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

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1. Introduction

Up to twenty percent of combat personnel in Iraq or Afghani-
stan experience mild traumatic brain injury—mTBI (Tanelian and
Jaycox, 2008). While conventional brain imaging is negative fol-
lowing mTBI (Vasterling et al., 2012b), mTBI is associated with
mechanical and metabolic damage to white matter tracts connect-
ing distant brain areas (Arfanakis et al., 2002; Davenport et al.,
2012; Jorge et al., 2012; Mac Donald et al., 2011; Matthews et al.,
2011; Rabinak et al., 2011; Sripada et al., 2012; Yin et al., 2011).

Posttraumatic stress disorder (PTSD) worsens prognosis follow-
ing mild traumatic brain injury (mTBI). Combat personnel with his-
tories of mTBI exhibit abnormal activation of distributed brain net-
works—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.

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In addition to DMN abnormalities, PTSD is associated with abnormal cortical-limbic regulation of emotional activity (Lanius et al., 2010b). 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 (Herringshaw et al., 2012; Mathews et al., 2011; Pannu Hayes et al., 2009; Roy et al., 2010; Scheibl et al., 2012; Simmons et al., 2011, 2013). Patients with PTSD also exhibit over-active 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., 2010; Carreño 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 + PTSD) during the Reading the Mind in the Eyes Test (RMET). As a validated test of empathy, the RMET requires emotional self appraisal in response to images of eyes cropped from portraits of human faces. Although RMET performance was not impaired in one study of individuals with civilian PTSD—assault, occupational accidents, natural disasters (Nietlisbach et al., 2010), individuals with PTSD from combat in Iraq exhibit impaired RMET performance (Mazza et al., 2012). To date, RMET performance has not been examined in patients with mTBI, including those with PTSD after mTBI.

2. Materials and methods

2.1. Subjects

Thirty-two (16mTBI only; 16 mTBI + PTSD) male Operation Iraqi Freedom/Operation Enduring Freedom (OEF/OIF) combat veterans provided written informed consent and completed this cross-sectional study, which was conducted from 2010 to 2012 and was approved by the University of California San Diego Human Research Protection Program and the Veterans Affairs San Diego Healthcare System (VASDHS) Research and Development Committee. Subjects were recruited from VASDHS clinical services through paper and electronic advertisements and word of mouth.

All subjects completed 2 sessions. During session 1, subjects completed a detailed clinical assessment, which involved administration of the Brief Traumatic Brain Injury Screen (Schwab et al., 2007), the Structured Clinical Interview for DSM-IV-TR (First et al., 2002), the Clinician-Administered PTSD Scale (CAPS) (Weathers et al., 2001) and Beck Depression Inventory 2 (BDI2) (Beck et al., 1996). Subjects were included if they reported experiencing 1 or more mTBI events during combat (i.e., a blast exposure or a blow or jolt to the head), that resulted in a loss or alteration of consciousness of 20 min or less. Health records related to mTBI were not available; therefore, subjects’ recall of trauma history could not be confirmed. Subjects meeting criteria for current PTSD – CAPS > 65 per Weathers and colleagues, 2001 (Weathers et al., 2001) – were included in the mTBI + PTSD group (n = 16). Subjects not meeting current PTSD criteria were included in the mTBI only group (n = 16)—though the mean (and standard deviation) for the mTBI only group being 36.8 (13.1) suggested subthreshold PTSD symptoms. Exclusion criteria included: (1) meeting criteria for an alcohol or substance use disorder within the past 30 days; (2) lifetime history of bipolar disorder, attention deficit hyperactivity disorder, or psychotic disorder; or (3) acute medical problems. During session 2, subjects completed the Reading the Mind in the Eyes Test (RMET) during EEG.

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 subjects’ button presses, were recorded in a simultaneously acquired event channel. Electrodes and water-based conductive gel were pressed into plastic wells on caps with a custom whole-head montage covering most of the skull, forehead, and superior temporal face surface.

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.

Fig. 1. Practice slide from Baron-Cohen’s Reading the Mind in the Eyes Test (www.autismresearchcentre.com/arc_tests).
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 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 trials 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 BDI2 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 N200 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.

Though we observed 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, Pz, 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 (Spearman’s $\rho = -0.564$, with $p < 0.001$; $-0.513$, 0.005; respectively). In fact, correlation between CAPS and N300 negativity remained significant after controlling for re-experiencing symptoms (Spearman’s $\rho = -0.499$; $p < 0.005$) but not after controlling for avoidance/numbing or hyperarousal (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 (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 not eliminate the significance of the correlation (Fig. 4).

4. Discussion

Patients with PTSD consistently exhibit larger ERPs during processing of trauma-related or emotionally-negative 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, patients with mTBI generally exhibit smaller or slower ERPs (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
hypothesis, we observed larger emotional face processing ERPs 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

Consistent with our results, ERP studies of patients with PTSD have observed larger ERPs during processing of trauma-related or emotional stimuli in patients with PTSD (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 ERPs 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 (Nardo 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; Sugiura 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

Fig. 3. All electrodes exhibiting significant correlations between N300 negativity and PTSD severity are colored red on scalp map in upper right hand corner. Electrode with strongest correlation is circled in lavender. For all veterans, peak negative N300 amplitudes from circled electrode is plotted along the y-axis against Clinician-Administered PTSD Scale (CAPS) scores on the x-axis (Spearman’s \( \rho = -0.0529; \ p < 0.001 \)).

Fig. 4. The 15 anatomic clusters of ICs with greatest contributions to N300 variance are plotted along the x-axis – in order of their contribution to the correlation between N300 negativity and PTSD severity – with lowest contributors on the far left, and the greatest contributors on the far right. For each cluster along the x-axis, the significance of the correlation with only that cluster removed from analysis is plotted along the y-axis. Mid-sagittal and mid-transverse images of the clusters are indicated by color-coordinated spheres—and arrows for clusters localizing to the precuneus (turquoise), bilateral occipital areas (navy blue), posterior cingulate (orange) and L sensorimotor area (fuschia). Removal of the cluster localizing to the precuneus lowers \( \rho \) to \( > 0.2 \); bilateral occipital areas, \( > 0.1 \); posterior cingulate, \( > -0.005 \); L sensorimotor (fuschia), \( > 0.004 \). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
activations may be specific to PTSD, and likely related to negative self-referralant 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.

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References

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