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## Veterans with PTSD Demonstrate Amygdala Hyperactivity while Viewing Threatening Faces: A MEG Study

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## Abstract

Posttraumatic stress disorder (PTSD) is a major psychiatric disorder that is prevalent in combat veterans. Previous neuroimaging studies have found elevated amygdala activity in PTSD in response to threatening stimuli, but previous work has lacked the temporal specificity to study fast bottom-up fear responses involving the amygdala. Forty-four combat veterans, 28 with PTSD and 16 without, completed psychological testing and then a face-processing task during magnetoencephalography (MEG). The resulting MEG data were pre-processed, transformed into the time-frequency domain, and then imaged using a beamforming approach. We found that veterans with PTSD exhibited significantly stronger oscillatory activity from 50–450 ms in the left amygdala compared to veterans without PTSD while processing threatening faces. This group difference was not present while viewing neutral faces. The current study shows that amygdala hyperactivity in response to threatening cues begins quickly in PTSD, which makes theoretical sense as an adaptive bottom-up fear response.

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## Keywords

posttraumatic stress; magnetoencephalography; fear; bottom-up: oscillatory activity; military

## 1. Introduction

Neuroimaging findings in posttraumatic stress disorder (PTSD; APA, 2013) indicate elevated amygdala activity, often in conjunction with inadequate prefrontal cortex modulation of such limbic hyperactivity (Etkin & Wager, 2007; Hayes et al., 2012; Koch et al., 2016; Patel et al., 2012). However, this literature typically utilizes neuroimaging tools (e.g. fMRI, PET) that are unable to measure fronto-limbic activations with high temporal specificity, preventing strong conclusions about the underlying time course. Recent research has focused generally on fast fear pathways (Diano et al., 2017; Méndez-Bértolo et al., 2016), but research about fast amygdala reactivity in PTSD is needed.

Automatic processing of threat-related cues is linked to threat reactivity responses in PTSD (Lanius et al., 2017). Interestingly, emotionally-neutral stimuli seem to require selective attention for processing, while emotionally-laden stimuli may be less dependent on attentional resources (Vuilleumier, 2005) and more rooted in amygdala responsivity (Diano et al., 2017). Magnetoencephalography (MEG) has excellent temporal specificity, and previous MEG studies using healthy participants have found early amygdala activation in response to emotional faces (Garrido et al., 2012; Garvert et al., 2014; Luo et al., 2007, 2010), consistent with face processing studies that used intracranial recordings (Hesse et al., 2016; Mendez-Bertolo et al., 2016; Pourtois et al., 2010; Sato et al., 2011). Substantial evidence supports the capability of MEG to detect neural activity in deep brain structures (Badura-Brack et al., 2017; Cornwell et al., 2012a, 2012b, 2014; Dalal et al., 2008; McDermott et al., 2016; Proskovec et al., 2016; Pu et al., 2017; Salvadore et al., 2009, 2010; Wilson et al., 2009, 2010, 2011, 2017). One such MEG study used a seed-based functional connectivity approach found that veterans with PTSD had increased functional connectivity relative to veterans without PTSD between the amygdala and ventromedial prefrontal cortex when viewing threatening faces (Dunkley et al., 2016); however, this study did not examine the time course or amplitude or amygdala responses, and thus such data remains unavailable in patients with PTSD.

We used a face-processing paradigm involving angry and neutral faces, as faces are known to elicit strong emotional reactivity (de Gelder et al., 2006; Johnson, 2005). Threatening expressions are a key primitive threat signal, which likely provoke an evolutionary alarm response (Tamietto & de Gelder, 2010). This innate alarm system has been of interest in PTSD (Lanius et al., 2017), with the amygdala being central to an automatic response to threat (e.g. fight or flight) and symptoms of PTSD (LeDoux & Pine, 2016). Given that PTSD is associated with neurocognitive deficits including speed of information processing and attention/working memory (see Scott et al., 2015), we expected the PTSD group to have slower reaction times than veterans without PTSD. Based on previous research, we hypothesized that amygdala activity would be present and occur shortly after stimulus onset

in threat trials in both groups, and specifically that amygdala activity would be significantly stronger in combat veterans with PTSD as compared to those without PTSD.

## 2. Materials and methods

#### 2.1. Participants

Twenty-eight male combat veterans with PTSD and 16 male combat veterans without PTSD participated in this study. All veterans served in Iraq or Afghanistan between 2003 and 2014, and were assessed using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). The two groups of men were matched on age (PTSD: M=33.50, SD=9.00; no-PTSD: M=33.56, SD=8.02), education (PTSD: M=14.71, SD=2.21; no-PTSD: M=14.27, SD=1.94), race (86%; 88% Caucasian), and handedness (all right-handed). Veterans diagnosed with PTSD had significantly higher (p > 0.001) CAPS scores (M=71.00, SD=17.20 than those without PTSD (M=23.5, SD=12.90). Exclusion criteria were medical diagnoses affecting central nervous system function, brain neoplasm or lesion, significant head trauma, current substance dependence and ferromagnetic implants. Veterans on medications were not excluded, and 32% of the PTSD group and 19% of those without PTSD were taking stable dosage of an SSRI, Xanax, or mood stabilizer. Written informed consent was obtained following the ethical guidelines of the Creighton University Institutional Review Board.

#### 2.2. Experimental paradigm

All participants completed a face-processing task (Britton et al., 2012) while seated inside the MEG chamber. Trials began with a fixation cross presented for 500 ms, followed by the presentation of a face pair for 500 ms. The stimuli varied between one angry and one neutral face (threat) or two neutral faces (neutral; Figure 1). Participants were instructed to respond with their right index or middle finger based on the location of a target that appeared in the space vacated by one of the faces. The target duration was 400 ms and a blank screen was presented between trials for an interval of 1250–1350 ms. Accuracy and response times were recorded.

#### 2.3. MEG Data Acquisition, Pre-Processing & Source Reconstruction

Neuromagnetic responses were sampled continuously at 1 kHz using an acquisition bandwidth of 0.1–330 Hz and Elekta system with 306 magnetic sensors (Helsinki, Finland). All MEG data were subjected to noise reduction using the signal space separation method with a temporal extension (tSSS; Taulu and Simola, 2006), coregistered with structural MRI, and transformed into standard space after beamforming (see below).

Cardiac artifacts were removed using signal-space projection (SSP; Uusitalo and Ilmoniemi, 1997). The continuous magnetic time series was divided into epochs of 2700 ms duration (-500 to 2200 ms), with 0.0 s defined as stimulus onset (i.e., faces) and the baseline defined as the -500 to -100 ms time window. Epochs containing artifacts were rejected based on a fixed threshold method, supplemented with visual inspection. Artifact-free epochs were transformed into the time-frequency domain using complex demodulation and the resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of mean spectral density, and then normalized using the mean power during the

baseline period. This revealed a broadband (4–40 Hz) oscillatory response in many MEG sensors that started shortly after stimulus onset (50 ms) and continued through the end of the face stimulus presentation period (450 ms).

Data were then imaged (4–40 Hz, 50–450 ms) using an extension of the linearly constrained minimum variance vector beamformer (Gross et al., 2001). The resulting 3-dimensional maps of functional brain activity were  $4.0 \times 4.0 \times 4.0$  mm resolution and were statistically evaluated using a mass univariate approach based on the general linear model. All statistical maps were displayed as a function of  $\alpha$  level, thresholded at p < 0.05, and adjusted for multiple comparisons using a spatial extent threshold (80 contiguous voxels). MEG preprocessing and imaging used the Brain Electrical Source Analysis (BESA version 6.1) software.

## 3. Results

Average accuracy in the task was 94.94% (SD: 4.61%) in the threatening condition and 95.36% (SD: 5.23%) in the neutral condition, and there were no group differences in either condition (ps > 0.23). Reaction time differed significantly on the Mann-Whitney U test between the groups for threatening (p = 0.013) and neutral (p = 0.022) conditions. Veterans with PTSD responded more slowly (neutral: M= 816.31ms, SD = 135.21; threat: M= 822.98ms, SD= 140.46) than their non-PTSD peers (neutral: M= 723.03ms, SD= 96.92; threat M= 721.62ms, SD= 101.14) in both conditions. Neither group showed a significant difference between conditions for accuracy or reaction time.

The MEG group comparisons showed that during threatening stimuli (50–450 ms), veterans with PTSD had significantly stronger oscillatory activity in the left amygdala (peak coordinate: -22, -1, -23; Tzourio-Mazoyer et al., 2002) compared to veterans without PTSD (p < .05, corrected; Figure 2). Follow-up analyses at the voxel level suggested that this amygdala response was primarily in the 6–10 Hz band from 100–300 ms. No neurophysiological differences were found between veterans with and without PTSD during neutral face processing.

## 4. Discussion

This study utilized the excellent temporal specificity of MEG in the context of threatening visual stimuli and PTSD. The key finding was stronger left amygdala oscillations in veterans with PTSD relative to those without PTSD during the processing of threatening, but not neutral faces. The left amygdala was the only brain region to show group MEG differences during threatening faces, and there were no group differences during neutral face processing. Thus, our amygdala findings were specific to threatening faces and argue against a generalized hyperactive amygdala in PTSD.

Preferential left amygdala activation is common in response to fearful and threatening facial stimuli as opposed to neutral faces in PET (Morris et al., 1996, 1998a, 1998b) and fMRI (Breiter et al., 1996; Carlson et al., 2009 Irwin et al., 1996; Whalen et al., 1998) studies, and our findings were consistent with such findings. Behaviorally, veterans with PTSD responded more slowly to both neutral and threatening faces relative to veterans without

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PTSD, consistent with previous speed of processing and attention studies (See Scott, et al., 2015). Our facial processing task did not specifically direct attention toward emotional stimuli (Diano et al., 2017), and thus may nicely model the cues that provoke PTSD symptoms in daily life. Further, only face pairs that included angry expressions triggered an early amygdala response, consistent with an immediate response to threat in PTSD (Lanius et al., 2017).

To our knowledge, only three previous MEG studies have identified the timing of cortical differences in threat-cue processing in patients with PTSD compared to traumatized controls, and no MEG study has reported amygdala activation differences. These studies found that veterans without PTSD engaged the anterior cingulate more than veterans with PTSD from 90–140 ms (Todd et al., 2015), and that veterans without PTSD engaged the right ventromedial prefrontal more than those with PTSD from 400–600 ms (Khanna et al., 2017) after emotional word presentation. These MEG studies used emotional words, which are not as primitive of a threat cue as angry faces and may be why amygdala differences were not noted. Another study found that patients with PTSD recruited right prefrontal regions more than controls at 130–160 ms after affective picture presentation (Adenauer et al., 2010), but these were pictures of various items which required more processing than simply viewing neutral versus angry faces.

Importantly, our findings are consistent with MEG studies of healthy participants identifying early amygdala activation in response to emotional faces (Garrido et al., 2012; Garvert et al., 2014; Luo et al., 2007, 2010). We have extended these findings, demonstrating that amygdala activation in response to angry but not neutral faces is stronger in veterans with PTSD than in those without. Thus clarifying an early (~50 ms) and specific amygdala activation to threatening stimuli in PTSD which may reflect a bottom-up amygdala drive on cortical functioning (Liddell et al., 2004, 2005) consistent with a fear response. Future research is necessary, using primitive threatening stimuli such as emotional faces and startling sounds, but our study suggests targeting early amygdala hyperactivity in the assessment and treatment of PTSD.

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**Figure 1.** Facial presentation task flow.

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## Figure 2.

Veterans with PTSD exhibited stronger oscillations in the left amygdala relative to veterans without PTSD. Image has been thresholded at p < 0.05, corrected.