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Neural correlates of attention bias in posttraumatic stress disorder

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HIGHLIGHTS

- Abnormal frontal brain responses in PTSD suggest increased resource allocation to routine stimuli.
- Disproportional resource allocation may prevent adequate processing of uncommon and sporadic events.
- Findings highlight the use of frontal brain activity measures as potential biomarkers for PTSD.

ABSTRACT

Objective: Patients suffering from posttraumatic stress disorder (PTSD) exhibit hyper arousal symptoms and attention problems which were frequently investigated using the P3 event-related potentials (ERPs). Our study aimed at providing more precise knowledge of the functional significance of the P3 alteration seen in PTSD by revealing its spatio-temporal dynamics.
Methods: Fifteen PTSD patients and fifteen healthy trauma-exposed controls participated in a three-tone "oddball" task while their brain activity was recorded by magnetoencephalography (MEG). They were asked to detect rare target tones and ignore standard tones and infrequent threatening distractors. An adaptive spatial-filter method (SAM beamformer) was applied for source estimation.
Results: Compared with controls, PTSD patients had more incorrect responses to standard stimuli. On the brain level, PTSD patients showed hyperactivity in the dorsolateral prefrontal cortex and anterior cingulate cortex in response to standard sounds, decreased activity in those regions in response to threatening distractors, and decreased orbitofrontal activity in response to target stimuli.
Conclusions: Increased frontal activation in response to standard, neutral, stimuli may reflect greater resource allocation dedicated to cognitive control mechanisms during routine functioning in PTSD. Decreased frontal activation in response to rare stimuli may reflect subsequently reduced residual resources for detecting rare stimuli and for emotion regulation. This may explain the hypervigilance and attention problems commonly reported by patients.
Significance: The current findings contribute to a better understanding of the mechanisms underlying the attention deficiency in PTSD, and highlight altered activity in specific frontal regions as potential biomarkers.

1. Introduction

Patients suffering from PTSD often exhibit difficulties in sustaining their attention on target tasks, together with hyper alertness and increased attention to potentially threatening cues in the environment. During the past decade, there has been a growing interest in applying event-related potentials (ERPs) to the study of cognitive impairments in PTSD. One ERP component in particular, the P300, has been widely used to study attentional processes in this disorder. This component is typically elicited using the oddball paradigm, in which individuals are instructed to attend to infrequent target stimuli (i.e., "oddball") and ignore

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other frequently presented standard stimuli. A variation of the oddball task includes presentation of infrequent distracting (i.e., "novel") stimuli as a third stimulus.

Most researchers today agree that the P300 (also known as "P3") consists of several functionally and topographically distinct components (Spencer et al., 1999; Goldstein et al., 2002; Volpe et al., 2007), and most frequently distinguish between the "Target P3" (P3b) and the "Novelty P3" (P3a). The P3b is mainly generated in response to attended target stimuli and is thought to represent the availability of attentional resources for stimulus processing (Donchin and Coles, 1988). Compared with the parieto-central distribution that characterizes the P3b, the P3a has a more anterior scalp distribution and is most prominently generated in response to rare non-target distracting stimuli or to deviant stimuli in an unattended series. The P3a precedes the P3b by approximately 50 ms (Courchesne et al., 1975), and was hypothesized to reflect a form of pre-attentive processing in which changes in the sensory environment evoke an automatic shift in attention (Näätänen, 1990). Although target and distractor stimuli are known to elicit distinct components, these components are not mutually exclusive. Both novel and rare stimuli have been shown to elicit parietal P3b and Novelty P3a components, differing only in their relative amplitude (Spencer et al., 1999).

Even though the P3a and P3b are hypothesized to reflect different cognitive functions and to be generated in different brain regions, many of the PTSD P300 studies fail to disentangle them. This distinction is particularly essential in PTSD, due to patients' distinctive impairment in the processing of relevant as opposed to irrelevant information. The diagnostic criteria (American Psychiatric Association, 2013) reflects this distinction by including symptoms indicative of disturbed attentional processing (which is tapped by the P3b component), and associated hyperarousal, such as hypervigilance and exaggerated startle response (tapped by the P3a component).

The most common finding regarding the P300 in PTSD population is of reduced amplitude (most likely P3b amplitude) to neutral target stimuli compared with controls (Karl et al., 2006). Reduced P3b amplitude is thought to reflect a reduction in the attentional resources allocated towards stimulus processing (Polich, 2003), hence providing electrophysiological support for the DSM-IV and V PTSD symptom of disturbed concentration (American Psychiatric Association, 1994, 2013). However, meta-analysis studies suggest that stimuli valence differentially affects the P300 amplitude, with trauma related stimuli leading to a sensitization of the P3b and P3a, and neutral stimuli leading to diminished P3a and P3b amplitudes in PTSD (Karl et al., 2006; Javanbakht et al., 2011; Johnson et al., 2013).

The brain regions involved in this altered processing are still under controversy. In healthy participants, multiple brain regions were found active in response to target stimuli depending on the measures employed, with two cortical regions found consistent across studies: the supramarginal gyri and the anterior cingulate cortex (ACC) (Ardekani et al., 2002; Clark et al., 2000; Kiehl and Liddle, 2001; Linden et al., 1999; McCarthy et al., 1997; Stevens et al., 2000; Halgren et al., 1998; Smith et al., 1990). The dorsolateral prefrontal cortex (dlPFC) is also believed to be involved in target detection (McCarthy et al., 1997; Clark et al., 2000; Stevens et al., 2000; Kiehl et al., 2001). Whereas there is considerable overlap of regions activated during distractor and target processing, bilateral superior temporal and right inferior frontal areas show pronounced activation related to distractors (Strobel et al., 2008). In PTSD, however, only few attempts have been made to localize the P300 source generators, yielding conflicting results. On the one hand, a recent ERP study using the oddball paradigm found decreased P300 activity in response to target stimuli among PTSD patients in multiple brain areas including the ACC (Bae et al., 2011). This finding is consistent with models of PTSD proposing that a failure of medial prefrontal/ACC networks to regulate amygdala activity results in the hyperactivity seen in PTSD patients (Bremner et al., 1999). On the other hand, fMRI studies using the oddball paradigm indicated increased ACC activity in PTSD subjects in response to target stimuli (Bryant et al., 2005) and emotional distractors (Pannu Hayes et al., 2009). These inconsistencies might be explained by the measuring techniques used in these studies and their different temporal resolutions. Whereas studies based on neuroimaging techniques such as fMRI allow for source localization in a time window of seconds after stimulus onset, EEG provides a temporal resolution in the millisecond range. Therefore, an optional explanation for these conflicting results is that the general enhanced activation of the ACC found in the fMRI oddball studies is preceded by a short phase of decreased activity in this region following stimulus presentation, which can be observed only by EEG.

The complex role of the ACC in PTSD emphasizes the importance of applying an imaging technique that can fully capture the dynamic brain function in high temporal resolution. Similar to the EEG, MEG provides millisecond temporal resolution allowing examination of the Novelty P3 and Target P3 components separately. In addition, MEG has a good spatial resolution allowing the estimation of the neural sources underlying these components. This high spatial resolution is a consequence of the fact that MEG signals, as opposed to EEG signals, travel through the various boundary layers of the brain and skull with relatively little distortion (Barth et al., 1986). Differences in the physical properties of the electric and magnetic fields arising from the same current source may lead to differences in source localization when EEG or MEG are applied. No studies using MEG to elucidate Novelty P3 and Target P3 neural correlates in PTSD have been conducted so far. It is therefore the aim of the present study to reveal the brain regions that show differential activity in PTSD patients and healthy trauma-exposed controls in response to neutral targets and threatening distractors. Identifying such sources should provide more precise knowledge of the functional significance of the P3 alteration seen in PTSD. To this end, MEG was recorded during an oddball paradigm comprising standard tones, rare target tones and rare threatening distractor sounds.

2. Methods and materials

2.1. Participants

Seventeen PTSD patients and sixteen healthy trauma exposed controls participated in the study. One subject from each group was excluded from analysis due to a magnetic artifact, and one PTSD patient dropped out due to difficulty in withstanding test conditions. Hence, MEG analysis was based on 30 participants, with 15 participants in each group. Exclusion criteria for both groups included symptoms or signs of psychosis or suicidality; drug/alcohol abuse in the previous 6 months; past history of brain injury, loss of consciousness or other neurological disease; and a contraindication to undergoing MRI or MEG. Groups were matched for age, gender and time since the occurrence of the trauma. Participants experienced diverse adult trauma, including motor vehicle accidents (PTSD $n = 4$, control $n = 8$), terror violence (PTSD $n = 2$, control $n = 1$) and military related trauma (PTSD $n = 9$, control $n = 6$). Comorbidity of anxiety and depression was allowed in the PTSD group, given that diagnosis of PTSD preceded the comorbid diagnosis (See Supplementary Methods in Supplementary Information for a complete description of the participants). The study was in compliance with the Helsinki Declaration and the Hadassah Hebrew University Medical Center Ethics Committee approved