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Research report

Reduced P3b brain response during sustained visual attention is associated with remote blast mTBI and current PTSD in U.S. military veterans

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HIGHLIGHTS

- Neural correlates of sustained visual attention in veterans with blast mTBI and/or PTSD were examined.
- P3b amplitude comparably reduced in veterans with blast mTBI and/or PTSD compared to controls.
- P3b amplitude reduction during a DS-CPT may index generalized brain pathology in mTBI/PTSD.

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ABSTRACT

Approximately 275,000 American service members deployed to Iraq or Afghanistan have sustained a mild traumatic brain injury (mTBI), with 75% of these incidents involving an explosive blast. Combat-related mTBI is frequently associated with comorbid mental health disorders, especially posttraumatic stress disorder (PTSD). Attention problems, including sustained attention, are common cognitive complaints of veterans with TBI and PTSD. The present study sought to examine neural correlates of sustained attention in veterans with blast mTBI and/or current PTSD. In 124 veterans of Operations Enduring and Iraqi Freedom (OEF/OIF), we examined event-related potentials (ERPs) elicited by targets and non-targets during performance of a degraded-stimulus continuous performance task (DS-CPT). Four groups, consisting of veterans with blast-related mTBI only, current PTSD only, both blast mTBI and PTSD, and a control group, were studied. Compared to all other groups, blast mTBI only participants were more likely to respond regardless of stimulus type during the DS-CPT. During target detection, the three mTBI/PTSD groups showed reduced amplitude of the P3b (i.e., P300) ERP at Pz compared to the control group. P3b of the three affected groups did not differ from each other. These results suggest that parietal P3b amplitude reduction during target detection in the DS-CPT task may be an index of brain pathology after combat trauma, yet the diminished brain response fails to differentiate independent effects of blast-related mTBI or severity of PTSD symptomatology.

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1. Introduction

The recent conflicts in Iraq and Afghanistan have had a significant impact on the physical and psychological well-being of American service members. Aspects of these engagements, including multiple and longer tours of duty, increased exposure to physical and mental stressors, as well as higher survival rates due to advances in body armor, have contributed to elevated rates of traumatic brain injury (TBI) and stress-related health problems, such as posttraumatic stress disorder (PTSD) in returning military service members [24,33].

Traumatic brain injury (TBI) is one of the most common injuries sustained by American service members deployed to Iraq and Afghanistan [55,58]. The Department of Defense reported that 333,169 service members sustained a traumatic brain injury between 2000 and 2015, with 82% of those being classified as mild TBI (mTBI) (http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi). Explosive blasts, such as those from improvised explosive devices (IEDs), are commonly involved in reported injuries to ser-

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vice members [55,58]. Of those veterans returning from these wars who experienced head injury, approximately 75% of incidents involved an explosive blast [20].

An mTBI in a combat environment often results from intense and emotionally traumatic events where threat of death or serious injury to self or others is prominent; thus, mTBI is frequently associated with comorbid mental health disorders, especially posttraumatic stress disorder (PTSD)[10,20]. Furthermore, mTBI-related postconcussive cognitive symptoms, such as memory and attention problems, have been shown to overlap with symptoms of PTSD [26,29,48]. [20] found that up to 44% of OIF service members who reported an mTBI also met criteria for PTSD, and that PTSD explained part of the relationship between mTBI and memory and concentration problems (see also [39,45]).

Attention problems are common complaints by veterans with mTBI and PTSD. For example, Lew et al. [26], in a group of 66 combat-related mTBI patients who had completed tours of military duty in Iraq or Afghanistan, found that about 50% reported problems with attention and concentration [26]. While self-reports by veterans with mTBI and/or PTSD indicate a large incidence of attention-related problems, fewer studies have investigated whether these veterans actually manifest attentional deficits on behavioral measures of attention [5]. Extant findings are somewhat inconsistent, but several reports indicate that mTBI patients have performed more slowly on attention tasks [54,56], show deficits in focused attention [11,54,56], and are impaired in attentional vigilance during tasks that require sustained attention [41,60]. Attentional problems are also a common complaint of patients with a PTSD diagnosis [19,22,31]. Studies have shown that veterans with PTSD perform worse than those without PTSD on tasks measuring focused and sustained attention [44,47,57]. Finally, a study by Barlow-Ogden and Poynter [5] found that subjects with comorbid mTBI and PTSD were less accurate, had slower reaction times, and showed higher variability in responses on focused and sustained attention tasks compared to both a PTSD and a healthy control group.

In the present study, we used the degraded stimulus version of the continuous performance task (DS-CPT) to examine neural correlates of sustained visual attention and vigilance in veterans with Blast mTBI and/or current PTSD. CPTs evaluate the ability to maintain continuous, focused readiness for detecting and responding to selected target stimuli over a prolonged time period. To our knowledge, no published studies have implemented the DS-CPT to characterize neural anomalies during sustained attention in veterans with blast mTBI with or without comorbid PTSD. We aimed to address whether these veterans exhibit diminished P3b event-related potential (ERP) amplitudes, compared to controls, in response to target stimuli, and whether they exhibit early processing abnormalities evident in early evoked potentials. The P3b, a subcomponent of the P300 brain response, is a well-known electrophysiological index of attentional allocation capacity and working memory updating [14,15,38]. Thus, P3b amplitude is sensitive to the amount of attentional resources allocated toward a stimulus [38]. Reduced P3b amplitude has been shown to reflect cognitive dysfunction in subjects with mTBI [9,13,16,25]. We hypothesized that the comorbid Blast mTBI + PTSD group would show a greater deficit in attention allocation capacity, as indexed by P3b amplitude reduction, than would the Blast mTBI and PTSD only groups.

2. Materials and methods

2.1. Participants

Participants consisted of 124 veterans of Operations Enduring and Iraqi Freedom (OEF/OIF), previously described [12,18], with self-reported traumatic combat experiences or exposure to explosive blasts during their most recent deployment (1–5 years before participation). Exclusion criteria included native language other than English, current or pre-deployment unstable medical condition that would reasonably be expected to significantly affect brain function (e.g., anoxic episode >10 s, stroke, seizures, multiple sclerosis, etc.), uncorrected visual problems or hearing loss, moderate or severe TBI not due to blast, any pre-deployment Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) [1] Axis I psychotic or mood disorder, current or past substance dependence other than nicotine or alcohol, and contraindications to MRI (e.g., metallic implants, shrapnel, and claustrophobia).

Participants provided written informed consent before enrollment in the study, and were compensated for participation after each study procedure. The study protocol was reviewed and approved by the University of Minnesota and Minneapolis Veterans Affairs Medical Center Institutional Review Boards, and the U.S. Army Medical Research and Materiel Command.

2.2. Clinical assessment

Participants completed a clinical interview that included the Structured Clinical Interview for DSM-IV-TR (SCID; [17], excluding the PTSD module, and the Clinician-Administered PTSD Scale for DSM-IV (CAPS) [8,59] by trained and supervised post-bachelor or graduate student staff. Consensus was reached by at least two individuals: one or more being a licensed Ph.D.-level clinical psychologist, and others being predoctoral-level graduate students. Due to an emphasis on assessing PTSD-specific symptomatology, the full CAPS (Criteria A–F) was only administered when Criterion A (traumatic exposure) and Criterion B (re-experiencing) were met, which yielded 86 participants with Criterion C (avoidance) and Criterion D (arousal) CAPS ratings for dimensional analyses (see Results section 3.3.3).

2.3. TBI assessment

Symptoms of mTBI were assessed by interview using the semi-structured Minnesota Blast Exposure Screening Tool (MN-BEST) [32]. These symptoms included altered consciousness (e.g., confusion and disorientation), loss of consciousness (LOC) less than 30 min, post-traumatic amnesia (PTA) up to 24 h, and neurological symptoms (e.g., headache, tinnitus, nausea, sensitivity to light or noise) immediately after the event. Blast-related injuries were defined as those in which the individual felt a blast wave and attributed the resultant concussion to its effects. Secondary blast effects, such as being hit by debris, were allowable as part of the overall blast-related injury. Tertiary blast effects, such as being thrown against the ground, were acceptable provided that the blast wave itself was experienced as the source of those effects. Participants were positive for blast-related mTBI when at least one blast-related mTBI event exceeded thresholds for plausible physical effects of blast (e.g., proximity) with significant post-concussive symptoms.

2.4. Blast TBI severity scoring

Ratings of TBI likelihood and severity were assigned by doctoral-level clinical neuropsychologists based on information secured by trained study interviewers using the MN-BEST. The three most significant potential blast-related TBI events were considered, each of which received a severity score ranging from 0 (no concussion) to a potential maximum of 30 (severe TBI), based on the severity rating scheme described below. No score was higher than 4 (the maximum within the mTBI range) in the current sample. Expand-

ing upon the concussion severity rating scheme initially proposed by Ruff and Richardson [43], concussions contributing to neurologic symptoms in the absence of LOC or PTA are rated as "Type 0" and assigned an overall blast-related TBI score of "1". Type I concussions are assigned an overall blast-related TBI score of "2" and include 'altered state or transient LOC', PTA of no more than 60 s and one or more neurologic symptoms. Type II and Type III concussions receive blast-related TBI scores of "3" and "4", respectively. Type II concussions consist of definite LOC of unknown duration to no more than 5 min, PTA from 60 s to 12 h and at least one neurologic symptom. Type III concussions consist of complete LOC for 5 to no more than 30 min, PTA greater than 12 h and one or more neurologic symptoms. Based upon this scheme, the total blast-related TBI severity score for mild uncomplicated blast TBI is quantified as the sum of the scores of the three blast-related events and ranges from 0 (no brain injury) to 12 (three Type III concussions) [32].

Individuals were separated into 4 groups: Blast mTBI (experience of blast-related mTBI during most recent deployment; n = 19), PTSD (sub- and supra-threshold criteria for current PTSD met at time of assessment, i.e. meeting at least 1 each of CAPS criteria B, C, and D; n = 33), Blast mTBI + PTSD (met criteria for both Blast mTBI and PTSD groups; n = 41), and Control (did not meet criteria for any other group; n = 31).

2.5. Vigilance assessment

During DS-CPT administration, participants were exposed to four 80 trial blocks within which 20 targets (the numeral "0") were embedded per block (320 total trials). Each trial was composed of a single-digit numeral ($4.3^\circ \times 3.4^\circ$ visual angle in size) presented for 29 ms followed by a 971-ms white display. The numbers and background were degraded, with 40% of the white numeral pixels switched to black and 40% of the black background pixels switched to white. Subjects were instructed to press the button only when they thought they saw the numeral "0." Twenty-five percent of the stimuli were targets ("0"), and 75% were non-targets (numerals "1"–"9"). Participant hit and false alarm rates were calculated using recommended adjustments for perfect performance [62]. Behavioral performance was characterized using standard signal detection indices including measures of target detection/perceptual sensitivity (d') as well as bias in overall tendency to respond during presented trials (ln(β) and c) [53]. In other words, we employed d' to reflect participants' efficacy at simultaneously maximizing hits and minimizing false alarms, and ln(β) and c to reflect participants' tendency to respond indiscriminately to all presented stimuli. Reaction time for correct hits was averaged across all four blocks. Mixed model ANOVAs were used to test for effects of Group (Controls, Blast mTBI, PTSD, and Blast mTBI + PTSD) and Block (Blocks 1–4) on behavioral outcome measures d', ln(β), and c. A univariate ANOVA was used to test for Group effects on Reaction Time.

2.6. Electrophysiological data collection and analyses

EEG was collected using 128 channel BioSemi ActiveTwo EEG system (http://www.biosemi.com/) with a 1024 Hz sampling rate during DS-CPT performances. To measure eye movements for the detection of bioelectrical artifacts vertical electro-oculograms (VEOG) were recorded from above and below the right eye and horizontal electro-oculograms (HEOG) were recorded from outer ocular canthi. Left and right forearm electromyographs (EMGs) and electrocardiograms (ECG) were recorded in order to identify and reduce artifact and quantify aspects of muscle contraction associated with button presses. All offline EEG processing was conducted using Matlab. EEG was first low-pass filtered with 256 Hz cut-off frequency, and high-pass filtering with 0.5 Hz cut-off frequency was also conducted to remove large DC offset voltage. Then, filtered EEG was down-sampled to 256 Hz using anti-aliasing resample function and referenced to linked earlobe signal. Noisy electrode signals were identified via visual inspection aided by measures of signal amplitudes and temporal correlations between adjacent electrodes, and then excluded. EEG was segmented to include 200 ms pre-stimulus and 1000 ms post-stimulus for every trials. Noisy epochs with strong low- (<8 Hz) and high-frequency (>25 Hz) artifacts were identified and excluded via semi-automated procedures aided by maximum amplitudes and spectral power measures of each epoch. Artifacts from physiological sources (e.g., eye-movements, electrocardiogram, and muscle artifacts) as well as environmental and electrode-specific electrical artifacts were removed using independent component analysis (ICA) that was conducted using the FastICA algorithm [21]. To obtain an optimal ICA decomposition and prevent under-fitting or over-fitting of EEG data [30], the data dimensionality was estimated using the Bayesian information criterion (BIC) [6,46] and principal component analysis (PCA) was conducted to reduce data dimensions to the estimated number of dimensions before applying ICA. ICs were inspected in terms of their topography, frequency power spectrum, and time course. ICs showing high temporal correlations with VEOG or HEOG signals and typical topography of high frontal polar activity were identified as eye-movement artifacts. ICs characterized by a pattern of periodic deflections in the component time series, persistent activity throughout the recordings, low-frequency (<3 Hz) peak power spectrum, and a unilateral or bilateral posterior topography were identified as cardiac artifacts. Muscle artifacts were characterized by spectra with broad peak from 20 to greater than 60 Hz, topography showing prominent activity restricted to marginal electrodes close to facial muscles, and periods of high frequency activations [30]. Brief periods of strong muscle artifact were removed, while longer periods of muscle artifact characterized by ICs were addressed through elimination of the IC from the reconstituted signal. EEG recordings were denoised by removing data variance of identified artifact ICs from the original recordings. Bad electrode signals were replaced with interpolated signals using spherical spline method [35] and optimal sets of interpolation parameters [23]. Finally, all scalp EEG signals were referenced to the average signal.

2.7. Analysis of ERP voltage data

Epochs from 300 ms pre-stimulus to 1000 ms post-stimulus were created, and baseline corrected using the 300 ms pre-stimulus period. Data were filtered using a 30-Hz low-pass filter. First, to identify components above baseline noise level, global field power (GFP) plots were derived for every subject and condition. GFP is the spatial standard deviation at a given time, which quantifies potential strength across all electrodes at each time point [50]. Grand averaged GFP plots were generated by averaging over all subjects within a condition. There were identifiable peaks in the GFP plots for each condition around 100 ms (corresponding to ERP component P1), 150 ms (N1), 180 ms (P2), 300 ms (N2), and 500 ms (P3b) ms post-stimulus. Component amplitudes were measured as the difference between the mean pre-stimulus baseline and maximum peak amplitude within time windows around peaks identified by GFP plots for components P1 (80–120 ms), N1 (100–200 ms), P2 (160–220 ms), and N2 (250–350 ms). P3b amplitude was quantified as the mean amplitude within the time window 350–650 ms.

We examined group differences in electrophysiological component amplitudes associated with target detection during vigilance. For analyses, target stimulus ERPs included only those elicited by correctly identified target stimuli (i.e. the "0" stimulus as described in Section 2.5). We conducted mixed model ANOVAs with one between subjects factor (Group: Controls, Blast mTBI, PTSD, and

Blast mTBI + PTSD) and one within subjects factor (Stimulus: Target, Non-Target), separately for each ERP component, at lateral parietal electrode sites P7 and P8 (over left and right hemisphere, respectively) for component P1, occipital midline site Oz for N1, and at midline sites Pz, Cz, and Fz for components P2, N2, and P3b.

3. Results

3.1. Demographics and clinical characteristics

Demographic and clinical characteristics of the sample are described in Table 1. Groups were similar with regard to age, gender, and education level. Also, both number of OEF/OIF deployments and the duration of those deployments did not significantly differ between groups, suggesting a similar level of military experience. Both current alcohol dependence and current major depressive disorder (MDD) were more common in the two groups that included individuals with PTSD than in those without PTSD. Entering these conditions as covariates in the mean P3b amplitude mixed model ANOVA somewhat reduced significance levels of group effects but did not change the overall pattern, supporting the interpretation that reported effects are not due to these comorbid conditions.

3.2. Behavioral performance

Means and standard deviations (SD) of behavioral performance measures, as well as statistical results, are displayed in Table 2. Consistent with previous investigations [52], a main effect of Block for d' indicated a decline in target sensitivity over time across all participant groups. No main effect or interaction with Group was observed for d', suggesting blast-related mTBI history and current PTSD symptom status did not influence perceptual detection of the degraded visual targets. Although no Block effects were observed for ln(β), a Block main effect for c indicated more conservative response tendencies for later experimental blocks. Participant groups differed on both ln(β) and c. Compared to all other groups, participants with positive histories of blast-related mTBI alone demonstrated more liberal response thresholds as indexed by reduced ln(β) and c. No interactions between Group and Block were observed for ln(β) or c, $p > 0.73$. Participant groups did not differ by mean reaction time to hits.

3.3. Electrophysiological components

Table 3 presents means, SDs, and results of statistical tests for electrophysiological component amplitudes evident during the DS-CPT. Figs. 1 and 2 depict DS-CPT target and non-target grand-averaged waveforms for Controls, Blast mTBI, PTSD, and Blast mTBI + PTSD groups.

3.3.1. Early component amplitudes: P1, N1, P2

Across the early ERP components (P1, N1, P2), results revealed main effects of Stimulus; amplitudes were generally larger in response to Non-Target stimuli compared to Targets. There were no main effects of Group, or Group × Stimulus interactions, for these early components (see Table 3).

3.3.2. N2 amplitude

For N2, there were also main effects of Stimulus at each of the midline sites. At Pz and Fz, N2 amplitudes were larger for Targets compared to Non-Targets, whereas, amplitudes were nominally ($p = 0.04$) larger for Non-Targets at Cz (see Table 3).

3.3.3. P3b amplitude

P3b amplitude analyses revealed main effects of Stimulus at each of the three midline sites, where amplitudes were significantly more positive for Targets compared to Non-Targets at Pz and Cz, and for Non-Targets compared to Targets at Fz. There were main effects of Group found at sites Pz and Fz, and a significant Group × Stimulus interaction at Cz (see Table 3). Follow-up univariate ANOVAs performed separately for Targets and Non-Targets at Cz revealed a significant effect of Group only for Targets ($F(3,120) = 4.04$, $p = 0.009$, *partial* $\eta^2 = 0.09$), in which the PTSD group P3b amplitude was reduced compared to Controls (Mean difference = 0.95, $p = 0.02$). Further, examining the main effect of group found at Pz, Tukey HSD tests revealed significantly reduced P3b amplitude in all three affected groups (Blast mTBI, PTSD, Blast mTBI + PTSD) compared to Controls (Blast mTBI mean difference = 0.80, $p = 0.02$; PTSD mean difference = 0.83, $p = 0.002$; Blast mTBI + PTSD mean difference = 0.63, $p = 0.03$). Fig. 2 shows ERPs to target and non-target stimuli from Controls, Blast mTBI, PTSD, and Blast mTBI + PTSD groups at Pz only.

To examine any relationships between behavioral measures and P3b amplitude, we correlated d', ln(β), c, and reaction time to hits with P3b amplitude at Pz. Larger P3b amplitude to targets was associated with shorter reaction times, $r = -0.27$, $p = 0.002$. No other behavioral measures were significantly correlated with P3b amplitude.

Using the 86 participants who had full CAPS ratings data (see Methods section 2.2), we conducted additional analyses to examine PTSD as a dimensional construct based on empirically derived symptom groupings [34,49,61]. Frequency (0–4) and intensity (0–4) CAPS ratings were summed to create severity scores, which were collapsed into the following groupings: Intrusions (B1–B5), Avoidance (C1–C2), Dysphoria (C3–D3), and Hyperarousal (D4–D5). We conducted multiple linear regressions to clarify any unique influences of the symptom groupings on P3b amplitude. We also included the blast TBI severity score derived from the MN-BEST to determine any unique influence blast mTBI had on P3b amplitude. This approach provided a direct contrast of the symptom

Table 1
Characteristics of the Sample.

	Control	Blast mTBI	PTSD	Blast mTBI + PTSD	Test Statistic (χ2 or F)	p
N	31	19	33	41		
Females (%)	4 (13%)	0 (0%)	2 (6%)	3 (7%)	3.5	n.s.
Age, years: Mean (SD)	33.0 (8.5)	34.9 (8.5)	33.2 (7.7)	31.0 (6.3)	1.25	n.s.
Education level: Mean (SD)[c]	5.5 (0.7)	5.4 (0.9)	5.2 (0.8)	5.2 (0.6)	1.26	n.s.
Number of OEF/OIF deployments: Mean (SD)	1.3 (0.8)	1.4 (0.5)	1.3 (0.5)	1.5 (0.6)	0.52	n.s.
Total duration of OEF/OIF deployments, months: Mean (SD)	19.1 (6.5)	20.5 (9.0)	16.9 (5.8)	17.4 (7.2)	1.36	n.s.
Current Alcohol Dependence: N (%)	2 (6%)	5 (26%)	10 (30%)[a]	14 (34%)[a]	8.03	0.045
Current MDD: N (%)	0 (0%)	4 (21%)[a]	20 (61%)[a,b]	14 (34%)[a,b]	23.02	<0.001

mTBI: mild Traumatic Brain Injury; PTSD: Post-Traumatic Stress Disorder; MDD: Major Depressive Disorder

[a] Different from Controls.

[b] Different from Blast mTBI.

[c] Education level was coded as follows: 1 = 7th Grade or less, 2 = Between 7th and 9th Grade, 3 = Between 10th and 12th, but not graduated, 4 = High School Graduate (includes GED), 5 = Partial College (includes business school, voc/tec), 6 = 4 year College/University Graduate, 7 = Graduate Degree (MA, PhD, MD, JD, etc.).

Table 2
Performance Measures (mean (SD)) and Analysis Results from the Degraded-Stimulus Continuous Performance Task.

	Control	Blast mTBI	PTSD	Blast mTBI + PTSD	Total	Model*	Test Statistic	p-value	Effect size (η_p^2)
Target detection (d')									
Block 1	2.87 (.95)	2.52 (.83)	2.44 (1.05)	2.56 (.93)	2.60 (1.09)[a]	Block	F(3,479) = 7.98	<0.001	0.05
Block 2	2.50 (1.15)	2.22 (1.22)	2.23 (1.04)	2.37 (1.12)	2.33 (1.08)[a,b]	Group	F(3,479) = 1.64	n.s.	
Block 3	2.20 (1.20)	2.07 (1.18)	2.11 (.99)	2.08 (1.00)	2.12 (1.08)[b,c]	Block × Group	F(9,479) = 0.16	n.s.	
Block 4	2.13 (1.04)	1.79 (1.08)	1.91 (.79)	2.02 (1.05)	1.96 (1.08)[c]				
Total	2.43 (.99)	2.12 (1.01)	2.17 (.89)	2.26 (.89)					
Response threshold (ln(β))									
Block 1	1.12 (1.06)	0.48 (.84)	.96 (.65)	1.32 (.72)	.91 (.88)[a]	Block	F(3,479) = 1.96	n.s.	
Block 2	1.13 (1.00)	0.53 (.73)	1.05 (0.90)	1.31 (.85)	1.01 (.87)[a]	Group	F(3,479) = 10.24	< 0.001	0.06
Block 3	1.02 (.90)	0.90 (.84)	1.32 (0.88)	1.28 (.78)	1.13 (.87)[a]	Block × Group	F(9,479) = 0.67	n.s.	
Block 4	1.30 (.83)	0.79 (.89)	1.38 (0.72)	1.36 (.79)	1.21 (.87)[a]				
Total	1.14 (0.75)[a]	0.67 (.70)[b]	1.18 (0.61)[a]	1.32 (.57)[a]					
Response threshold (c)									
Block 1	0.42 (0.36)	0.20 (0.30)	0.47 (0.36)	0.56 (.30)	0.41 (0.43)[a]	Block	F(3,479) = 11.94	<0.001	0.07
Block 2	0.53 (0.40)	0.29 (0.32)	0.58 (0.46)	0.65 (.36)	0.51 (0.43)[a,b]	Group	F(3,479) = 12.12	<0.001	0.07
Block 3	0.64 (0.50)	0.43 (0.33)	0.70 (0.41)	0.77 (.49)	0.63 (0.43)[b,c]	Block × Group	F(9,479) = 0.05	n.s.	
Block 4	0.73 (0.51)	0.51 (0.48)	0.81 (0.40)	0.82 (.48)	0.72 (0.43)[c]				
Total	0.58 (0.38)[a]	0.36 (0.31)[b]	0.64 (0.37)[a]	0.70 (.34)[a]					
Reaction time for Targets (ms)									
Total	395.7 (79.6)	406.8 (126.9)	426.9 (79.0)	428.71 (87.9)	416.6 (90.8)	Group	F(3,120) = 1.01	n.s.	

* Table shows results of mixed model ANOVAs with one between subjects factor (Group: Controls, Blast mTBI, PTSD, and Blast mTBI + PTSD) and one within subjects factor (Block: 1–4),performed separately for each behavioral measure; and of univariate ANOVA for reaction time. For each test, the F value, p value, and partial eta squared (ηp2) effect size are reported Performance outcome measures for each group are presented as mean (SD). In "Total" column (showing Block means) and within each "Total" row (showing Group means), means for each measure not sharing superscripts are significantly different at p < 0.05.

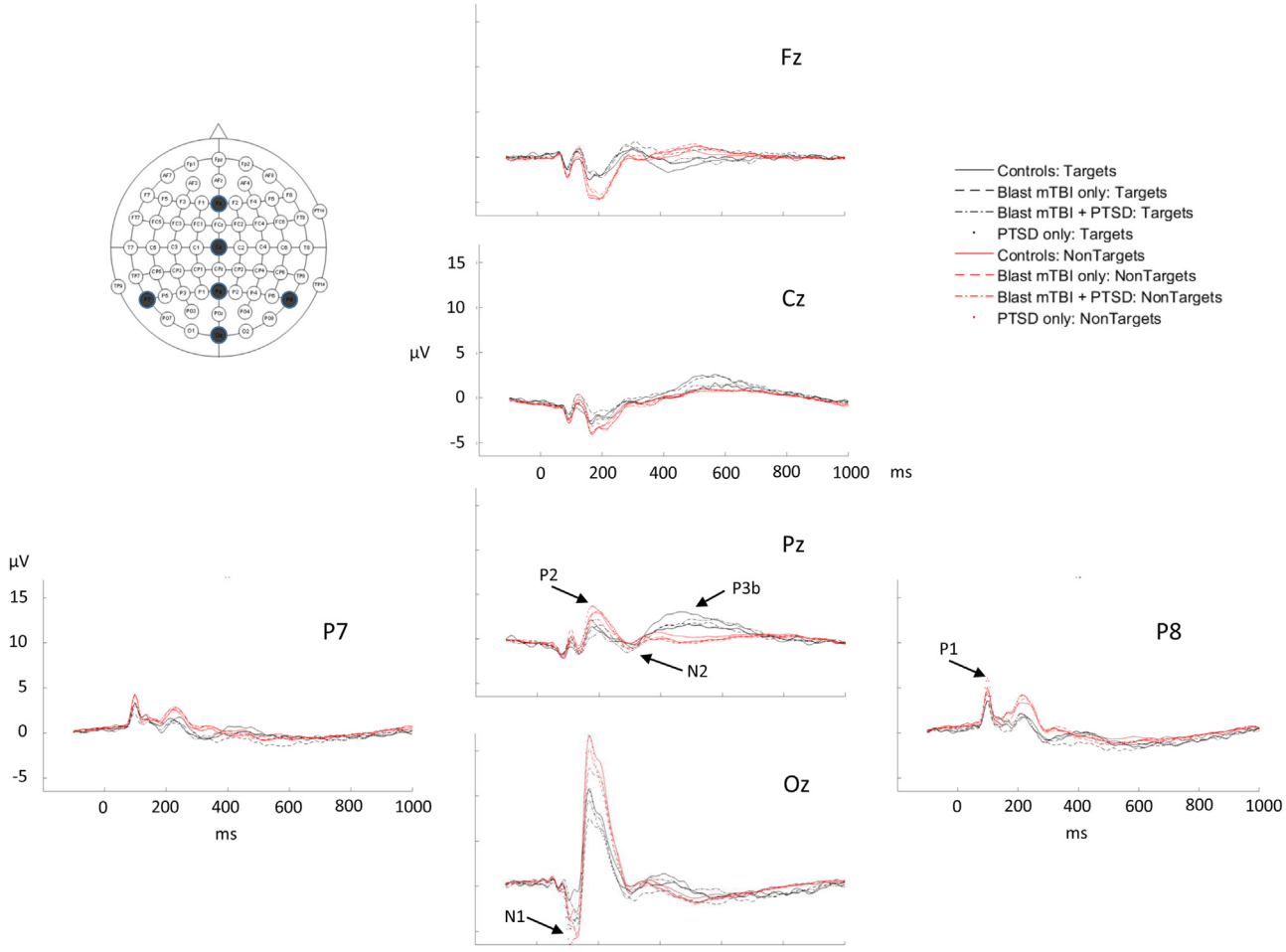

Fig. 1. Average event-related potentials elicited during the degraded-stimulus continuous performance task (DS-CPT) from Controls (solid lines), Blast mild traumatic brain injury (mTBI; dash lines), post-traumatic stress disorder (PTSD; dotted lines), and comorbid Blast mTBI + PTSD (dash-dot lines) groups for Target (the "0" stimulus that required a button-press response in the DS-CPT; black lines) and Non-Target (red lines) stimuli. All ERPs are presented on the same time and amplitude scales. Electrode locations are indicated by colored dots on the top-down 10-10 electrode site schematic map in upper left. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Mean (SD) Electrophysiological Component Amplitudes and Analysis Results from DS-CPT Trials.

Component	Model*	F	p	Effect size (η_p^2)	Site	Component Amplitudes (μV) Group							
						Controls		Blast mTBI		PTSD		Blast mTBI + PTSD	
						Targets	Non-Targets	Targets	Non-Targets	Targets	Non-Targets	Targets	Non-Targets
P1	Stimulus	30.07	<0.001	0.20	P7	3.80 (2.48)	4.56 (2.38)	2.90 (1.92)	3.66 (2.19)	3.92 (3.13)	4.34 (2.84)	3.60 (2.47)	4.58 (2.26)
	Group	0.67	n.s.										
	Stimulus × Group	0.92	n.s.										
	Stimulus	41.56	<0.001	0.26	P8	4.56 (3.55)	5.32 (3.30)	4.08 (2.91)	5.47 (3.27)	5.31 (3.83)	6.40 (3.90)	4.23 (2.52)	5.24 (2.40)
	Group	0.93	n.s.										
	Stimulus × Group	0.52	n.s.										
N1	Stimulus	39.43	<0.001	0.25	Oz	−4.21 (4.50)	−6.16 (5.73)	−6.29 (7.99)	−7.65 (8.10)	−8.18 (8.11)	−9.73 (7.77)	−5.84 (6.24)	−7.65 (7.18)
	Group	1.67	n.s.										
	Stimulus × Group	0.22	n.s.										
P2	Stimulus	111.40	<0.001	0.48	Pz	2.23 (2.47)	3.93 (3.08)	2.51 (3.28)	3.70 (3.34)	2.87 (2.34)	4.54 (2.24)	1.38 (2.02)	2.95 (2.06)
	Group	2.61	n.s.										
	Stimulus × Group	0.50	n.s.										
	Stimulus	112.96	<0.001	0.49	Cz	−3.44 (1.37)	−4.41 (1.47)	−2.28 (1.44)	−3.75 (1.53)	−3.52 (2.02)	−4.44 (1.74)	−3.72 (1.88)	−4.63 (1.63)
	Group	2.38	n.s.										
	Stimulus × Group	1.40	n.s.										
	Stimulus	207.02	<0.001	0.63	Fz	−3.30 (2.01)	−5.20 (2.19)	−3.00 (2.03)	−5.10 (2.35)	−3.66 (2.15)	−5.62 (2.08)	−3.01 (2.26)	−4.89 (2.03)
	Group	0.78	n.s.										
	Stimulus × Group	0.12	n.s.										
N2	Stimulus	31.14	<0.001	0.21	Pz	−1.65 (1.22)	−0.97 (.90)	−1.83 (1.22)	−1.63 (1.39)	−1.92 (1.53)	−1.05 (1.12)	−2.47 (1.79)	−1.53 (1.19)
	Group	2.31	n.s.										
	Stimulus × Group	1.60	n.s.										
	Stimulus	4.19	0.04	0.03	Cz	−2.13 (1.45)	−2.24 (1.04)	−1.38 (1.36)	−1.99 (1.24)	−1.89 (1.11)	−1.85 (0.97)	−1.93 (1.58)	−2.29 (1.10)
	Group	1.23	n.s.										
	Stimulus × Group	1.11	n.s.										
	Stimulus	81.96	<0.001	0.41	Fz	1.68 (1.91)	0.68 (1.12)	2.19 (0.96)	0.68 (0.77)	2.05 (2.12)	0.74 (1.09)	2.31 (1.93)	0.70 (1.24)
	Group	0.38	n.s.										
	Stimulus × Group	0.92	n.s.										
P3	Stimulus	183.07	<0.001	0.60	Pz	2.38 (1.32)	0.39 (0.68)	1.38 (1.54)	−0.21 (0.58)	1.18 (1.60)	−0.07 (0.70)	1.65 (1.38)	−0.12 (0.60)
	Group	5.38	0.002	0.12									
	Stimulus × Group	1.86	n.s.										
	Stimulus	38.34	<0.001	0.24	Cz	1.59 (1.28)	0.43 (0.76)	1.50 (1.06)	0.36 0(.51)	0.63 (1.23)	0.52 (0.73)	0.79 (1.53)	0.45 (0.80)
	Group	1.85	n.s.										
	Stimulus × Group	6.09	0.001	0.13									
	Stimulus	45.54	<0.001	0.28	Fz	−0.77 (1.40)	0.23 (0.52)	0.70 (0.94)	0.87 (0.57)	−0.22 (1.31)	0.70 (0.74)	−0.28 (1.37)	0.64 (0.87)
	Group	5.91	0.001	0.13									
	Stimulus × Group	2.34	n.s.										

* Table shows results of mixed model ANOVAs with one between subjects factor (Group: Controls, Blast mTBI, PTSD, and Blast mTBI + PTSD) and one within subjects factor (Stimulus: Targets, Non-Targets), performed separately for each ERP component (indicated in "Component" column) at the electrode sites indicated in "Site" column.For each test, the F value, p value, and partial eta squared (η_p^2) effect size are reported. Amplitude data of target and non-target stimuli for each group are presented as mean (SD) μV.

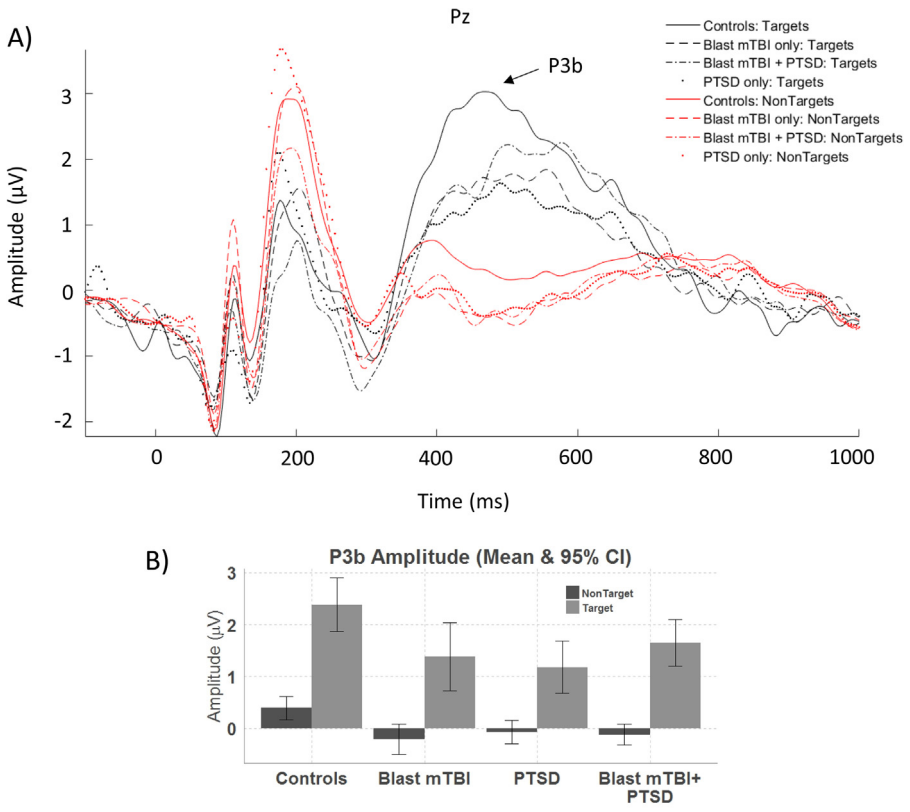

Fig. 2. A) Average event-related potentials elicited during the degraded-stimulus continuous performance task (DS-CPT), at midline parietal site Pz only, from Controls (solid lines), Blast mild traumatic brain injury (mTBI; dash lines), post-traumatic stress disorder (PTSD; dotted lines), and comorbid Blast mTBI + PTSD (dash-dot lines) groups for Target (the "0" stimulus that required a button-press response in the DS-CPT; black lines) and Non-Target (red lines) stimuli. B) Bar plot showing the mean P3b amplitude (calculated as the mean amplitude within the 350–650 ms time window (see Methods section); bars represent the 95% Confidence Interval) for each Group for both Target and Non-Target stimulus conditions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Results of multiple linear regression analysis.

	Zero-order correlations (r)							
	CAPS Avoidance	CAPS Dysphoria	CAPS Hyperarousal	Blast mTBI Severity Score	Target P3b amplitude at Pz	β	t	p
CAPS Intrusions	0.67*	0.76*	0.63*	0.003	0.008	0.06	1.31	0.19
CAPS Avoidance		0.62*	0.44*	−0.08	−0.09	−0.04	−0.72	0.48
CAPS Dysphoria			0.51*	0.15	−0.1	−0.04	−1.58	0.12
CAPS Hyperarousal				0.07	0.04	0.02	0.38	0.71
Blast mTBI Severity Score					0.02	0.11	1.1	0.28

β (beta weight), t-value, and p-value of each variable included in multiple regression model for predicting.
Target P3b amplitude at Pz from the CAPS and blast mTBI measures.
* $p < 0.001$.

dimensions in accounting for modulations of the P3b ERP. Multiple linear regression results showed that neither PTSD symptom scores nor blast mTBI severity score, either as a group or individually, explained a significant portion of variance in P3b amplitude to target stimuli at Pz ($R^2 = 0.057$, $p = 0.46$; see Table 4). These results lend further support to the hypothesis that P3b amplitude reduction during target detection in the DS-CPT task may be a marker of generalized brain pathology, and not be reflective of independent effects of blast-related mTBI or severity of PTSD symptomatology.

4. Discussion

The overall objective of this study was to investigate the neural correlates of sustained visual attention and vigilance in veterans with blast-related mTBI and/or current PTSD. We examined amplitudes of ERPs elicited by both target and non-target stimuli during the DS-CPT task. The amplitude of the early, sensory-related ERPs did not differ as a function of group membership (Blast mTBI, PTSD, Blast mTBI + PTSD, Controls), suggesting that sensory processing of stimuli was intact in the three affected groups. Neither did N2 amplitude differ between groups. P3b amplitude at site Pz, however, showed a group effect such that the Blast mTBI, PTSD, and Blast mTBI + PTSD groups showed a comparable reduction in P3b amplitude compared to Controls.

Variation in P3b amplitude reflects attentional allocation to stimulus processing and the updating of working memory for preceding stimulus events [14,38]. P3b amplitude is modulated by target stimuli that are infrequently presented, yet expected based on task demands [37]. The reduced P3b amplitude in the Blast mTBI, PTSD, and Blast mTBI + PTSD groups, compared to the Control group, may reflect reduced neural capacity in attentional resource allocation [38] compared to Controls. [37] has also theorized that

P3b generation might reflect neural inhibition. Effective attentional allocation, then, involves the suppression of extraneous neuronal activity, a process indexed by P3b amplitude. The reduced P3b amplitude exhibited by the three affected groups, then, would suggest a failure to inhibit extraneous neural activity, negatively affecting the allocation of attention towards target stimulus processing. These findings may be clinically relevant as attention and working memory problems are common cognitive sequelae of both mTBI [2,3] and PTSD [4]. mTBI and PTSD-related neural inhibitory dysfunction may relate to clinically-relevant symptoms that interfere with the ability to concentrate on a task, thus interrupting working memory, sustained attention, and inhibitory functions [4]. The P3b ERP may provide an objective index of these common cognitive dysfunctions.

Unexpectedly, we found comparable P3b amplitude reduction in all three affected groups. Based on previous findings (e.g. [5], we hypothesized that the comorbid Blast mTBI + PTSD group might show greater P3b reduction than the Blast mTBI only and PTSD only groups. Thus, P3b amplitude reduction during target detection in the DS-CPT task may be a marker of generalized brain pathology not reflective of independent effects of blast-related mTBI or severity of PTSD symptomatology. This proposition was further supported by results of multiple regression analyses investigating any unique influences on P3b amplitude by dimensional indices of PTSD symptomatology (i.e. Intrusions, Avoidance, Dysphoria, and Hyperarousal) or of blast-related mTBI severity, simultaneously. Results showed that P3b amplitude doesn't reflect independent effects of any of the PTSD-specific symptom groupings nor of blast mTBI severity. Associations between TBI severity and P3 amplitude have been shown, however, and typically are evident in moderate to severe TBI [27,42], and not in mild TBI [7,42], perhaps due to the restricted range of injury severity in mTBI [16]. One limitation of our approach using dimensional PTSD scores is that we only had full CAPS data on those subjects who met both Criterion A and Criterion B (see Methods section 2.2). This necessarily excluded many participants in the Control and Blast mTBI only groups. Thus, we were unable to have a complete view of the relationship between PTSD dimensional symptomatology and P3b amplitude.

Behavioral data showed that blast-related mTBI history and current PTSD symptom status did not influence perceptual detection of the degraded visual targets, consistent with our reporting above on the early, sensory-related ERPs. Having a positive history of blast-related mTBI without significant current PTSD symptoms, however, was associated with more liberal response thresholds when responding to targets, compared to all other groups. This result suggested that those with blast mTBI alone were more disinhibited in their behavioral responses during the task. Given that this effect was isolated to the blast mTBI only group, and, particularly, not seen in the blast mTBI + PTSD group, this effect is equivocal and should be replicated in another sample before further interpretation. Also, while reaction time to correctly identified targets did not differ between groups, it was significantly negatively correlated with P3b amplitude elicited by targets – faster reaction times were associated with larger P3b amplitudes. Thus, across groups, the increased allocation of attention, indexed by P3b amplitude, was associated with increased processing speed, suggesting that attentional capacity plays a key role in behavioral response variability (cf. [40].

While the non-specificity of P3b amplitude reduction may suggest it has limited utility as a diagnostic biomarker for mTBI and/or PTSD, P3b can provide information about cognition that is quantitatively comparable to other clinically-relevant measures [36]. Results of the current study suggest that P3b indexes a cognitive effort that is impaired across diagnostic groups. Alternatively, mTBI and PTSD may have different underlying traits that converge downstream to manifest as reduced amplitude P3b ERP. Further, the P3b is a complex ERP with a number of underlying neural generators including subcortical, frontal, and temporal-parietal areas [28,51]. mTBI or PTSD-related impairment in any of these neural generators may result in a reduced amplitude P3b. Thus, the P3b can provide valuable information with regards to characterization of psychopathology, especially within the context of a multivariate approach combining behavioral, psychological, and physiological measures. For example, while the current study lacked information on any underlying mTBI-related brain structural abnormalities in our subjects, that information would be beneficial to compare with the P3b abnormalities to get a fuller picture of impairment in mTBI and/or PTSD.

In conclusion, this study examined electrophysiological correlates of sustained attention and vigilance in veterans with blast-related mTBI and/or current PTSD. These disorders are commonly co-occurring, and are associated with alterations in the ability to effectively allocate attention, especially when sustained attention is necessary. The current study found that P3b amplitude elicited during the DS-CPT task was similarly reduced across groups with blast-related mTBI, PTSD only, and both blast mTBI + PTSD, when compared to a control group. Thus, the parietal P3b amplitude reduction during target detection in the DS-CPT task may be a marker of generalized brain pathology, not specific to either blast-related mTBI or to PTSD.

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