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Differential impact of post-deployment stress and PTSD on neural reactivity to emotional stimuli in Iraq and Afghanistan veterans

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ABSTRACT

For many veterans returning from combat in Iraq and Afghanistan, the transition from military to civilian life is complicated by an array of postdeployment stressors. In addition to significant stress associated with reintegration after deployment, many returning veterans also contend with the added burden conferred by PTSD symptoms. While the relationship between PTSD symptoms and the neurobiological substrates of emotion dysregulation has begun to be studied, even less is known about the effects of postdeployment stress on neural function. In order to assess the relationship among a neural measure of attention to emotion (i.e. the late positive potential; LPP), PTSD symptoms and postdeployment stressors, EEG was recorded and examined in a linear mixed model of 81 OEF/OIF/OND veterans. Results revealed a main effect for postdeployment stressors such that increased postdeployment stress was associated with a relatively *enhanced* LPP across all emotion types. There was also a main effect for PTSD symptoms such that greater symptoms were related to a relatively *blunted* LPP across all emotion types. Findings may have important implications for understanding how both current stress and PTSD symptoms affect motivated attention as measured by the LPP. Moreover, this work highlights the need to consider the effects of current stress, in addition to PTSD symptoms, on the functioning of returning veterans.

1. Introduction

As our men and women in uniform return from the wars in Iraq and Afghanistan, many encounter significant life stress as they transition back to civilian life. For example, many returning veterans of Operations Enduring Freedom, Iraqi Freedom and/or New Dawn (OEF/OIF/OND) struggle with impairments in family, financial, educational, occupational and social functioning (Spelman et al., 2012). Veterans may be especially sensitive to these types of post-deployment challenges because war-related stressors are known to increase vulnerability to subsequent stress, a process termed stress sensitization (Antelman et al., 1980; Post and Weiss, 1998). Thus, it is possible that post-deployment stressors are particularly salient for veterans as they work to reintegrate into their families, jobs, and communities.

In addition to contending with significant stress associated with the transition from military to civilian life, many returning veterans also contend with the added burden of posttraumatic stress disorder (PTSD). Of the more than 2 million U.S. soldiers that have been deployed to Afghanistan and Iraq, 23% have developed PTSD (Fulton et al., 2015). In addition to the study of PTSD as a discrete diagnostic category, recent work has also begun to highlight the strain created by subthreshold PTSD symptoms. For example, growing evidence has demonstrated that even subthreshold PTSD confers profound clinical and functional hardship, including heightened suicide risk and greater health problems (Eekhout et al., 2016; Jakupcak et al., 2011; Pietrzak et al., 2009).

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While substantial work from functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) has begun to elucidate the biological correlates of PTSD (e.g. Hughes and Shin, 2011; Lobo et al., 2015), few attempts have been made to examine the neural underpinnings of post-deployment stress. One method for elucidating the neurobiological correlates of post-deployment stressors is through the use of an event-related potential (ERP) component, known as the late positive potential (LPP). The LPP is a centro-parietal, positive-going ERP component that appears approximately 400 ms after stimulus onset and is larger for emotional (e.g., threatening) stimuli than neutral stimuli (Dolcos and Cabeza, 2002; Foti et al., 2009; Schupp et al., 2000). Because of its relation to emotional processing and motivated attention, the LPP has been examined in disorders of affect dysregulation, such as PTSD (Lobo et al., 2015). Specifically, earlier research examining a cohort of combat veterans with and without PTSD suggests that the diagnosis of PTSD is related to blunting of the LPP during processing of emotional faces (MacNamara et al., 2013).

Far fewer studies, however, have examined the LPP in the context of recent stress (as opposed to psychopathology). The LPP may be a particularly useful ERP component to examine current stress because it is fundamentally understood as a a means of tracking motivated attention toward emotionally salient information (Hajcak et al., 2013). As stress is known to disrupt attentional focus by increasing emotional vigilance at the cost of decreased attention toward non-emotional stimuli (Alomari et al., 2015), the LPP may be a strong neural marker to examine motivated attention. Although the LPP may be a useful measure to examine how stressors influence reactivity and regulation at the neural level, very few studies have examined the LPP in conjunction with current stress—and these studies have been focused on acute, provoked stress trials (e.g., response to physically uncomfortable stimulus) as opposed to the daily, routinized stressors with which returning veterans must content (e.g., marital problems, financial stress). In one study, Weymar and colleagues (Weymar et al., 2011) performed a stress trial on healthy volunteers in which they showed participants unpleasant images. In some trials, the images were preceded by a stressor (i.e., cold pressor test) and in other trials there was no preceding stressor. Results indicated viewing of unpleasant images evoked an enhanced LPP when participants were exposed to prior acute stress as compared to when they were not. Another study found that stress-related olfactory cues increased the salience of neutral and ambiguous faces in healthy adults as indicated by an enhanced LPP response (Rubin et al., 2012). Taken together, these prior studies suggest that stress enhances the LPP. Notably, however, no studies have examined how day-to-day psychosocial stressors, such as those during post-deployment, may be related to the LPP in veterans. Moreover, no study has examined the effect that current stressors and PTSD symptoms may be same or different on neural function; consequently, their unique and potentially interactive effects remain unknown.

Thus, this study sought to expand the current literature on the relation between current stress and PTSD symptoms. Specifically, in an independent cohort from that reported by MacNamara et al. (2013), we sought to examine the unique and interactive effects of post-deployment stressors and PTSD symptoms in OEF/OIF/OND veterans on neural reactivity as measured by the LPP. We examined all variables as continuous predictors in order to extend our understanding of the role of individual differences in the relationship between PTSD symptoms, stress, and LPP reactivity. Because LPP reactivity can be measured in various time windows, we examined neural reactivity in our sample in an early (i.e., 500–1500 ms) and late (i.e., 1500–3000 ms) time window. Analysis of two time windows was used to enrich understanding of the relationship between stress and PTSD symptoms on sustained, initial or late neural reactivity.

We hypothesized that both PTSD symptoms and post-deployment stressors would be related to emotional reactivity as measured by the LPP response to angry, fearful and happy faces. While we hypothesized that both PTSD would be related to blunting of the LPP based on prior research (DiGangi et al., 2017; MacNamara et al., 2013), we made no directional hypothesis for post-deployment stressors, given that no prior work has examined post-deployment stress in veterans with a range of psychiatric symptoms. Similarly, in terms of the interaction between stress and PTSD symptoms, no directional hypotheses were made because of the exploratory nature of this hypothesis.

2. Methods

This study was approved by the Institutional Review Boards at Jesse Brown VA Medical Center, Chicago IL and its university affiliate, the University of Illinois at Chicago. Research was conducted in accordance with the Helsinki Declaration.

2.1. Participants

Eighty-one participants with LPP data from EEG were included from a larger sample of OEF/OIF/OND veterans recruited at the Jesse Brown VA Medical Center and the University of Illinois Chicago. After completing informed consent procedures, participants completed the ERP task, a clinical assessment, and self-report measures. Exclusionary criteria for participants included: presence of a clinically significant medical or neurological condition, presence of an organic mental syndrome and/or psychotic disorder, intellectual disability or pervasive developmental disorder, and current substance abuse or suicidal ideation at a level that would interfere with the study protocol. Ages ranged from 21 to 53 years (mean: 33.99 SD: ±7.2); 80.2% of the sample was male. Average HAM-D score was 8.59 (SD: ±5.7; see Measures). Of the 81 participants, 4.8% (n = 4) had a primary diagnosis of an anxiety disorder that was not PTSD (e.g., Panic Disorder), 31% (n = 26) had a primary diagnosis of mood disorder and 9.5% (n = 8) had a current or past substance use disorder. At the time of enrollment, 41.7% of the sample was prescribed psychiatric medications (see Table 1).

2.2. Measures

All clinical measures were administered by a psychologist or a master's level research assistant under the supervision of a licensed psychologist. Post-deployment stressors were assessed through self-report, using the Post-Deployment Stressors (PDS) subscale of the Deployment Risk and Resilience Inventory-2 (DRRI-2) (Vogt et al., 2013). The PDS subscale is scored on a dichotomous (i.e., yes/no) scale and includes stressors that have occurred post-deployment (e.g., I lost my job or had serious trouble finding a

Table 1
Demographic and clinical characteristics.

n = 81	AGE	CAPS	HAM-D	DRRI/PDS
Mean (+/− SD)	33.99 (7.2)	40.37 (31.4)	8.59 (5.7)	4.05 (2.9)
			n	%
Gender	Male		65	80.2
	Female		16	19.8
Primary Dx	Other Anxiety Disorder (not PTSD)		4	4.8
	Mood Disorder		26	31
	Substance Use Disorder		8	9.5
Current Psych Med Use			35	41.7

job). Items endorsed as "yes" are summed for a possible score ranging from 0 to 14, with higher scores indicative of more exposure to additional life stressors after deployment. Earlier work with the PDS subscale has been shown to have good internal consistency (i.e., $\alpha = 0.85$; Flanagan et al., 2014). In order to examine the unique effects of postdeployment stress, we also included a measure of pre-deployment stress to examine what, if any, effect it would have on the model. Thus, the Prior Stressors subscale of the DRRI-2 was also used. The Prior Stressors subscale of the DRRI-2 has also been shown to have good internal consistency (i.e., $\alpha = 0.73$; Flanagan et al., 2014).

2.2.1. Clinical assessment

Psychiatric diagnoses were established using the Mini International Neuropsychiatric Interview 6.0 (Sheehan et al., 1998). The M.I.N.I. is a well-validated, semi-structured interview for the assessment of current and lifetime DSM-IV Axis I disorders. It was administered to every participant in order to establish other psychiatric diagnoses. PTSD was assessed using the CAPS-IV (Blake et al., 1995). The CAPS is a clinician-administered interview that dimensionally evaluates 17 PTSD on frequency and intensity. Ratings are summed to create a severity score for each of the 3 clusters and a total PTSD score. Given that our study focused on combat-related PTSD, all reported Criterion A events were related to OEF/OIF/OND deployments. Depression was assessed using the clinician administered Hamilton Depression Rating Scale (Hamilton, 1960).

2.2.2. Emotional faces task

Participants completed an EEG version of the Emotional Face-Matching Task (EFMT; Hariri et al., 2002), which has proven useful in characterizing threat-processing in anxious and non-anxious participants (Labuschagne et al., 2010) and facilitates comparison with prior ERP work in PTSD (Felmingham et al., 2008; MacNamara et al., 2013). On each trial, three faces or shapes were presented for 3000 ms, in a triangular arrangement – i.e., one image was centered in the top-half of the screen and the other two images were presented in the bottom-half of the screen (one to the left and one to the right). On each face-matching trial, the faces of three different actors were presented: two were always emotional and one always neutral. Participants were instructed to select one of the faces at the bottom of the screen that bore the same emotional expression as the 'target' face centered in the top portion of the screen. Face-matching trials could be fearful, angry or happy. On shape-matching trials, participants were instructed to choose the shape at the bottom of the screen that matched (i.e., had the same form as) the target shape at the top of the screen. In line with previous studies (e.g., Labuschagne et al., 2010; Phan et al., 2008), we used geometric shapes as control stimuli instead of neutral faces, because neutral faces may be more influenced by individual differences (Somerville et al., 2004). The task was divided into two runs, with each block having 12 angry, 12 fearful, 12 happy and 12 shape-matching trials; trials were presented randomly within each run. The inter-trial interval varied between 1000 and 3000 ms, during which time a white fixation cross was centrally presented on a black background. Participants performed six practice trials prior to beginning the experiment. The task was administered on an Intel(R) Core(tm) i7 @ 1.60 GHz computer with a 19-in. (48.3 cm) monitor, using Presentation software (Presentation, 2016).

2.2.3. EEG data recording

Continuous EEG was recorded using the ActiveTwo BioSemi system (ActiveTwo, 2016). Thirty-four electrode sites (standard 32 channel setup, as well as FCz and Iz) were used, based on the 10/20 system; in addition, one electrode was placed on each of the left and right mastoids. The electrooculogram (EOG) generated from eye movements were recorded from four facial electrodes. The EEG signal was pre-amplified at the electrode to improve the signal-to-noise ratio. The data were digitized at 24- bit resolution with a Least Significant Bit (LSB) value of 31.25 nV and a sampling rate of 1024 Hz, using a low-pass fifth order sinc filter with a −3 dB cutoff point at 204.8 Hz. The voltage from each active electrode was referenced online with respect to a common mode sense active electrode producing a monopolar (non-differential) channel. Off-line analyses were performed using Brain Vision Analyzer software (Brain Vision Analyzer 2, 2006). Data were re-referenced to the average of the two mastoids, segmented 200 ms before stimulus onset and continuing for the 3000 ms stimulus duration, and band-pass filtered with high-pass and low-pass filters of 0.01 and 30 Hz, respectively. Eye blink and ocular corrections used the method developed by (Miller et al., 1988). Semi-automated artifact rejection procedures were used to identify a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. Trials were also inspected visually for any remaining artifacts, and data from individual channels containing artifacts were rejected on a trial-to-trial basis.

2.3. Data analyses

The LPP was scored based on prior literature as well as prior studies from our lab and from visual depiction of the current data indicating the LPP is maximal at centro-parietal sites (e.g., DiGangi et al., 2017); specifically, the LPP was scored at Cz, CP1, CP2, Pz, P3 and P4, and it was apparent in the overall sample beginning at approximately 500 ms and continuing throughout the stimulus duration of 3000 ms; thus, the LPP was scored across this entire window. Fig. 1 depicts scalp distributions and grand-average waveforms for all emotions at centro-parietal pooling. In order to isolate the variance in the LPP related to emotional picture processing, our analyses focused on emotional faces (i.e., angry, fearful, and happy separately) minus shapes difference scores; the decision to separate the emotional faces was supported by results from earlier work in which there was only an effect for angry faces (MacNamara et al., 2013). Behavioral data were analyzed using a repeated measures analysis of variance (ANOVA). Significant omnibus findings were followed up using independent *t*-tests for planned comparisons; post-hoc tests used the Bonferroni correction. Greenhouse Geisser corrections were applied as necessary for violations of sphericity.

A multilevel mixed model was conducted to examine the unique and interactive effects of current stress as measured by the DRRI-2 postdeployment index and PTSD and symptoms on LPP magnitude. Given the high comorbidity between PTSD and depression, and to ensure that effects were specific to symptoms of PTSD, BDI scores were entered into the model. Also, to ensure that the effects of postdeployment stress were distinct from prior stress, predeployment stressors were also entered into the model. Task condition was specified as a three-level within-subject variable – angry, fearful, and happy faces. Psychotropic medication use (yes/no) and biological sex were included as covariates. The main effects of current stress and psychopathology (i.e., PTSD and depression symptoms) were modeled, as well as all possible two- and three-way interactions. The multilevel model used restricted maximum likelihood (REML) estimation and an unstructured covariance matrix. Statistical analyses were conducted in SPSS (IBM Corp, 2013).

3. Results

3.1. Behavioral

Participants performed well on the EFMT as average accuracy

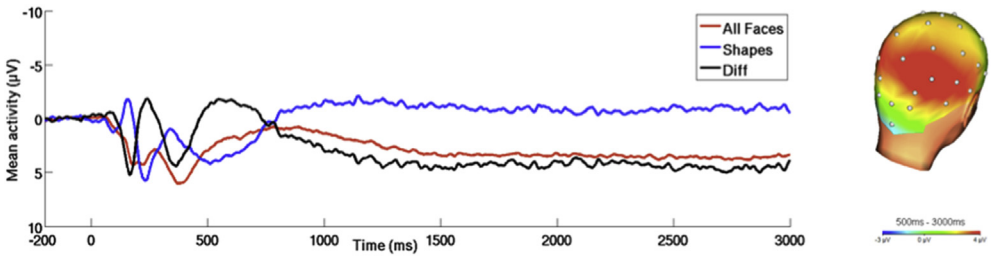

Fig. 1. Scalp Distributions for all emotional faces condition (minus shapes) during 500–3000ms window and ERPs (negative up) at centro-parietal sites.

was 94% SD: ±0.04 There was an effect of condition on reaction time (F (2.42, 195.81) = 548.55, $p < 0.001$, $\eta^2 = 0.87$). Post-hoc analyses indicated that trials with faces elicited slower reaction times than those with shapes. Specifically, angry faces elicited the slowest reaction time (i.e., angry > fear > happy > shapes; Bonferroni-corrected $p < 0.001$). Similarly, there was an effect of condition on accuracy ($F(1.84, 149.0) = 117.37$, $p < 0.001$, $\eta^2 = 0.60$), such that trials with faces elicited worse performance that trials with shapes. Consistent with earlier research (MacNamara et al., 2013), angry faces elicited the worst performance of all conditions (i.e., shapes > happy > fear > angry; Bonferroni-corrected $p < 0.001$). There were no significant relationships between reaction times, PTSD or stress.

3.2. Results of multilevel modeling/linear mixed model

3.2.1. Early time window (500–1500 ms)

Results in the early time window revealed one main effect. Specifically, there was a main effect of current stress as measured by the DRRI post-deployment stressors index ($b = 0.71$, t (192.54) = 2.17, $p = 0.03$), such that current levels of postdeployment stress *enhanced* the magnitude of the LPP across emotion types (Fig. 2). There was no effect for PTSD in the early time window.

3.2.2. Late time window (1500–3000 ms)

Results in the late time window revealed two main effects. Specifically, there was a main effect of current stress as measured by the DRRI post-deployment stressors index ($b = 1.1$, t (200.14) = 2.20, $p = 0.03$), such that current levels of postdeployment stress *enhanced* the magnitude of the LPP across emotion types (Fig. 2). There was no effect for PTSD in the early time window. Additionally, there was a main effect of PTSD as measured by the CAPS ($b = -0.11$, t (200.14) = −2.00, $p = 0.05$), such that PTSD *blunted* the magnitude of the LPP across emotion types (Fig. 3).

There was no effect of depression in either model (early: $p = 0.39$; late: $p = 0.20$). None of the interactions (i.e., emotional expression x stress; emotional expression x PTSD; emotional expression x depression) was significant. Medication use, age and sex did not change model results.

4. Discussion

The primary aim of the current study was to examine the impact of post-deployment stressors and PTSD symptoms on a neural measure of motivated attention to socio-emotional cues (i.e., angry, fearful, and happy faces) in a sample of OEF/OIF/OND veterans. Results revealed a main effect for current stress as measured by an inventory of post-deployment stressors across both an early and late time window, such that increased postdeployment stress was associated with a relatively enhanced LPP across all emotion types. Conversely, there was a main effect for PTSD symptoms such that greater symptoms were related to a relatively blunted LPP across all emotion types in only the late time window. This has important implications for understanding how both current stress and PTSD symptoms may affect motivated attention as measured by the LPP

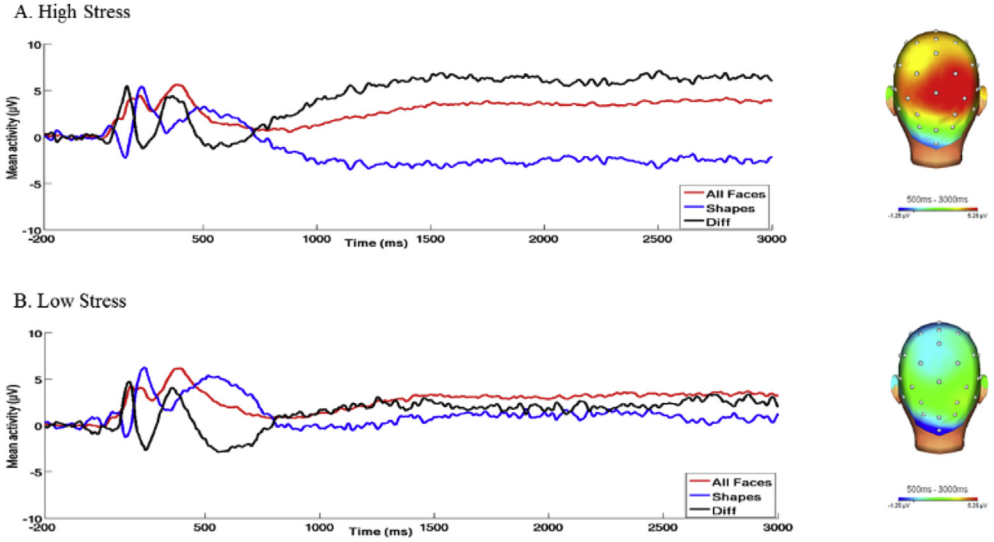

Fig. 2. Scalp distributions depicting responses to all faces minus shapes among: A. participants with high post-deployment stressors score (n = 42), B. participants with low post-deployment stressors score (n = 39).

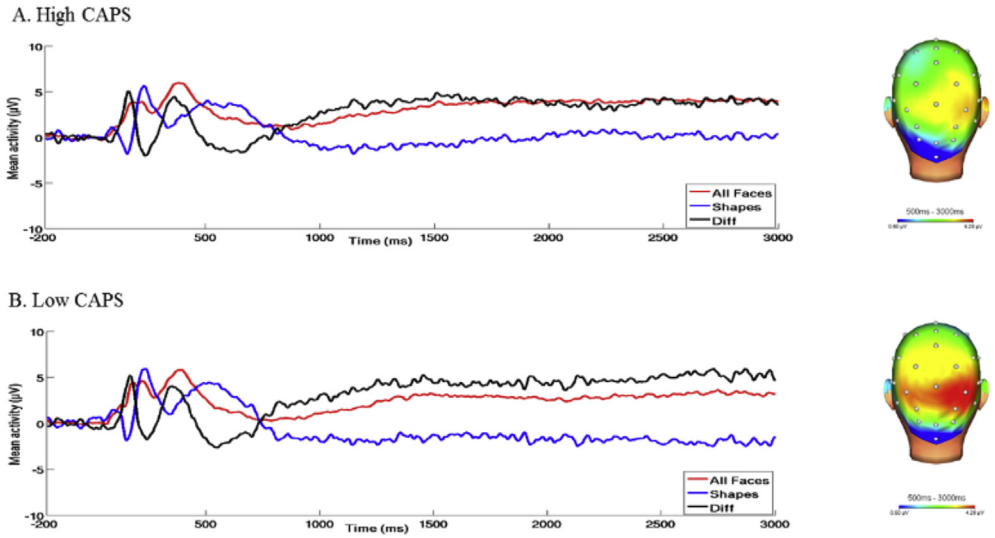

Fig. 3. Scalp distributions depicting responses to all faces minus shapes among: A. participants with high CAPS score (n = 41), B. participants with low CAPS score (n = 40).

in different ways. Specifically, the results suggest that post-deployment stressors were associated with sustained responding to emotional stimuli. It may be that postdeployment stress is associated with non-specific, broader reactivity whereas PTSD may have a different neural signature that is associated with slower reactivity to emotional content.

In terms of PTSD, the few available studies that have examined the LPP in the context of PTSD and emotional face processing provide preliminary evidence that blunting of the LPP may be a neurobiological correlate of PTSD (DiGangi et al., 2017; MacNamara et al., 2013). However, it is also important to note that one study found PTSD was associated with increased reactivity to threat as measured by the LPP in response to images of mutilated bodies (Lobo et al., 2014). The reason for these discrepant findings is unclear. A possible explanation in the heterogeneity of findings may be due to methodological differences. While all studies used emotionally provocative stimuli, Lobo et al. (2014) used disturbing images of mutilated bodies and the other two studies used emotional faces (i.e., happy, fearful, angry; (DiGangi et al., 2017; MacNamara et al., 2013). Findings from the present study are consistent with theory of PTSD—most notably that affect dysregulation is a core feature of PTSD (Hayes et al., 2012). As the LPP is considered a means to track motivated attention toward emotional stimuli (Hajcak et al., 2013), it is possible that greater PTSD symptoms in this cohort reflects attentional disengagement from these affective stimuli (i.e., emotional faces).

Even less is known about the effects of current stress on the LPP. Most fundamental to the current study, it was unknown if current stress would be related to a distinct pattern of neural functioning than has been previously described for PTSD. Our results suggest that post-deployment stressors have different effects from PTSD as assessed by the LPP. Although PTSD has its etiological roots in (traumatic) stress, the subsequent pathways by which PTSD and current stress are related to motivated processing of socioemotional stimuli suggest that they are underpinned by some distinct processes. While we have already speculated that PTSD may be related to affective disengagement, the construct of major life stress (e.g., foreclosure, divorce) may be more related to hyperreactivity to emotional cues. In other words, PTSD—consistent with new nosology put forth by DSM-5—may be a disorder of broad emotion dysregulation (e.g., reactivity and blunting; Etkin and Wager, 2007), whereas major life stress may be related more discretely to hyperreactivity.

In terms of current stressors, OEF/OIF/OND veterans contend with significant levels of reintegration stress—and the transition back to civilian life after deployment is often is associated with non-psychiatric features of irritability, anxiety, and sadness (e.g., Adler et al., 2011). Prior work indicates that stress can increase emotional vigilance at the cost of a decrease in attention towards non-emotional stimuli (Alomari et al., 2015). Our study provides evidence that common, post-deployment stressors lead to heightened emotional reactive among veterans. Importantly, psychiatric stress (i.e., PTSD symptoms) and post-deployment related stressors are related to neural activity in important and distinct ways. Also noteworthy, the heightened and blunted reactivity were demonstrated across emotion types, suggesting that returning veterans may be more reactive to a broad range of emotion as opposed to specific emotions only (e.g,. anger).

There are also important limitations and future directions that need to be considered. The experimental design is cross-sectional and, importantly, it is not clear whether blunting or reactivity are results of PTSD and current stress, respectively, or if these neural features predate psychopathology and stress. Second, future work that examines other types of emotionally provocative and neutral stimuli (e.g., non-social threatening and non-threatening material) would further develop understanding and generalizability of the relationship between stress (both psychiatric and non-psychiatric) and neural response. Likewise, future studies that consider other biological measures of physiological reactivity (e.g., blood pressure) to postdeployment stress and PTSD would enhance our understanding of these complex biological and environmental relationships. Finally, our sample did not solely contain PTSD symptoms, as individuals with a history of other affective and anxiety disorders (e.g., panic disorder) were also included. Because our modest sample size precluded us from controlling for all possible confounding variables, the degree to which comorbid conditions contributed to the present findings remains unclear. However, given our heterogeneous sample, the findings are more likely to generalize to a diverse cohort of OEF/OIF/OND veterans.

In conclusion, this study provides evidence that emotion processing in the context of PTSD and post-deployment stress have differential impact on neural reactivity to socio-emotional signals. Specifically, PTSD is associated with an attenuated neural response to emotional faces whereas the current stressors that are common to veterans in their post-deployment lives are associated with an enhanced neural response to emotional faces as measured by the

LPP. Many veterans content with great hardship conferred by *both* PTSD symptoms and significant life stress. Elucidating how these distinct stressors affect processing and, therefore, functioning may ultimately yield new and useful psychophysiologic targets for treatment and early interventions after military deployment and during transitioning back to civilian life.

Financial disclosures

The authors report no financial interests or potential conflicts of interest.

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