Naval Health Research Center

Combat Veterans With PTSD After Mild TBI Exhibit Greater ERPs from Posterior–medial Cortical Areas While Appraising Facial Features

I-Wei Shu
Julie A. Onton
Nitin Prabhakar
Ryan M. O'Connell
Alan N. Simmons
Scott C. Matthews

Naval Health Research Center

Report No. 12-49

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government. Approved for public release; distribution unlimited.

This research was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

Naval Health Research Center
140 Sylvester Road
San Diego, California 92106-3521
Research report

Combat veterans with PTSD after mild TBI exhibit greater ERPs from posterior–medial cortical areas while appraising facial features

I-Wei Shua,b, Julie A. Ontone, Nitin Prabhakarc, Ryan M. O’Connellb,c, Alan N. Simmonsb,d, Scott C. Matthewsa,d

b VISN-22 Mental Illness, Research, Education and Clinical Center, 3350 La Jolla Village Drive, #116A, San Diego, CA 92161, USA
c Veterans Affairs San Diego Healthcare System, 3350 La Jolla Village Drive, #116A, San Diego, CA 92161, USA
d Department of Psychiatry, University of California San Diego, 9500 Gilman Drive #116A, La Jolla, CA 92037, USA

a Veterans Affairs San Diego Healthcare System Center of Excellence for Stress and Mental Health, 3350 La Jolla Village Drive, #116A, San Diego, CA 92161, USA

A R T I C L E   I N F O

Article history:
Received 24 May 2013
Accepted 14 June 2013
Available online 17 November 2013

Keywords:
PTSD
Mild TBI
N300
Posterior cingulate cortex
Precuneus
Biomarker

A B S T R A C T

Posttraumatic stress disorder (PTSD) worsens prognosis following mild traumatic brain injury (mTBI). Combat personnel with histories of mTBI exhibit abnormal activation of distributed brain networks—including emotion processing and default mode networks. How developing PTSD further affects these abnormalities has not been directly examined. We recorded electroencephalography in combat veterans with histories of mTBI, but without active PTSD (mTBI only, n = 16) and combat veterans who developed PTSD after mTBI (mTBI + PTSD, n = 16)—during the Reading the Mind in the Eyes Test (RMET), a validated test of empathy requiring emotional appraisal of facial features. Task-related event related potentials (ERPs) were identified, decomposed using independent component analysis (ICA) and localized anatomically using dipole modeling. We observed larger emotional face processing ERPs in veterans with mTBI + PTSD, including greater N300 negativity. Furthermore, greater N300 negativity correlated with greater PTSD severity, especially avoidance/numbing and hyperarousal symptom clusters. This correlation was dependent on contributions from the precuneus and posterior cingulate cortex (PCC). Our results support a model where, in combat veterans with histories of mTBI, larger ERPs from over-active posterior–medial cortical areas may be specific to PTSD, and is likely related to negative self-referential activity.

1. Introduction

Up to twenty percent of combat personnel in Iraq or Afghanistan experience mild traumatic brain injury—mTBI (Tanelian and Jaycox, 2008). While conventional brain imaging is negative following mTBI (Vasterling et al., 2012b), mTBI is associated with mechanical and metabolic damage to white matter tracts connecting distant brain areas (Arfanakis et al., 2002; Davenport et al., 2012; Jorge et al., 2012; Mac Donald et al., 2011; Matthews et al., 2012; Morey et al., 2012). Consistent with white matter damage, patients with histories of mTBI exhibit abnormal connectivity within distributed, rest brain networks, including the default mode network (DMN) – with generally decreased connectivity among DMN areas including the anterior and posterior cingulate – ACC, PCC (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012).

PTSD is common in combat personnel with histories of mTBI and further worsens outcomes following mTBI (Polusny et al., 2011; Vasterling et al., 2012a). Functional magnetic resonance imaging (fMRI) studies of patients with active PTSD or histories of mTBI suggest these populations share abnormalities in dorsolateral prefrontal, middle frontal and orbitofrontal brain activity (Simmons and Matthews, 2012; Stein and McAllister, 2009). In contrast to generally decreased DMN connectivity in patients with histories of mTBI, PTSD is generally associated with increased DMN connectivity (Daniels et al., 2010; Lanius et al., 2010a; Rabain et al., 2011; Sripada et al., 2012; Yin et al., 2011). Processing trauma-related stimuli is also associated with increased activation of posterior DMN areas—precuneus, PCC, retrosplenic cortex (Ramage et al., 2012; Sartory et al., 2013), raising the possibility that increased resting DMN activity in patients with PTSD arises from more negative self-referential activity, including recall of traumatic memories.

Corresponding author. Tel.: +1 858 922 9907; fax: +1 858 345 3887.
E-mail addresses: iwei@ucsd.edu, iweishumdphd@gmail.com, I-Wei.Shu@va.gov (I.-W. Shu).
0165-0327/$ - see front matter Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.jad.2013.06.057
In addition to DMN abnormalities, PTSD is associated with abnormal cortical-limbic regulation of emotional activity (Lanious et al., 2010). For example, fMRI studies of emotion processing in combat personnel with PTSD have observed over-active ventromedial, cingulate and limbic activity, and deficient frontal activity, including in subjects with histories of mTBI (Herrington et al., 2012; Matthews et al., 2011; Pannu Hayes et al., 2009; Roy et al., 2010; Scheibel et al., 2012; Simmons et al., 2011, 2013). Patients with PTSD also exhibit over-acute event-related potentials (ERPs) when presented with trauma-related stimuli during electroencephalography—EEG (Javanbakht et al., 2011). More specifically, trauma-related distractors during oddball tasks consistently produce increased P3 amplitudes in veterans with combat-related PTSD (Attias et al., 1996; Stanford et al., 2001). P3 and related ERPs also source localize to areas abnormally activated in patients with PTSD, including the ACC and PCC (Albert et al., 2012; Campanella et al., 2013; Zhang and Lu, 2012).

To date, there are no published ERP studies of emotion processing in patients with PTSD after mTBI. ERP studies involving patients with histories of only mTBI have focused primarily on civilian injuries from sports, accidents or assaults, without specifically examining PTSD. These studies have involved primarily cognitive tasks, generally finding normal, attenuated or slower brain responses in patients with histories of mTBI only (Broglio et al., 2011; Larson et al., 2012; Larson et al., 2011).

Studies directly examining differences in brain activity between patients with histories of mTBI only and patients with PTSD after mTBI would improve our understanding of neural mechanisms underlying the negative effects of PTSD on outcomes following mTBI. Patients with PTSD generally exhibit over-active ACC and PCC activity, at rest or when processing trauma-related or emotional stimuli. Thus, we hypothesized that, compared to veterans with histories of mTBI only, veterans with PTSD after mTBI would exhibit over-active P3 or related ERPs that source localize to the cingulate cortex. To test our hypothesis, we recorded EEG in veterans with histories of mTBI only (mTBI only) or PTSD after mTBI (mTBI þ PTSD) during the Reading the Mind in the Eyes Test (RMET). As a validated test of empathy, the RMET requires subjects to choose, from the 4 words at the corners, the one word that best matches the other’s mental state. The images, 4 possible answers, and the 1 correct answer were selected from field trials where healthy controls chose the correct answer 70–80% of the time (Baron-Cohen et al., 2001). The task is not timed and is scored on accuracy.

2.2. Task

During the RMET (www.autismresearchcentre.com/arc_tests), subjects were presented, in a series, 36 different images of eyes cropped from photographs of human faces (Fig. 1). Subjects were instructed to choose, from the 4 words at the corners, the one word that best matches the other’s mental state. The images, 4 possible answers, and the 1 correct answer were selected from field trials where healthy controls chose the correct answer 70–80% of the time (Baron-Cohen et al., 2001). The task is not timed and is scored on accuracy.

2.3. EEG acquisition and preprocessing

EEG data were collected synchronously from 132 scalp and 4 infra-ocular electrodes with an active reference (BioSemi Instrumentation, Amsterdam) at a sampling rate of 512 Hz with 24-bit A/D resolution. Onsets and offsets of RMET visual stimuli, as well as EEG data were analyzed by custom MATLAB (The MathWorks, Inc., Natick, MA, USA) scripts built on the open source EEGLAB environment (http://sccn.ucsd.edu/eeGLab) (Delorme et al., 2011). Data were re-referenced to average reference and digitally filtered to emphasize frequencies above 1 Hz. Data periods containing broadly distributed, high-amplitude muscle noise and other irregular artifacts were removed from analysis using EEGLAB functions. Eye blinks, other eye movements, and tonic muscle tension artifacts were not removed at this stage of preprocessing.

![Figure 1](image_url)

Fig. 1. Practice slide from Baron-Cohen’s Reading the Mind in the Eyes Test (www.autismresearchcentre.com/arc_tests).
2.4. Artifact removal using independent component analysis (ICA)

Data were then concatenated and submitted to full-rank decomposition by extended InfoMax ICA as implemented in EEGLAB. Independent components (ICs) characteristic of non-brain artifact (e.g., eye, muscle, or line noise) by visual inspection of their scalp topographies, time courses, and activity spectra were excluded. Next, equivalent dipole models for each IC were computed using a boundary element model that included Oostenveld FieldTrip functions as implemented by EEGLAB's DIPFIT plug-in. Pairs of bilaterally symmetric dipoles were permitted to exclude. Next, equivalent dipole models for each IC were computed using a boundary element model that included Oostenveld FieldTrip functions as implemented by EEGLAB's DIPFIT plug-in. Pairs of bilaterally symmetric dipoles were permitted to fit ICs with bilaterally symmetric scalp maps. ICs with scalp projections having less than 15% residual variance from the best-fit dipole scalp projection were considered brain ICs. Dipoles that localized outside the brain volume were excluded.

2.5. Analysis

All ICs, except known artifacts (e.g., eye blinks, eye movements, electrocardiogram, and muscle) were back-projected to Fz, FCz, Cz, Pz, Oz, P7, and P8. For each subject, onset of REMT visual stimuli was set as time 0 ms, average activity between -100 and 0 ms was subtracted as baseline, and the epochs between 0 and 625 ms from all 36 clusters were averaged to generate single-subject event-related potentials (ERPs). For each group, single-subject ERPs were averaged to generate group ERPs. Two-tailed independent sample t-tests were computed for each channel.

Peak amplitudes for single-subject ERPs were computed by identifying the most negative (or positive) ERP value within the window starting 100 ms before and ending 100 ms after the characteristic ERP latency (i.e., 200–400 ms for N300/P300). There being no evidence to assume linear relationships between peak amplitudes and PTSD severity, correlations between single subject peak amplitudes and single-subject CAPS scores were tested using Spearman’s ρ.

For source localization, we first identified dominant ICs—those responsible for the greatest variance between 200 and 400 ms. In addition, ICs responsible for variances > half that of dominant ICs were also included. ICs were then clustered based on anatomical location, by calculating the Euclidean distance between all dipole locations and then clustering the results using linkage and dendrogram functions in MATLAB. Back-projections of clustered components to Fz, FCz, Cz, Pz, Oz, P7, and P8 allowed for the same analysis of ERPs and peak amplitudes as previously described for raw EEG signals for each cluster.

3. Results

3.1. Clinical and behavioral results

Per selection criteria, PTSD severity was significantly higher in veterans with mTBI+PTSD (mean + SD CAPS scores: mTBI only, 36.8 ± 13.1; mTBI+PTSD, 82.0 ± 17.1; p < 0.001; see Table 1). Groups did not differ on demographic variables including, age or education; or on head injury variables, such as mechanism of mTBI, number of blasts, or mTBI-related changes in mental status, including loss of consciousness or retrograde amnesia (Table 1). Behaviorally, groups did not differ on total number of errors during REMT performance (Table 1).

Groups did not differ on the clinical variables of comorbid major depressive disorder (MDD), other anxiety disorders, comorbid alcohol or substance use or treatment with psychoactive medications (Table 1). Groups did differ, however, on depression severity; more specifically, veterans with mTBI+PTSD exhibited greater depression severity (mean ± SD BDZ scores: mTBI only, 7.1 ± 7.8; mTBI+PTSD, 21 ± 9.9; p < 0.001; see Table 1).

3.2. ERP results

We observed four ERPs commonly associated with emotional face processing: more specifically, N1 (P1 at posterior electrodes), vertex positive potential (VPP; N170 at posterior electrodes), N300 (P300 at posterior electrodes) and late positive potential (LPP) (Frühholz et al., 2011; Luo et al., 2010; Schutter et al., 2004). The N170 ERP during emotional face processing tasks is related to the N2 ERP that immediately precedes the P3 in oddball tasks described above. Not unexpectedly, we did not observe prominent P3s during the REMT which, in contrast to oddball tasks, primarily requires emotional appraisal of facial features.

There were no group differences for P1/N1 amplitudes. In contrast, compared to mTBI only veterans, mTBI+PTSD veterans exhibited significantly larger VPP/N170 amplitudes at Fz, FCz, Cz, Pz, Oz, and P8 (t-test; p < 0.05; Fig. 2), N300/P300 amplitudes at Cz, Pz, and Oz (t-test; p < 0.05; Fig. 2), and significantly larger LPP amplitudes at Fz, FCz, Cz, Oz, and P8 (t-test; p < 0.05; Fig. 2).

Though we observed group differences for both VPP/N170 and N300/P300 ERPs during the REMT, only the N300 consistently source localizes to our region of interest—the cingulate cortex (Albert et al., 2012; Campanella et al., 2013; Zhang and Lu, 2012). Thus, we focus on N300 negativity in subsequent analyses.

3.3. Correlations

Peak N300 amplitudes from single-subject ERPs were computed by identifying the most negative ERP value between 200 and 400 ms latencies. For all veterans, greater central–medial N300 negativity correlated with greater PTSD severity (Spearman’s ρ = –0.529 with p < 0.001 at most significant central–medial electrode; Fig. 3). Strength of correlation was smaller (–0.466) but remained significant (p < 0.01) after controlling for depression severity. Within group correlations were significant, though smaller, for mTBI+PTSD veterans (Spearman’s ρ = –0.432 with p < 0.05; data not shown) but only trended towards significance for mTBI only veterans (Spearman’s ρ = –0.390 with p=0.094; data not shown).

For all veterans, correlations were significant for all PTSD symptoms clusters (re-experiencing, avoidance/numbing, hyperarousal...
subscores on the CAPS), but strongest and most significant for avoidance/numbing and hyperarousal \( (\text{Spearman's } \rho = -0.564, \text{ with } p < 0.001; -0.513, 0.005; \text{ respectively}) \). In fact, correlation between CAPS and N300 negativity remained significant after controlling for re-experiencing symptoms \( (\text{Spearman's } \rho = -0.499; p < 0.005) \) but not after controlling for avoidance/numbing or hyperarousal \( (\text{data not shown}) \).

From the 15 anatomic clusters of ICs responsible for the greatest N300 variance, we tested the significance of the correlation between N300 negativity and PTSD severity when any one cluster was removed from the analysis \( (\text{Fig. 4}) \). Greater N300 negativity no longer correlated with PTSD severity after removal of cluster 8, which localizes to the precuneus, and cluster 12, which localizes to bilateral occipital areas. Cluster 2, which localizes to the PCC, and cluster 16, which localizes to L sensorimotor areas, were the third and fourth most significant contributors to the correlations, though removing either attenuated but did not but did not eliminate the significance of the correlation \( (\text{Fig. 4}) \).

4. Discussion

Patients with PTSD consistently exhibit larger ERPs during processing of trauma-related or emotionally-negative stimuli \( (\text{Attias et al., 1996; Bae et al., 2011; Javanbakht et al., 2011; Johnson et al., 2013; Stanford et al., 2001; Yun et al., 2011}) \). In contrast, patients with mTBI generally exhibit smaller or slower ERPs \( (\text{Broglio et al., 2011; Larson et al., 2012; Larson et al., 2011}) \). These studies suggest that, in combat veterans with histories of mTBI, larger ERPs may be specific to PTSD. Consistent with this
In contrast, patients with histories of mTBI only do not exhibit over-activation of posterior–medial cortical areas, including in studies directly examining the DMN (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012). These results raise the possibility that increased posterior–medial cortical activations may be specific to PTSD symptoms in combat veterans with histories of mTBI, and is likely related to negative self-referential activity, including recall of traumatic memories.

4.1. PTSD-related ERP differences

We further observed that larger ERPs in veterans with PTSD after mTBI compared to those with histories of mTBI only.

The role of the PCC in fear processing is well-established (Tanev, 2003). Consistent with its role in fear processing, the PCC is generally over-activated in patients with PTSD during processing of trauma-related stimuli (Attias et al., 1996; Bae et al., 2011; Javanbakht et al., 2011; Johnson et al., 2013; Stanford et al., 2001; Yun et al., 2011). In contrast, ERP differences during processing of neutral stimuli have been mixed, though patients with PTSD generally exhibit smaller ERP responses under neutral conditions, leading both Javanbakht and colleagues and Johnson and colleagues to hypothesize that patients with PTSD allocate greater neural resources towards processing emotional stimuli at the expense of, and actually depleting, resources available for processing neutral stimuli. Specific to ERP studies of face processing in patients with PTSD, Felmingham and colleagues did not observe larger ERPs (Felmingham et al., 2003), in contrast to our results, though only temporal–occipital electrodes were reported. Consistent with our results, Ehlers and colleagues reported larger ERPs consistent with cingulate over-activity (Ehlers et al., 2006), though potential N300 differences were not discussed.

4.2. Posterior–medial cortical activity in patients with PTSD

The role of the PCC in fear processing is well-established (Tanev, 2003). Consistent with its role in fear processing, the PCC is generally over-activated in patients with PTSD during processing of trauma-related stimuli (Bremner et al., 1999a, 1999b; Driessen et al., 2004; Lanius et al., 2007). The precuneus is highly anatomically and functionally connected with the PCC (Cavanna and Trimble, 2006) and is similarly over-activated in patients with PTSD during processing of trauma-related or emotionally-negative stimuli (Nardos et al., 2011; Whalley et al., 2009). In fact, 2 recent meta-analyses identified both the PCC and precuneus as among areas most consistently activated in patients with PTSD during processing of trauma-related stimuli (Ramage et al., 2012; Sartory et al., 2013).

Physiologically, both the PCC and precuneus are consistently and jointly activated during tasks involving self representation, e.g., visual-spatial orientation, autobiographical memories, appraisal of self versus others, and as part of the DMN (Lombardo et al., 2010; Shannon and Buckner, 2004; Sugiuara et al., 2005). Closely related to their roles in self representation, the PCC and precuneus are also involved in evaluating threats to physical or mental integrity (Farrow et al., 2012; Mechias et al., 2010; Pantazatos et al., 2012; Wood et al., 2012). Specific to patients with PTSD, over-activation of posterior–medial cortical areas during trauma-related tasks most likely arises from increased sensitivity to trauma-related stimuli, or increased responses to trauma-related memories and associated thoughts and feelings (Ramage et al., 2012; Sartory et al., 2013). In contrast, patients with histories of mTBI only generally do not exhibit over-activation of posterior–medial cortical areas, including in studies directly examining the DMN (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012) —raising the possibility that increased posterior–medial cortical activity in veterans with PTSD after mTBI compared to those with histories of mTBI only.

We further observed that larger ERPs in veterans with PTSD after mTBI primarily arise from the PCC and precuneus—consistent with posterior–medial cortical areas being over-activated during processing of trauma-related stimuli in patients with PTSD (Ramage et al., 2012; Sartory et al., 2013). Though results from resting studies of patients with PTSD are more mixed, PTSD is also generally associated increased connectivity between posterior DMN areas including the PCC and precuneus (Daniels et al., 2010; Lanius et al., 2010a; Rabinak et al., 2011; Sripada et al., 2012; Yin et al., 2011). In contrast, patients with histories of mTBI only do not exhibit over-activation of posterior–medial cortical areas, including in studies directly examining the DMN (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012). These results raise the possibility that increased posterior–medial cortical activations may be specific to PTSD symptoms in combat veterans with histories of mTBI, and is likely related to negative self-referential activity, including recall of traumatic memories.

4.1. PTSD-related ERP differences

We further observed that larger ERPs in veterans with PTSD after mTBI primarily arise from the PCC and precuneus—consistent with posterior–medial cortical areas being over-activated during processing of trauma-related stimuli in patients with PTSD (Ramage et al., 2012; Sartory et al., 2013). Though results from resting studies of patients with PTSD are more mixed, PTSD is also generally associated increased connectivity between posterior DMN areas including the PCC and precuneus (Daniels et al., 2010; Lanius et al., 2010a; Rabinak et al., 2011; Sripada et al., 2012; Yin et al., 2011). In contrast, patients with histories of mTBI only do not exhibit over-activation of posterior–medial cortical areas, including in studies directly examining the DMN (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012). These results raise the possibility that increased posterior–medial cortical activations may be specific to PTSD symptoms in combat veterans with histories of mTBI, and is likely related to negative self-referential activity, including recall of traumatic memories.

4.1. PTSD-related ERP differences

We further observed that larger ERPs in veterans with PTSD after mTBI primarily arise from the PCC and precuneus—consistent with posterior–medial cortical areas being over-activated during processing of trauma-related stimuli in patients with PTSD (Ramage et al., 2012; Sartory et al., 2013). Though results from resting studies of patients with PTSD are more mixed, PTSD is also generally associated increased connectivity between posterior DMN areas including the PCC and precuneus (Daniels et al., 2010; Lanius et al., 2010a; Rabinak et al., 2011; Sripada et al., 2012; Yin et al., 2011). In contrast, patients with histories of mTBI only do not exhibit over-activation of posterior–medial cortical areas, including in studies directly examining the DMN (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012). These results raise the possibility that increased posterior–medial cortical activations may be specific to PTSD symptoms in combat veterans with histories of mTBI, and is likely related to negative self-referential activity, including recall of traumatic memories.

4.1. PTSD-related ERP differences

We further observed that larger ERPs in veterans with PTSD after mTBI primarily arise from the PCC and precuneus—consistent with posterior–medial cortical areas being over-activated during processing of trauma-related stimuli in patients with PTSD (Ramage et al., 2012; Sartory et al., 2013). Though results from resting studies of patients with PTSD are more mixed, PTSD is also generally associated increased connectivity between posterior DMN areas including the PCC and precuneus (Daniels et al., 2010; Lanius et al., 2010a; Rabinak et al., 2011; Sripada et al., 2012; Yin et al., 2011). In contrast, patients with histories of mTBI only do not exhibit over-activation of posterior–medial cortical areas, including in studies directly examining the DMN (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012). These results raise the possibility that increased posterior–medial cortical activations may be specific to PTSD symptoms in combat veterans with histories of mTBI, and is likely related to negative self-referential activity, including recall of traumatic memories.

4.1. PTSD-related ERP differences

We further observed that larger ERPs in veterans with PTSD after mTBI primarily arise from the PCC and precuneus—consistent with posterior–medial cortical areas being over-activated during processing of trauma-related stimuli in patients with PTSD (Ramage et al., 2012; Sartory et al., 2013). Though results from resting studies of patients with PTSD are more mixed, PTSD is also generally associated increased connectivity between posterior DMN areas including the PCC and precuneus (Daniels et al., 2010; Lanius et al., 2010a; Rabinak et al., 2011; Sripada et al., 2012; Yin et al., 2011). In contrast, patients with histories of mTBI only do not exhibit over-activation of posterior–medial cortical areas, including in studies directly examining the DMN (Johnson et al., 2012; Mayer et al., 2011; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012). These results raise the possibility that increased posterior–medial cortical activations may be specific to PTSD symptoms in combat veterans with histories of mTBI, and is likely related to negative self-referential activity, including recall of traumatic memories.
activations may be specific to PTSD, and likely related to negative self-referential activity.

4.3. Limitations

Similar to other published studies of combat-related mTBI, we rely on subject recall of injuries and course of symptoms. This limitation, combined with this study being cross-sectional, precludes a definitive answer to whether greater N300 negativity preceded, or followed, traumatic events or onset of symptoms. In addition, similar to veterans receiving treatment at VAs nationally, subjects in this study were comorbid for multiple psychiatric problems. Importantly, prevalence of MDD, other anxiety disorders, alcohol or substance use, treatment with psychiatric medications and head injury variables were not significantly different between the groups. Correlations also remained significant after controlling for depression severity, allowing us to conclude that observed differences primarily arise from PTSD. While our subjects with histories of mTBI only did not meet categorical and severity criteria for PTSD, mean CAPS score (and standard deviation) for the this group was 36.8 (13.1), suggesting presence of subthreshold PTSD symptoms. This limitation suggests greater N300 negativity is primarily a marker of greater PTSD severity rather than a categorical marker of PTSD diagnosis—a conclusion also supported by our correlation analysis.

5. Conclusion

To better understand the neural mechanisms underlying the negative effects of PTSD on outcomes following mTBI, we tested the hypothesis that combat veterans with PTSD after mTBI, compared to those with histories of mTBI only, would exhibit larger ERPs from the cingulate cortex during a test of empathy requiring emotional appraisal of facial features. Consistent with our hypothesis, veterans with PTSD after mTBI exhibited larger emotional face processing ERPs, including greater N300 negativity. Furthermore, greater N300 negativity correlated with greater PTSD severity. The significance of this correlation depended on contributions from the PCC and precuneus—posterior—medial cortical areas responsible for self representation. These results are consistent with a model where the negative effects of PTSD on outcomes following mTBI are associated with over-activation of posterior—medial cortical areas. Future studies will focus on how PTSD-related differences in posterior—medial cortical activity may augment evaluation and treatment of PTSD, including in combat veterans with histories of mTBI.

Role of funding source

This work represents Report No. 12-xx and was supported by BUMED under Work Unit 61032. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government. Approved for public release; distribution is unlimited. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocols NHRC.2010.0022 and NHRC.2010.0023). The authors are grateful to Elena Kosheleva, and Jenny Marks for their contributions to this research, which was supported by the VA Mental Illness Research, Education and Clinical Center, VA Office of Academic Affiliations, VA Advanced Fellowship Program in Mental Illness Research Treatment, and the VA Center of Excellence for Stress and Mental Health, and by grants from the University of California San Diego Academic Senate, Department of Veterans Affairs, and the Congressionally Directed Medical Research Program. Dr. Matthews is supported by a CDA-2 from the VA CSBRD.

Conflict of interest

The authors have no potential conflicts of interest to report.

Acknowledgements

This work represents Report No. 12-xx and was supported by BUMED under Work Unit 61032. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government. Approved for public release; distribution is unlimited. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocols NHRC.2010.0022 and NHRC.2010.0023). The authors are grateful to Elena Kosheleva, and Jenny Marks for their contributions to this research, which was supported by the VA Mental Illness Research, Education and Clinical Center, VA Office of Academic Affiliations, VA Advanced Fellowship Program in Mental Illness Research Treatment, and the VA Center of Excellence for Stress and Mental Health, and by grants from the University of California San Diego Academic Senate, Department of Veterans Affairs, and the Congressionally Directed Medical Research Program. Dr. Matthews is supported by a CDA-2 from the VA CSBRD.

The authors have no potential conflicts of interest to report.

References


Posttraumatic stress disorder (PTSD) worsens prognosis following mild traumatic brain injury (mTBI). Combat personnel with histories of mTBI exhibit abnormal activation of distributed brain networks—including emotion processing and default mode networks. How developing PTSD further affects these abnormalities has not been directly examined. We recorded electroencephalography in combat veterans with histories of mTBI, but without active PTSD (mTBI only, n=16) and combat veterans who developed PTSD after mTBI (mTBI+PTSD, n=16)—during the Reading the Mind in the Eyes Test (RMET), a validated test of empathy requiring emotional appraisal of facial features. Task-related event related potentials (ERPs) were identified, decomposed using independent component analysis (ICA) and localized anatomically using dipole modeling. We observed larger emotional face processing ERPs in veterans with mTBI+PTSD, including greater N300 negativity. Furthermore, greater N300 negativity correlated with greater PTSD severity, especially avoidance/numbing and hyper arousal symptom clusters. This correlation was dependent on contributions from the precuneus and posterior cingulate cortex (PCC). Our results support a model where, in combat veterans with histories of mTBI, larger ERPs from over-active posterior–medial cortical areas may be specific to PTSD, and is likely related to negative self-referential activity.