AN INVESTIGATION OF MASKED FACIAL AFFECT IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER USING ELECTROENCEPHALOGRAPHY AND FUNCTIONAL MAGNETIC RESONANCE IMAGING

by

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ABSTRACT

The research detailed within this dissertation investigates the neurobiological changes associated with emotional processing of backward masked emotional faces in veterans with and without posttraumatic stress disorder (PTSD). PTSD affects millions of Americans, including approximately 20% of veterans, and is associated with a number of negative symptoms, including hyperarousal, avoidance, and flashbacks.

In this dissertation, we examined a group of 15 veterans with PTSD and a group of 12 veterans without PTSD using both functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Using fMRI, the blood oxygen level dependent (BOLD) signal of the amygdala and extrastriate cortex was measured, and using EEG, the P1 event-related potential (ERP) was recorded in response to masked affect. The veteran group with PTSD exhibited increased extrastriate BOLD signal but decreased P1 ERP amplitude in the right hemisphere. This was evidence of a right hemisphere specific visuosensory modulation in veterans with PTSD, which is most evident using EEG. Unexpectedly, the P1 ERP and extrastriate BOLD signal did not display a significant linear relationship in either veteran group, which indicates that although activity was measured from similar regions, the two methodologies provided distinct information regarding neuronal activity in this study.

In addition, a relationship was observed between the BOLD signal of the amygdala and extrastriate cortex and the degree of combat exposure, based on the Combat Exposure Scale (CES). A veteran group without PTSD displayed a negative correlation between the extent of combat exposure and amygdalar BOLD activity. This was not the case for a veteran group with PTSD, who instead exhibited a negative correlation between the degree of combat exposure and extrastriate BOLD activity. When the total score of the CES was used as a covariate, the veteran group with PTSD displayed significantly increased amygdalar BOLD and extrastriate BOLD activity, compared to the veteran group without PTSD.

This research highlights the importance of multimodal research, as differences between the two groups were observed using both methodologies. Our results suggest a relationship between the degree of combat exposure and the processing of masked emotional stimuli, even in veterans without PTSD.

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CHAPTER 1

INTRODUCTION

This study aimed to add to the characterization of posttraumatic stress disorder (PTSD) by applying neuroimaging approaches and clinical assessments to study the response to backwardly masked emotional faces in a veteran population. Using functional magnetic resonance imaging (fMRI), we investigated the blood oxygen level dependent (BOLD) response of the amygdala and extrastriate cortex, two regions associated with both the processing of emotion and PTSD. We also used surface electroencephalography (EEG) to examine the P1 event-related potential (ERP), which reflects attentional and emotional visual processes that may be affected by PTSD. In addition, we sought to determine if there was a direct relationship between the degree of combat exposure and the neuronal response to backwardly masked emotional faces. PTSD negatively impacts the lives of numerous veterans and this research may lead to a better understanding of the neurobiological underpinnings of the disorder, with the ultimate goal of improving treatment efficacy. This research may also contribute to the identification of neurobiological markers of PTSD, which could allow medical professionals to target individuals at risk for developing the disorder.

There are more than 21 million veterans in the United States, with an

estimated prevalence of PTSD of approximately 20% (Fulton et al., 2015; U.S. Census Bureau, 2014). Although a strong focus is placed on veterans, PTSD can develop from a number of traumatic experiences including motor vehicle accidents (Beck & Coffey, 2007), sexual assault (Dunmore, Clark, & Ehlers, 1999), natural disasters (Hensley & Varela, 2008), and terrorist attacks (Shalev & Freedman, 2005). PTSD is unique among anxiety disorders in that it requires a person to experience a specific traumatic event for the disorder to be diagnosed. Although the types of events that can cause PTSD are well studied, the changes to the brain's structure, function, and connectivity are not fully understood.

As well known as PTSD is today, it was only explicitly defined in 1980 as a part of the DSM-III (APA, 1980). Not only was the disorder undefined for many years, but there has been, and continues to be, stigma associated with PTSD. This stigma makes patients less likely to seek treatment, especially those with a military background (Brown & Bruce, 2016; Greene-Shortridge, Britt, & Castro, 2007). Returning veterans have not always received needed medical care, with many remaining isolated, particularly those with mental disorders (Institute of Medicine, 2010; Kulka et al., 1990). However, the Veterans Health Administration has worked hard to create outreach programs, and with the return of veterans from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF), there has been an increased emphasis on PTSD research and treatment.

The amygdala has been the focus of many PTSD neuroimaging investigations as evidence from multiple scientific approaches indicates this region plays a role in the disorder. The amygdala has also been shown to play an

important role in the response to fearful and threatening stimuli (Bremner, 2007; Hughes & Shin, 2011; Rauch et al., 2000). The amygdala's role in an implicit fear network is thought to contribute to the hyperarousal seen in patients with PTSD. This fear network allows the brain to respond to threatening objects and situations before the conscious brain is aware of them (Adolphs, 2008; LeDoux, 2012). The direct subcortical pathway to the amygdala involves the superior colliculus and thalamus, and is faster and independent from the conscious cortical pathway (Liddell et al., 2005; Ohman, 2005). The amygdala is strongly linked with the appraisal and processing of emotional expressions, especially fear, as damage to the amygdala results in the inability to recognize fearful expressions in others (Adolphs, Tranel, Damasio, & Damasio, 1994). When healthy subjects are shown fearful stimuli, the amygdala and the visual cortex display increased activity compared to neutral stimuli (Morris et al., 1998; Pizzagalli et al., 2002). The amygdala and visual cortex are structurally and functionally connected (Amaral, Behniea, & Kelly, 2003; Fairhall & Ishai, 2007), but can act independently. When the visual cortex is damaged, the amygdalar response to emotional stimuli is unaltered (Morris, DeGelder, Weiskrantz, & Dolan, 2001; Vuilliemier et al., 2002). However, when the amygdala is damaged, the fear-related increase in the visual cortex is not observed, suggesting that the amygdala is required for this response (Vuilliemier, Richardson, Armony, Driver, & Dolan 2004).

Emotional stimuli can be masked below conscious perception by using a process called backward masking. An emotional stimulus, the target, is shown for

a brief amount of time, between 10 and 30 milliseconds (ms), and is immediately followed by a neutral stimulus, the mask, for a longer period of time, typically between 100 and 500 ms. Despite backward masking preventing conscious awareness of the target stimuli, fMRI studies have shown that the amygdala responds more strongly when the target is expressing fear, compared to when the target is expressing neutral or positive emotions (Morris et al., 1998; Whalen et al., 1998).

Using masked emotional faces as opposed to overtly presented emotional faces has distinct advantages, particularly when studying patients with PTSD. Firstly, it reduces the impact of cortical regions, such as the anterior cingulate cortex (ACC) and medial prefrontal cortex (PFC), from modulating amygdala activity, as these and other prefrontal regions have been shown to be involved in conscious emotional processing (Etkin, Egner, & Kalisch, 2011; Shin et al., 2005). In addition, PTSD symptom severity has been shown to correlate with amygdala activity in response to fearful faces, but only when stimuli are masked below conscious perception (Armony, Corbo, Clement, & Brunet, 2005; Rauch et al., 2000; Shin et al., 2005).

One of the aims of this work was to expand on the findings of previous research to determine if there were differences in the response between extrastriate cortex BOLD signal and the P1 ERP in veterans with and without PTSD, in response to backwardly masked affective faces. An additional objective was to determine if a linear relationship between extrastriate cortex BOLD signal and the P1 ERP was present. The final aim was to examine the influence of

combat exposure on the BOLD signal of the amygdala and extrastriate cortex in response to masked affect in both veterans with and without PTSD.

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CHAPTER 2

COMBAT VETERANS WITH PTSD DISPLAY DIFFERENCES IN THE RESPONSE TO MASKED AFFECT USING EEG AND FMRI

Abstract

Posttraumatic stress disorder (PTSD) affects millions of Americans and has a particularly high prevalence among combat veterans. Previous work using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) has shown that the response to masked emotional stimuli is altered in veterans with PTSD. However, to date, no one has used both methodologies to examine the response to masked affect in combat veterans. It is also unclear if the extent of combat exposure influences the response to masked affect in veterans with PTSD, as well as veterans without PTSD.

A group of 15 veterans with PTSD and a control group of 12 veterans without PTSD were shown masked fearful, happy, and neutral faces while undergoing EEG recording and, separately, fMRI scanning. The P1 event-related potential (ERP), collected during EEG recording, and blood oxygen level dependent (BOLD) signal of the amygdala and extrastriate cortex, measured while subjects underwent fMRI scanning, were used to determine whether there were differences between veterans with and without PTSD in response to

masked affect. The Combat Exposure Scale (CES) was used to determine if the degree of combat exposure influenced the response to masked affect in either group.

Veterans with PTSD, compared to veterans without PTSD, exhibited increased right extrastriate BOLD signal in response to masked happy faces (p = .018). In addition, the veterans with PTSD displayed decreased right hemisphere P1 ERP amplitude for all three emotional conditions (Fear: p = .002; Happy: p < .001; Neutral: p = .010). Both veteran groups failed to display significant relationships between P1 ERP amplitude and extrastriate BOLD activity. The veteran group with PTSD displayed a negative relationship between the degree of combat exposure and bilateral extrastriate BOLD signal, but only in response to masked fearful faces. The veteran group without PTSD exhibited a negative relationship between the extent of combat exposure and right amygdala BOLD signal for masked fear, happy, and neutral faces. When using ANCOVA to control for the degree of combat exposure, the veteran group with PTSD displayed significantly greater right amygdala BOLD activity in response to fearful and happy masked faces, and greater bilateral extrastriate cortex BOLD signal when shown fearful, happy, and neutral masked faces.

These findings indicate a right hemispheric visual processing alteration in veterans with PTSD, evident using both EEG and fMRI. However, the direction of these effects differed between methodologies, likely reflecting the differences in temporal resolution between the two methods and highlighting the importance of multimodal imaging in clinical populations. Additionally, a relationship between

the degree of combat exposure and the response to masked affect was observed, which differed depending on PTSD diagnosis. When controlling for the extent of combat exposure, the veteran group with PTSD displayed increased right amygdala activity in response to emotion, and a general hyperactivity of the bilateral extrastriate cortex compared to the veteran group without PTSD. These findings support previous work in which alterations in the processing of masked affect is present in veterans with PTSD, extending these findings by displaying this effect using both EEG and fMRI. Finally, these findings provide strong evidence that the degree of combat exposure influences the neuronal response to masked affect in veterans with and without PTSD.

Introduction

Posttraumatic Stress Disorder (PTSD) occurs at some point in the lifetime of roughly 7% of individuals in the United States (Kessler, Sonnega, Hughes, & Nelson, 1995; Kessler et al., 2005), with the lifetime prevalence among those in the military being even higher, with some estimates above 20%, in large part due to the effects of combat exposure (Fulton et al., 2015; Kang, Natelson, Mahan, Lee, & Murphy, 2003; Kulka et al., 1990; Tanielian & Jaycox, 2008; U.S. Census Bureau, 2014). PTSD is associated with a number of disruptive symptoms including nightmares, panic attacks, hyperarousal, aversion to trauma-related situations, and flashbacks (Sher, 2004).

When considering recent OEF/OIF/OND veterans, there is a concern among experts that the limited time between deployments, as well as the length

of deployments, may relate to the high incidence of PTSD in these individuals (American Psychological Association, 2007; MacGregor, Han, Dougherty, & Galarneau, 2012). The clinical and biological correlates of PTSD have been difficult to study due to the high prevalence of comorbid diagnoses, including depression, suicide, and traumatic brain injury, among others (Depue et al., 2014; Flory & Yehuda, 2015; Legarreta et al., 2015; Rytwinski, Scur, Feeny, & Youngstrom, 2013). Additionally, PTSD is heterogeneous, and even in studies that are limited to veterans, there is evidence of differing symptom profiles depending on the kind of trauma that triggers the disorder (Graham et al., 2016). This adds to the challenge of studying PTSD. The high prevalence of PTSD among veterans and the lack of a clear understanding of the disorder is why additional PTSD research in veteran populations is needed. The goal of this research is to more fully understand the neurobiological changes associated with PTSD, particularly in the visuosensory and affective networks, through the use of masked emotional stimuli. This research was performed with the objective of contributing to the identification of neuronal markers that can detect individuals at risk for developing PTSD before it is acquired.

In addition, this study aimed to evaluate the quantifiable influence of the degree of combat exposure on the neuronal response to masked affect in veterans with and without PTSD. This area of research is important, as experiencing combat in and of itself is associated with a number of negative health outcomes. Those with a greater extent of combat exposure and multiple deployments are more likely to use alcohol, nicotine, and illicit substances

(Hermes et al., 2012; Jacobson et al., 2008; Larson, Wooten, Adams, & Merrick, 2012), have a higher prevalence of hypertension (Granado et al., 2009), and have an increased incidence of one or more mental health diagnoses. According to the Veterans Association (VA), between October 2001 and June 2015, 58% of the 1.21 million Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND), veterans who sought treatment through the VA health care system were diagnosed with a mental disorder (VA Office of Public Health, 2017). Even in those who do not develop PTSD, combat exposure may influence the brain's response to emotional stimuli, negatively impacting the lives of these individuals, who are not necessarily being given treatment or support. Thus, there is a great need for research that attempts to determine if the degree of combat exposure has any effect on the brain, behavior, or psychology of veterans with and without diagnosed psychiatric disorders.

Functional Magnetic Resonance Imaging (fMRI) uses the principles of MRI to measure the amount of blood oxygen in different areas of the brain (Buxton, 2013). When the brain is active, it requires large amounts of oxygen, which is removed from the blood stream by neurons and glia (Kim & Ogawa, 2012). When oxygen is resupplied to the area, there is an overshoot in the amount of oxygen needed and, for a brief time, the area contains more oxygenated hemoglobin than elsewhere in the brain, referred to as the blood oxygen level dependent (BOLD) response (Ogawa, Lee, Kay, & Tank, 1990).

Early fMRI studies showed that the amygdala, a limbic region involved in emotional processing, emotional memory formation, and fear conditioning

(LeDoux, Cicchetti, Xagoraris, & Romanski, 1990; Phelps, 2004; Sergerie, Chochol, & Armony, 2008), is hyperactive in individuals with PTSD (Hendler et al., 2003; Rauch et al., 2000; Shin et al., 2005). Increased amygdalar activity in individuals with PTSD has been shown to be associated with PTSD symptoms, including hyperarousal (Ronzoni, Arco, Mora, & Segovia, 2016), flashbacks to the traumatic event (Rauch et al., 1996), and difficulties with emotional processing (Bruce et al., 2013). The amygdala is part of the subcortical limbic system and responds most strongly to emotional stimuli. It is often associated with an internal alarm system that orients a person to prospective danger in the environment and is strongly linked with fear conditioning and the formation of fearful memories (LeDoux, 2012; Ohman, 2005).

Evidence suggests that combat-exposed individuals without a diagnosis of PTSD exhibit increased amygdala activity in response to emotional stimuli. Simmons and colleagues (2011) used functional MRI (fMRI) to show that a combat-exposed veteran group with no Axis I diagnoses, including PTSD, produced exaggerated amygdala activity in response to angry, happy, and fearful faces compared to a group of healthy civilians. A veteran group with PTSD displayed a fear-specific amygdalar enhancement, above and beyond both the civilian group and the group of veterans without PTSD. These findings indicate the presence of an amygdalar hyperresponsivity to fear in participants with PTSD, but also an amygdalar hyperresponsivity to facial stimuli that may be related to the degree of combat exposure, regardless of PTSD diagnosis.

Another region that has shown alterations in BOLD activity between

individuals with and without PTSD, and which is particularly important in visual studies, is the extrastriate cortex (Hendler et al., 2003; Jatzko, Scmitt, Demirakca, Weimer, & Braus, 2005; Mueller-Pfeiffer et al., 2013; Williams et al., 2006). The extrastriate cortex is part of the visual cortex and is responsible for processing visual information including faces. This predominately occurs in the fusiform face area, located in the fusiform gyrus. Because faces are processed in the extrastriate cortex makes it an ideal target when using emotional faces as stimuli.

Similar to the amygdala, the extrastriate cortex responds more strongly to emotional expressions (Vuilleumier, Armony, Driver, & Dolan, 2001; Vuilleumier et al., 2002). In addition, the two regions are structurally connected (Amaral et al., 2003), and lesion studies provide additional evidence that the amygdala is functionally connected to the extrastriate cortex during emotional facial processing. Vuilleumier et al. (2004) observed that when the amygdala is damaged, the typical increase in extrastriate BOLD signal in response to fearful faces is not observed.

Jatzko and colleagues (2005), as well as Mueller-Pfeiffer and associates (2013), observed reduced extrastriate cortex activity in individuals with PTSD, while Hendler and collaborators (2003) and Williams and colleagues (2006) found that extrastriate cortex activity was increased in individuals with PTSD. The noted divergences in the findings of these papers highlight the need for further research into the visuosensory processes of visual information in the extrastriate cortex in individuals with PTSD.

In addition to fMRI, electroencephalography (EEG) has also been used to study the response to emotional stimuli. EEG measures global brain activity from the surface of the head. These signals often are driven by pyramidal neurons that are oriented perpendicular to the surface of the skull (Olejniczak, 2006; Pfurtscheller & Silva, 1999). Event-related potentials (ERPs) are a measure of the EEG response produced by a specific stimulus (Luck, 2014). When healthy control subjects are shown fearful stimuli, such as trauma-related words, trauma-related images, or fearful faces, an amplified positive event-related potential (ERP) is recorded approximately 120 ms later over the posterior portion of the head, referred to as the P1 ERP (Luo, Feng, He, Wang, & Luo, 2010; Pourtois, Dan, Granjean, Sander, & Vuilleumier, 2005; Pourtois, Grandjean, Sander, & Vuilleumier, 2004).

This response is augmented in individuals with high trait anxiety and those diagnosed with anxiety disorders (Frenkel & Bar-Haim, 2011; Rossignol et al., 2012). Evidence from studies using source localization suggests the extrastriate cortex is the primary generator of the P1 ERP (Di Russo, Martinez, & Hillyard, 2003; Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002; Pourtois et al., 2004). Therefore, we chose to study the P1 ERP, as it provided a complementary measure of extrastriate cortex activity in response to masked affective faces, and has been shown to be altered in individuals with anxiety disorders.

Both EEG and fMRI methods have been employed separately to study subliminal fearful stimuli in healthy and patient populations including a range of anxiety disorders (Felmingham, Bryant, & Gordon, 2003; Killgore et al., 2014;

Klimova, Bryant, Williams, & Felmingham, 2013); however, no investigation has examined the response to masked emotional stimuli using both of these methods in the same study cohort. We aimed to expand on the findings of previous research to determine if there was a relationship between extrastriate BOLD signal and the P1 ERP in response to masked fearful faces, particularly in a sample of veterans diagnosed with PTSD. We hypothesized that veterans with PTSD would display significant differences in BOLD activity in the extrastriate cortex and, additionally, would exhibit significantly different P1 ERP amplitude in response to masked affective faces. We also hypothesized that extrastriate BOLD activity and P1 ERP amplitude in response to masked affective faces would correlate significantly.

Materials and Methods

Subjects

The Institutional Review Boards at the George E. Wahlen VA Medical Center and the University of Utah approved this study. All subjects provided written informed consent prior to participation in the study. A total of 27 subjects were recruited through the George E. Wahlen Department of Veterans Affairs (VA) Medical Center and the surrounding community. Prior to admittance into the study, participants completed a phone screen for inclusion and exclusion criteria with an experienced staff member (EB). Volunteers were included in the study if they were male veterans between the ages of 18-55. Exclusionary criteria included major sensorimotor deficits (e.g., blindness, deafness, paralysis),

estimated full-scale IQ below 80, history of autism, claustrophobia, schizophrenia or other psychotic disorders, anorexia nervosa or bulimia, history of electroconvulsive therapy, current substance abuse, or the presence of any metal fragments or implants that would be contraindicated in an MRI. Twelve subjects were categorized as controls (non-PTSD) and 15 subjects were categorized as PTSD (lifetime) using the DSM-IV (American Psychiatric Association, 1994).

Assessment Measures

Clinical measures were performed by a licensed clinician with extensive experience in working with a veteran population (ML). The Structured Clinical Interview for DSM-IV Patient Version (SCID-I/P; First, Spitzer, Gibbon, & Williams, 2002) was used to determine the presence of Axis I disorders. The Hamilton Anxiety Inventory (HAM-A; Hamilton, 1959) and Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) were used to evaluate the severity of symptoms of anxiety and depression symptoms, respectively. The State and Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, & Jacobs, 1983) was used to assess trait anxiety. The Clinician Administered PTSD Scale for DSM-IV (CAPS; Blake et al., 1995) was used to measure PTSD symptom presence and symptom severity. The Combat Exposure Scale (CES; Keane, Fairbank, Caddell, Zimmering, & Al, 1989) was utilized to measure the extent of combat exposure reported by study participants.

Magnetic Resonance Imaging Acquisition

All subjects were scanned using a Siemens Trio 3T MRI system at the University Neuropsychiatric Institute in Salt Lake City, Utah. Before scanning, subjects confirmed the absence of metal implants, pacemakers, or any internal object that could influence data collection or be dangerous for personnel or subjects. Participants were guided onto the MRI machine table and a trained technician placed a 12-channel head coil around the head of the subject. A T1-weighted 3D MPRAGE GRAPPA (TE = 3.42 ms, TR = 2 s, TI = 1.1 s, flip angle = 8°, 256 x 256 acquisition matrix, 256 mm^2 FOV, 160 slices, 1 mm slice thickness) was used for the structural scan. The masked emotional faces paradigm was performed during a BOLD EPI sequence (TE = 28 ms, TR = 2, flip angle = 90°, acquisition matrix = 64 x 64, FOV = 220 mm, 40 slices, 3 mm slice thickness). Subjects viewed the task using a mirror placed on the head coil, which allowed them to see the task projected onto a screen at the back of the scanner. After scanning, images for each subject were read by a neuroradiologist to rule out gross pathology.

FMRI data were analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). Images were converted from the original DICOM format to the NIFTI format using the built-in SPM tool. Next, images were realigned, coregistered to each subject's structural image, normalized to MNI space, resliced into 2 mm voxels, and smoothed with a 6 mm Gaussian kernel. One control subject was excluded from further analyses due to movement greater than 3 mm. During first-level analyses, each subject's images were

convolved with a canonical hemodynamic response (HRF) function. Serial correlations were corrected using an autoregressive model. A high-pass filter of 128 seconds was used to remove the effects of scanner drift, as well as physiological changes over the course of each scanning session. Contrast images for each condition were created for each subject and used for second-level analyses. Second-level analyses were composed of one-sample *t* tests, using the contrast images for each condition, for each subject. The resulting images, one for each condition, were used to extract region of interest (ROI) parameter estimates (Poldrack, 2007). ROI masks of left hemisphere and right hemisphere Brodmann areas 18 and 19 based on the Talairach Daemon atlas (Lancaster, Summerlin, Rainey, Freitas, & Fox, 1997; Lancaster et al., 2000), were made using the Wake Forest Pick Atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003), and used to extract BOLD signal for each condition using the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002). Mean intensity values for each ROI, for each condition, for each individual, were then imported into SPSS 20. Within SPSS, parameter estimates for left and right Brodmann areas 18 and 19 were averaged to derive an extrastriate BOLD signal measure, as these Brodmann areas have been shown to align with the extrastriate cortex (Kastner, De Weerd, Desimone, & Ungerleider, 1998; Rottschy et al., 2007).

Event-Related Potential Recording

EEG data were acquired continuously using a 136-channel amplifier (ANT Neuro, Netherlands) at a sampling rate of 2048 Hz, and re-referenced offline to

an average reference. A breathable and flexible Waveguard cap (ANT Neuro), embedded with 128 small, sintered Ag/AgCl electrodes, was placed on the head of each subject. The cap was positioned such that the electrodes adhered to the extended 10-20 system. Grass EC2 electrode cream was used to reduce the resistance between the scalp and electrodes. The impedance for each electrode was observed to be below 50 kOhm before EEG recording began. Eye movements were monitored using two electrooculogram (EOG) electrodes. EOG electrodes were placed 1 cm above and 1 cm below the right eye to measure eye movement and blinking.

EEG data were analyzed offline using the Brainstorm toolbox (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011). First, signals were passed through a bandpass filter, which kept data that was between 0.1 Hz and 30 Hz. Next, signal space projection was used to detect eye blink-related components and remove them. Afterwards, events were divided into epochs: 100ms before to 700 ms after the initial masked facial stimuli were displayed. Epochs were then baseline corrected for the 100 ms preceding stimulus presentation (Eimer & Kiss, 2007; Holmes, Nielsen, & Green, 2008; Rossignol et al., 2012). Trials were removed from analysis if any electrodes over the occipital or parietal cortex displayed activity less than -60 uV or greater than 60 uV (Holmes et al., 2008). One veteran with PTSD and one veteran without PTSD were removed from analyses because less than 50 trials remained after trial removal. Trials were then averaged within each condition and P1 peak amplitudes and latencies were extracted using MATLAB and imported into SPSS 20. In SPSS, P1 ERP amplitudes were three

left hemisphere electrodes (O1, PO7, P7) were averaged for each subject to create an average left hemisphere P1 measure. The same procedure was performed on right hemisphere electrodes (O2, PO8, P8).

Masked Faces Paradigm

Stimuli were composed of black and white images of five male and five female actors, taken from the Ekman set of facial photographs (Ekman & Friesen, 1976). A masked emotional face, either fearful, happy, or neutral, was presented for 16.7 ms, and followed by an image of the same actor with a neutral expression for 183.3 ms. Neutral masked images were flipped 90 degrees to ensure there were differences between the target and the mask, even in the neutral condition. A fixation cross was then presented for 1800 ms, during which time subjects were instructed to press the button under their index finger if they believed the person was a male and to press the button under their middle finger if they thought the person was a female. In total, each trial lasted for a total of 2000 ms.

Runs were comprised of emotional blocks ordered pseudo-randomly, such that every three blocks contained one fear block, one happy block, and one neutral block. Within blocks, stimuli were presented randomly without replacement, so that each actor was shown once per block. Each block lasted for a total of 20 seconds. During fMRI scanning, the task was composed of 6 blocks per condition, for a total of 18 blocks and a total running time of 6 minutes. During EEG recording, each block also lasted for a total of 20 seconds. The task

was composed of 10 blocks per condition, for a total of 30 blocks, lasting for 10 minutes. The neuroimaging acquisition techniques were randomized among subjects. More blocks were performed during EEG recording due to a priori knowledge that eye blinks and movement would prevent the use of a portion of EEG trials. During analysis, trials were divided by condition into fear, happy, and neutral groups.

Statistical Analysis

After data were entered into SPSS, Shapiro-Wilk tests for normality were performed on each variable, for each group, to determine if independent sample *t* tests, which assume a normal distribution, could be performed. If the Shapiro-Wilk test provided evidence that both variables were normally distributed, independent group two-sample *t* tests were performed between the veteran group with PTSD and the veteran group without PTSD. If a variable, for either group, was determined not to be normally distributed based on the Shapiro-Wilk test, nonparametric Mann-Whitney U tests were performed to determine if between group effects were significant.

Pearson correlations were performed as part of an exploratory analysis to investigate the relationship between extrastriate BOLD signal and P1 ERP amplitude. If either variable was not normally distributed according to the Shapiro-Wilk test, Spearman Rho correlations were implemented instead. Pearson correlations were also performed to compare the relationship between amygdala and extrastriate BOLD signal, as well as the relationship between the

extent of combat exposure and neuroimaging measures. ANCOVA, with to total score of the CES used as a covariate, was performed to determine group differences when controlling for the degree of combat exposure.

Results

Shapiro-Wilk Tests for Normal Distribution

In the control group, HAM-A ($W(11) = .570$, $p < .001$, Mean = 3.83, SD = 4.86, Skewness = 1.49, Kurtosis 1.25), and HAM-D, ($W(11) = .787$, $p = .006$, Mean = 2.67, SD = 4.72, Skewness = 2.99, Kurtosis = 9.48), were significant for the Shapiro-Wilk test for normality, indicating non-normality. For the group composed of veterans with PTSD, age was determined to not be normally distributed according to the Shapiro-Wilk test, $W(14) = .872$, $p = .044$. Left extrastriate BOLD signal, for the Happy condition, in the group consisting of veterans without PTSD, also was significant for the Shapiro-Wilk test, $W(11) = .839$, $p = .042$, as was right amygdalar BOLD signal, for the fear condition, in the group of veterans without PTSD, $W(11) = .839$, $p = .030$.

Demographics, Clinical and Behavior

Age and the number of years of education did not differ significantly between the two groups. The group of veterans with PTSD displayed significantly higher trait anxiety, based on the STAI, $t(24) = 4.38$, $p < .001$. This group also displayed greater HAM-A, $U = 18$, $p < .001$, and HAM-D scores, $U = 13$, $p < .001$. Finally, the group of veterans with PTSD displayed a significantly greater degree

of combat exposure, based on the total score of the CES, $t(25) = 2.95$, $p = .007$. The reports of two subjects without PTSD failed to reach the threshold for the minimal extent of combat exposure using the CES, resulting in these subjects receiving scores of zero. Veterans with and without PTSD failed to display behavioral differences in accuracy or response time when identifying the gender of the facial stimuli that were presented to them during EEG recording and fMRI scanning. Demographic and behavioral measure statistics can be found in Table 2.1.

ERP Group Differences

The veteran group with PTSD ($N = 14$) displayed significantly reduced P1 ERP amplitudes for all three conditions compared to the veteran group without PTSD ($N = 11$) at electrodes positioned over the right hemisphere (Fear: $t(23) = -3.92$, $p = .002$; Happy: $t(23) = -4.38$, $p < .001$; Neutral: $t(23) = -3.06$, $p = .010$). Electrodes located over the left hemisphere failed to display group differences in P1 ERP amplitude. These results are summarized in Table 2.2.

BOLD Parameter Group Differences

The veteran group with PTSD displayed significantly increased BOLD signal in the right extrastriate region, for the Happy condition, $t(24) = 2.54$, $p = .018$, although activation in the region was not significantly different between groups for the Fear or Neutral conditions. Left extrastriate activity was not significantly different between groups for any condition. In addition, no group

differences were observed for the left or right amygdala for any of the three conditions. These results can be seen in Table 2.3.

Relationship Between Extrastriate BOLD Signal and P1 ERP Amplitude

Pearson correlation coefficients were used to test the linear relationship between the P1 ERP and extrastriate BOLD signal. Spearman's rho rank correlation, a nonparametric correlation test that does not require both variables to be normally distributed, was used in cases where a variable failed the Shapiro-Wilk test for normal distribution. No significant correlations were observed between these measures within either group, for any of the three conditions. These results can be found in Table 2.4 and Table 2.5.

Relationship Between Amygdala and Extrastriate BOLD Signal

In the group of veterans with PTSD, right amygdala BOLD signal correlated positively with right extrastriate BOLD signal, $r(13) = .580$, $p = .023$ for the fear condition. A similar relationship between the right amygdala and right extrastriate cortex was observed for the happy condition, $r(13) = .523$, $p = .045$ but not the neutral condition.

For participants of the study without PTSD, right amygdala BOLD signal correlated positively with left, $r(9) = .643$, $p = .033$, and right extrastriate BOLD signal, $r(9) = .620$, $p = .042$, in the fear condition but not the happy or neutral conditions.

Correlation Between FMRI BOLD Activity and the Degree of Combat Exposure

The extent of combat exposure negatively correlated with left amygdala BOLD signal for the fear condition in the veteran group without PTSD, $r(9) = -.629$, $p = .038$ (Table 2.6). Moreover, this group exhibited significant negative correlations between right amygdala BOLD signal and the degree of combat exposure for all three emotional conditions; fear, $r(9) = -.763$, $p = .006$, happy, $r(9) = -.808$, $p = .003$, and neutral, $r(9) = -.641$, $p = .034$. No significant correlations were observed for the group of veterans without PTSD between the extent of combat exposure and extrastriate BOLD signal.

Veterans with PTSD displayed no significant relationships between amygdala activity and the degree of combat exposure. However, the veteran group with PTSD did display significant correlations between the extent of combat exposure and left extrastriate cortex, $r(13) = -.554$, $p = .032$, and right extrastriate cortex, $r(13) = -.567$, $p = .028$, for the fear condition.

ANCOVA With CES Total Score as a Covariate

When the extent of combat exposure was used as a covariate in multivariate ANCOVA to investigate group differences in amygdala and extrastriate BOLD signal, the groups displayed significantly different right amygdala BOLD signal for the fear, $F(1, 25) = 4.875$, $p = .037$ and happy conditions, $F(1, 25) = 9.747$, $p = .005$ (Table 2.7) with veterans with PTSD displaying increased activity compared to the veterans without PTSD. Veterans with PTSD also displayed increased activity in the left extrastriate cortex for the

fear, $F(1, 25) = 5.380$, $p = .030$, happy, $F(1, 25) = 11.713$, $p = .002$, and neutral conditions, $F(1, 25) = 7.548$, $p = .011$. Veterans with PTSD also exhibited increased activity for the right extrastriate cortex for the fear, $F(1, 25) = 7.155$, $p = .014$, happy, $F(1, 25) = 10.880$, $p = .003$, and neutral conditions, $F(1, 25) = 9.986$, $p = .004$.

Discussion

In this study, we observed that a group of veterans with PTSD exhibited reduced right hemisphere P1 ERP amplitude in response to masked emotional faces in comparison to a group of veterans without PTSD. We also found that veterans with PTSD displayed increased right hemisphere extrastriate BOLD signal in response to backwardly masked happy faces. Contrary to our hypothesis, we failed to find evidence that P1 ERP amplitude and extrastriate BOLD signal were related in either group.

The fMRI BOLD results of the present study suggest increased right hemisphere extrastriate activity in veterans with PTSD. Previous investigations studying the visual system of individuals with PTSD have been inconsistent. Some studies have observed reduced visual cortex activity, including the extrastriate cortex, in individuals with PTSD. For example, Jatzko et al. (2005) observed reduced left hemisphere parahippocampal and fusiform gyrus activity in civilians with PTSD in response to positive valence movie clips, and Mueller-Pfeiffer et al. (2013) reported reduced bilateral visual cortex activity in civilians with PTSD when viewing both positive and negative stimuli. In contrast, an

investigation by Bremner et al. (1999) found veterans with PTSD displayed increased blood flow in the right lingual gyrus, a region located in the extrastriate cortex when viewing traumatic images. However, none of these studies used facial stimuli or stimuli that were masked below conscious perception. Hendler et al. (2003) found that combat veterans with PTSD displayed increased activity in the lateral occipital complex (LOC) when viewing combat-related imagery, but only when stimuli were backwardly masked. Although this result was in the LOC, which is a higher order visual processing region as compared to the extrastriate cortex, the findings of Hendler et al. (2003) are consistent with greater activity in the associative visual cortex in PTSD. Given that the activation differences occurred only when combat images were displayed, the cortical activation may reflect a specific response to trauma-related imagery. The findings presented in the current study suggest a more generalizable extrastriate effect in response to emotional faces. However, when comparing the present study and the one reported in Hendler et al. (2003), different regions related to visual processing were examined, making it difficult to determine if the results are contradictory or represent the activity of different visual regions to masked stimuli. Similar to the present study, Williams et al. (2006) used emotional faces as stimuli. The authors found increased bilateral visual cortex BOLD activity in the extrastriate cortex (Brodmann areas 18 and 19) in civilians with PTSD in response to overt fearful stimuli. The current study supports the findings of increased extrastriate cortex activity in subjects with PTSD.

While the veteran group with PTSD displayed increased extrastriate BOLD

signal when compared to the veteran group without PTSD, the EEG results of the study indicated decreased right hemisphere P1 ERP amplitude. When taken together, previous studies of the ERP response to emotional facial stimuli in patients with PTSD are varied. Reports by MacNamara, Post, Kennedy, Rabinak, and Phan, (2013) and Shu et al. (2014) present conflicting results when displaying emotional faces overtly to combat veterans with PTSD. MacNamara et al. (2013) found that the vertex positive potential (VPP), an ERP associated with facial processing, was reduced in veterans with PTSD compared to veterans without PTSD in response to fearful, happy, and angry faces. Conversely, Shu et al. (2014) found an increased VPP for veterans with PTSD for negative and trauma-related images; however, faces were restricted to the eye region in the study. The differences in stimuli between the two studies, as well as the presence of comorbid mild traumatic brain injury (TBI) in the Shu et al. (2014) study, may explain the discrepancy in the results of the two studies. It also should be noted that MacNamara et al. (2013) and Shu et al. (2014) used overt facial stimuli, in contrast to the present study. The findings of the current study most closely correspond to those reported in MacNamara et al. (2013) and suggest a right hemisphere specific P1 ERP suppression when viewing facial stimuli.

Other studies have investigated the ERP response to facial affect stimuli in civilians with PTSD. Felmingham et al. (2003) found that, compared to a control group, participants with PTSD produced a smaller negative ERP at around 100 ms, the N1 ERP, in response to angry faces, for sensors placed over

the temporal cortex. The timeframe of this result was similar to the P1 ERP used in the present study. The authors of the study did not find evidence of a general processing deficit, but their results do suggest a dampened response to negative emotions in individuals with PTSD. Ehlers et al. (2006) found an enhanced N1 ERP in frontal electrodes in response to sad faces in civilians with PTSD, suggestive of hyperarousal in response to negative stimuli. A previous study also found evidence of a reduced P1 ERP in response to visual stimuli in veterans with PTSD. Kounios et al. (1997) observed that veteran participants with PTSD exhibited reduced right hemisphere P1 ERP amplitude in response to both threatening and neutral words. Similar to the current study, subject participants were not studied prior to the traumatic event that elicited PTSD symptomology, so it cannot be determined if this response predates the development of PTSD, stems from PTSD itself, or is a learned coping mechanism. Longitudinal EEG studies studying the response to stimuli before and after they acquire PTSD are necessary to study the chronology of this effect. While the findings from the current investigation are not able to address this because of the cross-sectional design, the results lend further support to the hypothesis of a PTSD-related sensory dampening, demonstrated by decreased right hemisphere P1 amplitude in response to visual stimuli.

Because the present study used faces as stimuli, it is possible that the observed effect is due to irregular facial processing in veterans with PTSD. When activity in the right fusiform gyrus is disrupted, the processing of faces is altered to a greater degree than when left fusiform gyrus activity is affected (Rossion et

al., 2003; Tsapkini, Vindiola, & Rapp, 2011). The fusiform face area (FFA), located within the fusiform gyrus, is so named due to the observation that this region demonstrates a preference for facial stimuli (Gauthier et al., 2000; Kanwisher, McDermott, & Chun, 1997). Damage to the right hemisphere FFA can result in prosopagnosia, a disorder in which patients are unable to recognize the faces of others (Renzi, Perani, Carlesimo, Silveri, & Fazio, 1994). In addition, EEG studies have found that faces produce greater activity in the right hemisphere than objects or words (Rossion et al., 2003). It should be noted, however, that some researchers dispute the theory that facial processing occurs primarily in the right hemisphere, and suggest that it is a bilateral process (Behrmann & Plaut, 2014; Levine, Banich, & Koch-Weser, 1988). Nevertheless, there is a large body of work, as detailed above, that indicates that facial processing occurs predominantly in the right hemisphere, which may explain the right hemisphere P1 ERP amplitude inhibition reported in the present study.

When investigating the within-group correlations between extrastriate BOLD signal and P1 ERP amplitude, no significant correlations were observed. The lack of a correlation between extrastriate BOLD signal and P1 ERP amplitude was unexpected as the P1 ERP has been shown to emanate from the extrastriate cortex (Di Russo et al., 2002; Di Russo et al., 2003). It is possible that the differences in temporal resolution played a role in the lack of a relationship between EEG and fMRI measures. Previous studies using simultaneous EEG and fMRI have found positive correlations between ERPs and extrastriate BOLD signal in response to facial stimuli (Iidaka, Matsumoto,

Haneda, Okada, & Sadato, 2006; Sadeh, Podlipsky, Xhdanov, & Yovel, 2010; Sadeh, Zhdanov, Podlipsky, Hendler, & Yovel, 2008). However, in the current study, EEG and fMRI were performed sequentially rather than simultaneously. Also, to date, no simultaneous EEG and fMRI studies have been performed that have studied the response to masked affect.

The significant relationship between the total score of the CES and BOLD signal in veterans with and without PTSD, presented in the current study, suggests that the extent of combat exposure influences brain activity long after combat is experienced, and this effect differs depending on the presence of PTSD. Veterans with PTSD displayed a negative correlation between the CES total score and bilateral extrastriate cortex activity in response to masked fear. This indicates a decrease in visuosensory activity in response to fearful imagery as the degree of combat exposure increases. A possible explanation for this effect may be associated with the vigilance-avoidance hypothesis (Mogg, Bradley, Miles, & Dixon, 2004; Mogg, Mathews, & Weinman, 1987). This theory details an initial hyperactivity quickly followed by hypoactivity in response to threatening or negative stimuli. A study that explored the time frame of this effect was performed by Adenauer and colleagues (Adenauer et al., 2010) using magnetoencephalography. The authors observed that in response to negative-valence images, individuals with PTSD produced exaggerated right hemisphere activity at around 150 ms, which was quickly followed by a sharp decrease in activity at around 230 ms. The authors postulated that the early hyperactivity was related to subcortical regions responding to the negative stimuli, while the

hypoactivity seen shortly after was evidence of disengagement from these stimuli.

The observed reduction in amygdala BOLD activation as the degree of combat exposure increased may reflect an amygdalar numbing or inhibition in subjects exposed to combat. It may also be an indication of resilience to traumatic stimuli, which may have helped to protect these individuals from developing PTSD after experiencing combat. This resilience may be the result of genetic factors that modulate amygdala activity in response to threat (Bertolino et al., 2005; Hariri et al., 2002); environmental influences, including past experiences, social support, and level of education (Bonanno, Galea, Bucciarelli, & Vlahov, 2007; Curtis & Cicchetti, 2003; Ozbay et al., 2007; Rutter, 2012); or epigenetic responses to trauma (Fleshner, Maier, Lyons, & Raskind, 2011; Russo, Murrough, Han, Charney, & Nestler, 2012). Most likely, it is a combination of these aforementioned factors, which is reflected by the present finding of a reduction in amygdalar activity in response to masked affect in veterans without PTSD as the extent of combat exposure increased.

Given the significant relationships observed between the degree of combat exposure and both amygdalar and extrastriate activity, the CES total score was used as a covariate in multivariate ANCOVA to investigate group differences in amygdalar BOLD signal. Group effects were observed in the right amygdala and bilaterally in the extrastriate cortex. The veteran group with PTSD produced significantly stronger activity than the participants without PTSD, after controlling for the total score of the CES. This finding indicates that the extent of

combat exposure may be mediating the response to masked affect, and therefore the observed lack of group differences.

While researchers have investigated the response to emotional faces in combat veterans with and without PTSD (Herringa, Phillips, Fournier, Kronhaus, & Germain, 2013; Rauch et al., 2000, Simmons et al., 2011), few have attempted to examine how variation in the degree of combat exposure impacts the neuronal response to emotional stimuli. Rauch et al. (2000) did not observe a relationship between the extent of combat exposure and amygdala BOLD signal in response to masked fearful faces. However, the sample in Rauch et al. (2000) included eight veterans with PTSD and eight veterans without PTSD, which may have restricted the power of the study. Simmons et al. (2011) did not explicitly report correlations between BOLD signal and the degree of combat exposure, but the authors found that in response to overt facial stimuli, a group of veterans without PTSD displayed amygdala activity that was similar to a veteran group with PTSD. Finally, Herringa et al. (2013) found a positive correlation between the extent of combat exposure and dorsal anterior cingulate cortex (ACC) activity when veterans with a range of posttraumatic stress symptoms (PTSS) viewed overt angry faces. In the sample, the degree of combat exposure was significantly related to PTSS; however, no group comparisons were performed as subjects were studied as one sample. The dorsal ACC was not an ROI in the present investigation, but its relationship to both the amygdala and the extent of combat exposure (Herringa et al., 2013; van Wingen, Geuze, Vermetten, & Fernandez, 2011) make it a target for future investigations studying the influence of combat

on neuronal activity.

Combat differs from other types of acute traumas that can lead to PTSD, such as car accidents, natural disasters, and terrorist attacks, because it can take place over months or years. Combat often involves repeated trauma over prolonged periods, making it more similar to complex trauma such as child abuse and domestic violence. Previous work has found that long-term stress leads to decreased long-term potentiation (LTP) in the hippocampus (Artola et al., 2006), alterations in cortisol and norepinephrine functioning (Bremner, 2006), as well as changes in functional connectivity throughout the brain (Nephew, Huang, Poirier, Payne, & King, 2017). It is likely that combat elicits some or all of these changes, which lead to the results of the present investigation.

Limitations and Future Directions

There are several limitations that should be considered in interpreting the results of this study. The number of participants in each group was modest, limiting the statistical power and generalizability of the study results. Furthermore, subjects were not matched for the degree of combat exposure, which may have influenced the results. Another limitation was that we did not include a healthy civilian control group who had not experienced combat or trauma. Previous studies have shown alterations between combat veterans without PTSD and control subjects who have not experienced combat. Therefore, including a control group of civilians may have provided greater insight into how the extent of combat exposure influenced the response to masked affect

(Simmons et al., 2011). Additionally, EEG and fMRI were not performed concurrently, although they were performed on the same day. Future studies may attempt to perform this task during simultaneous EEG/fMRI, despite disadvantages such as artifacts (Huster, Debener, Eichele, & Herrmann, 2012; Yan, Mullinger, Brookes, & Bowtell, 2009).

Our masked faces paradigm also had a few limitations. Firstly, it did not include angry faces, which have been used previously in PTSD research and shown unique effects in individuals with PTSD (Felmingham et al., 2003). Also, facial stimuli were the only type of stimulus used in our paradigm, so we were unable to determine if the effects seen in this manuscript were because of a general response to visual stimuli or a specific response to facial stimuli. Future studies could examine if the effects seen in the present study are observed when faces are presented overtly, as the present study only investigated masked emotional faces.

During the masked faces paradigm, subjects were instructed to perform a gender discrimination task and press a button in response to the gender of the person displayed. We used this task to determine if subjects were paying attention to the stimuli, distract them from the actual task, and gauge behavioral response times. Nevertheless, it is possible that the act of planning the button press, performing the button press, or determining the gender of the individual on the screen influenced the results of the study in some way. Future studies could perform an additional passive viewing task where no button presses are required and no gender discrimination is performed. Finally, we did not modulate the

amount of time the masked faces were displayed; target stimuli were always presented for 16.7 ms. This time period used because it was the shortest possible duration due to the refresh rate of the paradigm computer monitor, and therefore was the least likely to produce conscious processing of masked stimuli. By using the same display length between trials, we were able to reduce the amount of variance as much as possible. However, future studies may elect to study how variations in target display length influence the neuronal response to masked emotion in individuals with PTSD.

The impact of other brain regions, including the amygdala and prefrontal cortex, which have both been shown to modulate activity in the extrastriate cortex during similar tasks, bears consideration (Barcelo, Suwazono, & Knight, 2000; Rotshtein et al., 2010). Future studies should investigate activity in these distal yet functionally connected regions to determine if the effects seen in the present study are restricted to the extrastriate cortex or extend elsewhere. Further, a number of the veterans in the study with PTSD were diagnosed with comorbid disorders, such as depression and history of substance abuse. The effects of comorbid diagnoses on these results, although not part of our initial hypotheses, requires future study.

Conclusion

To our knowledge, this was the first experiment to study surface EEG brain patterns in response to masked emotional faces in a veteran population with PTSD. In addition, it was also the first to directly compare EEG and fMRI

results during a masked facial affect paradigm. The results suggest a sensory dampening in response to masked facial stimuli in veterans with PTSD that is evident using EEG. This sensory dampening was not reflected by extrastriate cortex BOLD signal, which was increased in veterans with PTSD, possibly due to differences in temporal resolution between the two methodologies.

This study also found associations between neuronal activity in response to masked emotional stimuli and the total score of the CES. The regions that displayed relationships with the degree of combat exposure differed based on PTSD diagnosis. Veterans with PTSD displayed a significant correlation between extrastriate cortex BOLD activity and the extent of combat exposure, while veterans without PTSD exhibited a significant correlation between amygdala BOLD activity and the CES total score. In both groups, the degree of combat exposure was most strongly associated with regional activation in response to masked fear. Repeated combat exposure, and the associated neurobiological and psychological effects, in combination with genetic influences, may be the root cause of the change in BOLD activation seen in the present investigation.

This study demonstrates that veterans with PTSD can be differentiated using both EEG and fMRI and allows for the opportunity to use these methodologies to study individuals at risk for developing PTSD as well as to monitor treatment efficacy in those who have developed the disorder. It also highlights the influence of combat exposure on the neuronal activity of veterans with and without PTSD and the importance of accounting for the extent of combat exposure when studying veterans.

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Table 2.1

Summary of demographics and clinical measures

	PTSD		Control		Significance
	M	*SD*	*M*	*SD*	
Age	38.9	8.47	38.2	11.07	*P* = .840
Education	14.4	1.45	14.8	1.90	*P* = .508
HAM-A	12.7	5.35	3.8	4.86	***P* < .001**
HAM-D	11.9	5.56	2.7	4.72	***P* < .001**
STAI-Trait	51.4	13.39	32.6	6.99	***P* < .001**
CES Total Score	18.2	6.95	9.3	8.45	***P* = .007**

Note. Bolded signifies significance < .05

Table 2.2

P1 ERP group differences

	PTSD		Control		Significance
	M	*SD*	*M*	*SD*	
Left Hemisphere Fear Amplitude	2.49	1.62	3.38	1.70	*P* = .212
Right Hemisphere Fear Amplitude	1.69	1.76	4.63	1.72	***P* = .002**
Left Hemisphere Happy Amplitude	2.89	1.36	3.36	1.55	*P* = .519
Right Hemisphere Happy Amplitude	1.86	1.55	4.67	1.08	***P* < .001**
Left Hemisphere Neutral Amplitude	2.58	2.29	3.23	1.09	*P* = .288
Right Hemisphere Neutral Amplitude	1.93	1.09	4.62	2.06	***P* = .010**

Note. Bolded signifies significance < .05

Table 2.3

Extrastriate and amygdala BOLD signal group differences

	PTSD		Non-PTSD		Significance
	M	*SD*	*M*	*SD*	
Left Amygdala BOLD Fear	.191	.506	.224	.813	*P* = .901
Right Amygdala BOLD Fear	.202	.477	.124	.684	*P* = .540
Left Amygdala BOLD Happy	.228	.571	.236	.798	*P* = .978
Right Amygdala BOLD Happy	.244	.413	-.008	.406	*P* = .134
Left Amygdala BOLD Neutral	.169	.539	.247	.753	*P* = .759
Right Amygdala BOLD Neutral	.298	.471	.203	.489	*P* = .622
Left Extrastriate BOLD Fear	.107	.601	-.066	.592	*P* = .469
Right Extrastriate BOLD Fear	.228	.577	-.012	.634	*P* = .323
Left Extrastriate BOLD Happy	.170	.516	-.241	.319	*P* = .061
Right Extrastriate BOLD Happy	.315	.314	-.166	.529	***P* = .018**
Left Extrastriate BOLD Neutral	.107	.520	-.186	.428	*P* = .139
Right Extrastriate BOLD Neutral	.268	.475	-.094	.467	*P* = .064

Note. Bold signifies significance < .05

Table 2.4

Relationship between extrastriate BOLD signal and P1 ERP amplitude – veteran group with PTSD

	Left P1 ERP Fear	Right P1 ERP Fear	Left P1 ERP Happy	Right P1 ERP Happy	Left P1 ERP Neutral	Right P1 ERP Neutral
Left Extrastriate BOLD Fear	*r* = -.088 *p* = .765					
Right Extrastriate BOLD Fear		*r* = -.282 *p* = .329				
Left Extrastriate BOLD Happy			*r* = -.058 *p* = .843			
Right Extrastriate BOLD Happy				*r* = -.107 *p* = .716		
Left Extrastriate BOLD Neutral					*r* = .035 *p* = .904	
Right Extrastriate BOLD Neutral						*r* = -.074 *p* = .801

Pearson correlation unless otherwise noted

Table 2.5

Relationship between extrastriate BOLD signal and P1 ERP amplitude – veteran group without PTSD

	Left P1 ERP Fear	Right P1 ERP Fear	Left P1 ERP Happy	Right P1 ERP Happy	Left P1 ERP Neutral	Right P1 ERP Neutral
Left Extrastriate BOLD Fear	*r* = .092 *p* = .801					
Right Extrastriate BOLD Fear		*r* = -.562 *p* = .072				
Left Extrastriate BOLD Happy			*rho* = .430 *p* = .214 (Spearman)			
Right Extrastriate BOLD Happy				*r* = -.009 *p* = .980		
Left Extrastriate BOLD Neutral					*r* = .010 *p* = .978	
Right Extrastriate BOLD Neutral						*r* = -.365 *p* = .269

Pearson correlation unless otherwise noted

Table 2.6

Pearson correlations between combat exposure and BOLD signal

	PTSD		Non-PTSD	
Source	Pearson's *r*	Significance	Pearson's *r*	Significance
Left Amygdala BOLD Fear	.043	.880	-.629	**.038**
Right Amygdala BOLD Fear	-.398	.142	-.763	**.006**
Left Amygdala BOLD Happy	.162	.564	-.471	.144
Right Amygdala BOLD Happy	-.312	.257	-.808	**.003**
Left Amygdala BOLD Neutral	.031	.913	-.530	.094
Right Amygdala BOLD Neutral	-.410	.129	-.641	**.034**
Left Extrastriate BOLD Fear	-.554	**.032**	-.529	.094
Right Extrastriate BOLD Fear	-.567	**.028**	-.546	**.**082
Left Extrastriate BOLD Happy	-.476	.073	-.460	**.**154
Right Extrastriate BOLD Happy	-.442	.099	-.299	.372
Left Extrastriate BOLD Neutral	-.480	.070	-.464	.150
Right Extrastriate BOLD Neutral	-.490	.064	-.452	.163

Note. Bold signifies significance < .05

Table 2.7

Analysis of covariance with combat exposure as covariate

Source	Sum of Squares	*df*	Mean Square	*F*	Partial Eta squared
Left Amygdala BOLD Fear	.250	1	.250	.639	.027
Right Amygdala BOLD Fear	1.071	1	1.071	**4.875**	.175
Left Amygdala BOLD Happy	.089	1	.089	.194	.008
Right Amygdala BOLD Happy	1.217	1	1.217	**9.747**	**.**298
Left Amygdala BOLD Neutral	.076	1	.076	.194	.008
Right Amygdala BOLD Neutral	.692	1	.692	3.960	.147
Left Extrastriate BOLD Fear	1.419	1	1.419	**5.380**	.190
Right Extrastriate BOLD Fear	1.867	1	1.867	**7.155**	.237
Left Extrastriate BOLD Happy	1.936	1	1.936	**11.713**	.337
Right Extrastriate BOLD Happy	2.218	1	2.218	**10.880**	.321
Left Extrastriate BOLD Neutral	1.448	1	1.448	**7.548**	.247
Right Extrastriate BOLD Neutral	.806	1	1.806	**9.986**	.303

Note. Bold signifies significance < .05

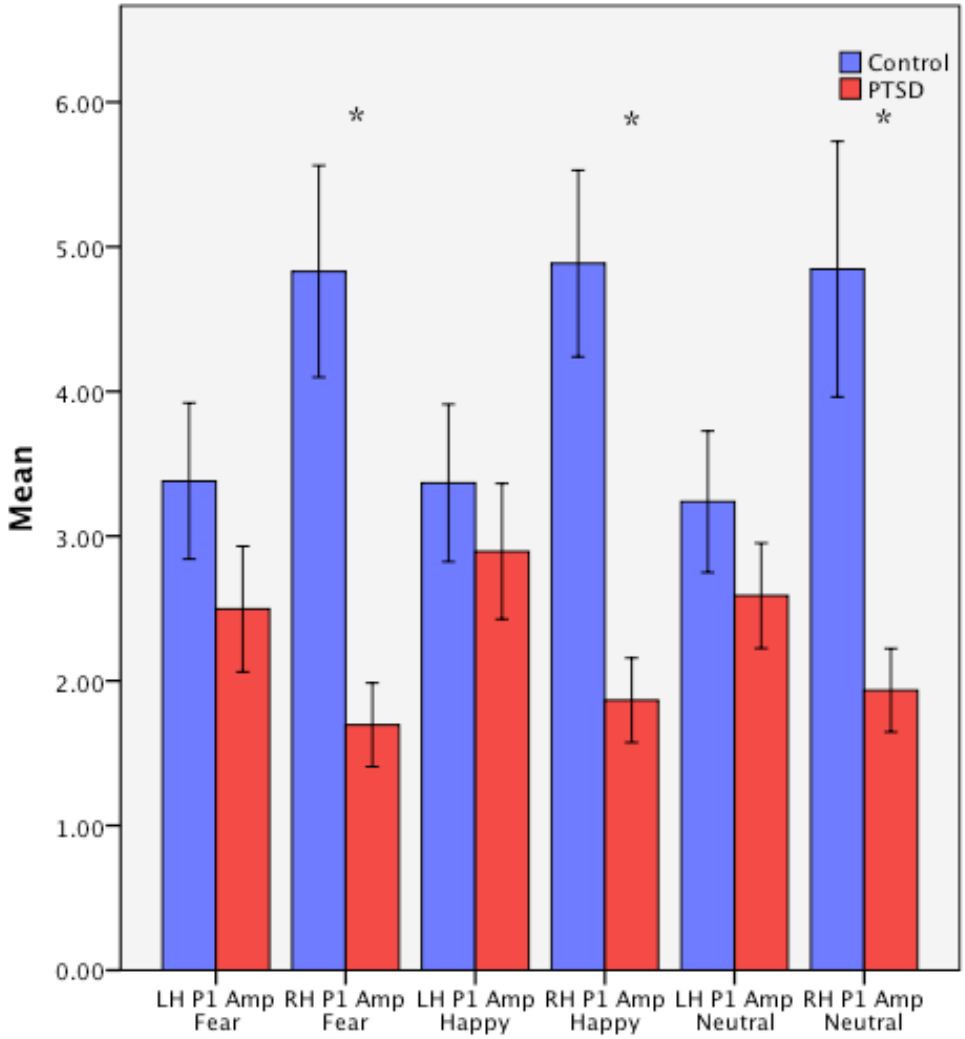

Figure 2.1. P1 ERP amplitude by group. Significantly greater P1 ERP amplitude recorded over the right hemisphere in veterans without PTSD. This was observed for all three masked affect conditions, fear, happy, and neutral.

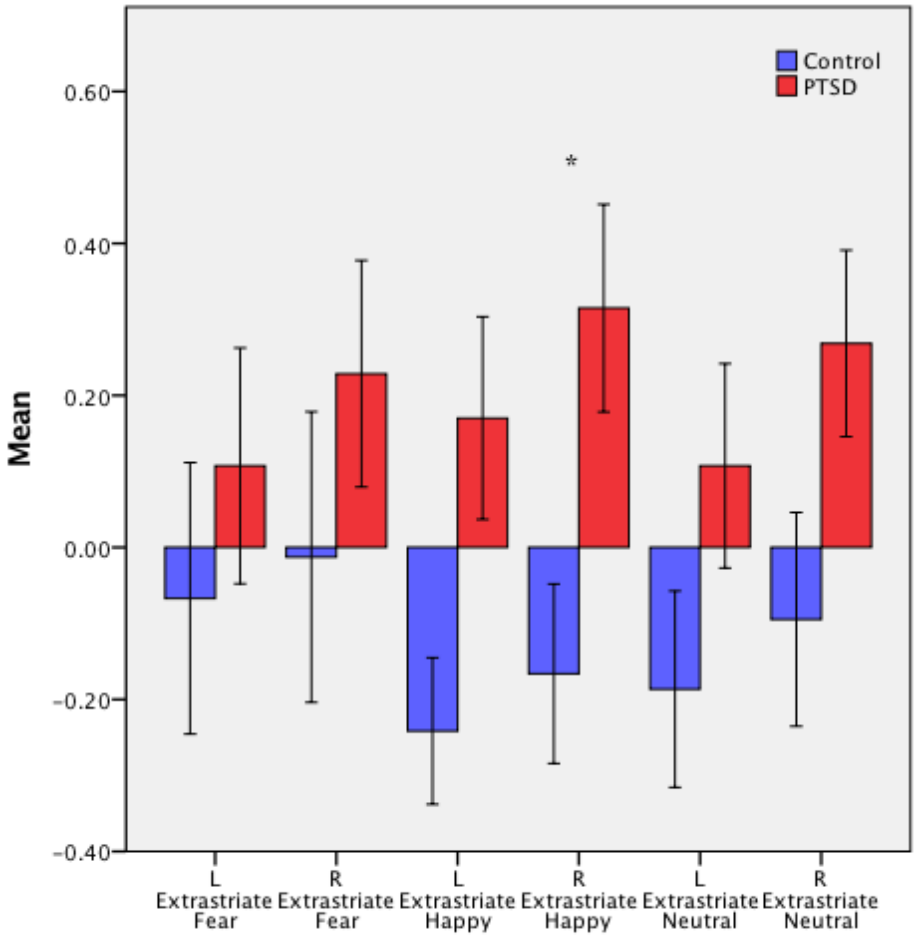

Figure 2.2. Extrastriate BOLD signal by group. Significantly greater BOLD activity observed in the right extrastriate cortex in the veteran group with PTSD during the masked happy condition. This effect was not observed for the masked fear or neutral conditions.

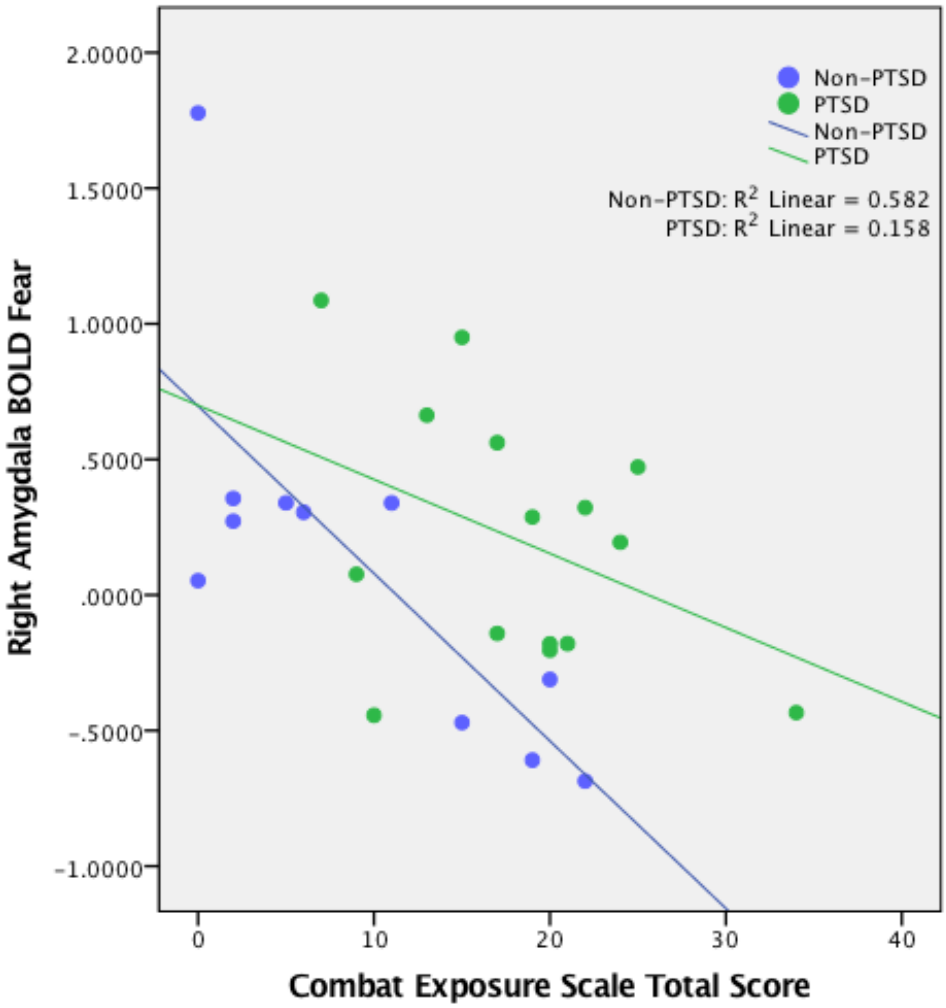

Figure 2.3. Scatterplot of CES total score and right amygdala BOLD signal for the fear condition, by group. A significant negative correlation was observed for the relationship between right amygdala BOLD activity and the degree of combat exposure during the masked fear condition, but only in the veteran group without PTSD.

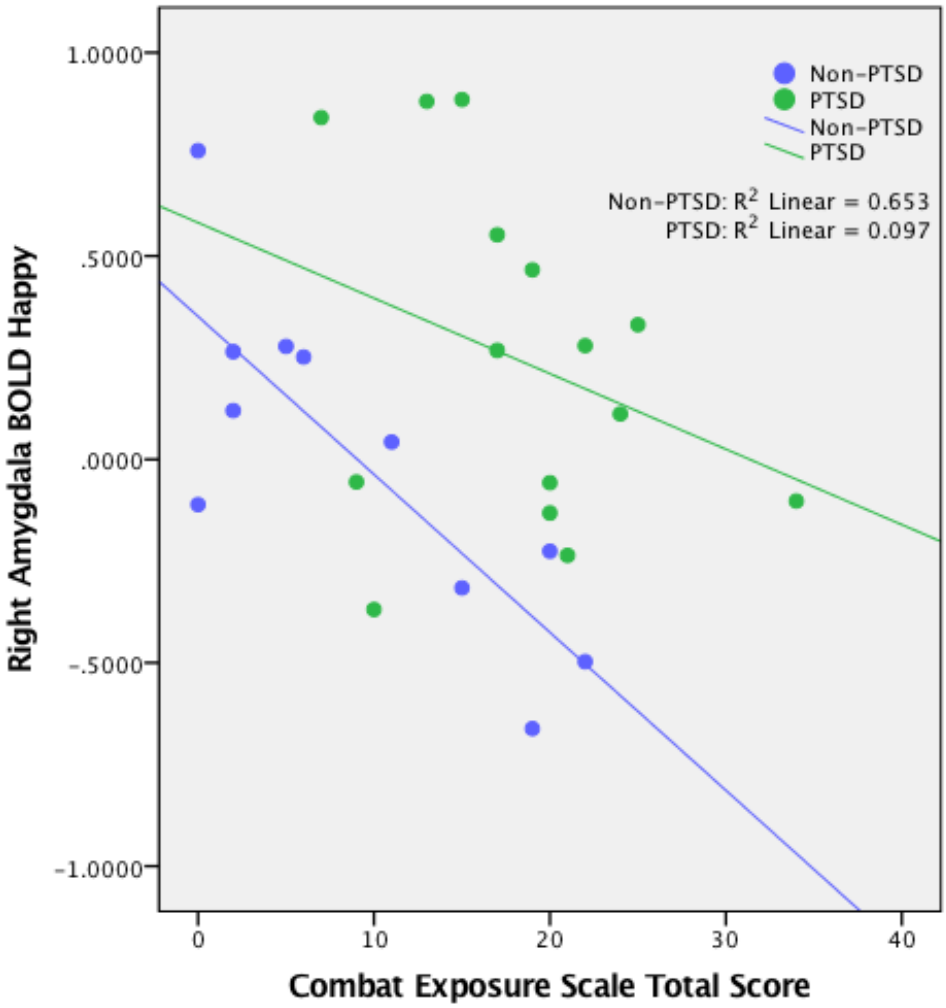

Figure 2.4. Scatterplot of CES total score and right amygdala BOLD signal for the happy condition, by group. A significant negative correlation was observed for the relationship between right amygdala BOLD activity and the degree of combat exposure during the masked happy condition, again only in the veteran group without PTSD.

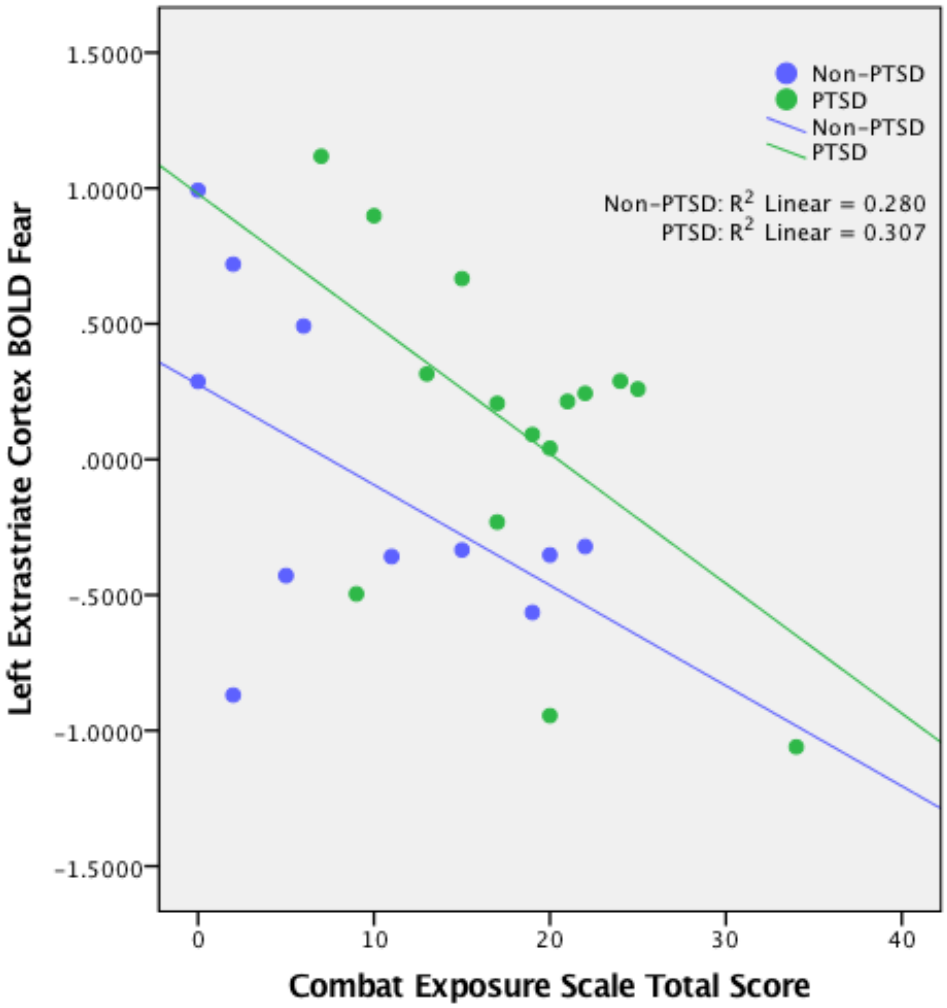

Figure 2.5. Scatterplot of CES total score and left extrastriate BOLD signal for the fear condition, by group. A significant negative correlation was observed for the relationship between left extrastriate BOLD activity and the degree of combat exposure during the masked fear condition, but was only significant for the veteran group with PTSD.

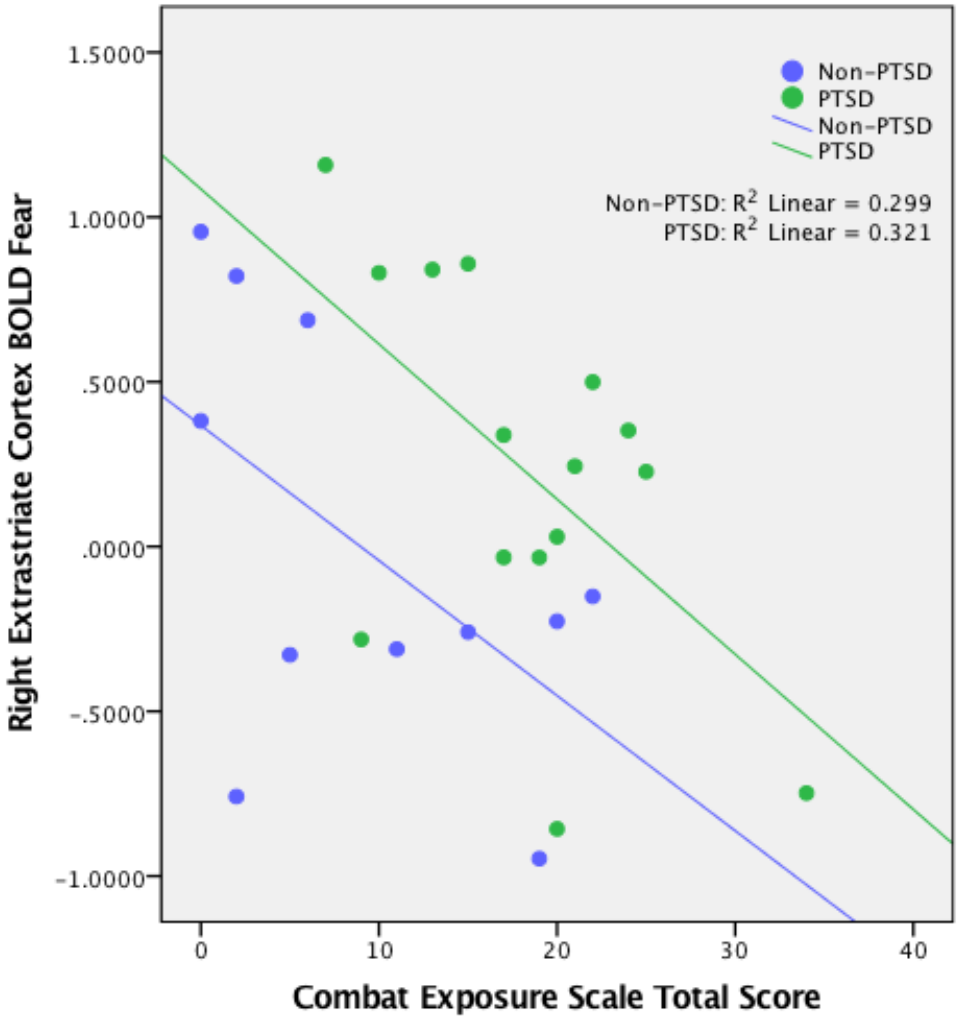

Figure 2.6. Scatterplot of CES total score and right extrastriate BOLD signal for the fear condition, by group. A significant negative correlation was observed for the relationship between right extrastriate BOLD activity and the degree of combat exposure during the masked fear condition, but again, this effect was only significant for the veteran group with PTSD.

CHAPTER 3

DISCUSSION

Summary

This work sought to increase our understanding of emotional processing in veterans with PTSD by characterizing responses to masked affect stimuli using neuroimaging approaches. We predicted that a veteran group with PTSD would produce enhanced P1 ERP amplitude as a result of increased activity in the extrastriate portion of the visual cortex. This hypothesis was based on evidence of enhanced extrastriate and visual cortex BOLD signal and exaggerated P1 ERP amplitude in response to fearful faces in healthy controls (Carlson, Reinke, Lamontagne, & Habib, 2010; Pourtois et al., 2004; Pourtois et al., 2005), an augmented P1 ERP amplitude response to fearful faces in individuals with high trait anxiety (Holmes et al., 2008; Li, Xinbarg, Boehm, & Paller, 2008), and studies that indicated amygdalar damage prevents the standard increases in P1 ERP amplitude and visual cortex BOLD signal produced by fearful stimuli (Rotshtein et al., 2010; Vuilleumier et al., 2004). Based on this previous work, we hypothesized that increased amygdalar activity, a frequent finding in PTSD literature (Hendler et al., 2003; Rauch et al., 2000; Shin et al., 2005), would lead to increased P1 ERP amplitude in response to fearful stimuli as a result of

augmented extrastriate cortex activity. Instead, we observed reduced P1 ERP amplitude over the right hemisphere in veterans with PTSD when compared to veterans without PTSD.

This unexpected result may be related to a visuosensory disruption or possible visual processing deficit in combat veterans with PTSD. Similar alterations to the processing of visual stimuli have been observed in psychiatric disorders, such as schizophrenia, and developmental disorders, such as autism (Behrmann, Thomas, & Humphreys, 2006; Butler, Silverstein, & Dakin, 2008; Marco, Hinkley, Hill, & Nagarajan, 2011; Norton, McBain, Holt, Ongur, & Chen, 2009). Previous studies measuring the sensory response to stimuli in individuals with PTSD have observed decreased ERP amplitude in response to sensory stimuli. Kounios and colleagues (1997) found that Vietnam-era veterans with PTSD displayed reduced right hemisphere P1 ERP amplitude when viewing both threatening and nonthreatening words. This result is similar to that of the present study in that the effect was specific to the right hemisphere and was evident for multiple stimulus types: both threatening and neutral stimuli. When the results of Kounios et al. (1997) are taken together with the results of the present study, they suggest a general visuosensory deficit in veterans with PTSD that is not specific to facial stimuli and seems to be present across emotional valence. Further, the stimuli in Kounios et al. (1997) were overtly presented, suggesting this effect applies to both backward masked and overtly presented stimuli. Because the work of Kounios and colleagues (1997), and the present study, were cross-sectional in nature, we are unable to determine whether this effect

predates or follows the trauma that led to the development PTSD in these individuals. Longitudinal studies performed before and after trauma would be useful to determine the time course of this effect. It is important to understand whether this effect is an adaptive process that restricts the amount of visual information that is sent to downstream regions, which may help prevent individuals with PTSD from being overwhelmed by sensory stimuli, or a factor that is present prior to the traumatic event.

Electrophysiological studies examining the response to auditory stimuli in individuals with PTSD have also found alterations in sensory processing. Felmingham and colleagues (2002) observed that civilians with PTSD exhibited a reduced P300 ERP during an auditory oddball task, which correlated negatively with numbing symptoms. This indicates an attentional deficit during sensory processing, reflected by the P300 ERP, that is related to the extent of numbing reported by individuals with PTSD. This attentional deficit may help to reduce the amount of sensory information that is received and processed, thereby reducing the burden on the individual. Despite the observation that the P300, which occurs later than the P1, was reduced in individuals with PTSD, the results of the study by Felmingham et al. (2002) support a broad, multisensory, attentional deficit that may be reflected in both veterans and civilians with PTSD. Araki et al. (2005) also examined the response of civilians with PTSD using an auditory oddball task. The authors found a similar result as Felmingham et al. (2002), a reduced P300 ERP in civilians with PTSD. Further, the authors found that the amplitude of the P300 was positively correlated with the size of the anterior cingulate cortex

(ACC). Although the present study did not investigate the ACC, future studies should investigate the morphometry and activity of the ACC in relation to the auditory P300 ERP, as well as the visual P1 ERP, which was the focus of the present study. Future work is also needed to directly compare civilians with PTSD to veterans with PTSD, to see if these groups differ in their electrophysiological response to both auditory and visual stimuli.

While the P1 ERP was reduced in a group of veterans with PTSD, extrastriate BOLD signal was increased in the sample, during the same masked affect task. This disparity may be related to the temporal differences in these measures, as the P1 ERP occurs roughly 130 ms after stimuli are presented, while the BOLD signal occurs multiple seconds after stimuli are presented (Ogawa et al., 1990). While simultaneous EEG/fMRI studies have displayed strong correlations between BOLD signal and ERPs, the ERPs that correlate tend to be slow ERPs, that occur hundreds of milliseconds to seconds after stimuli are presented, similar in timeframe to the BOLD signal itself (Schicke et al., 2006). As a result, the P1 ERP, which occurs after approximately 100 ms, may not reflect extrastriate activity as measured by BOLD signal to the degree that was predicted, which may explain the discrepancy in findings between the two methodologies in the present investigation. In addition, the participants of the present study were not presented with the masked affect task during simultaneous EEG/fMRI, but rather these methodologies were performed separately. It is possible that a stronger relationship would have been observed if these methods were performed simultaneously; however, doing so could have

introduced other forms of variance and noise such as an increased number of artifacts (Huster et al., 2012; Yan et al., 2009). It is also possible that clinical factors including psychopharmacotherapy, history of mild traumatic brain injury, and comorbid psychiatric disorder may have introduced confounding effects.

In addition, we observed significant negative correlations between combat exposure and both amygdalar and extrastriate BOLD signal, which differed depending on PTSD diagnosis. The veteran group with PTSD displayed a negative correlation between the degree of combat exposure and extrastriate BOLD signal in response to fearful faces, while the veteran group without PTSD exhibited a negative correlation between amygdalar activity and the extent of combat exposure. The negative correlation between the degree of combat exposure and amygdalar BOLD signal in veterans without PTSD may reflect an avoidance to emotional stimuli that contributed to these individuals being resilient to the development of PTSD following trauma (Russo et al., 2012). There is evidence to suggest that Increased amygdalar activity is both a predisposing factor for PTSD (McLaughlin et al., 2014), as well as positively related to PTSD symptom severity (Armony et al., 2005), so decreased amygdalar activity may protect against the development of PTSD after trauma. However, because the present study was cross-sectional and performed after trauma was experienced, we cannot determine whether the amygdalar effect observed in the veteran sample without PTSD was present before, or only after, combat was experienced. Although these individuals may not have PTSD, they may still be behavioral and clinical effects due to the neurobiological changes of the

amygdala that could be detrimental to their health and well-being. More research focusing on trauma-exposed individuals who do not go on to develop PTSD is needed, particularly those exposed to chronic trauma such as child abuse, domestic violence, and combat.

Taken together, the results of this investigation suggest a sensory dampening in response to masked facial stimuli in veterans with PTSD, which was most evident using the P1 ERP. This dampening is likely located in the visual cortex and may not be directly related to amygdalar activity, as we observed increased amygdalar BOLD signal in veterans with PTSD when controlling for the degree of combat exposure. We had proposed that the amygdala and visual cortex would be connected to a greater degree in veterans with PTSD, but our results indicate these regions may be less functionally connected compared to combat veterans without PTSD. This altered functional connectivity may also relate to the observed P1 ERP amplitude inhibition in that a reduction in input or aberrant input from the amygdala may result in less attentional and visual resources being allocated to the processing of facial stimuli, and likely other visual stimuli as well. Additional studies using methods such as DTI and resting state functional connectivity are needed to further evaluate the input from other brain regions and to examine both resting and task-related network activity.

Conclusion

In this investigation, we found evidence of increased extrastriate BOLD signal and decreased P1 ERP amplitude in veterans with PTSD in response to masked emotional faces compared to veterans without PTSD. This work is significant because it provides evidence that veterans diagnosed with PTSD can be distinguished from veterans without PTSD using the P1 ERP and extrastriate BOLD signal. This allows for the opportunity to use these methods to study individuals at risk for developing PTSD, as well as monitor treatment efficacy in those who have been diagnosed with the disorder. However, we did not observe a direct linear relationship between extrastriate BOLD signal and the amplitude of the P1 ERP in either veteran group. The observed lack of a relationship may be the result of differences in temporal resolution between the two methods, which led to greater intermethod incongruity than predicted.

In addition, we found evidence of a negative relationship between the degree of combat exposure and amygdala BOLD signal in a veteran group without PTSD in response to masked affect. This preliminary finding suggests that the extent of combat exposure may influence the amygdalar response to masked emotional facial stimuli. One implication of this observation is that combat-exposed veterans who do not meet the full criteria for a diagnosis of PTSD may process and potentially respond abnormally to emotional cues. Future investigations, including longitudinal and behavioral studies, are needed to determine if these amygdalar BOLD effects change over time or impact behavior. Nevertheless, this research provides important insights into the potential effects

of combat on the neurobiological response to masked emotional affect. Finally, the observation of a negative relationship between the degree of combat exposure and extrastriate BOLD signal in a veteran group with PTSD indicates a visuosensory alteration in PTSD related to the extent of combat exposure, which is independent of PTSD symptom severity. Additional studies are needed to evaluate if there is an influence of combat exposure on PTSD treatment outcomes.

This investigation sought to examine the neurobiological and electrophysiological response to masked affect in veterans with and without PTSD. While this research produced several exciting findings that were predicted, some results were unexpected. Medical and psychiatric comorbidities may have introduced variance that prevented the isolated study of PTSD. In addition, while there are numerous ways to examine fMRI and EEG results, we chose to limit the scope of the investigation to address the specific hypotheses that were formulated. However, the findings of this work, including the observation of decreased right hemisphere P1 ERP amplitude in veterans with PTSD in response to masked affect, provide intriguing insights into the neurobiology of PTSD in combat veterans.

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