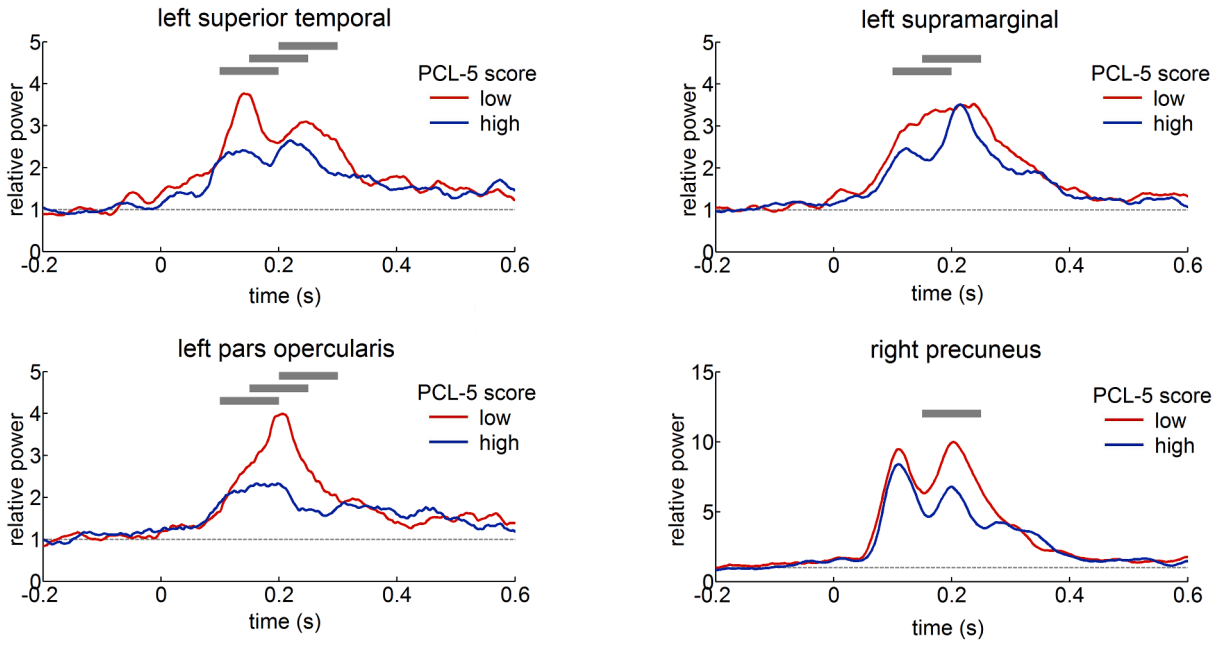

Fig. 4. The mean relative power of the evoked signal is exemplified in four cortical regions for subgroups of patients with low PCL-5 scores (n = 23, PCL5 ≤ 22) and high PCL-5 scores (n = 17, PCL5 ≥ 26). Horizontal bars mark the 100 ms long temporal intervals with significant correlations between the relative power and PCL-5 scores.

Table 1
Brain regions showing significant correlations between the PCL-5 scores and the relative power of the evoked responses on at least one 100 ms-long temporal interval. *p*-values marked with (*) are significant after correction to control the FDR.

Brain region	correlation with PCL-5 scores					
	100 ms–200 ms		150 ms–250 ms		200 ms–300 ms	
	r_s	*p*	r_s	*p*	r_s	*p*
left hemisphere						
pars opercularis	−0.45	0.0032*	−0.61	<0.0001*	−0.53	0.0004*
pars triangularis	−0.25	0.1265	−0.47	0.0021*	−0.55	0.0002*
pars orbitalis	−0.33	0.0350	−0.45	0.0038*	−0.47	0.0023*
rostral middle frontal	−0.14	0.3799	−0.45	0.0037*	−0.35	0.0283
supramarginal	−0.54	0.0003*	−0.50	0.0010*	−0.37	0.0205
posterior superior temporal	−0.53	0.0005*	−0.54	0.0003*	−0.48	0.0015*
banks superior temp. sulcus	−0.45	0.0040*	−0.39	0.0125	−0.42	0.0075
right hemisphere						
pars triangularis	−0.44	0.0049	−0.65	<0.0001*	−0.42	0.0077
posterior superior temporal	−0.46	0.0027*	−0.30	0.0605	−0.17	0.3090
Precuneus	−0.36	0.0231	−0.46	0.0025*	−0.28	0.0793

may be related to what has been conceptualized as *implicit* memory (Graf and Schacter, 1985) involving an automatic (effortless) re-activation of the neuronal ensembles that were active when an item was previously encountered. During the first presentation of an image (in the study session), a memory trace can be established in a latent form in some neuronal ensembles by means of physiological mechanisms that lead to changes in synaptic weights lasting over temporal scales in the range of minutes or longer. As a result, these neuronal ensembles may exhibit changes in the evoked neuronal activity during subsequent presentations of the image compared to its first presentation or compared to the presentation of novel stimuli. These early changes in neuronal activity may reflect both enhanced spiking rates in some neurons and reduced spiking rates in others, which leads to *sharpening* of the neuronal representation of a repeated item (Norman and O'Reilly, 2003). Computational studies and electrophysiological findings suggest that after multiple exposures to a sensory stimulus, overall neuronal population activity in regions of the sensory processing hierarchy up to and including perirhinal cortex as the final stage of object recognition is decreased compared with novel stimuli (Brown and Xiang, 1998), whereas our results suggest an early overall increase in neuromagnetic signal power after a single exposure to scene images. Notably, regional signal power estimated from MEG recordings can increase with the presence of oscillations that reflect rhythmic activity and temporal synchronization within local populations of neurons and may not be directly compared with measures of population activity based on average neuronal spiking over certain temporal intervals. The timing of the old/new effect observed in our study is in a range of latencies when single neurons show scene-selective spiking activity in occipitotemporal neurons (starting at ~ 125 ms after stimulus onset, Bell et al., 2011), peak spiking rates occur in the inferior temporal cortex encoding object information (recorded from 100 ms to 200 ms after image onset, Hung et al., 2005; DiCarlo et al., 2012), and repetition-sensitive responses are found in perirhinal and entorhinal areas (with onset latencies of ~105 ms to 135 ms, Xiang and Brown, 1998). The old/new effects observed during the earliest temporal interval (50–150 ms) were not accompanied by significant correlations with the PCL-5 scores, suggesting that, at least within the constraints of our paradigm, this early evoked activity is not affected in PTSD. Therefore, this suggests that any enhancement of perceptual priming for neutral scenes as a result of a long term effect of psychological trauma in PTSD does not seem to manifest as a prolonged effect on repetition priming in early visual processing regions, which, if present, would have been indicative of a the maintenance of strong inflexible sensory representations as described by the dual representation theory.

An old/new effect was also present during the following temporal interval, from 100 ms to 200 ms, in the posterior part of the left inferior frontal gyrus (*pars opercularis*) and bilaterally in the *caudal anterior cingulate*, which showed higher activity for the correctly recognized old

images compared to novel images. Whereas the earliest old/new effect observed in visual processing regions between 50 ms and 150 ms would likely be the outcome of feedforward inputs and local recurrent processing within each region, the immediately following activity in downstream prefrontal neuronal populations (100 ms to 200 ms) may reflect a *read out* of the information encoded in lower-level visual processing regions as well as the initiation of feedback (bias) signals to visual processing regions in support of higher level, goal-oriented or task-relevant cognitive functions (Desimone and Duncan, 1995).

The relative power evoked by original images in *pars opercularis* and other prefrontal regions was lower in participants with high PTSD symptom severity on consecutive temporal intervals between 100 ms and 300 ms, as was the activity in other regions of the lateral posterior temporal cortex, lateral parietal cortex and *precuneus*. The lateral and dorsal prefrontal regions along with parietal regions that belong to the fronto-parietal attention network may contribute to a subsequent *explicit* recognition of the original scenes, which involves elaboration on familiar cues and strengthening of the neuronal representation of discriminative information, which was bound during encoding in the first session to episodic contextual information associated with the experimental study session (Diana et al., 2006), and facilitate the recognition of the original images with relatively high confidence. Multiple fMRI studies (reviewed in Wagner et al., 2005) in healthy participants have indicated that the prefrontal cortex, left lateral parietal cortex (including the supramarginal gyrus) and *precuneus* are more active for correctly recognized, previously seen items compared to new items (these findings generalized across word and picture stimuli). In our study, however, with the exception of the left *pars opercularis*, we did not observe an old/new effect on the evoked responses from these regions in our sample of participants. Notably, the latency range selected for our analysis was limited to the first 350 ms due to the presence of behavioral responses with short latencies in some trials and for some participants in our study. It is conceivable that the early evoked activity in these regions may be mainly associated with the *initiation* of effortful attempts to access discriminative features that can help in the recognition of an image, which should be present for both old and novel images.

A decrease in prefrontal activation observed in this timeframe in participants with higher PTSD symptom severity, especially in ventral lateral regions including the pars opercularis and pars triangularis (Scalici et al., 2017), may also be related to alterations in the process of *attribution* involved in the recognition of scene familiarity (the fluency heuristic) which assesses the rapidity of sensory processing and may consciously attribute the more rapid processing of previously experienced stimuli (an otherwise implicit process) as an index of familiarity (Whittlesea and Wiliams, 2000). This could account, at least in part, for a negative correlation between recognition of original scenes and PTSD symptom severity that we found in our study. This fluency heuristic process may be unlearned in certain patient populations (Geurten and Willems, 2017), resulting in poorer explicit recognition performance even in the presence of a sensory priming effect that produces significantly more rapid stimulus processing. Additionally, more rapidly processed neutral stimuli are biased toward having a somewhat more positively valenced affective tag (Willems et al., 2007), an effect that may be reduced or lost in PTSD in association with the phenomenon of emotional numbing. Finally, we propose that the fluency heuristic process may be actively suppressed in patients with PTSD as a component of hyperarousal and hypervigilance, as stimulus processing speed in general may be upregulated. Patients may additionally unconsciously suppress this process to avoid the potential of mislabeling familiar stimuli with an artificially positive affective valence.

Several lines of evidence provide support to the potential contribution of prefrontal, medial parietal (*precuneus*) and lateral parietal (*supramarginal gyrus*) regions, which in our study showed reduced relative power of the evoked response for patients with high PTSD symptom severity, to an effortful search for discriminative attributes or contextual associations that help explicit recognition. Activations of multiple neuronal representations in visual processing regions may send inputs to frontal and parietal regions and receive feedback from those regions in a process of search and selection of relevant features that involves recurrent activation through local collateral connections and bias signals from other (distant) areas. Previous studies have observed that the left lateral prefrontal cortex can play a role in the selection of relevant information and inhibition of irrelevant information according to the current task (Nolde et al., 1998; Thompson-Schill et al., 1999; Fletcher and Henson, 2001). This role can be conceptualized as a goal-oriented control over the search for discriminative features during recognition of visual scenes, with recognition being facilitated when neuronal representations of the same features or associations that were activated during the study session (*i.e.* at encoding) are re-activated during the recognition (test) session, whereas a correct categorization of a novel item is facilitated when the degree of mismatch between the representation of a current stimulus with respect with those of previously seen stimuli is maximized. Notably, the search for discriminative features during analysis of complex visual scenes requires that selective attention is dynamically redistributed across individual scene elements or configurations of elements. Parietal regions that showed reduced power of the evoked response in patients with high PTSD symptom severity in our study are known to exhibit activation levels modulated by attention and are likely recruited in this search process. For example, fMRI and PET studies reported higher activation of the *precuneus* during tasks that required shifting attention between object features (Le et al., 1998; Nagahama et al., 1999) or between local and global levels of complex visual figures (Fink et al., 1997). Since shifting attention is often required during the search for discriminative attributes of a stimulus, these findings could be related to reports of activation in *precuneus* and prefrontal regions during re-generation of previous contextual associations that is sensitive to the amount and quality of information retrieved (Rugg et al., 1998; Takahashi et al., 2002; Dobbins et al., 2002; Lundstrom et al., 2003, 2005). The lateral parietal region, encompassing the *supramarginal gyrus* and the lateral bank of the intraparietal sulcus, has been traditionally viewed as a component of the visual attention network (Corbetta and Shulman, 2002; Cabeza et al., 2008). Activity in the left lateral parietal cortex has been proposed to be modulated by the bottom-up capture of attention triggered by the re-activation of (mnemonic) neuronal representations that were previously activated during encoding (Wagner et al., 2005). This suggests a potential role in the integration of bottom-up mnemonic information with top-down modulation, providing "attentional support" to these mnemonic neuronal representations (the *attention-to-memory* hypothesis, Wagner et al., 2005; Cabeza et al., 2008; Ciaramelli et al., 2008, 2010; Kahn et al., 2004). According to this hypothesis, the effectiveness of the encoding (which may benefit also from a process of elaboration during the study session) would influence the recruitment of neuronal ensembles in lateral parietal regions during recognition. Hence, an ineffective encoding in memory in PTSD due to alterations in brain oscillatory activity during the study session, as reported in one of our previous studies (Popescu et al., 2020), may contribute in part to the observed alterations in evoked responses during recognition, with deleterious effects on recognition accuracy. However, an analysis carried out to investigate the potential association between the evoked response over early temporal intervals in the recognition session and the oscillatory brain activity indicative of ineffective encoding in PTSD did not provide clear evidence for their association (Supplementary material). Therefore, the reduced activation levels observed during the recognition session in those participants with high PTSD symptom severity do not appear to be simply a manifestation of poor encoding at the time of first stimulus presentation, but rather suggest an additional deficit inherent to the process of stimulus recognition. A possible explanation for this finding comes from the fact that salient features of complex scenes (which may include global spatial layout as well as non-spatial properties such as prominent features of single objects defined *e.g.* by distinctive color or high contrast) are more likely processed during

early temporal intervals following the image onset (Itti and Koch, 2001). The re-activation of the neuronal representation of these salient features that are selectively processed during the early temporal intervals may be influenced by ineffective encoding to a lesser degree compared to neuronal representations of additional (fine-grained) scene details that may encode for example information about local spatial layout or about less prominent features of single objects which can be used to recognize an old scene. Selective processing of the less salient scene details, which may be disproportionately affected by ineffective encoding, may occur predominantly at longer latencies, *i.e.* outside of the latency range used in our analysis (which was limited by the presence of behavioral responses with short latencies for some participants in our study). Nevertheless, it is important to note that if the contribution of ineffective encoding of both salient and fine-grained image features to impaired recognition is mediated by reduced bottom-up capture of selective attention by reactivations of (mnemonic) neuronal representations, then a general dysfunction related to selective attention orienting to sensory inputs in PTSD can potentiate the negative effects of ineffective encoding on recognition. Two observations suggest that dysfunction of the distributed network including frontal, parietal and posterior lateral temporal regions may contribute to the lower recognition performance irrespective of (or in addition to) the alterations in brain activity observed during encoding. First, there is an absence of a significant correlation in the recognition session between the PCL-5 scores and brain activity during the early temporal intervals in bilateral ventral and medial temporal regions and left orbitofrontal cortex (*i.e.* the regions with altered electrophysiological patterns during the encoding session) which would be expected to be simultaneously present or precede the alterations seen in the activity of the frontal, parietal and posterior lateral temporal regions. Second, there is a lack of an old/new effect in the evoked responses in lateral parietal cortex, which suggests that the early evoked activity in this region may be primarily associated during these temporal intervals with the *initiation* of effortful attempts to access discriminative features through dynamical allocation of selective attention, which would be present for both old and novel images. This would be consistent with observations of other previous studies, which provided evidence that activity in lateral parietal cortex may reflect an effortful *recollection attempt* (which was also referred to as *retrieval orientation)* that is present for all (old and novel) test items (Dobbins et al., 2003). In turn, the difficulty with elaboration on visual cues due to ineffective control of selective attention and/or attention-shifting may prevent cortical processing modules from providing appropriate bias inputs to the hippocampal pattern separation and pattern completion. This may contribute to overgeneralization of trauma reminders if pattern completion is favored over pattern separation in PTSD for cues that share some similarities with stimuli experienced during the traumatic event (Lange et al., 2017). Relevant mechanisms and possible causes of attention dysfunction in PTSD are discussed in the Supplementary material.

Our findings can be also discussed from the perspective of the *predictive processing* framework proposed to characterize perception and learning (Friston, 2009; Friston and Kiebel, 2009), which has recently became a popular theory in neuroscience. According to this theory, predictions of sensory information encountered in the environment are formulated in higher order cortices and are fed back to sensory cortices. Differences between predictions and incoming sensory inputs are dynamically encoded as *prediction errors* at different levels within the sensory processing hierarchy. These prediction errors are fed forward in the cortex from lower sensory areas, and contribute to update previous predictions in a recursive process. Ascending prediction errors that are not suppressed by descending prediction representations will be used to update one's "generative model" of the world for use in future predictions, which defines the process of learning. Notably, the mechanisms described by the predictive processing framework do not function independently from other recognition memory mechanistic systems described above, but rather function in concert with them to optimize behavior. In the predictive processing framework, the construct of attention in sensory processing is recast as the *precision* or confidence in feed-forward and feedback information within the sensory processing hierarchy; in the case of visual processing, this hierarchy extends from the lateral geniculate nucleus and V1 up to the highest levels of cognitive and emotional processing in association cortex and limbic cortices in both ascending and descending directions.

In our recognition paradigm, in which any given scene has an equal probability of being old or new, initial predictions regarding the categorization of each image may be formed at high-levels of the processing hierarchy (prefrontal cortex) based on a level of familiarity induced by scene elements or on particular configurations of elements. Subsequently, participants must use visual search and attention strategies to confirm or refute the initial prediction. The overlap between elements that were present in original and novel scenes from the same category increases task difficulty and participants should theoretically be increasing the precision of sensory information and decreasing the precision of predictions that were formulated based on the early processed (incomplete) sensory data. An inability in PTSD to properly shift the balance of precision from an emphasis on top-down prediction to an emphasis on bottom-up prediction error, which would facilitate the update of predictions following, for example, the processing of disconfirmatory information, may lead to lower discrimination between old and new images. Hence, it is possible that the impairment in recognition memory we have demonstrated using neutral scenes may represent a more subtle or nuanced manifestation of disturbed predictive coding in PTSD. Predictive processing has indeed been theorized to be dysfunctional in PTSD, at least in the case of sensory information that could be a reminder of the traumatic event (Wilkinson et al., 2017; Kube et al., 2020). When exposed to stimuli with some overlap of sensory features with a prominent sensory component of the trauma, a perceptual process that favors feedback activity (predictions) over feed-forward activity and over a drive to acquire additional disconfirmatory sensory information may lead to sensory flashbacks. In these cases, the prediction error associated to processing of disconfirmatory information will be erroneously suppressed and the prediction of a flashback will become a self-fulfilling prophecy; avoidance behavior and hypervigilance may also ensue.

To summarize our findings with respect to the dual representation theory, we did not find evidence of persistent enhanced perceptual priming for trauma-unrelated and emotionally neutral stimuli in early sensory cortices in patients with chronic PTSD. We did, however, find evidence consistent with ongoing dysfunction of a distributed cortical system involving prefrontal, parietal and lateral temporal cortices that likely supports the hippocampally based retrieval of complex, contextual and flexible information. This suggests that dysfunction in this system that either precedes the psychologically traumatic event and predisposes to the development of PTSD or is a direct result of the traumatic stress that produced sustained PTSD symptoms and contributed to a fragmentation of the explicit memory of the traumatic event, is to some degree persistent in patients with chronic PTSD symptoms. These results help advance our understanding of potential neurophysiological mechanisms that may contribute to core symptoms of PTSD. Whereas previous research has linked the overgeneralization of trauma reminders/fear in PTSD to deficits in sensory discrimination that were mostly attributed to dysfunction of the hippocampus (Kheirbek et al., 2012), our findings highlight the additional involvement of a distributed brain network including frontal, parietal and posterior lateral temporal regions that supports visual recognition, including the recognition of trauma-unrelated and emotionally neutral stimuli. Our findings are consistent with a diminished ability to elaborate on visual cues during visual recognition, which undermines processing of discriminative sensory features for stimuli with overlapping neuronal representations and in this way may contribute to overgeneralization of trauma reminders in PTSD. Since elaboration on visual cues during visual recognition involves the ability to dynamically allocate attention across local

and global scene features (which include contextual associations between scene elements), our findings may be related to previous reports of deficits of selective attention orienting in PTSD (*e.g.* reviewed in Block and Liberzon, 2016). The significance of the ability to process discriminative sensory features becomes apparent when an individual who was exposed to psychological trauma is confronted with the presence of strong predictions associated with memories of the traumatic event, since difficulties with attention control may prevent the effective processing of dis-confirmatory sensory information regarding the threatening nature of a cue. Our cross-sectional study does not allow us to draw conclusions about the etiology or chronicity of the alterations in brain activity seen during the visual recognition task and the dual representation theory does not specify if some pre-trauma cognitive deficits may represent risk factors for the memory dysfunction in PTSD. Our findings do not exclude, for example, the possibility of a preexisting alteration in the evoked brain activity of this brain network prior to the experience of severe psychological trauma, which may or may not be exacerbated by exposure to psychological trauma and by the presence of post-traumatic stress symptoms. Such preexisting alterations in network function that may contribute to attentional dysfunction may have a developmental or genetic basis and be long standing or may be due to some preexisting acquired pathology and represent a risk factor that may predispose those individuals to develop (more severe) PTSD symptoms upon exposure to psychologically traumatic events. Since deficits of attention and sensory discrimination may constitute a potential target for treatment in PTSD (Kube et al., 2020), our findings provide support for future research into the effectiveness of pharmacological or non-pharmacological therapies that are designed to address these deficits (Tang and Posner, 2009; Hakamata et al., 2010; Badura-Brack et al., 2015) and can be tested as *add-on* interventions for improving the outcome of cognitive-behavioral therapy in PTSD. Future studies can utilize the methodology described in our study to investigate the effects of such therapeutic interventions on the brain activity underlying recognition memory and to assess the correlation between a normalization of such brain activity and a decrease in the frequency of intrusive memories. Such studies may help elucidate if the identified alterations in brain activity for patients with PTSD are clinically actionable (Woo et al., 2017). Furthermore, the reductions in evoked brain activity during visual recognition may also be tested in these studies as a biomarker for the identification of those patients with PTSD who may benefit from such treatments or for the identification of individuals who are predisposed to the development of PTSD after exposure to a psychologically traumatic event.

CRediT authorship contribution statement

Mihai Popescu: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. **Elena-Anda Popescu:** Methodology, Software, Formal analysis, Writing - review & editing. **Thomas J. DeGraba:** Conceptualization, Writing - review & editing. **John D. Hughes:** Conceptualization, Methodology, Writing - original draft, Supervision.

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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, DoD, or any component agency.

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Appendix A. Supplementary data

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