Combat Veterans with Comorbid PTSD and Mild TBI Exhibit a Greater Inhibitory Processing ERP from the Dorsal Anterior Cingulate Cortex

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ABSTRACT

Posttraumatic stress disorder (PTSD) is common among combat personnel with mild traumatic brain injury (mTBI). While patients with either PTSD or mTBI share abnormal activation of multiple frontal brain areas, anterior cingulate cortex (ACC) activity during inhibitory processing may be particularly affected by PTSD. To further test this hypothesis, we recorded electroencephalography from 32 combat veterans with mTBI—17 of whom were also comorbid for PTSD (mTBI+PTSD) and 15 without PTSD (mTBI-only). Subjects performed the Stop Task, a validated inhibitory control task requiring inhibition of initiated motor responses. We observed a larger inhibitory processing eventrelated potential (ERP) in veterans with mTBI+PTSD, including greater N200 negativity. Furthermore, greater N200 negativity correlated with greater PTSD severity. This correlation was most dependent on contributions from the dorsal ACC. Support vector machine analysis demonstrated that N200 and P300 amplitudes objectively classified veterans into mTBI-only or mTBI+PTSD groups with 79.4% accuracy. Our results support a model where, in combat veterans with mTBI, larger ERPs from cingulate areas are associated with greater PTSD severity and likely related to difficulty controlling ongoing brain processes, including trauma-related thoughts and feelings.

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1. Introduction

Posttraumatic stress disorder (PTSD) is especially common in combat personnel with mild traumatic brain injury (mTBI) and further worsens outcomes following mTBI (Polusny et al., 2011; Tanelian and Jaycox, 2008; Vasterling et al., 2012a). Functional magnetic resonance imaging (fMRI) studies of patients with active PTSD or mTBI suggest that while these patients share abnormalities in dorsolateral prefrontal, middle frontal, and orbitofrontal brain activity, abnormalities in medial frontal and anterior cingulate cortex brain activity may be especially common in patients with PTSD (Stein and McAllister, 2009; Simmons and Matthews, 2012). If so, neural mechanisms underlying the compounding effects of PTSD on

outcomes in personnel with comorbid mTBI likely involve medial frontal and anterior cingulate brain areas.

Medial frontal and anterior cingulate areas (MFC and ACC) are consistently activated during cognitive control tasks requiring conflict monitoring and response inhibition (Ridderinkhof et al., 2004). During these tasks, patients with PTSD generally exhibit increased MFC and ACC activity, and increased errors—abnormalities that likely contribute to difficulties controlling ongoing brain processes, including trauma-related thoughts and feelings in patients with PTSD (Stein et al., 2002; Carrion et al., 2008; Jovanovic et al., 2012; Matthews et al., 2012; Swick et al., 2012; Thomaes et al., 2012). In contrast, patients with mTBI only generally do not exhibit significant errors or differences in brain activation during these tasks (Stewart and Tannock, 1999; Potter et al., 2002; DeHaan et al., 2007; Larson et al., 2011, 2012; Mayer et al., 2012; Terry et al., 2012).

Electroencephalographic (EEG) studies of event-related potentials (ERPs) have also demonstrated generally larger ERPs during

inhibitory processing in patients with PTSD. More specifically, during Go/No-Go or Stop Tasks, patients with PTSD consistently exhibit greater N200 (or N2) and P300 (or P3) ERPs (Shucard et al., 2008; Wu et al., 2010; Covey et al., 2013). N200 and P300 ERPs have been repeatedly associated with conflict monitoring and response inhibition (Nieuwenhuis et al., 2003; Donkers and van Boxtel, 2004; Enriquez-Geppert et al., 2010; Huster et al., 2013). In contrast, ERP studies of inhibitory processing in patients with mTBI only have focused primarily on civilians with injuries from sports, accidents, or assaults— without specifically examining PTSD—and have generally observed normal or attenuated error-related ERPs (Potter et al., 2002; Pontifex et al., 2009; Larson et al., 2011, 2012; De Beaumont et al., 2013).

To date, there are no published ERP studies of inhibitory processing in patients with comorbid PTSD and mTBI. We hypothesized that, among combat veterans with mTBI, those with PTSD would exhibit larger ERPs during inhibitory processing, as compared with those without PTSD. To test our hypothesis, we recorded EEG from veterans with mTBI and a few or no symptoms of PTSD (mTBI-only) and from veterans with mTBI and PTSD (mTBI+PTSD). Subjects performed the Stop Task, a validated inhibitory control task requiring inhibition of initiated motor responses. Consistent with fMRI studies demonstrating increased ACC activity in patients with PTSD during inhibitory processing, and studies localizing the N200 and P300 to the ACC (Huster et al., 2011), we hypothesized that the larger ERPs in our mTBI+PTSD group would localize to the cingulate cortex.

2. Materials and methods

2.1. Subjects

Thirty-two (15 mTBI-only; 17 mTBI+PTSD) male combat veterans from the military conflict in Iraq or Afghanistan provided written informed consent and completed this cross-sectional study, which was conducted from 2010 to 2012 and 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 two sessions. During session 1, subjects completed a detailed clinical assessment, which involved administration of the Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2007), the Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR; First et al., 2002), the Clinician-Administered PTSD Scale (CAPS) (Weathers et al., 2001), and the Beck Depression Inventory II (BDI-II) (Beck et al., 1996). Subjects were included if they: (1) reported experiencing one or more concussive events (mTBI) during combat (i.e. a blast exposure or a blow or jolt to the head) that resulted in a loss or alteration of consciousness for 20 min or less, on the BTBIS; and (2) met criteria for mTBI based on questions adapted from Vasterling et al. (2012b). Each case was also reviewed by Drs. Shu and Matthews, VA psychiatrists who together have over 8 years of experience evaluating and treating veterans with mTBI. Health records related to mTBI were not available; therefore, subjects' recall of trauma history could not be confirmed. TBI variables assessed during Session 1 are presented in Table 1.

Subjects who developed PTSD during or after combat, as determined by the SCID-IV-TR and CAPS score >65 (Weathers et al., 2001), were included in the mTBI+PTSD group (n=17). Subjects who developed PTSD prior to combat were excluded from the study. Subjects without PTSD were included in the mTBI-only group (n=15); however, the mean ± standard deviation (S.D.) CAPS score for the mTBI-only group was 37.3 ± 13.2, suggesting subthreshold PTSD-related symptoms. Exclusion criteria included: (1) meeting criteria for an alcohol or substance use disorder within the past 30 days; (2) history of developing PTSD prior to combat; (3) history of bipolar disorder, attention deficit hyperactivity disorder, or psychotic disorders; or (4) acute medical problems. Included subjects returned for Session 2, where they performed the Stop Task (see Section 2.2 below) while EEG was recorded (see Section 2.3 below).

2.2. Task

During the Stop Task (Matthews et al., 2005), subjects were presented with the letter "X" or "O", in bold, white font, on a black background. Subjects were instructed to press the right mouse button for "X" and the left mouse button for "O". In 25% of the trials (Stop Trials), four separate delays of ∼15, ∼65, ∼115, or

Table 1
Clinical and behavioral variables.

	mTBI-only (n=15) Mean ± S.D.	mTBI+PTSD (n=17) Mean ± S.D.	P
Age, years	29.5 ± 5.7	30 ± 5.4	0.74
Education, years	14.0 ± 1.1	14.0 ± 1.3	0.61
Stop, % errors	12.4 ± ± 13.8	10.3 ± 8.4	0.61
CAPS	37.3 ± 13.2	81.0 ± 17.4	**< 0.001**
CAPS-intrusions	10.9 ± 5.3	20.6 ± 7.1	**< 0.001**
CAPS-avoidance	3.7 ± 3.3	11.1 ± 3.2	**< 0.001**
CAPS-dysphoria	17.8 ± 9.2	38.1 ± 9.5	**< 0.001**
CAPS-hyperarousal	7.9 ± 3.7	12.1 ± 2.0	**< 0.001**
BDI-II	7.1 ± 7.9	21 ± 10.1	**< 0.001**
MDD	n=9	n=15	0.11
Other anxiety disorders	n=4	n=9	0.17
Psychoactive medications	n=4	n=6	0.71
Blast-related	n=13	n=14	1.00
Number of blasts	13.8 ± 20.1	6.2 ± 7.3	0.20
LOC	n=7	n=6	0.72
Retrograde amnesia	n=3	n=2	0.65
PCS	n=10	n=11	0.70

BDI-II, Beck Depression Inventory II; CAPS, Clinician-Administered PTSD Scale; LOC, loss of consciousness; MDD, major depressive disorder; mTBI, mild traumatic brain injury; PCS, post-concussive symptoms; PTSD, posttraumatic stress disorder; and S.D., standard deviation. Significant group differences in bold (independent sample *t*-test or Fisher's exact test).

∼165 ms (depending slightly on stochastic software delays but not scaled by subject response time) after "X" or "O" presentation, subjects were presented with a Stop Signal (auditory beep), instructing subjects to inhibit the button press. Subjects were given four blocks to practice the task, after which, when all subjects were likely to be at the plateau of their learning curve, they began the trials used for further analyses. Each trial lasted 1800 ms (or until subject response). Trials were separated by a jittered inter-trial interval of between 700 and 1200 ms (black background only). During successful Stop Trials, subjects correctly inhibited button presses when presented with the Stop Signal; during Error Trials, subjects incorrectly responded with button presses when presented with the Stop Signal (Fig. 1). After artifact removal, the number of successful Go Trials used for subject ERP averages ranged from 283 to 542; Stop Trials ranged from 69 to 154; Error Trials ranged from 3 to 41. Given the low number of Error Trials, ERP results from Error Trials should be interpreted with caution. However, the analysis showed a logical trend away from successful Stop activity and toward no beep, or Go Trial activity (i.e. no button press), which seemed worth reporting for future rigorous validation. Please refer to Online Supplementary materials (Online Supplementary Figs. 1–3).

2.3. EEG acquisition and preprocessing

EEG data were collected synchronously from 132 scalp and four infra-ocular electrodes with an active reference (BioSemi Instrumentation, Amsterdam, NL) at a sampling rate of 512 Hz with 24-bit analog-to-digital resolution. Onsets and offsets of Stop Task 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). In addition, data were re-referenced to average reference and high-pass filtered 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.

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 nonbrain artifact (e.g. eye, muscle, and line noise) by visual inspection of 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
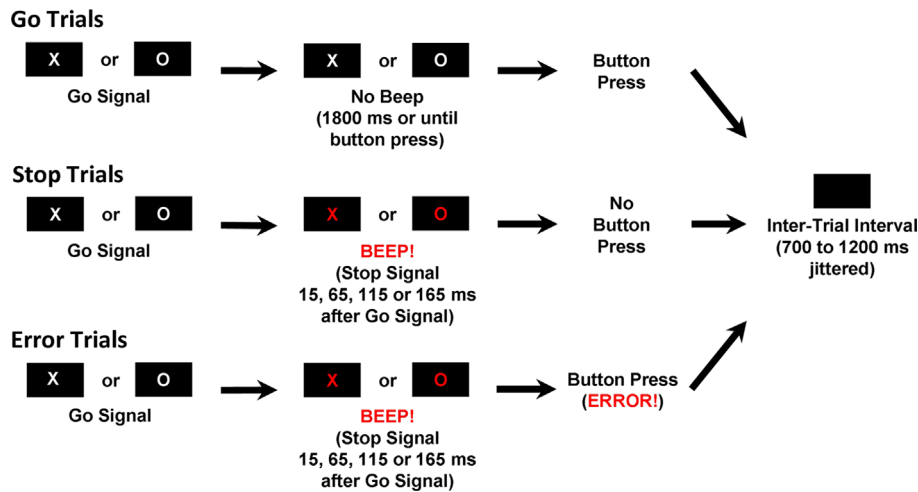
Go Trials

X or O → X or O → Button Press

Go Signal   No Beep
(1800 ms or until
button press)

Stop Trials

X or O → X or O → No Button Press → Inter-Trial Interval (700 to 1200 ms jittered)

Go Signal   BEEP!
(Stop Signal
15, 65, 115 or 165 ms
after Go Signal)

Error Trials

X or O → X or O → Button Press (ERROR!)

Go Signal   BEEP!
(Stop Signal
15, 65, 115 or 165 ms
after Go Signal)

Fig. 1. Schematic for three likeliest outcomes during Stop Task. During Go Trials, subjects are presented with Go Signal ("X" or "O") without Stop Signal (beep) and responded with corresponding button press (right for "X"; left for "O"). During successful Stop Trials, subjects are presented with Go Signal followed by Stop Signal (beep) and responded correctly by inhibiting button press. Error Trials are Stop Trials where subjects are presented with Go Signal followed by Stop Signal but fail to inhibit, and incorrectly respond with button press. See *Materials and methods* for details.

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 activity), were back projected to scalp electrode positions. For each subject, onset of Stop Signal 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 Stop Trials were averaged to generate single-subject ERPs. For each group, single-subject ERPs were averaged to generate group ERP. Two-tailed independent sample t-tests were also 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. 100–300 ms for N200). 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 putative brain ICs or those with < 15% residual variance from an equivalent dipole model and localized within the brain volume. 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.

More specifically, a hierarchical clustering was performed based on a distance measurement between dipole locations. The only variable in this process is the number of clusters, which is true of many clustering algorithms. The number 15 was arrived at by clustering with a wide range of cluster numbers and choosing the number that was in the middle of a fairly stable stretch of cluster numbers (that is, very well-defined clusters were relatively intact, but minor changes in the peripheries of clusters accounted for the variations among cluster numbers). Essentially, the final number of clusters (within reason) would not have altered our result significantly, but may have spread or narrowed the physical spread of the cluster dipoles of interest. There is no exact science to clustering dipoles at the present moment. The head models themselves use an average MNI brain, which makes exact anatomical localization impossible, though general placement is quite reliable. Furthermore, variations in IC expression across subjects can make clustering an extra challenge because the distributions of dipoles across subjects do not always line up exactly. Nevertheless, we believe that the clusters that we have identified are reasonably homogeneous and fairly well-localized to the locations we have identified. But because we understand that these are slightly imperfect estimations, we intended to express that these cluster locations are 'in or near' the stated locations, but this terminology gets dropped when we begin to discuss what is known about the brain regions that we think are involved in the phenomenon of interest. We added the phrase 'in or near' to the manuscript where the localization of our clusters in particular is discussed.

To determine which clusters contributed most to the observed correlation with PTSD severity, each cluster was removed from the raw data back projection individually, and the correlation was recalculated. The clusters that caused the largest decrease in the correlation P-value were considered the highest contributors to the observed scalp correlation.

To test whether inhibitory processing ERPs can objectively classify combat veterans with mTBI into groups with and without PTSD, a support vector machine (SVM) analysis

is performed in R (http://www.r-project.org) using the e1071 library (cran.r-project.org/web/packages/e1071). Machine learning methods can be used to find the unknown decision function f that maps EEG signals to groups: $f(\nu) \rightarrow g$, where ν represents the EEG data (N200/P300) and g is the predicted group of allocation (mTBI/mTBI+PTSD). Once the decision function is learned from the training data, it can be used to predict the group assignment in a new set of data. The SVM algorithm corresponds to an optimal classifier with strong generalization (Boser et al., 1992). For a detailed description of the SVM, see Burges (1998). The SVM was performed on the full set of 32 subjects to test how well the group could be optimally classified. Thus, peak single-subject N200 and P300 amplitudes are utilized to develop an algorithm that optimally segregates subjects into mTBI-only and mTBI+PTSD groups. Due to the limited number of subjects, a general model that used a different cohort of subjects for training and testing could not be performed.

3. Results

3.1. Clinical and behavioral results

Based on selection criteria, PTSD severity was significantly higher in veterans with mTBI+PTSD (mean ± S.D. CAPS scores: mTBI-only, 37.3 ± 13.2; mTBI+PTSD, 81.0 ± 17.4; P < 0.001; see Table 1). Groups did not differ on demographic variables, including age or education, or on head injury variables, such as mechanisms of mTBI, number of blasts, or mTBI-related changes in mental status (e.g. loss of consciousness or retrograde amnesia) (Table 1). Behaviorally, groups did not differ on total number of errors during Stop Trials. One low-scoring mTBI-only subject who scored 47% increased the standard deviation of the mTBI-only group to three times that of the PTSD+mTBI group. Examination of the results with and without this subject confirmed that, despite his low behavioral score, his brain activity was comparable to the other subjects and was left in the analysis (Table 1; also see Online Supplementary Fig. 3).

As shown in Table 1, groups do not differ on the clinical variables of comorbid major depressive disorder (MDD) and other anxiety disorders or treatments with psychoactive medications. However, groups did differ on depression severity; more specifically, veterans with mTBI+PTSD exhibited greater depression severity (mean ± S.D. BDI-II scores: mTBI-only, 7.1 ± 7.7; mTBI+ PTSD, 21 ± 10.1; P < 0.001; see Table 1).

3.2. ERP results

During successful Stop Trials, both groups exhibited two ERPs (N200 and P300) consistently associated with conflict monitoring

and response inhibition (Huster et al., 2010). While peak N200 amplitudes did not correlate with behavioral accuracy (due to all subjects exhibiting high accuracy), N200 ERPs were not observed during Go or Error Trials – consistent with previous reports that N200 is associated with response inhibition (also see Online Supplemental Fig. 4). Compared with mTBI-only veterans, mTBI+PTSD veterans exhibited significantly larger N200 amplitudes at the vertex channel, Cz (t-test; $P < 0.0003$; Fig. 2). Of note, this group difference remained significant ($P < 0.03$) after covarying for depression severity. Removal of Go Signal locked ERP activity decreased amplitude of Stop Signal locked N200 (Figs. 3 and 4); however, the magnitude of decrease – on the order of ∼1 μV – is comparable in both mTBI-only and mTBI+PTSD veterans (Fig. 5). Note that group N200 differences remain significant after correcting for ERP responses to the Go Signal ($P < 0.05$). Furthermore, peak Go Signal locked N300 amplitudes were not correlated with PTSD severity, in contrast to Stop Signal locked N200 – either corrected or uncorrected for Go Signal locked ERP activity (Online Supplementary Fig. 5). Correction for auditory N1 (in response to Stop Signal) is not necessary given the latency of the observed N200 and the source separation and localization results below.

While P300 amplitudes were greater in mTBI+PTSD veterans compared with mTBI-only veterans, the differences were not statistically significant. For all veterans, no N200 or P300 ERPs were observed during Error Trials (Fig. 2), which is consistent with N200 and P300 arising from brain processes necessary for response inhibition. Since group differences were only observed for N200 ERPs, we focused on N200 negativity in the subsequent analysis.
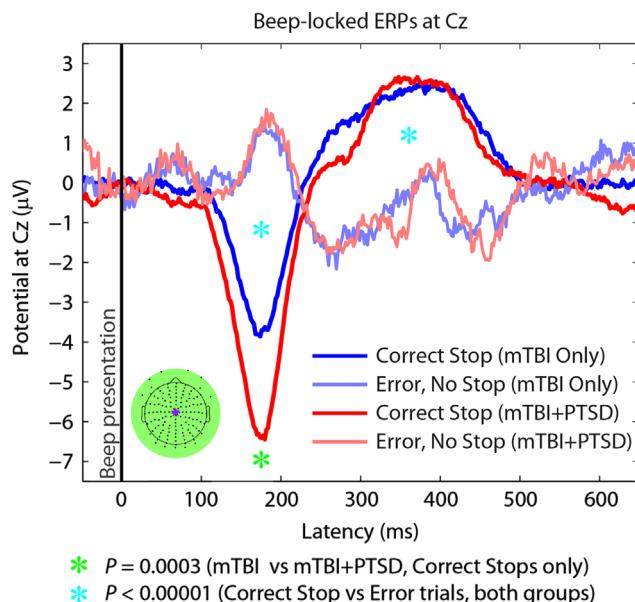

Fig. 2. Grand average Stop Signal locked ERPs at Cz for mTBI-only (blue) and mTBI+PTSD (red) veterans, during Stop (solid lines) and Error (lightened lines) trials. Green asterisk indicates latency with significant group differences during successful Stop Trials (t-test, $P = 0.0003$). Turquoise asterisk indicates latencies with significant trial-type differences (t-test, $P < 0.00001$). The word latency is used here to indicate the time point when groups were significantly different from one another. Using the word 'component' in this manuscript would be confusing because of our use of 'independent components', which has a completely different meaning. We have therefore left the word 'latency' as is since it is technically correct, though may not be the conventional terminology. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Correlations

Peak N200 amplitudes from single-subject ERPs were computed by identifying the most negative ERP value between 100 and 300 ms latencies. For all veterans, greater central-medial N200 negativity was correlated with greater PTSD severity (Spearman's $\rho = -0.573$ with $P < 0.001$ at Cz; Fig. 6). Correlation strength was smaller (-0.374) but remained significant ($P < 0.02$) after controlling for depression severity.

For all veterans, correlations were significant for all PTSD symptoms clusters (re-experiencing, avoidance/numbing, and hyperarousal subscores on the CAPS). However, the strongest and most significant correlations were for avoidance/numbing (Spearman's $\rho = -0.522$, $P < 0.001$) and hyperarousal (Spearman's $\rho = -0.593$, $P < 0.0002$). The correlation with re-experiencing was lower, but still significant (Spearman's $\rho = -0.394$, $P < 0.04$). For both avoidance/numbing and hyperarousal, strength of correlation was smaller but remained significant after controlling for depression severity (Spearman's $\rho = -0.330$, with $P < 0.04$; -0.447, 0.006; respectively). Dividing the CAPS test differently into four subclusters as described by Simms et al. (2002)—intrusions (B1–5), avoidance (C1–2), dysphoria (C3–7, D1–3), and hyperarousal (D4–5)—we similarly found all subcluster scores to significantly correlate with N200 magnitude, although the intrusion subcluster was again less significant (intrusions: Spearman's $\rho = -0.32$, $P < 0.04$; avoidance: Spearman's $\rho = -0.42$, $P < 0.008$; dysphoria: Spearman's $\rho = -0.6$, $P < 0.0001$; hyperarousal: Spearman's $\rho = -0.42$, $P < 0.008$). Dysphoria and hyperarousal subclusters were still significant after correcting for depression, but intrusions and avoidance were not (dysphoria: Spearman's $\rho = -0.42$, $P < 0.01$; hyperarousal: Spearman's $\rho = -0.31$, $P < 0.05$).

Within-group correlations were significant only for N200 negativity and total CAPS score among mTBI+PTSD veterans (Spearman's $\rho = -0.305$ with $P < 0.05$). This correlation trended toward significance among mTBI-only veterans (Spearman's $\rho = -0.324$ with $P = 0.11$).

From the 15 anatomic clusters of ICs responsible for the greatest N200 variance, we tested the significance of the correlation between N200 negativity and PTSD severity when any one cluster was removed from the analysis (Fig. 7). Strength of correlation was most affected by removing cluster 9 (which localizes to or near the dorsal ACC) from the analysis, which decreased Spearman's ρ from -0.57 to -0.49. Strength of correlation was also affected by clusters 12, 8, 16, and 3, which localize to or near the bilateral occipital areas, precuneus, L sensorimotor areas, and anterior ACC, respectively and which decreased Spearman's ρ to order of -0.50 to -0.56. Please see Online Supplementary Figs. 6 and 7 for more detailed information on how clusters 9 (dorsal ACC) and 12 (occipital areas) contribute to observed N200 differences.

3.4. Clinical classification

The above results suggest that, among combat veterans with mTBI, a larger inhibitory processing ERP is associated with greater PTSD severity. To test the hypothesis that larger N200 and P300 ERPs can objectively classify combat veterans with mTBI into groups with and without PTSD, we used SVM, a multivariate pattern recognition technique. Further, SVM was used to develop an algorithm that, with peak single-subject N200 and P300 amplitudes as inputs, optimally segregates subjects into mTBI-only and mTBI+PTSD groups. Consistent with the hypothesis, peak single-subject N200 and P300 amplitudes allowed discrimination with an accuracy of 81% ($P < 0.002$, sensitivity=70.6%, specificity=88.2%; see Table 2).
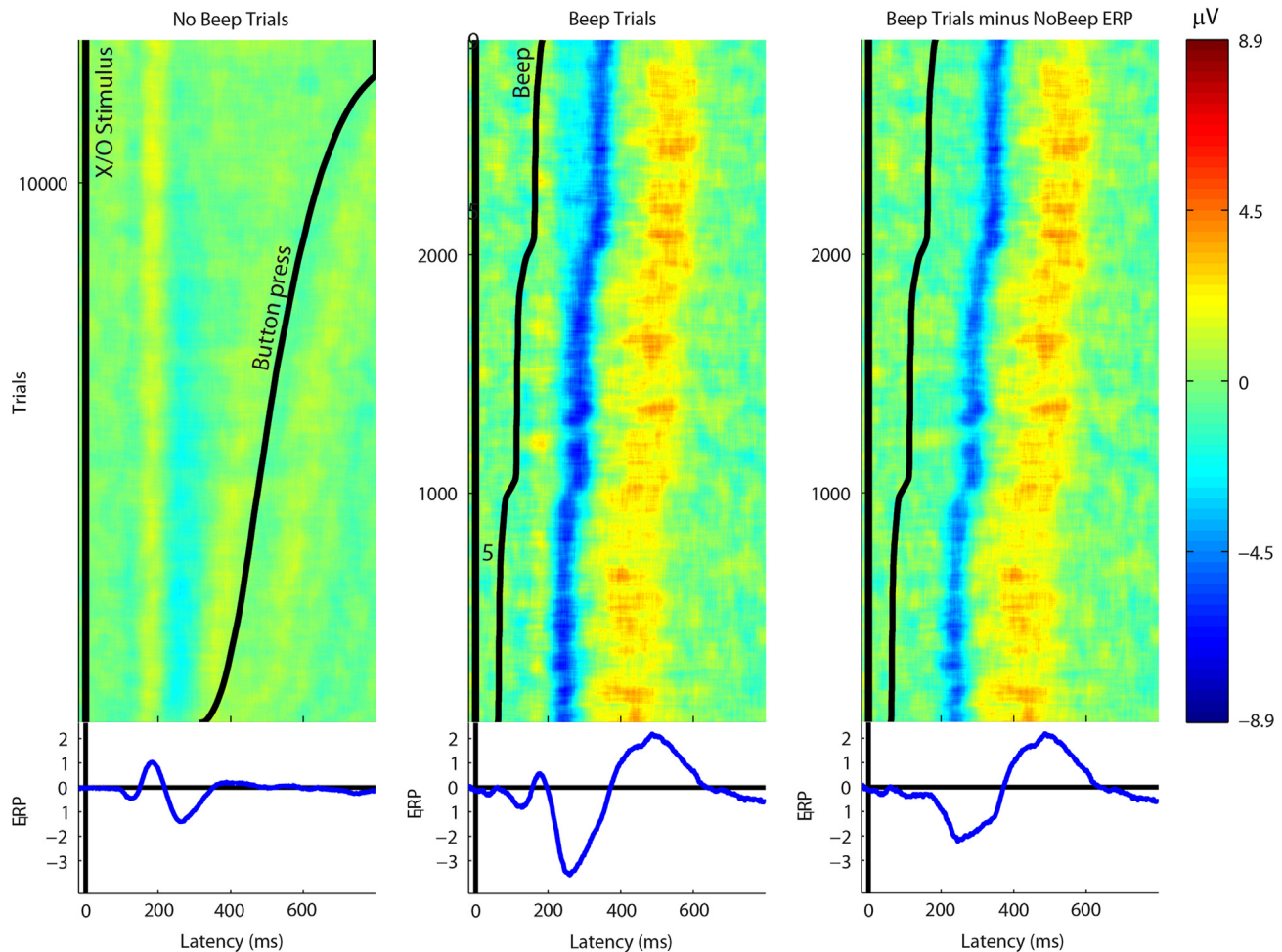
Fig. 3. Go Signal locked ERP images: Left, Go Trials for all subjects sorted by response latency; Middle, Stop Trials for all subjects sorted by Stop Signal latency; Right, Stop Trials for all subjects sorted by Stop Signal latency with Go Signal locked ERP responses removed.

4. Discussion

Patients with PTSD consistently exhibit larger ERPs during inhibitory processing (Shucard et al., 2008; Wu et al., 2010; Covey et al., 2013). In contrast, mTBI-only subjects generally exhibit normal, smaller, or slower inhibitory processing ERPs (Potter et al., 2002; Pontifex et al., 2009; Larson et al., 2011, 2012; De Beaumont et al., 2013). These studies suggest that, among combat veterans with mTBI, greater inhibitory processing ERPs may be especially common in patients with PTSD. Consistent with this hypothesis, we observed greater N200 negativity during the Stop Task in veterans with comorbid PTSD and mTBI, compared with mTBI-only subjects. Furthermore, greater N200 negativity correlated with greater PTSD and stress-related symptom severity in all mTBI+ veterans. In an exploratory analysis, we found that inhibitory processing ERPs can objectively classify combat veterans with mTBI into groups with and without PTSD.

We further observed that larger ERPs in veterans with PTSD and mTBI primarily arose from (or from near) the dorsal ACC; this observation is consistent with studies demonstrating medial frontal and cingulate overactivation during inhibitory processing in patients with PTSD (Stein et al., 2002; Carrion et al., 2008; Jovanovic et al., 2012; Matthews et al., 2012; Swick et al., 2012; Thomaes et al., 2012). In contrast, patients with mTBI-only generally do not exhibit medial frontal and cingulate overactivation during inhibitory processing (Stewart and Tannock, 1999; DeHaan

et al., 2007; Larson et al., 2011, 2012; Mayer et al., 2012; Terry et al., 2012). These results raise the possibility that, in combat veterans with mTBI, increased medial frontal and cingulate activity during inhibitory processing may be especially common in patients with PTSD, and may be related to hypervigilance and/or difficulties controlling ongoing brain processes.

4.1. PTSD-related ERP differences

Consistent with previous studies (Shucard et al., 2008; Wu et al., 2010; Covey et al., 2013), our results indicate that mTBI+PTSD veterans exhibit larger inhibitory processing ERPs than mTBI-only veterans. In contrast to our results, Covey et al. (2013) and Shucard et al. (2008) observed greater P300, but not N200, in patients with PTSD. This difference may arise from our subjects generally exhibiting more severe PTSD symptoms from combat-related trauma, while subjects in Covey et al. (2013) and Shucard et al. (2008) studies generally exhibited less severe PTSD symptoms from civilian-related trauma. While N200 and P300 are closely related, there is evidence that N200 primarily arises from brain processes responsible for conflict monitoring, while P300 primarily arises from brain processes responsible for response inhibition (Nieuwenhuis et al., 2003; Donkers and van Boxtel, 2004; Enriquez-Geppert et al., 2010; Huster et al., 2013). This distinction raises the possibility that observed N200 processing differences in veterans with more severe combat-related PTSD symptoms are
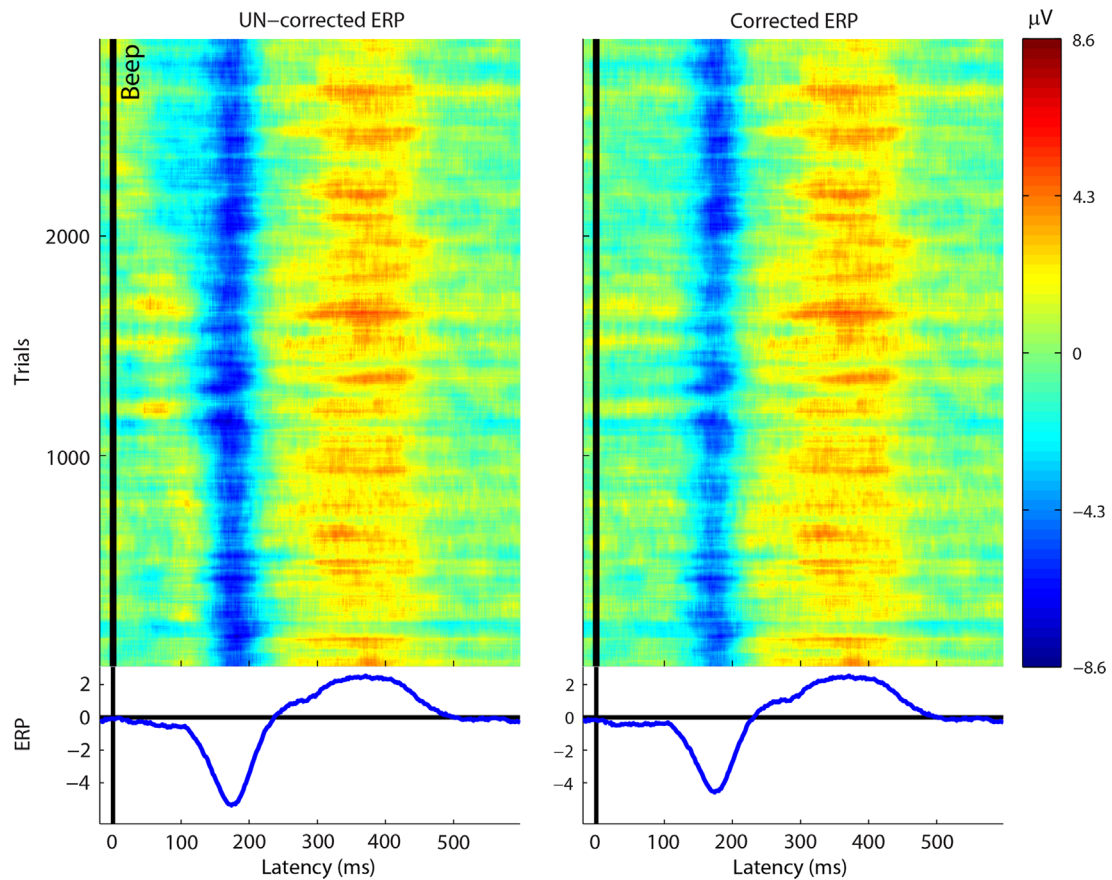
Fig. 4. Stop Signal locked ERP image: Left, Stop Trials for all subjects sorted by Stop Signal latency; and Right, Stop Trials for all subjects sorted by Stop Signal latency with Go Signal locked ERP responses removed.
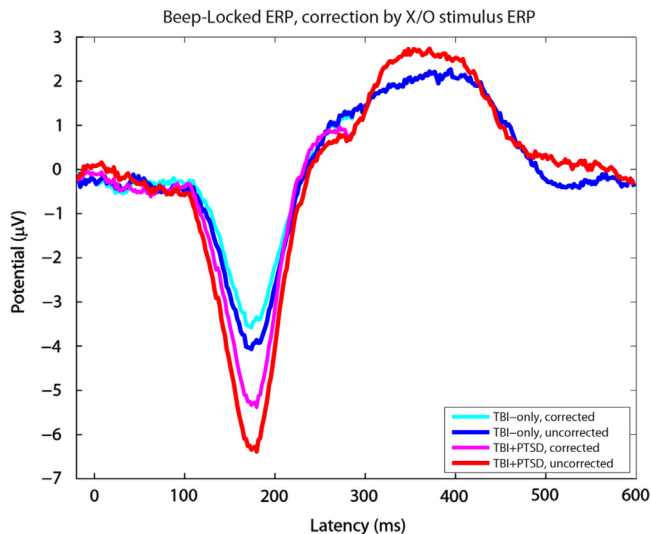

Fig. 5. Grand average Stop Signal locked ERPs at Cz for mTBI-only veterans uncorrected (blue) and corrected (turquoise) for Go Signal locked ERP activity, and for mTBI+PTSD veterans uncorrected (red) and corrected (magenta) for Go Signal locked ERP activity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 6. For all veterans, peak negative N200 amplitudes at Cz (from successful Stop Trials only) are plotted along the y-axis against Clinician-Administered PTSD Scale (CAPS) scores on the x-axis – mTBI-only veterans in blue; mTBI+PTSD veterans, red (Spearman's $\rho = -0.573$; $P < 0.001$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

primarily influenced by difficulty managing conflicting thoughts and feelings. Consistent with this model, we observed that in all mTBI+PTSD veterans, greater N200 negativity was correlated with greater PTSD severity, especially in the avoidance/dysphoria and hyperarousal symptom clusters. Furthermore, in all mTBI+
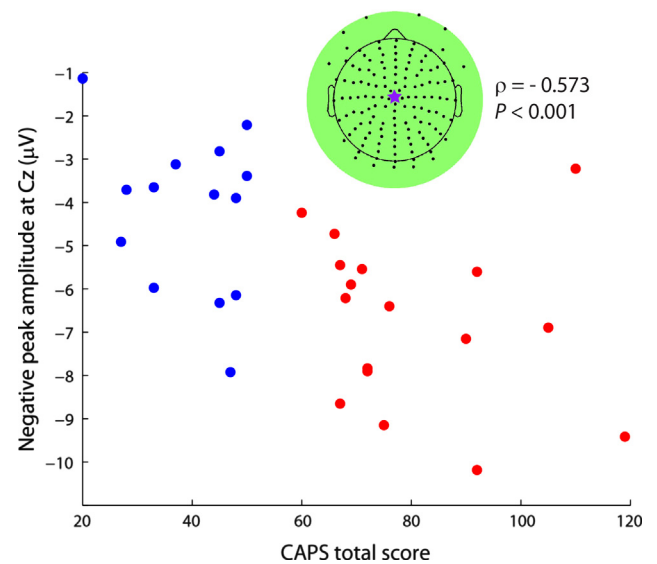
veterans (with and without clinical PTSD), greater N200 negativity was correlated with greater CAPS scores—raising the possibility that greater N200 negativity might reflect greater stress-related distress in general.
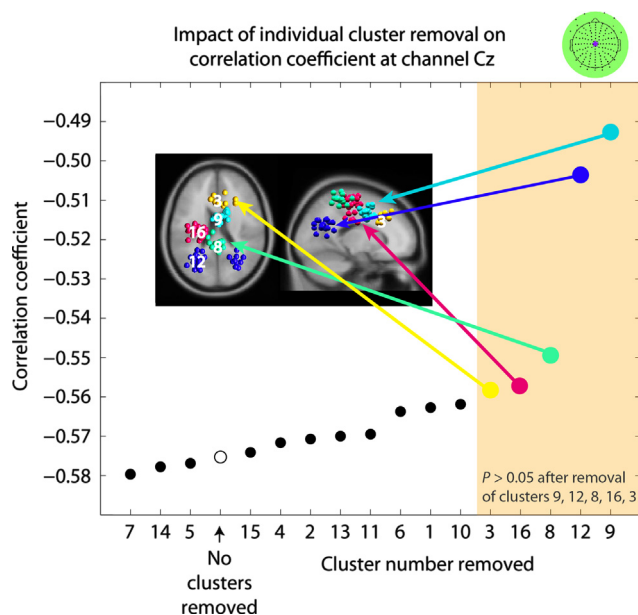
Fig. 7. The 16 anatomic clusters of ICs with greatest contributions to N200 variance are plotted along the *x*-axis in the order of their contribution to the correlation between N200 negativity and PTSD severity—with lowest contributors on the far left, and the greatest contributors on the far right. For each cluster along the *x*-axis, the significance of the correlation with only that cluster removed from the analysis is plotted along the *y*-axis. Midsagittal and midtransverse images of the five clusters with greatest contributions to the correlations are indicated by arrows: dorsal ACC (turquoise), bilateral occipital areas (navy blue), precuneus (sea green), and L sensorimotor area (fuchsia) and a more anterior ACC (yellow). Removal of the cluster localizing to the dorsal ACC decreases Spearman's ρ from -0.57 to -0.49. Removal of clusters in the shaded (salmon color) region of the plot eliminates statistical significance of correlation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
SVM classification into groups with and without PTSD.

	PTSD+ (SVM)	PTSD− (SVM)	Sens/Spec
PTSD+ (CAPS > 65)	15	2	88% (Sens)
PTSD− (CAPS < 65)	4	11	73% (Spec)
Accuracy			81%
Corrected χ^2: 10.1			$P < 0.002$

PTSD, posttraumatic stress disorder; SCID-IV-TR, Structured Clinical Interview for the Diagnostic and Statistical Manual IV-TR; Sens, sensitivity; Spec, specificity; and SVM, support vector machine.

4.2. Medial cortical inhibitory processing activity in patients with PTSD

The role of the ACC in inhibitory control is well established (Ridderinkhof et al., 2004). Since patients with PTSD commonly report difficulties controlling ongoing brain processes, including trauma-related thoughts and feelings (Lanius et al., 2010), abnormal inhibitory processing by the ACC may play a role in the pathophysiology of PTSD. Consistent with this model, patients with PTSD generally exhibit increased ACC activity, as well as increased errors, during inhibitory control tasks and related areas that are generally overactivated during inhibitory processing (Stein et al., 2002; Carrion et al., 2008; Jovanovic et al., 2012; Matthews et al., 2012; Swick et al., 2012; Thomaes et al., 2012). Furthermore, two recent meta-analyses identified the ACC as among the areas most consistently activated in patients with PTSD during processing of trauma-related stimuli (Ramage et al., 2012; Sartory et al., 2013). The most parsimonious model of these results suggests that PTSD is associated with difficulties inhibiting both neutral and trauma-related thoughts and feelings, which

are characterized by increased ACC activity. Consistent with this model, we observed that the correlation between greater N200 negativity and PTSD severity among mTBI+ veterans arises principally from the ACC.

We also observed significant contributions to the correlation between N200 negativity and PTSD severity from the precuneus. While multiple fMRI studies have demonstrated precuneus activation during inhibitory processing (Menon et al., 2001; O'Connell et al., 2007; Brown et al., 2007, 2008), the precuneus may be more responsible for behavioral engagement vs. frank response inhibition (Barber and Carter, 2005; Zhang and Li, 2012). Specific to patients with PTSD, the precuneus is among brain areas—along with the ACC, posterior cingulate, and retrosplenial cortex—most consistently activated during processing of trauma-related stimuli (Ramage et al., 2012; Sartory et al., 2013). In contrast, patients with mTBI-only generally do not exhibit overactivation of medial cortical areas at rest (Mayer et al., 2011; Johnson et al., 2012; Stevens et al., 2012; Zhang et al., 2012; Zhou et al., 2012) or during inhibitory processing (Stewart and Tannock, 1999; DeHaan et al., 2007; Larson et al., 2011, 2012; Mayer et al., 2012; Terry et al., 2012). These results raise the possibility that increased medial cortical activity among mTBI+ veterans may be due to comorbid PTSD, and may be related to difficulties inhibiting PTSD-related symptoms, such as hyperarousal, which was correlated with N200 magnitude in the present report.

4.3. Limitations

Similar to other published studies of combat-related mTBI, we relied on subject recall of injuries and course of symptoms. This limitation, combined with this study's cross-sectional design, precludes a definitive answer to whether greater N200 negativity preceded, or followed, traumatic events or onset of symptoms. In addition, similar to veterans receiving treatment at Veterans Affairs facilities nationally, subjects in this study were comorbid for multiple psychiatric problems. It is also important to note that our findings are relative only to individuals who have experienced an mTBI event and have some level of combat-related PTSD since no mTBI- and PTSD-free controls were included in this study.

While prevalence of MDD did not differ between groups, veterans with PTSD after mTBI exhibited both greater PTSD and depression severity. Thus, greater N200 amplitudes in this group may arise from the effects of both PTSD and depression. Most studies of inhibitory ERPs demonstrate decreased or equal, including N200, amplitudes in depressed subjects (Kaiser et al., 2003; Zhang et al., 2007b; Holmes and Pizzagalli, 2008; Ruchsow et al., 2008; Vanderhasselt and De Raedt, 2009; Quinn et al., 2012; Vanderhasselt et al., 2012; Clawson et al., 2013); this finding is consistent with greater N200 amplitudes in mTBI+PTSD veterans being specific to PTSD. However, four studies have demonstrated increased N200 amplitudes in depressed subjects (Ogura et al., 1991; Zhang et al., 2007a; Krompinger and Simons, 2009, 2011). The varying effects of depressive symptoms on N200 amplitudes likely arise from depression being a heterogeneous disorder, with some patients exhibiting more melancholic features and other patients more anxious features. Though not fully examined in previous studies, we would hypothesize that patients with melancholic depression exhibit normal or decreased N200 amplitudes, while patients with anxious depression would exhibit increased N200 amplitudes (similar to patients with anxiety disorders including PTSD). We plan to specifically test these hypotheses in future studies of inhibitory ERPs in patients with mTBI by recruiting adequately powered samples of mTBI+ patients with MDD only, MDD+PTSD, and PTSD only.

Importantly, prevalence of MDD, other psychiatric disorders, treatment with psychiatric medications, and head injury variables

were not significantly different between the groups. ERP differences and correlations also remained significant after controlling for depression severity; thus allowing us to conclude that observed differences largely arise from PTSD. While our subjects with mTBI-only did not meet categorical and severity criteria for PTSD, the mean $\pm$ S.D. CAPS score for this group was 37.3 ± 13.2, suggesting presence of subthreshold PTSD symptoms. As such, this limitation suggests greater N200 negativity is primarily a marker of greater PTSD severity rather than a categorical marker of PTSD diagnosis—a conclusion also supported by our correlational analysis. Nevertheless, peak single-subject N200 and P300 amplitudes did objectively classify subjects into mTBI-only or mTBI+PTSD groups with 79.4% accuracy.

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 comorbid PTSD and mTBI, compared with those having mTBI-only, would exhibit larger inhibitory processing ERPs from the cingulate cortex during the Stop Task, a validated inhibitory control task requiring inhibition of initiated motor responses. Consistent with our hypothesis, veterans with comorbid PTSD and mTBI exhibited a larger inhibitory processing ERP (N200 negativity). Furthermore, N200 negativity correlated with greater PTSD severity. The significance of this correlation depended on contributions from (or from near) the dorsal ACC and precuneus, both medial cortical areas responsible for managing conflicting stimuli and planned responses. These results are consistent with a model where the negative effects of PTSD on outcomes following mTBI are associated with a relative overactivation of medial cortical areas during inhibitory processing. Future studies will focus on how PTSD-related differences in medial cortical activity during inhibitory processing may improve diagnosis and treatment of PTSD, particularly in combat veterans with mTBI.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2014.07.010.

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Posttraumatic stress disorder (PTSD) is common among combat personnel with mild traumatic brain injury (mTBI). While patients with either PTSD or mTBI share abnormal activation of multiple frontal brain areas, anterior cingulate cortex(ACC) activity during inhibitory processing may be particularly affected by PTSD. To further test this hypothesis, we recorded electroencephalography from 32 combat veterans with mTBI—17 of whom were also comorbid for PTSD (mTBIþPTSD) and 15 without PTSD (mTBI-only). Subjects performed the Stop Task, a validated inhibitory control task requiring inhibition of initiated motor responses. We observed larger inhibitory processing event related potential (ERP) in veterans with mTBIþPTSD, including greater N200 negativity. Furthermore, greater N200 negativity correlated with greater PTSD severity. This correlation was most dependent on contributions from the dorsal ACC. Support vector machine analysis demonstrated that N200 and P300 amplitudes objectively classified veterans into mTBI-only or mTBIþPTSD groups with 79.4% accuracy. Our results support a model where, in combat veterans with mTBI, larger ERPs from cingulate areas are associated with greater PTSD severity and likely related to difficulty controlling ongoing brain processes, including trauma-related thoughts and feelings.

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Mild traumatic brain injury, posttraumatic stress disorder, EEG, ICA, biomarker, N200, P300, conflict monitoring, response inhibition

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