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Posttraumatic Stress Symptom Dimensions and Brain Responses to Startling Auditory Stimuli in Combat Veterans

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Posttraumatic stress disorder (PTSD) is marked by alterations in emotional functioning, physiological reactivity, and attention. Neural reactivity to acoustic startle stimuli can be used to understand brain functions related to these alterations. Investigations of startle reactivity in PTSD have yielded inconsistent findings, which may reflect the heterogeneity of the disorder. Furthermore, little is known of how the common co-occurrence of mild traumatic brain injury (mTBI; i.e., concussion) may influence neural reactivity. We examined the event-related potentials (ERPs) of combat veterans (n = 102) to acoustic startle probes delivered during viewing of pleasant, neutral, unpleasant, and combat-related pictures. Interview-based assessments yielded dimensional characterizations of PTSD and mTBI. The P3 ERP response to startle probes was reduced during all affective relative to neutral pictures but failed to be associated with a PTSD diagnosis. However, two separable domains of PTSD symptomatology were associated with startle ERPs regardless of the picture conditions. Maladaptive avoidance was associated with smaller N1, P2, and P3 amplitudes, while intrusive reexperiencing was associated with larger P2 amplitudes. There were no main effects of mTBI. Findings suggest that level of symptomatology rather than a formal diagnosis of PTSD better explains alterations in neural reactivity after traumatic events, while mild brain injuries have little impact. Avoidance symptoms of PTSD may dampen neural functions that facilitate reorientation to threat while intrusive reexperiencing of traumatic events appears to heighten sensory reactivity. Considering specific aspects of symptomatology provides insight into the neural basis of trauma-related psychopathology and may help guide individualization of clinical interventions.

General Scientific Summary

Brief white noise bursts were used to produce startle reactions among military veterans, which were measured using electroencephalography (EEG) recordings. Two separate PTSD symptom dimensions were independently associated with startle-related neural processing. Different PTSD symptom domains may map onto separable brain systems.

Keywords: PTSD, mTBI, veterans, startle, EEG

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Traumatic warfare experiences can affect the long-term physical and psychological wellbeing of military veterans (Hoge et al., 2007; Pizarro et al., 2006). Although posttraumatic growth and resilience are common, a significant minority of individuals experience trauma-related impairment in emotional functioning that may develop into posttraumatic stress disorder (PTSD; Bonanno et al., 2012; Maguen et al., 2006). Modernized combat with improvised explosive devices has created additional dangers and elevated the rates of mild traumatic brain injuries (mTBIs) among military personnel (Taber et al., 2006; Warden, 2006). It has proved difficult to delineate how combat blast events may affect later social, occupational, and cognitive functioning (Disner et al., 2017; Mattson et al., 2019). Veterans with blast mTBI histories often present with clinical complaints resembling aspects of posttraumatic stress such as impaired concentration, mood changes, and fatigue (Sayer, 2012). Furthermore, blast exposures typically occur during psychologically traumatic circumstances (e.g., roadside bombings of convoys), which can complicate efforts to understand the neural correlates of blast-related mTBI and obscure the sources of poor reintegration into civilian society (Vasterling et al., 2009).

Consequently, there is a pressing clinical need to determine which aspects of postdeployment impairment are associated with PTSD as compared to mTBI. Such a determination will facilitate clinical interventions that more effectively target the underlying neural and psychological bases of impairment (e.g., fear conditioning processes vs. sequelae of a concussed brain). In this study, we investigated neural reactivity in United States military veterans while they were presented with pictures designed to elicit emotional responses. Specifically, we recorded event-related potentials (ERPs) to auditory startle probes during free viewing of pleasant, neutral, unpleasant, and combat scenes to understand how neural reactivity during various emotional states may be associated with PTSD and/or mTBI.

Exaggerated startle responses are frequently self-reported as a symptom of PTSD (American Psychiatric Association, 2013). Startle reflexes are also important, protective, and adaptive biological phenomena that prepare the body to respond to sudden environmental changes (Graham, 1979; Miller et al., 2002). In laboratory settings, noxious auditory bursts of static (i.e., white noise) consistently evoke increases in heart rate and blood pressure, elevated electrodermal activity, and muscle contractions (Bakker et al., 2009; Grillon & Baas, 2003; Holand et al., 1999; Koch, 1999). Rapid electrophysiological changes in the central nervous system accompany these peripheral reflexes (Putnam & Roth, 1990; Roth et al., 1984). Approximately 300 ms after a startling auditory stimulus, a P3 response is evident within the ERPs. P3 responses at posterior scalp electrode sites (e.g., Pz) are commonly associated with goal-directed attention toward the motivational aspects of evocative images, infrequently presented targets, and conditioned stimuli (Franken et al., 2011; Iaconoet al., 2003; Polich, 1989; Roth et al., 1984; Rozenkrants & Polich, 2008). The P3 in response to an auditory startle probe (i.e., "startle P3") is thought to specifically correspond to the degree of reorientation of attention toward processing the probe in preparation for defensive behavioral responding (Drislane et al., 2013; Perkins et al., 2017).

Startling auditory stimuli (e.g., gunshot, explosion) often indicate an urgent need for greater situational awareness (Drislane et al., 2013). The acuteness of this need is reduced if attention is already allocated toward the external environment such as when processing an affect-eliciting visual scene. Accordingly, the startle P3 is smaller when people are already engaged with the hedonic or aversive content of their immediate surroundings. The most studied example of this is an "arousal" effect whereby viewing of affect-eliciting images reduces startle P3 relative to neutral images (Bradley et al., 2006; Cuthbert et al., 1998; Engelmann et al., 2011; Ferrari et al., 2011; Keil et al., 2007; Schupp et al., 2004; Schupp et al., 1997). Additionally, individuals who report high trait levels of perceptual absorption with environmental stimuli also exhibit reduced responses within the P3 component window (Benning et al., 2015). Thus, startle P3 reflects overall attentional reorienting to sudden auditory probes, which may be dampened when attention has already been drawn to the external environment (Bradford et al., 2017).

At present, disparate clinical phenomena have been associated with reduced startle P3, ranging from features of psychopathy to anxiety (Drislane et al., 2013; B. D. Nelson, Hodges, et al., 2015). Lang and colleagues (2018) examined a heterogeneous clinical cohort and concluded that startle P3 effects across different measures of mood and anxiety may be explained by an association with the broader clinical construct of negative emotionality. Among this participant sample, P3 attenuation was seen for disorders of "anxious misery" (e.g., mood disorders, PTSD, and generalized anxiety disorder; although, see Stevens et al., 2018), but P3 enhancement was observed for obsessive–compulsive disorder. This theme of contrasting P3 effects mimics findings from Perkins and colleagues (2017) who used a single participant sample to show that greater disinhibition predicted smaller P3 while greater threat sensitivity simultaneously predicted larger P3. Therefore, startle ERP responses may be differentially associated with several clinical phenomena of possible relevance to trauma-related psychopathology and postdeployment functioning.

Earlier features of acoustic startle ERPs may be useful for understanding additional aspects of defensive responding related to emotional experience. The auditory N1 component recorded at frontal electrode sites (e.g., Fz, FCz) is sensitive to task manipulations involving early attentional processes. Cuthbert and colleagues (1998) described selective enlargement of N1 during exposure to unpleasant visual stimuli, but only when probes contained task-relevant information. Visual cues indicating the potential for danger may similarly potentiate N1. Nelson and colleagues (Nelson & Hajcak, 2017; B. D. Nelson, Hajcak, & Shankman, 2015) reported that anticipatory uncertainty regarding threat of electric shock selectively enlarged N1. However, others have noted N1 enlargement when task conditions convey threat certainty, with stepwise increases in N1 as threat becomes more imminent (Krause et al., 2018; Stevens et al., 2018). Modulation of the N1 response was not observed using affective word stimuli (Herbert et al., 2006). Additional examination of early startle ERP components during manipulations of threat may clarify the relevance of N1 to defensive responding.

Another early electrophysiological response of interest is the P2, which becomes amplified as auditory stimuli are presented with increasing intensity (Buchsbaum & Pfefferbaum, 1971). P2 is thought to increase in amplitude until a neurophysiological response limit is reached and sensory inhibition mechanisms are triggered (Pritchard, 1986). P2 amplitude differences related to PTSD are most evident when acoustic stimuli are of intensities similar to white noise startle probes (i.e., dB $\geq$ 95). Two studies have found PTSD to be associated with P2 attenuation consistent

with a possible overapplication of protective mechanisms (Lewine et al., 2002; Paige et al., 1990). In contrast, PTSD-related P2 potentiation has also been reported (McPherson et al., 1997; Metzger et al., 2002) and these larger responses have been associated with intrusive reexperiencing symptoms of posttraumatic stress (Metzger et al., 2008). Further investigation is needed to understand how facets of PTSD symptomatology are related to the startle P2 component.

To summarize, research to date suggests startle ERPs simultaneously index several electrophysiological phenomena related to neural reactivity: anticipation of threat (N1; B. D. Nelson, Hajcak, & Shankman, 2015), sensory response inhibition (P2; Lewine et al., 2002); an overall shift of attention toward the startle stimuli (P3; Drislane et al., 2013; Perkins et al., 2017); and ongoing motivated engagement with the external environment (P3 attenuation; Cuthbert et al., 1998). We are not aware of any studies examining how neural reactivity to auditory startle probes is related to PTSD symptomatology while also considering potential chronic effects of brain injuries that often occur during psychologically traumatic events. We sought to address this by quantifying brain responses to auditory startle in military veterans after deployments to combat zones. Participant recruitment was designed to ensure sufficient representation of PTSD and mTBI in the study sample.

In this experiment, we assessed both the magnitude of responses to the startle probes as well as how viewing affect-eliciting pictures modulated the responses. Based on evidence for PTSD-related startle P3 reductions, our previous report of PTSD and mTBI being associated with diminished P3 during a continuous performance task, and associations between P3 and nonspecific pathophysiological disruptions (Bernat et al., 2020; Gilmore et al., 2018; Lang et al., 2018), we predicted reduced overall startle P3 magnitude with PTSD and mTBI. Given the importance of traumatic memories and fear conditioning (Foa & Kozak, 1986; Rothbaum & Davis, 2003); we also predicted individuals with PTSD would exhibit the greatest P3 attenuation to combat scenes (i.e., PTSD-by-picture condition interaction). We tested how alternative dimensional characterizations of mTBI and PTSD may explain categorical findings or reveal associations not observed with categorical diagnoses alone (Cuthbert, 2005; Grove, 1991). Based on the past literature, we also predicted that larger P2 responses would be associated with intrusive reexperiencing symptoms of PTSD (Metzger et al., 2008).

Methods and Materials

Participants

Participants were a cross-sectional sampling of United States Military veterans who had served in Iraq and/or Afghanistan as part of Operations Enduring and Iraqi Freedom (OEF/OIF; Gilmore et al., 2018; Marquardt et al., 2018), Recruitment focused on individuals from a longitudinal study of Minnesota National Guard members and patients at the Minneapolis Veterans Affairs Health Care System (VAHCS). Written consent was provided following protocol approval by the Minneapolis VAHCS and University of Minnesota Institutional Review Boards (4043-A). Veterans with likely PTSD and/or mTBI histories as well as nontreatment seeking veterans with similar deployment experiences were targeted for recruitment. Individuals with a predeployment history of major *DSM–IV–TR* (American Psychiatric Association, 2000) Axis I psychopathology were excluded. Of the 135 individuals who consented, a total of 118 participants completed the electroencephalographic portion of this task and were eligible based on study inclusion/exclusion criteria (see online supplementary materials for details).

Clinical Assessment

Interview assessments were completed by postbachelors research assistant or clinical psychology doctoral student staff using the Structured Clinical Interview for *DSM–IV–TR* Axis I Disorders (SCID-I; First et al., 2002) and the Clinician-Administered PTSD Scale for *DSM–IV* (CAPS; Blake et al., 1995; Weathers et al., 2001). Diagnostic consensus for psychopathology was reached by assessment teams, which included at least one licensed Ph.D.-level clinical psychologist. To decrease participant burden, the full CAPS (Criteria A—F) was only administered when Criterion B (reexperiencing) was met, which yielded 70 participants with Criterion C (avoidance/numbing) and Criterion D (arousal) CAPS ratings. Assessment of mTBI focused on participants' three most consequential deployment-related blast exposures using the semistructured Minnesota Blast Exposure Screening Tool (MN-BEST; N. W. Nelson et al., 2011). TBI consensus based on severity (e.g., loss of consciousness, posttraumatic amnesia, neurologic signs) and plausibility (e.g., proximity to blast) of participant self-report was reached by neuropsychological consensus teams of at least one licensed clinical neuropsychologist (N. W. Nelson, Davenport, & Sponheim, 2015). Four participant groups were formed based on these assessment procedures: no PTSD/no mTBI, no PTSD/mTBI, PTSD/no mTBI, and PTSD/mTBI (see Table 1).

Experimental Procedure

Participants were instructed to passively view 15 pleasant (e.g., pets, erotic scenes), 15 neutral (e.g., appliances, household scenes), and 15 unpleasant (e.g., threatening animals, violence) images from the International Affective Picture System selected based on normative ratings (online supplementary materials; Lang et al., 2005). An additional category of 15 combat-related OIF scenes was created (e.g., roadside bomb explosions, combat injuries), which participants perceived as highly unpleasant and arousing (Marquardt et al., 2018). Images were presented using an LCD monitor and E-prime control software (Sharpsburg, PA) for 6 s during two 30-picture blocks using pseudorandom ordering. Intertrial intervals (ITIs) were of 18, 21, or 24 s durations. White noise bursts (50 ms, near instantaneous rise time) occurred during 12 of each picture category presentations 2.5 or 4.5 s after image onset, which participants were instructed to ignore. Startle probes were either 95 or 103 dB for participants. Differences in probe level had no effect on N1, P2, or P3 amplitude (see online supplementary materials for analyses).

Physiological Data Preprocessing

Recordings were collected at 1024 Hz using a 128-channel BioSemi (Amsterdam, Netherlands) ActiveTwo EEG system. After resampling at 256 Hz, visual inspection took place using in-house MATLAB software to exclude epochs and electrodes

Table 1
Demographics and Clinical Characteristics

	Participant status											
	No PTSD						PTSD					
	No mTBI			mTBI			No mTBI			mTBI		
Variable	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*
Total	35			19			19			29		
Female	6			2			0			0		
Minority	4			1			2			1		
Age, years[a]		33.3	8.6		33.8	8.3		33.4	9.7		29.9	6.7
Education, years[a]		14.7	1.6		14.3	1.6		14.5	1.7		14.4	1.7
time since blast mTBI, months[a]					47.7	19.0					54.2	21.0
GAF[a]		70.1	11.6		65.3	12.6		58.5	4.1		55.2	6.9
Depressive disorder[b]	5			6			6			16		
Alcohol dependence[c]	4			5			2			10		
Full CAPS completed	10			12			19			29		
CAPS Intrusions severity[a]		9.4	4.6		8.4	4.4		15.6	5.8		18.3	5.7
CAPS Avoidance severity[a]		4.8	2.9		3.1	2.7		8.7	3.2		8.8	3.2
CAPS Dysphoria severity[a]		9.8	8.6		10.3	5.2		23.8	8.5		29.3	7.9
CAPS Hyperarousal severity[a]		4.8	3.7		5.4	4.2		6.8	3.1		9.0	3.1
MN-BEST Total Blast mTBI severity[a]		.0	.0		3.4	1.1		.0	.0		3.7	3.0

Note. CAPS severity calculated by summing frequency and intensity symptom scores. PTSD = posttraumatic stress disorder; mTBI = mild traumatic brain injury; GAF = *DSM–IV–TR* Global Assessment of Functioning Scale; CAPS = Clinician-Administered PTSD Scale for *DSM–IV*; MN-BEST = Minnesota Blast Exposure Screening Tool.
[a] Presented as group mean values using all available participant data. [b] Current *DSM–IV–TR* major depressive disorder or dysthymia. [c] Current *DSM–IV–TR* alcohol dependence.

dominated by artifact. Remaining EEG preprocessing was undertaken using BESA Research 6.0 (Gräfelfing, Germany). Given the overlap between N1 and startle-induced muscular blinks, we employed an independent component analysis-based adaptive correction method (Ille et al., 2002). Custom time-series segments were created for each participant from spontaneous blinks not evoked by startle probes, and the dominant component of this time-series was used to correct vertical blink artifacts. Thus, startle-related blink activity could be extracted leaving behind startle-related brain activity. Template horizontal eye movement components were also employed when contributing nonredundant corrections. We applied .1 – 30 Hz 24 db/oct filters (zero-phase) and a $>$ 110 μV amplitude exclusion criterion. Probe ERPs were calculated using 500 ms preprobe and 1000 ms postprobe epochs with preprobe baseline correction. After preprocessing, there were no significant associations between frontal ERPs and orbicularis oculi muscle reflexes (see online supplementary materials for analyses).

Participant waveforms from the 128-channel montage were interpolated into an average referenced 25-channel montage (Figure S1). Midline electrodes Fz, Cz, and Pz were examined to facilitate comparison to similar studies (e.g., Cuthbert et al., 1998). The following values were extracted: N1 peak amplitude (50 – 150 ms), P2 peak amplitude (150 – 250 ms), and P3 mean amplitude (260 – 340 ms). Peak latency findings are discussed in the online supplementary materials. Participants were included for analysis when at least seven valid trials were available per condition, yielding a final sample of 102 individuals (valid cases: pleasant, n = 110; neutral, n = 109; unpleasant, n = 108; combat, n = 104). Past research suggests seven trials produces acceptable internal consistency for startle N1 and P3 (B. D. Nelson, Hajcak, & Shankman, 2015).

Analysis

Group differences on demographics variables were tested with chi-square tests, *t*-tests, and PTSD (2) * mTBI (2) between-subjects ANOVAs in SPSS 23.0. To examine group differences in startle probe ERPs, we completed PTSD (2) * Blast mTBI (2) * Picture Type (4; pleasant, neutral, unpleasant, combat-related) * Electrode (3; Fz, Cz, and Pz) MANOVAs. We carried out follow-up analyses of significant effects for each electrode site. Follow-up analyses included a Bonferroni-corrected threshold of α = .016 to account for the three recording sites examined for each ERP of interest (nonsignificant $p \leq .05$ findings are noted).

To address study hypotheses about independent effects of intrusive reexperiencing symptomatology, additional general linear models (GLMs) were constructed in SPSS 23.0 using PTSD symptoms and blast-related mTBI severity as dimensional model predictors of N1, P2, and P3 amplitude. Based on factor analytic evidence (Yufik & Simms, 2010), frequency (0 – 4) and intensity (0 – 4) CAPS ratings were summed to create severity scores within the following symptom groupings: Intrusions (B1 – B5), Avoidance (C1 – C2), Dysphoria (C3 – D3), and Hyperarousal (D4 – D5). Blast severity ratings were obtained from the MN-BEST adaptation of Ruff and Richardson's (1999) ratings scheme. Mean-centered model predictors of Intrusions, Avoidance, Dysphoria, Hyperarousal, and Blast mTBI Severity were included as well as within-subjects factors of Picture Type (4) and Electrode (3). This allowed testing of the effect of each

dimensional symptom or mTBI variable taking into consideration the influence of the other dimensional predictors. We carried out follow-up analyses of significant effects for each electrode site. The same statistical significance thresholds were used for the dimensional and categorical models. Unstandardized effect estimates with 95% confidence intervals are reported to describe directionality of the associations.

As a secondary follow-up for the above analyses, we executed a time-domain principal component analysis (PCA) to more fully separate specific aspects of the ERPs of interest (Dien, 2010b; Foti et al., 2009). These results are presented in the online supplementary materials and confirm the findings relevant to posttraumatic avoidance and intrusive reexperiencing symptomatology.

Results

Participant Characteristics

Participant characteristics are reported in Table 1. No female participants ($n = 8$) had current PTSD. Blast head injury status did not differ by gender, $p = .193$. Groups were similar in ethnic minority status, age, education, and months since experiencing a deployment-related blast mTBI, $ps \geq .245$. Lower levels of functioning as measured by the Global Assessment of Functioning (GAF) ratings (American Psychiatric Association, 2000) were associated with PTSD, $F(1, 98) = 29.87$, $p < .001$, $\eta_p^2 = .234$, and mTBI, $F(1, 98) = 4.12$, $p = .045$, $\eta_p^2 = .040$. PTSD was also associated with a greater likelihood of a comorbid depressive disorder, $\chi^2 = 7.53$, $p = .006$, *Cramer's V* = .27, but not comorbid alcohol dependence, $p = .299$. Participants with mTBIs more frequently reported a comorbid depressive disorder, $\chi^2 = 7.53$, $p = .006$, *Cramer's V* = .27, and comorbid alcohol dependence, $\chi^2 = 6.30$, $p = .012$, *Cramer's V* = .25. Follow-up analyses demonstrated that depressive disorder and alcohol dependence were not associated with PTSD within each mTBI group (mTBI present, mTBI absent), p's $\geq .061$, nor with mTBI within each PTSD group (present, absent), p's $\geq .109$, suggesting that when specific subgroups of combat-related conditions were independently examined the co-occurrence with other disorders was less prominent.

Startle N1: Early Cortical Reactivity

We examined the amplitude of the N1 response to assess whether early cortical processes varied based on affective picture content or clinical status. Analysis across frontal, central, and parietal (Fz, Cz, and Pz, respectively) recording sites yielded main effects of Picture Type, $F(3, 96) = 9.90$, $p < .001$, $\eta_p^2 = .236$, and Electrode, $F(2, 97) = 202.67$, $p < .001$, $\eta_p^2 = .807$, and an interaction of Picture Type and Electrode, $F(6, 93) = 4.88$, $p < .001$, $\eta_p^2 = .240$. There were no other main or interaction effects indicating an absence of associations between N1 amplitude and categorical classifications of PTSD and mTBI, $ps \geq .079$. Follow-up analyses at each electrode site revealed a within-subjects effects of Picture Type for N1 amplitude at Fz, $F(3, 96) = 6.61$, $p < .001$, $\eta_p^2 = .171$, and Cz, $F(3, 96) = 10.61$, $p < .001$, $\eta_p^2 = .249$ (Figures 1 and 2 depict ERP modulation by affective picture content). N1 at Fz and Cz was smaller during pleasant compared to neutral pictures ($ps \leq .005$), and also smaller at Cz during combat-related compared to neutral pictures ($p = .002$). N1 was additionally smaller at Fz and Cz during the pleasant and combat-related pictures compared with the unpleasant pictures ($ps \leq .008$).

Analysis of PTSD symptom dimensions and mTBI severity across Fz, Cz, and Pz electrode sites yielded a main effect of Avoidance symptomatology, $F(1, 64) = 8.09$, $p = .006$, $\eta_p^2 = .112$, as well as an interaction of Avoidance and Electrode, $F(2, 63) = 3.17$, $p = .049$, $\eta_p^2 = .091$. As with the categorical analysis, there were main effects of Picture Type, $F(3, 62) = 9.14$, $p < .001$, $\eta_p^2 = .307$, and Electrode, $F(2, 63) = 151.66$, $p < .001$, $\eta_p^2 = .828$, and an interaction of Picture Type and Electrode, $F(6, 59) = 4.22$, $p = .001$, $\eta_p^2 = .236$, but there were no other main or interaction effects, $ps \geq .092$. Follow-up analyses at each electrode site revealed effects of Avoidance at Cz, $F(1, 64) = 7.99$, $p = .006$, $\eta_p^2 = .111$, and Pz, $F(1, 64) = 9.09$, $p = .004$, $\eta_p^2 = .124$ (Figures 3 and 4 depict the effects of clinical dimensions for ERP components). Smaller N1 responses at both electrode sites were associated with increased Avoidance irrespective of the Picture Type condition (Cz, $B = 1.913$, 95% CI [.561 3.264]; Pz, $B = .736$, 95% CI [.248 1.224]) indicating that individuals who engage in avoidance of trauma reminders had diminished early cortical reactivity to startle probes that was independent of the affective content of pictures. There was an interaction between Intrusions and Picture Type at Fz that did not survive Bonferroni correction, $F(3, 62) = 3.55$, $p = .019$, $\eta_p^2 = .147$, and posthoc simple effects were not significant ($ps \geq .168$). When dimensional analyses were restricted to individuals meeting full diagnostic criteria for PTSD the effect of Avoidance on N1 amplitude was no longer significant, Site Cz: $F(1, 42) = 2.28$, $p = .138$, $\eta_p^2 = .052$; Site Pz: $F(1, 42) = 4.00$, $p = .052$, $\eta_p^2 = .087$.

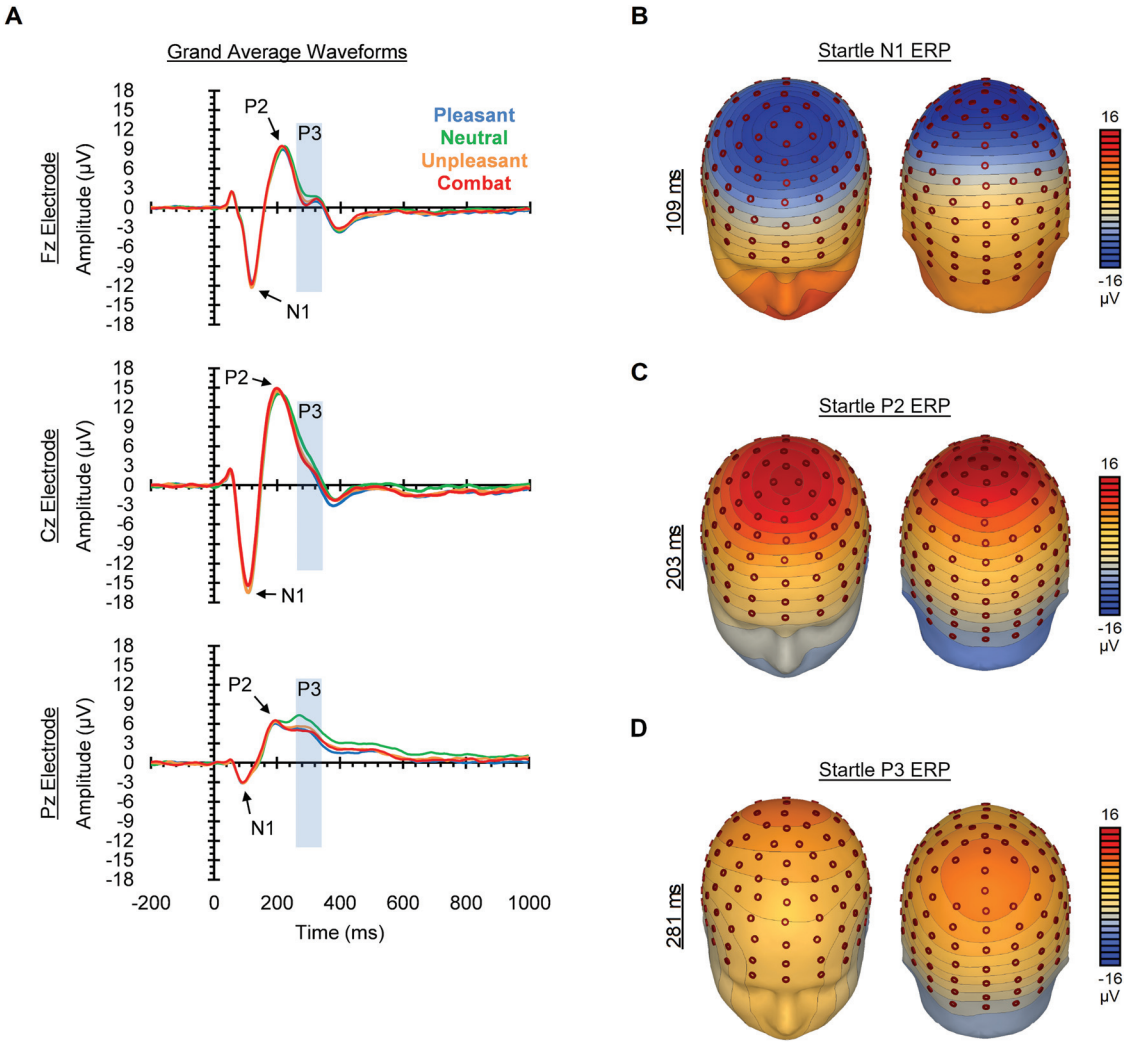
Startle P2: Midlatency Sensory Inhibition

We examined P2 peak amplitude to assess the processing of startle probes that may reflect sensory inhibition. Analysis across the three electrode sites yielded main effects of Picture Type, $F(3, 96) = 2.94$, $p = .037$, $\eta_p^2 = .084$, and Electrode, $F(2, 97) = 149.27$, $p < .001$, $\eta_p^2 = .755$, and an interaction of Picture Type and Electrode, $F(6, 93) = 2.50$, $p < .027$, $\eta_p^2 = .139$. An interaction between PTSD and mTBI was also evident, $F(1, 98) = 4.64$, $p = .034$, $\eta_p^2 = .045$. There were no other main or interaction effects for P2 amplitude, $ps \geq .287$. Follow-up analyses revealed within-subjects effects of Picture Type for P2 amplitude were observed at the frontal Fz, $F(3, 96) = 4.43$, $p = .006$, $\eta_p^2 = .122$ and the posterior Pz electrodes, $F(3, 96) = 4.67$, $p = .004$, $\eta_p^2 = .127$, but not at Cz, $F(3, 96) = .27$, $p = .846$, $\eta_p^2 = .008$ (see Figure 2). P2 responses at Fz and Pz during the pleasant pictures were smaller than during neutral pictures ($ps \leq .001$). There was an interaction between PTSD and blast mTBI at Pz, $F(1, 98) = 6.75$, $p = .011$, $\eta_p^2 = .064$ (see Figure 5). Posthoc comparisons revealed that among individuals without mTBI, participants with PTSD showed smaller P2 amplitudes than participants without PTSD, $F(1, 98) = 5.90$, $p = .017$, $\eta_p^2 = .057$. Simple effects for PTSD for individuals with mTBI were absent, $p = .209$.

Analysis of PTSD symptom dimensions and mTBI severity in relation to the P2 response across the three electrode sites yielded a main effect of Intrusions symptomatology, $F(1, 64) = 4.73$, $p = .033$, $\eta_p^2 = .069$, as well as an interaction of Dysphoria symptomatology, Picture Type, and Electrode, $F(6, 59) = 2.61$, $p = .026$, $\eta_p^2 = .210$. As with the categorical analysis there were main

Figure 1

Grand Average ERPs to Affective Pictures, Calculated to the Onset of the Acoustic Startle Probes Across All Participants (n = 102)



Note. [A] Within-subject condition differences are displayed at midline frontal (Fz), central (Cz), and parietal (Pz) electrodes sites. Baseline is truncated to −200 to 0 milliseconds for display purposes. [B—D] Topographical depictions of the grand average startle ERPs during the neutral image condition are also displayed. μV = microvolts; ms = milliseconds. See the online article for the color version of this figure.

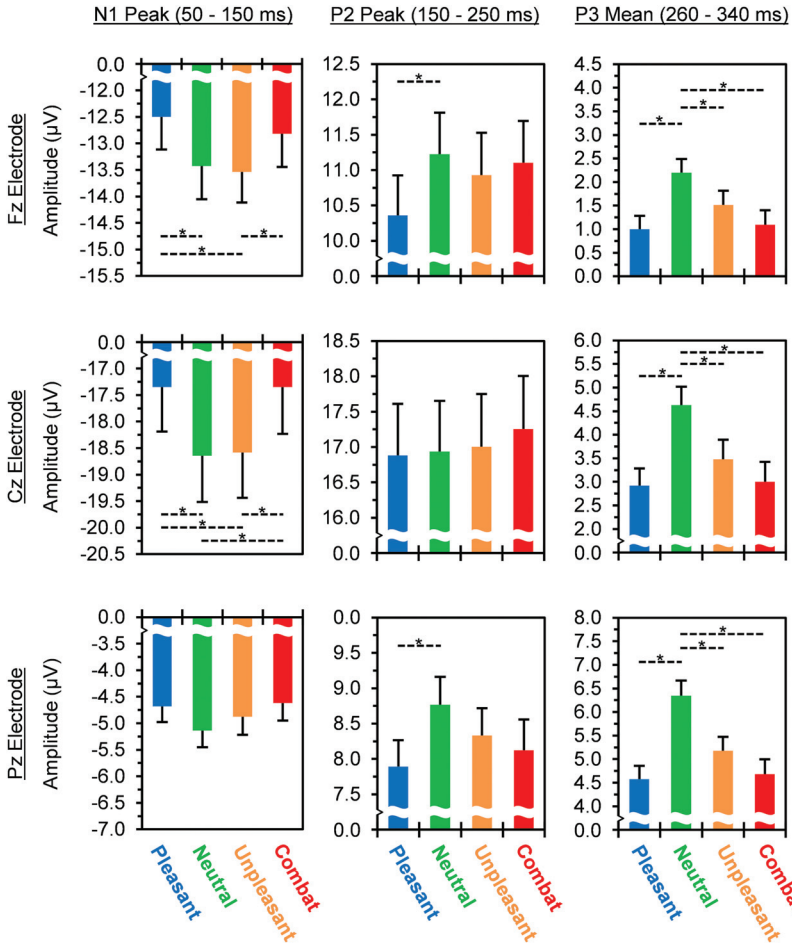
effects of Picture Type, $F(3, 62) = 9.14$, $p < .001$, $\eta_p^2 = .307$, and Electrode, $F(2, 63) = 151.66$, $p < .001$, $\eta_p^2 = .828$, and an interaction of Picture Type and Electrode, $F(6, 59) = 4.22$, $p = .001$, $\eta_p^2 = .236$. There were no other main or interaction effects, $ps \geq .092$. Follow-up analyses revealed effects of Intrusions, $F(1, 64) = 7.58$, $p = .008$, $\eta_p^2 = .106$, and Avoidance, $F(1, 64) = 8.25$, $p = .006$, $\eta_p^2 = .114$, at the Pz site (see Figure 3). Consistent with alterations in sensory processing of startle probes, P2 amplitudes were larger when intrusive reexperiencing symptoms were prominent ($B = .423$, 95% CI [.116 .730]); however, P2 amplitudes were smaller when avoidance symptoms were prevalent ($B = -.587$, 95% CI [−1.129 -.203]). These opposing associations indicated that independent symptom-related effects on neural reactivity were manifesting in the P2 response. There was a main effect of Intrusions at Cz that did not survive Bonferroni correction, $F(1, 64) = 3.98$, $p = .050$, $\eta_p^2 = .059$ ($B = .740$, 95% CI [-.001 1.482]). Follow-up analyses failed to reveal any effects for Dysphoria at specific electrode sites, and no other main or interaction effects were observed at any electrode sites, $ps \geq .061$. When dimensional analyses were restricted to individuals meeting full diagnostic criteria for PTSD the effect of Intrusions on the P2 response remained, Site Pz: $F(1, 42) = 4.60$, $p = .038$, $\eta_p^2 = .099$.

Startle P3: Reorientation of Attention

We examined the startle P3 response to assess how attentional reorienting to the startle probe varied based on affective picture content and clinical status. Analysis across the three electrode sites

Figure 2

Modulation of Startle Probe ERPs by Affective Picture Type

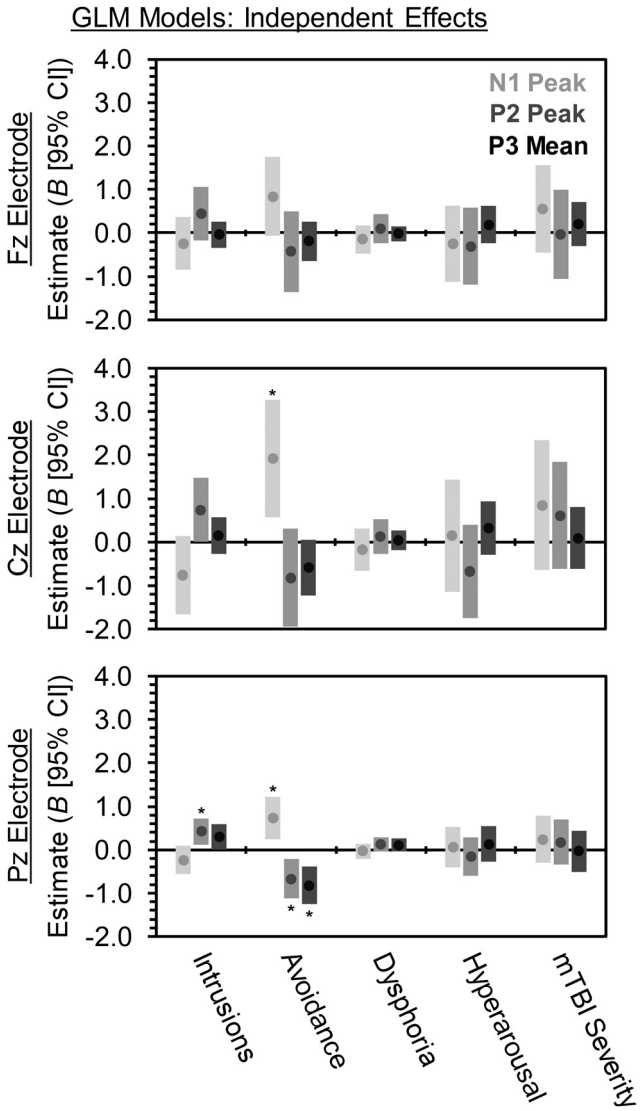


Note. Average amplitudes for N1 peak, P2 peak, and P3 mean are displayed for each picture condition at midline frontal (Fz), central (Cz), and parietal (Pz) electrodes sites. Standard error bars are depicted. Significant posthoc differences after applying a Bonferroni-corrected threshold are depicted using dashed lines and asterisks. μV = microvolts; ms = milliseconds. See the online article for the color version of this figure.

yielded main effects of Picture Type, $F(3, 96) = 25.81$, $p < .001$, $\eta_p^2 = .446$, and Electrode, $F(2, 97) = 53.19$, $p < .001$, $\eta_p^2 = .523$. There was a nonsignificant interaction of PTSD, mTBI, and Electrode, $F(2, 97) = 2.97$, $p = .056$, $\eta_p^2 = .058$. The absence any other main or interaction effect suggested a lack of associations between P3 amplitude and categorical classifications of PTSD and mTBI, $ps \geq .122$. Follow-up analyses revealed within-subjects effects of Picture Type for P3 amplitude at Fz, $F(3, 96) = 12.08$, $p < .001$, $\eta_p^2 = .274$, Cz, $F(3, 96) = 18.82$, $p < .001$, $\eta_p^2 = .370$, and Pz, $F(3, 96) = 25.58$, $p < .001$, $\eta_p^2 = .444$ (Figures 1 and 2). Startle P3 during the viewing of all affective picture types (pleasant, unpleasant, combat) was smaller than during viewing of neutral pictures ($ps \leq .001$; Fz, Cz, Pz). There was an interaction between PTSD and blast mTBI for P3 amplitude at Pz that did not withstand Bonferroni correction, $F(1, 98) = 5.80$, $p = .018$, $\eta_p^2 = .056$ (see Figure 5). Among individuals without mTBI, P3 amplitude was marginally reduced for those with PTSD compared to those without PTSD, $F(1, 98) = 6.72$, $p = .011$, $\eta_p^2 = .064$. There was no effect of PTSD within the mTBI group, $p = .400$. No other main or interaction effects were observed, $ps \geq .075$.

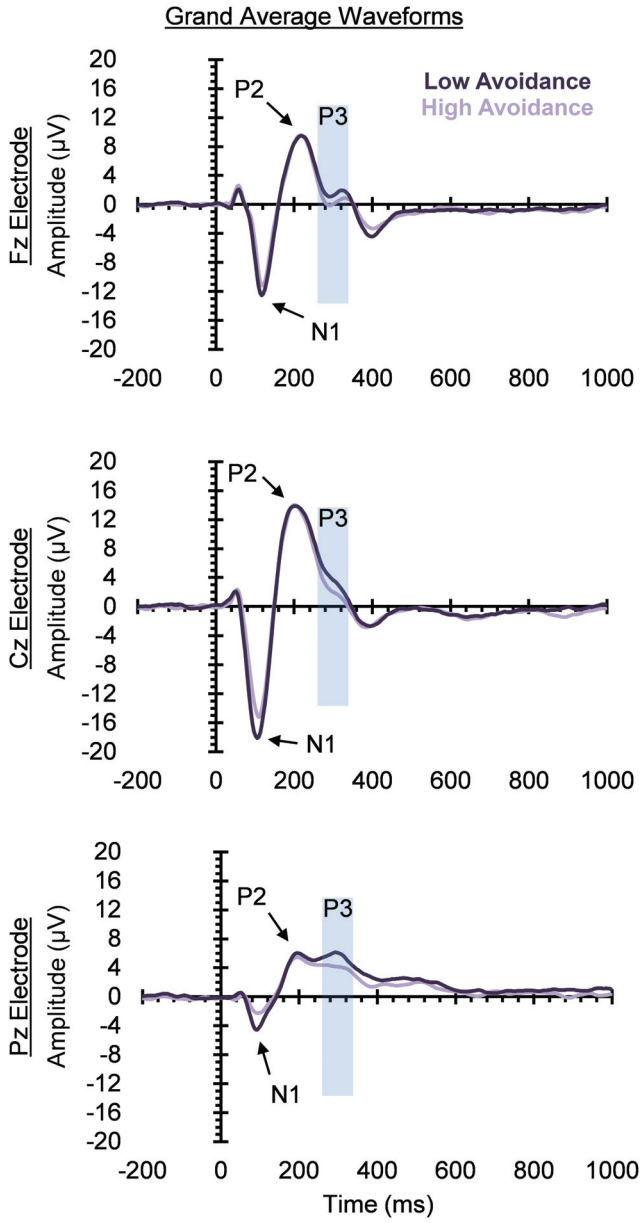
Analysis or PTSD symptom dimensions and mTBI severity across the three electrode sites yielded a main effect of Avoidance symptomatology, $F(1, 64) = 6.53$, $p = .013$, $\eta_p^2 = .093$. As with the categorical analysis there were main effects of Picture Type, $F(3, 62) = 16.87$, $p < .001$, $\eta_p^2 = .449$, and Electrode, $F(2, 63) = 38.04$, $p < .001$, $\eta_p^2 = .547$. There were no other main or interaction effects, $ps \geq .093$. Follow-up analyses of the relationship of P3 amplitude with PTSD symptom dimensions and mTBI severity revealed effects of Avoidance at site Pz, $F(1, 64) = 14.29$, $p < .001$, $\eta_p^2 = .182$ (Figures 3 and 4). Participants with elevated symptoms of avoidance exhibited smaller posterior P3 responses ($B = -.823$, 95% CI [−1.258 -.388]) consistent with lesser reorientation of attentional resources toward the startle probes. On the other hand, Intrusions were associated with increased P3 at Pz, but this association did not survive multiple comparisons correction, $F(1, 64) = 4.12$, $p = .047$, $\eta_p^2 = .060$ ($B = .293$, 95% CI [.005 .582]). No other main or interaction effects were observed at any

Figure 3
Effect of PTSD Symptomatology on Startle Probe ERPs



Note. Unstandardized estimates of the independent effects are displayed using 95% confidence intervals. Significant model effects are designated with asterisks. GLM = general linear model; mTBI = mild traumatic brain injury.

Figure 4
Avoidance Symptomatology and Diminished ERPs



Note. Grand average event-related potentials to the acoustic startle probes collapsed across all affective picture conditions. For the purpose of visualizing the multivariate model effects, waveforms are selectively depicted using individuals with the lowest (n = 18) and highest (n = 22) posttraumatic avoidance symptom scores. Baseline is truncated to −200 to 0 milliseconds for display purposes. μV = microvolts; ms = milliseconds. See the online article for the color version of this figure.

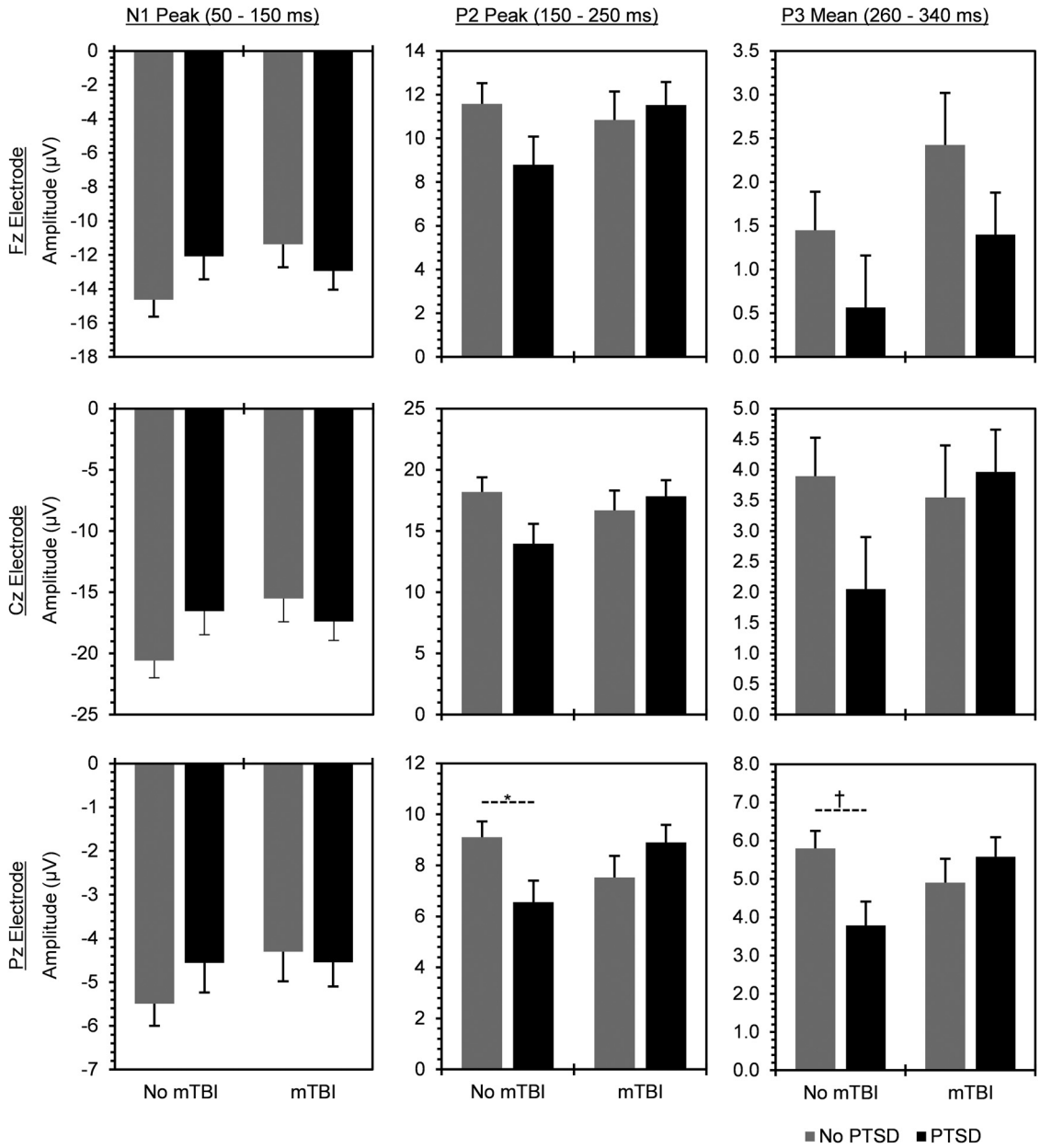
electrode sites, $ps \geq .064$. When dimensional analyses were restricted to individuals meeting full diagnostic criteria for PTSD the effect of Avoidance on P3 amplitude remained, Site Pz: $F(1, 42) = 9.78$, $p = .003$, $\eta_p^2 = .189$.

Discussion

We investigated the neural reactivity of U.S. military war zone veterans to auditory startle stimuli while they viewed emotionally arousing pictures. Analysis of PTSD symptomatology revealed that avoidance of trauma reminders was associated with diminished posterior brain responses consistent with diminished early reactivity (N1), greater sensory inhibition (P2), and reduced reorientation of attention to the startle stimulus (P3). Reduced startle P3 was the largest effect and findings suggest that maladaptive avoidance contributes to a limited shift in attentional resources toward external alarming stimuli. Intrusive reexperiencing of traumatic events was associated with less sensory inhibition as suggested by larger P2

Figure 5

Diagnostic Category Differences for Startle Probe ERPs



Note. Standard error bars are depicted. μV = microvolts, ms = milliseconds, mTBI = blast-related mild traumatic brain injury, PTSD = posttraumatic stress disorder.

* Posthoc significant difference for model effect surviving Bonferroni correction. † Posthoc significant difference for model effect not surviving Bonferroni correction.

amplitudes—opposite the direction of association between P2 and avoidance symptoms of PTSD. Thus, separate domains of PTSD symptomatology demonstrated opposing associations with neural reactivity, which could not be explained by the severity of mTBIs. Overall, this investigation revealed that compared to a formal diagnosis of PTSD or history of mTBI, dimensions of PTSD symptomatology better explained variability in the brain responses of combat veterans to startling auditory stimuli.

Because all dimensions of PTSD symptomatology and mTBI severity were included in the same analysis, effects of symptom dimensions on measures of neural reactivity were independent of other aspects of symptomatology. The relationship between startle P3 and avoidance symptomatology may reflect P3 reductions that have been associated with negative emotionality and reported by Lang and colleagues (2018). Maladaptive avoidance is often conceptualized as a dysfunctional coping strategy (Bryant & Harvey,

1995). When faced with painful reminders of traumas many people learn to avoid unpleasant affect and cognitions tied to the events as a way to regulate emotions in the short-term (i.e., "experiential avoidance"; Hayes et al., 1996). The unpredictable combat images or noxious startle probes in the current study may have created a threatening context that activated avoidance states typically used to prepare for potential environmental threat. In clinical treatment settings increased avoidance symptomatology is predictive of poorer outcomes in individuals with PTSD (Benotsch et al., 2000). Moreover, well-established PTSD treatment protocols such as prolonged exposure therapy consider avoidance a primary intervention target (Foa et al., 2007). Exposure may set the stage for altering fear learning by circumventing the avoidance processes that maintain symptoms (Foa & Kozak, 1986; Foa & Meadows, 1997). Findings of the current study support a focus on avoidance symptomatology as part of psychotherapeutic interventions, and the possible use of startle ERPs to predict outcomes or track progress during exposure therapy.

Consistent with past findings (Drislane et al., 2013; Lang et al., 2018; Vaidyanathan et al., 2014); results indicate that overall startle magnitude may be more relevant to individual differences in neural reactivity and symptomatology than affective modulation to the startle probes. The findings parallel Krause and colleagues' (2018) investigation among healthy controls, which revealed decreased startle P3 when participants expected upcoming opportunities to avoid electric shock. When people seek to evade threat, cognitive resources shift toward processing the external world. Given that startle stimuli probe the degree to which individuals are maintaining an external orientation of attention in preparation for a possible defensive behavioral response, attenuated startle ERPs may index preparatory mental stances among individuals chronically engaged in "persistent" and "effort[ful]" (p. 468, American Psychiatric Association, 2000) avoidance of potential threat. Future studies of neural reactivity and posttraumatic stress would benefit from including unambiguous safety cues or more enduring manipulations of experimental conditions through a block design that may more strongly modulate avoidance states. Also, it may be informative to compare the startle P3 to P3 responses elicited by other goal-directed task paradigms free of startle to identify factors that uniquely influence startle P3 (e.g., Perkins et al., 2017).

The present investigation indicated that separate domains of posttraumatic symptomatology were differentially associated with startle ERPs, which may explain inconsistent findings of past studies that simply examined a categorical diagnosis of PTSD (Lewine et al., 2002; McPherson et al., 1997; Metzger et al., 2002; Metzger et al., 2008; Paige et al., 1990). In addition to avoidance-related amplitude reductions, symptoms of intrusive reexperiencing were related to increased P2 responses. Thus, individuals who reported heightened sensitivity to trauma cues exhibited amplified neural responsiveness to the noxious startle stimuli, which may implicate impaired protective mechanisms important to basic sensory reactivity. Differential relationships of symptom domains with P2 in the current study are similar to previous findings suggesting that several behavioral traits and neurophysiological systems may explain individual differences in startle ERPs (Perkins et al., 2017). It appears necessary to consider dimensions of symptomatology in order to parse PTSD in ways that more directly map onto biological phenomena (Cuthbert, 2005; Grupe et al., 2016; Lieberman et al., 2017; Marquardt et al., 2018; Moran et al., 2017).

The lack of a main effect of blast mTBI on brain responses to acoustic startle contributes to an emerging consensus regarding long-term outcomes in military populations. Maladaptive adjustment to civilian life after deployment that is commonly attributed to mild head injury can often be accounted for by psychopathology including PTSD (Disner et al., 2017; Polusny et al., 2011; Wilk et al., 2012). Recruitment of individuals with wide ranges of PTSD symptomatology and mTBI exposure in the current study allowed for statistical modeling of the possible confound of psychiatric impairment concomitant with traumatic brain injury from a war zone. Results point to potential brain-based markers of posttraumatic stress symptomatology that are independent of mTBI and provides additional evidence for relatively greater functional disruption associated with PTSD than from mTBIs incurred during military deployments.

A limitation of the current investigation was the absence of collateral information from the battlefield on brain injury sequelae (e.g., loss of consciousness) beyond retrospective self-report from the veterans. We attempted to mitigate some of the uncertainty by using semistructured tools and consensus procedures (N. W. Nelson, Davenport, & Sponheim, 2015; N. W. Nelson et al., 2011). An isolated interaction effect was observed between PTSD and mTBI for the amplitude of the P2 ERP component (see Figure 5). There may be unique aspects to individuals with PTSD and mTBI related to sensory inhibition as captured be the P2 response. Also, comorbidity of depressive disorder and alcohol dependence with PTSD and mTBI complicates attempts to isolate symptom effects to a specific categorical diagnosis. Future studies of PTSD might implement targeted recruitment of individuals with and without these comorbidities. Additionally, the cross-sectional study design cannot definitively distinguish between symptom markers or risk factors. Our exclusion of individuals with predeployment psychopathology provides some support for neural reactivity to startle probes as an expression of current psychopathology. Finally, when dimensional analyses were restricted to study participants who met full criteria for PTSD ($n = 48$) the N1 association with Avoidance fell to below significance (Cz: $p = .138$; Pz = $p = .052$), but associations with P2 and P3 components remained. Additional subtle influences on the ERPs may also be considered such as nicotine withdrawal (Engelmann et al., 2011); potential signal habituation over time (B. D. Nelson, Hajcak, & Shankman, 2015), and differences based on picture composition or complexity (Bradley et al., 2007).

In conclusion, enduring abnormalities in physiological reactivity following psychological trauma are predictive of impaired psychosocial functioning in traumatized individuals. For the current investigation we characterized neural reactivity after trauma by examining ERPs to acoustic startle probes to better understand how variation in brain responses explains posttraumatic psychopathology. In a sample of U.S. Military war zone veterans, select domains of posttraumatic stress symptomatology predicted neural reactivity as measured by N1, P2, and P3 ERP components. Specifically, amplitudes of all three ERP components to acoustic probes were reduced for individuals with maladaptive avoidance symptomatology, while the P2 component was larger for individuals with intrusive reexperiencing symptoms. Level of symptomatology rather than a formal diagnosis of

PTSD better explained alterations in neural reactivity after traumatic events, while mild brain injuries had little impact on such brain responses. Considering specific aspects of symptom expression after traumatic events is important for understanding the neural basis of trauma-related psychopathology.

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