Relationship between Stress Exposure and a Neural Measure of Emotional Response in Combat Veterans

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THESIS

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
CAPS	Clinician Administered PTSD Scale
CES	Combat Exposure Scale
DRRI	Deployment Risk and Resilience Inventory
EEG	Electroencephalography
ERP	Event Related Potential
ERT	Emotion Regulation Task
IAPS	International Affective Picture System
IRB	Institutional Review Board
LPP	Late Positive Potential
OEF	Operation Enduring Freedom
OFC	Orbitofrontal Cortex
OIF	Operation Iraqi Freedom
OLS	Ordinary Least Squares
PTSD	Posttraumatic Stress Disorder
VPP	Vertex Positive Potential

SUMMARY

A study of the neural processes contributing towards hyper-reactivity to threatening stimuli was carried out in combat-exposed military veterans and inter-individual variability in neural response was measured in relation to current symptoms of posttraumatic stress disorder (PTSD), severity of combat exposure, combat-associated stress, and non-combat-associated stress. Participants completed self-report measures related to illness state and experiences during combat and, following, completed an Emotion Regulation Task (ERT) during electroencephalogram (EEG) recording. The Late Positive Potential (LPP), an event related potential (ERP), was extracted as a neurophysiological index of arousal during the ERT throughout directed (1) maintenance and (2) voluntary regulation of reactivity to negative imagery. In order to test predictive associations between magnitude of the LPP during sustained reactivity and regulation of reactivity with variables of-interest, bivariate ordinary least squares (OLS) regressions were performed.

Condition effects across subjects indicate that the LPP during maintenance did not change in amplitude while it decreased in positive amplitude during regulation. In examining regression results, it was determined that pre-deployment stress exposure (a non-combat-associated stressor) and a lack of unit support (a combat-associated stressor) both increased the positive amplitude of the LPP during regulation alone, counter to desired effects. These findings demonstrate that additional life stressors (e.g., not combat per se) impair neural processes during the regulation of reactivity. Study limitations, implications and a summary of findings in the context of existing literature are discussed.

I. INTRODUCTION

Exposure to a traumatic event can alter the way in which the body ordinarily responds to stress by impacting physiological functioning of the stress response system. One byproduct of this alteration involves the development of hyper-reactivity, or heightened physiological arousal following exposure to cues that relate to the original trauma or are generally fear-producing (Blanchard et al., 1982; Carson et al., 2000; Foa et al., 1989; Gerardi et al., 1989; Keane et al., 1985; Kimura et al., 2013; Liberzon et al., 1999; Malloy et al., 1983; McCaffrey et al., 1993; McDonagh-Coyle et al., 2001; McFall et al., 1990; Orr et al., 1993, 1998; Pallmeyer et al., 1986; Pitman et al., 1987; Pitman and Orr, 1990; Seundermann et al., 2010; Vedantham et al., 2000; Wolfe et al., 2000). While reactivity to stimuli in the environment that signal threat is itself a normal and expected reaction in all individuals in order to ready the body for danger, the initiation of arousal eventually subsides in normal instances once threat has abated. In contrast, the initiation of arousal may begin exaggerated and persist well beyond the removal of the threat in individuals who have been exposed to severely traumatic experiences (Riggs et al., 1995; Rothbaum et al., 1992), sometimes persisting as a symptom for many years after the traumatic event (McDonagh-Coyle et al., 2001). Measured most commonly by probing functioning of the autonomic nervous system (ANS) during perceived threat, hyper-reactivity may also be studied within the central nervous system (CNS) by observing changes in brain processes during electroencephalogram (EEG) recording. While many studies of ANS functioning suggest that hyper-reactivity is defined by an over-engagement of this system, the study of event related potentials (ERP's) extracted from EEG additionally suggest that the brain during this time is unable to accurately discern threat, as evidenced by atypical ERP response during the deployment of attention and processing of negative imagery. Thus, a more complete understanding with regard to physiological response during hyper-reactivity involves hyper-

responsiveness of the ANS that, itself, may be dependent on deficient brain processes in the ability to distinguish threat.

Even so, consistent with the discovery of individual variability in the generation of arousal itself (Belsky et al., 1998; Canli et al., 2001; Carson and Bittner, 1994; Eugene et al., 2003; Hamann and Canli, 2004; Hasnain et al., 1998; Hunton et al., 1996; Nadeau et al., 1998; Silvers et al., 2012; Stollstorff et al., 2013), individual differences also exist in the extent to which hyper-reactivity is present following trauma exposure (Abramson et al., 1989; Chang, 2002; Charbonneau et al., 2009; Smith et al., 1993; Wagner et al., 2007). Further, this variability has been suggested to depend on both biological (Gillespie et al., 2009b; White et al., 2012) and environmental (Gillespie et al., 2009b; Grant et al., 2011; Heim et al., 2008; Shonkoff et al., 2009) influences. To-date, identifiable environmental risk-factors have centered on the relationship between hyper-reactivity and qualities particular to the trauma exposure. With respect to veterans exposed to combat in particular, functional magnetic resonance imaging (fMRI) studies have determined that severity of combat experiences may alter functioning in brain regions involved in extended emotional processing (Aupperle et al., 2013; Herringa et al., 2013; van Wingen et al., 2011a, 2011b). Additionally, neuroimaging studies have also uncovered a correlation between exposure to early life trauma and these same aberrations, suggesting that trauma experienced during development may be additionally influential in shaping the symptom.

While the association to environmental factors that may ultimately affect hyper-reactivity is itself informative, inter-individual differences in the symptom are also defined by variability in brain processes during both the initiation of arousal and regulation of arousal, occurring either

implicitly or explicitly prior to a behavioral response. Even so, while the aforementioned research suggests that environmental precursors may increase risk for hyper-reactivity in general, there is no study to-date testing these associations during the independent initiation and regulation of reactivity in order to discern whether these environmental factors selectively impair one or both of these processes. The current study aimed to address this gap by testing the relationship between exaggerated emotional reactivity, measured via brain processes during EEG recording, and stress particular to combat exposure alongside the incidence of stress experienced outside of military operations. Importantly, these associations were tested with respect to inter-individual differences in the initiation of reactivity to negative imagery and during the voluntary regulation of this reactivity. Additionally, the relationship to current symptom presentation of posttraumatic stress disorder (PTSD) was examined in all individuals given prior evidence that reactivity itself is over-exaggerated in this population (Pole, 2007). The exact aim of this work was to independently identify sources for atypical functioning within the brain that contribute towards hyper-reactivity as a symptom of trauma exposure by systematically studying the influence of psychopathology and trauma factors on both reactivity itself and the regulation of reactivity.

II. CONCEPTUAL FRAMEWORK

A. Defining Emotional Hyper-reactivity following Trauma Exposure

Emotional reactivity is the initiation of arousal following the appraisal of cues in the environment that signal potential threat, a sequence of actions that has been documented via numerous studies of healthy individuals following exposure to negative imagery (Adolphs, 2002; Calder et al., 2001; LeDoux, 2000; Phan et al., 2002, Williams et al., 2005; Zald, 2003). Following the experience of a traumatic event, however, this process may become altered in a more permanent way via exaggeration of this reactivity during exposure to subsequent stressors. This exaggerated emotional hyper-reactivity, defined as atypical, most commonly occurs following exposure to stimuli that recall the initial traumatic event itself (Blanchard et al., 1982; Carson et al., 2000; Gerardi et al., 1989; Liberzon et al., 1999; Malloy et al., 1983; McCaffrey et al., 1993; McDonagh-Coyle et al., 2001; McFall et al., 1990; Orr et al., 1993, 1998; Pallmeyer et al., 1986; Pitman et al., 1987; Pitman and Orr, 1990; Suendermann et al., 2010; Vedantham et al., 2000; Wolfe et al., 2000) but may also occur following exposure to general fear-inducing cues (Foa et al., 1989; Keane et al., 1985; Kimura et al., 2013).

With regard to the prevalence of the symptom following trauma, it has been documented in cases involving the loss of loved ones (Carmassi et al., 2013; Pfefferbaum et al., 2013), the diagnosis of a terminal illness (Rzeszutek et al., 2012; Oniszczenko and Laskowska, 2014), motor vehicle accidents (Kazantizis et al., 2012), and exposure to combat (Paulus et al., 2013). While the exact cause of hyper-reactivity may be assumed to follow from the acute stress experience itself, individual variability exists in presentation, indicating that simple exposure

to trauma cannot fully explain the symptom's existence (Abramson et al., 1989; Chang, 2002; Charbonneau et al., 2009; Klanecky and McChargue, 2009; Smith et al., 1993; Wagner et al., 2007). In terms of determining sources for such individual differences, research varies widely on the cause, with correlations drawn to differences in depressive and temperamental traits (Lauterbach, 2006; McFarlane, 2006; Oniszczenko et al., 2014; Smith et al., 1999; Strelau, 2010), age, gender (Charbonneau et al., 2009), and genetic precursors (White et al., 2012). In terms of environmental influences, the severity of trauma exposure has been associated with severity of hyper-reactive symptoms (Aupperle et al., 2013; Herringa et al., 2013; Kimble et al., 2010; Pfefferbaum et al., 2013; van Wingen et al., 2011a, 2011). Additionally, exposure to early childhood trauma or maltreatment has also been attributed to disrupting individual capacity to perceive and differentiate threat later in life, thus altering emotional reactivity by exaggerating this response when exposed to subsequent trauma (Chapman et al., 2004; Dube et al., 2001; Felitti et al., 1998; Gillespie et al., 2009a; Gladstone et al., 2004; Glaser et al., 2006; Grant et al., 2011; Heim et al., 2008; Jovanovic et al., 2009; McCauley et al., 1997). Individual variability in expression of hyper-reactivity has also been found to mediate the relationship between stress exposure and the development of depression (Charbonneau et al., 2009) trait-anxiety (Grillon et al., 2005) and PTSD (Pole, 2007; Keane et al.., 1998; Laor et al.., 1998; Shalev et al., 1993).

B. **Measuring Emotional Hyper-reactivity**

Hyper-reactivity may be measured a number of ways. Self-report measures of subjective distress following re-exposure to trauma-related cues have been used with success (Badour et al., 2011; Liberzon et al., 1999; Wolfe et al., 2000). In some cases, this distress can be measured in terms of subjective feelings of various emotions, including unpleasantness, arousal, vividness, sadness, anger, fear, disgust and surprise (Badour et al., 2011; Pitman et

al., 1987, 1990; Pineles et al., 2013; Shin et al., 2004). In attempting to measure physiological response directly, many investigations rely on probing the functioning of the autonomic nervous system (ANS) immediately following exposure to trauma-related or fear-inducing cues. The ANS controls visceral organs, containing two complementary branches. One branch, the sympathetic division, instigates “fight or flight” responses to stress while the parasympathetic performs “rest and digest” functions in the absence of stress. Observable “fight or flight” responses following threat may be completed by measuring skin conductance response (SCR) - a measure of perspiration on the skin’s surface as a result of sweat gland secretion - heart rate variability, increased blood pressure and the contraction of muscles, all processes that function to promote immediate behavioral responses to threat (Brierley-Bowers et al., 2011). Startle response to an aversive stimuli, in most cases a noxious auditory sound, has also been used as exaggerated startle has been found to correlate with increased SCR and heart rate variability (Pole et al., 2007).

In women that were once victims of childhood sexual abuse, elevated heart rate, muscle tension, and slowed habituation of SCR has been reported following an acute stress test performed in adulthood (Metzger et al., 1999; McDonagh-Coyle et al., 2001; Orr et al., 1998). Additionally, in individuals exposed to physical assault and motor vehicle accidents, increased SCR has also been observed following exposure to a novel stimulus not associated with either trauma or fear (Felmingham et al., 2012). This suggests that increased functioning of the ANS as a measure of reactivity may occur outside exposure to fear-related cues. Specific to investigating ANS functioning in those exposed to combat, it has also been reported that both veterans with and without a PTSD diagnosis demonstrate an exaggerated startle response in comparison to healthy controls (Grillon et al., 1998). This suggests that hyper-reactivity may also be better associated with trauma exposure irrespective of the development of PTSD. Even

so, most of the studies investigating characteristics of hyper-reactivity have solely studied this phenomenon in individuals diagnosed with PTSD. Here, it has been confirmed that individuals with PTSD do show increased autonomic reactivity following exposure to scripts (Carson et al., 2000; Orr et al., 1993, 1998; McDonagh-Coyle et al., 2001; Pitman et al., 1987; Pitman and Orr, 1990; Seundermann et al., 2010) sounds (Blanchard et al., 1982; Gerardi et al., 1989; Liberzon et al, 1999; Pallmeyer et al, 1986; Wolfe et al, 2000), sights, (McFall et al, 1990; Malloy et al, 1983; McDonagh-Coyle et al., 2001; Wolfe et al., 2000) and smells (McCaffrey et al., 1993) associated with the trauma itself (Vedantham et al., 2000).

While this evidence suggests that hyper-reactivity is defined by an overactive ANS in response to potential threat, because hyper-reactivity also relies on operations within the central nervous system (CNS), the symptom may also be measured via changes in brain functioning. Electroencephalogram (EEG) recording has been a useful tool in determining response of the CNS during arousal with prior research demonstrating a strong association between cortical activation measured via EEG and heart rate variability and SCR (Falconer et al., 2008; Lim et al., 1996, 1999; Prinsloo et al., 2013; Yu et al., 2009), supporting the notion that EEG provides additional insight with regard to the biological underpinnings of the symptom. Event related potentials (ERP's), extracted from the EEG recording, are time-locked to a particular task execution with signal characteristics defining brain processes associated with that task function, such as stimulus viewing. Additionally, as EEG recording allows for the study of brain processes on a timescale of milliseconds, the measure allows for exceptional temporal resolution towards understanding the dynamic process of reactivity.

Early engagement of attention towards stimuli that may signal threat and subsequently evoke emotional reactivity has been measured most closely via the P300, an ERP that is characterized by a positive deflection at a central-parietal location and occurring approximately 300 milliseconds after the viewing of a stimulus. This component is believed to relate to the actual deployment of attention as changes in the amplitude and temporal characteristics of the P300 following stimulus onset have been related to changes in attentional processing following the perception of a novel stimulus (Karl et al., 2006; Picton, 1992). Across many studies, the P300 amplitude has been found to be increased in trauma-exposed individuals with (Donchin and Coles, 1998; Felmingham et al., 2012; Kaufman, 2002; Kimble et al., 2000; Johnson, 1986; Nieuwenhuis et al., 2005; Polich, 2007; Polich and Kok, 1995) and without PTSD (Covey et al., 2013; Karl et al., 2006; Kimble et al., 2010; Kimura et al., 2013; Qiu et al., 2010), suggesting that increased attention processing is occurring. Individuals with acute stress syndrome following trauma also demonstrate similar increased P300 amplitudes to novel, non-fear-provoking cues (Karl et al., 2006). In individuals with PTSD, atypical latencies of the P300 also suggest slowed attention capabilities (Shucard et al., 2008) alongside decreased P300's during the viewing of distractor stimuli (McFarlane et al., 1993), with this last finding suggesting that stimulus differentiation may also be impaired.

With respect to the processing of emotionally-specific stimuli, there is a dearth of research involving individuals exposed to trauma outside the development of PTSD. However, increased P300's following the viewing of negative stimuli and decreased P300's following the viewing of neutral stimuli in individuals with PTSD have been documented, suggesting that attention may be over-deployed with regard to affective stimuli and under-deployed with regard to non-affective stimuli (Bryant and Harvey, 1995; Kaspi et al., 1995; Kimble et al., 2000, 2010; McNally et al., 1990). The study of other ERP's that are specifically related to extended

emotional processing, rather than attention allocation, have also been used. The Late Positive Potential (LPP) has been identified as uniquely related to the processing of emotion (Cuthbert et al., 2000; Hajcak and Nieuwenhuis, 2006; Keil et al., 2002; Lang et al., 1997b; Schupp et al., 2000, 2003b) and is defined by a positive-going deflection occurring approximately 300 ms after the viewing of an emotionally-salient stimulus at a central-parietal location. This component is distinct from the P300 in its sensitivity to affective stimuli and is believed to relate to longer cognitive processes during the appraisal of emotional cues. Increases in LPP amplitude are hypothesized to relate to greater processing related to the assessment of emotional cues (Cuthbert et al., 2000; Diedrich et al., 1997; MacNamara et al., 2009; Azizian and Polich, 2007; Codispoti et al., 2001; Foti et al., 2009; Hajcak and Olvet, 2008; Olofsson et al., 2008; Olofsson and Polich, 2007) while decreases in amplitude during voluntary emotional regulation may reflect successful ability to dampen reactivity following emotional appraisal (Hajcak and Nieuwenhuis, 2006; Krompinger et al., 2008; Moser et al., 2006). Further, decreases in LPP amplitude during voluntary regulation have been found to correlate with self-report ratings of reactivity (Hajcak and Nieuwenhuis, 2006), suggesting that the component is accurately measuring reactive response.

In combat-veterans with PTSD, decreased amplitude of the LPP has been demonstrated (MacNamara et al., 2013), theorized to represent decreased capabilities in the processing of emotional cues that – in turn – may alter the appropriate initiation of arousal. Similarly, decreased Vertex Positive Potentials (VPP)’s have been documented, theorized to demonstrate impairment in the detection of the social signals of threat, as this component is uniquely tied to the processing of faces (MacNamara et al., 2013). Altogether, this evidence suggests that brain processes involved in the evaluation of emotional cues in the environment may be altered in individuals exposed to trauma. Specifically, over-engagement of attention to non-emotional

stimuli, coupled with an even greater heightened response to affective stimuli in particular, suggests that the brain is acutely perceptive of stimuli that may signal threat. However, decreased cognitive processing suggests that cognitive mechanisms that allow for the true deciphering of threat (and eventual initiation or dampening of behavioral responses) may be impaired. In turn, this deficiency has been theorized to relate to the over-engagement of the ANS, as reported prior (Brierley-Bowers et al., 2011).

C. **Emotion Regulation following Hyper-reactivity**

While heightened emotional reactivity may be due to atypical functioning during the initiation of arousal, it may also be due to impaired ability in regulating this arousal. The first reason this may be so relies on the temporal dynamics of emotion processing, with both unconscious and conscious modulation of arousal occurring prior to any behavioral output (Gross, 2002; Gross and Thompson, 2007; Thompson, 1990, 1994). Additionally, evidence from developmental and longitudinal studies demonstrate that individual differences exist with respect to how effectively arousal can be regulated (Lee et al., 2012; Stifter, 2002), suggesting that inter-individual variability in emotional reactivity may follow from impairments in regulatory capacity. Emotion regulation is broadly defined as modulating or changing arousal when done automatically or under voluntary control. One voluntary emotion regulation strategy that is commonly used is cognitive reappraisal, a technique in which individuals re-evaluate the context of an emotional stimulus so as to view a potentially threat-provoking situation in a more positive or emotionally-neutral light. In healthy individuals, the use of cognitive reappraisal has been shown effective in dampening physiological response to negative stimuli (Adam et al., 2014; Kim and Hamann, 2012; McRae et al., 2012) and, further, in decreasing self-report in the experience of negative affect (Denny and Ochsner, 2014; Hayes et al., 2010; Moore et al.,

2008). In terms of the systems in place during the execution of reappraisal, neuroimaging work has demonstrated that successful reappraisal recruits prefrontal cortical regions, sometimes during the simultaneous deactivation of regions in the brain involved in the instigation of arousal (Ochsner et al., 2002, 2004; Phan et al., 2005).

Exposure to childhood maltreatment has been shown to predict impairment in regulating emotions, as evidenced by behavioral problems associated with lack of emotional control (Briere and Rickards, 2007; Choi and Oh, 2014) and self-reported difficulties in regulating arousal (Carvalho Fernando et al., 2013). Sexual assault experienced during adulthood has also been shown to predict emotion regulation disturbances (Ullman et al., 2014) as has exposure to severely traumatic events such as mass shootings (Bardeen et al., 2013). With regard to the association between impairment in regulatory capacity in trauma survivors, the majority of this research, however, has focused on the link between trauma and PTSD. Individuals with PTSD commonly self-disclose an inability to voluntarily regulate arousal (Badour and Feldner, 2013; Chemtob et al., 1997; Cloitre et al., 2005; Ehring and Quack, 2010; Klemanski et al., 2012; Price et al., 2006, New et al., 2009; Tull et al., 2007) and, in studies where specific training on emotion regulation is targeted for treatment, improvements in symptom reduction have been reported (Cloitre et al., 2002; Price et al., 2006). Self-reported difficulty in regulating emotions, along with the interaction between high self-reported feelings of anxiety and low emotion regulation skills, has also been found to predict PTSD symptom severity (Badour and Feldner, 2013). Additionally, an interaction between high SCR following exposure to trauma-related scripts and high emotion regulation difficulties has also been found to predict PTSD symptom severity (Badour and Feldner, 2013). Investigations using fMRI have also discovered that individuals with PTSD show impairment in the prefrontal cortical regions that are engaged during cognitive reappraisal (Lang et al., 2012; Rabinak et al., 2014).

D. The Potential Causes of Emotional Hyper-Reactivity Specific to Combat-Exposed Veterans

It is clear that there remain individual differences in the development of emotional hyper-reactivity following trauma exposure and the fact that hyper-reactivity exists in individuals who fail to report subjective feelings of distress further suggests that the body's atypical physiological reaction to perceived threat may predate any development of psychopathology (D'Andrea et al., 2011). Yet, despite this, there is little research independently examining the precursors or causes of emotional hyper-reactivity in the trauma-exposed outside the study of PTSD. Recent work, summarized here, has begun to uncover associations to environmental pre-cursors that may affect hyper-reactivity outside the development of illness, specifically in veterans exposed to combat. However, while this research lays the framework for the current investigation, it also demonstrates a gap in knowledge with respect to the relationship between environmental influences and the ongoing neural processes that define hyper-reactivity beyond the study of reactivity as a discrete and temporally-constrained phenomenon. While correlations between environmental precursors and hyper-reactivity has been established using fMRI and MRI investigations, these relationships have never yet been tested using ERP's in order to tease apart these influences on the dynamic process of reactivity itself as well as regulation of reactivity over a timescale of milliseconds.

In investigating sources of dysfunction in individuals exposed to war, the extent to which individuals were exposed to combat has itself been shown to correlate with attention towards threatening stimuli by predicting variance in P300 amplitudes (Kimble et al., 2010), again suggesting that severity of combat experiences may selectively impair the brain's ability in

perceiving threat. Additional evidence involving fMRI documents further that perceived threat during combat is correlated to increased activation within the amygdala, a region involved in the initiation of arousal. Further, this aberration was not linked to symptoms of PTSD (van Wingen et al., 2011a) and may persist for years following combat exposure (van Wingen et al., 2011b). Finally, during combat, the severity of negative experiences has also been found to positively correlate with activation of the anterior cingulate cortex (ACC; Aupperle et al., 2013; Herringa et al., 2013), a region important for automatic emotional processing. Thus, heightened activation within this region may signal greater threat detection and, given strong anatomical connections between the amygdala and ACC (Etkin et al., 2011), may also reflect a measure of exaggerated reactivity itself (Herringa et al., 2013). In investigating the association to early life trauma within combat veterans specifically, evidence from fMRI again demonstrates a positive correlation between the experience of childhood trauma and activation within the ACC (Herringa et al., 2013). With regard to structural abnormalities, correlations between early childhood maltreatment and size of the amygdala (Kuo et al., 2012) and ACC (Woodward et al., 2013) have also been reported.

E. **Summary and Current Study**

In review of the literature to-date on hyper-reactivity in trauma survivors, three gaps in knowledge were identified. First, in terms of identifying causes of dysfunction, little research to-date has yet investigated environmental precursors of brain functioning during hyper-reactivity. While some neuroimaging work has determined a correlation between trauma-factors and additional stress exposure with atypical neural functioning during emotional processing, this work has yet to be investigated via EEG where the temporal dynamics of hyper-reactivity can be more closely investigated. Second, despite evidence that trauma exposure may produce hyper-

reactivity by way of atypical functioning during early initiation of reactivity and regulation of reactivity, there are no studies to-date that investigate both aspects of the symptom within one study design, selectively exploring the relationship between environmental precursors and brain functioning during both the initiation and regulation of reactivity. Finally, while emotional reactivity may be present in individuals who develop PTSD following trauma, the fact that the trait exists in trauma-exposed controls suggests that the symptom is common following trauma and not inherently tied to the development of psychopathology. Even so, the majority of work on hyper-reactivity has studied this development in the context of PTSD without investigating sources of hyper-reactivity itself.

III. METHODS

The outcome measure of the current study was the extraction of the LPP as a measure of arousal during (1) emotional reactivity and (2) regulation of emotional reactivity and studied in individuals exposed to combat. Previous literature demonstrates that both reactivity and regulation are themselves dynamic processes that involve constant cognitive re-evaluation of emotionally-salient stimuli (Hajcak et al., 2010), thus the temporal resolution of EEG allowed for a more comprehensive investigation of functioning as it unfolded over time. Current findings promote EEG research as a viable cost-effective and portable alternative to other neuroimaging techniques (e.g., fMRI) by demonstrating that changes to neural processes during reactivity and regulation can be isolated, quantified, and meaningfully interpreted - perhaps ultimately promoting the opportunity for EEG to serve as a 'brain test' of stress and trauma in the outpatient clinical setting.

A. **Participants**

Participants were 28 Operation Enduring Freedom (OEF) and/or Operation Iraqi Freedom (OIF) combat veterans that were recruited and tested at the Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI between 2009 and 2011. Inclusion criteria for all veterans included documented and sufficient exposure to combat per a Combat Exposure Scale (CES; Keane et al.., 1989) score of ≥ 17, aged 18-55, discharged from active military service, deemed physically healthy enough to participate in research procedures following a medical examination, free from a history of head trauma, a negative urine toxicology screen and pregnancy test (if applicable), an ability to read and speak English, and an ability to provide written consent. No participants were taking psychiatric medication for a duration of at least four weeks prior to testing. Study procedures were approved by the Institutional Review Board (IRB)

of VA Ann Arbor as well as the University of Michigan Medical School IRB and participants were monetarily compensated for their time.

B. **Materials**

1. **Experimental Task**

During continuous EEG recording, participants completed the Emotion Regulation Task (ERT; Figure 1), a modified version of a task used previously by Davidson et al. (2003) and Ochsner et al. (2002). In previous studies, this task successfully elicited the LPP (Cuthbert et al., 2000; Keil et al., 2002; Lang et al., 1997b; Schupp et al., 2000, 2003b) and, further, was used as a method to study observable changes in the LPP following voluntary emotional control (Hajcak and Nieuwenhuis, 2006; Krompinger et al., 2008; Moser et al., 2006). Our modification of the task allowed for the study of neural activation during (1) sustained emotional reactivity and (2) voluntary emotion regulation following the comparison of LPP amplitude changes during three experimental conditions.

During the task, participants were seated comfortably 60 centimeters before a computer screen, which subsequently presented negative and neutral images from the International Affective Picture System (IAPS; Lang et al., 1997a). Each trial of the task was divided into two stages (Figure 1). First, each image was shown on screen for 1000 ms, during which time participants were asked to view the image as they normally would. Next, at 1000 ms for negative images, an auditory instruction was received to either “maintain” (i.e., to continue

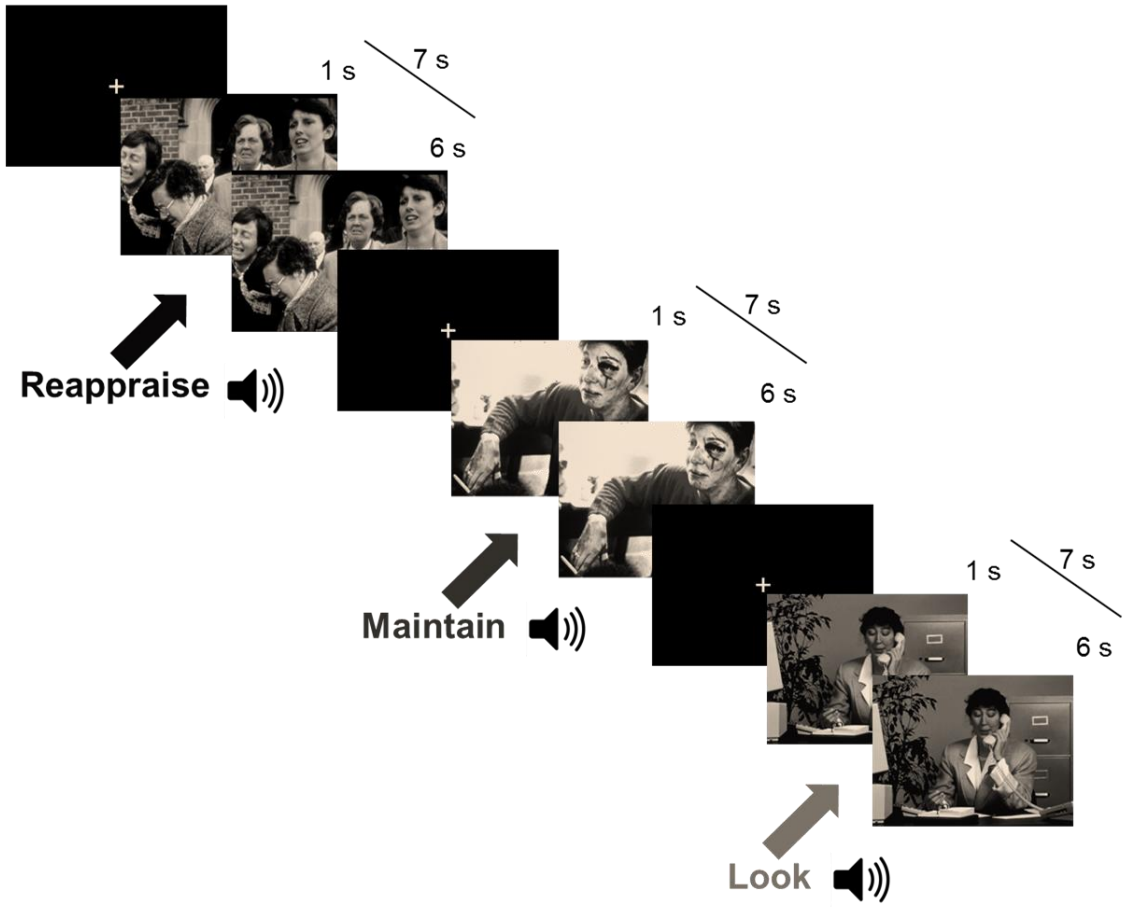


Figure 1. Emotion regulation task

viewing the picture without trying to change reaction) or “reappraise” (i.e., to reduce reaction by making the picture seem less emotional). For neutral images, the auditory instruction to “look” (i.e., continue viewing pictures) was given. In all three conditions following instruction, the image remained on-screen for 6000 ms, resulting in a total trial length of 7000 ms. Trials were presented in valence-specific pseudo-randomized blocks comprised of 25 trials with a fixation presented on screen between trials for 1000 ms. After a block, a researcher manually advanced the task after a brief pause to allow for periods of rest. During the task, a total of one “maintain”, one “reappraise” and two “look” blocks were presented for a task length of 13 minutes and 20 seconds. Prior to task execution, participants were given ten practice trials with IAPS images not used in the actual task, during which time they verbalized their strategies for each condition to a researcher. Verbal feedback from the researcher was given in response to whether the participant used appropriate cognitive strategies to either “maintain” or “reappraise” their emotional reactivity.

2. **Electroencephalogram Recording and Initial Data Reduction**

Continuous EEG recording during the task was completed using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, The Netherlands). Thirty-four electrode sites were placed on the scalp for recording neural activity based on the 10/20 system. Four facial electrodes were used in order to record electrooculogram (EOG) generated from eye blinks and eye movements: two of these electrodes were located approximately one cm outside the outer edge of the right and left eyes to monitor horizontal eye movements while two electrodes were placed approximately one cm above and below the right eye to measure vertical eye movements. The data were digitized at 24-bit resolution with a sampling rate of 1024 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 204.8 Hz. Each active

electrode was measured online with respect to a common mode sense (CMS) active electrode producing a monopolar (non-differential) channel.

Initial offline data processing included band-pass filtering for both low and high frequencies of .01 and 30 Hz, respectively. All electrodes were referenced to the average of the left and right mastoids and artifact analysis was used to identify and remove voltage steps of more than 50 μV between sample points, a maximally allowed difference of values within an interval of 300 μV, and activity lower than 0.50 V μV within 100 ms intervals. All trials were additionally visually inspected and remaining artifacts subsequently removed on a trial-by-trial basis. Electrophysiological activity for each condition was measured by averaging signal from all relevant trials while correcting for noise using a 200 ms pre-stimulus baseline. Only trials retaining at least 80% or more of data were included in averaging.

3. **Electroencephalogram Measure: Late Positive Potential**

The LPP was measured at separate electrode poolings representing a central-parietal and frontal site (Figure 2), given evidence that while the LPP begins at a central-parietal location, it may shift forward along the midline as a function of time (Hajcak et al., 2010). The component was defined as a positive amplitude during the viewing of negative images (e.g., either during “maintain” or “reappraise” conditions) in comparison to the viewing of neutral images (e.g., “look” condition). Characteristics of the LPP were assessed pre-instruction, representing a measure of initial reactivity. Changes to the LPP post-instruction represented either the ability to sustain reactivity or voluntarily regulate reactivity. Prior work has shown that the LPP is sensitive to the voluntary control of reactivity via cognitive reappraisal, with an immediate decrease in the positive deflection of this component indicative of successful

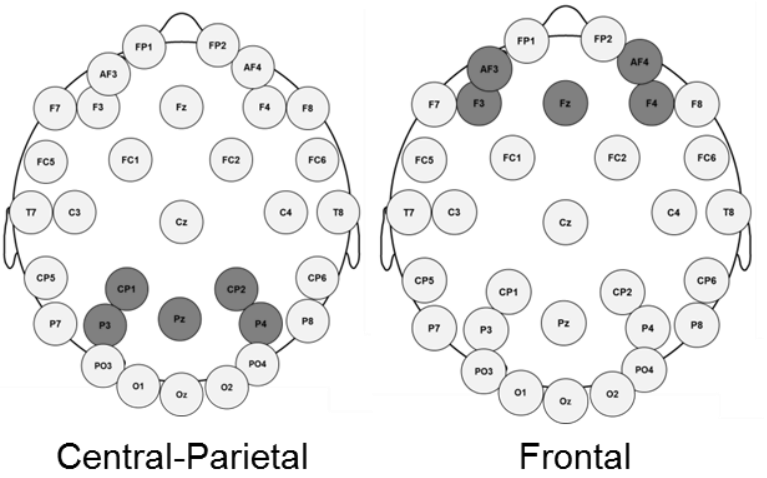


Figure 2. Electrode map

regulation (Dunning and Hajcak 2009; Hajcak et al., 2009). Thus, the component post-instruction was measured as either a maintained positive deflection during the “maintain” condition or a decrease in the positive deflection during the “reappraise” condition, again indicating successful voluntary regulation. Post-instruction, in order to assess whether the maintenance of the positive deflection occurred, a difference wave was calculated to measure amplitude of the LPP during the “maintain” condition in comparison to amplitude changes during the “look” condition in order to subtract out signal related to picture viewing. Similarly, in order to assess whether decreases in the positive deflection occurred during voluntary regulation, a difference wave was calculated to measure amplitude of the LPP during the “reappraise” condition in comparison to amplitude during the “maintain” condition, again to subtract out inter-individual differences in signal related to level of reactivity. Due to the elongated recording time by which the LPP was allowed to fluctuate, separate analyses were first completed with respect to early (1500 – 3000 ms), middle (3000 – 4500 ms), and late (4500 – 7000 ms) phases of each difference wave, consistent with prior research (Parvaz et al., 2012).

4. **Current Symptoms of Posttraumatic Stress Disorder**

A measure of current PTSD symptom severity was captured via the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995), a 30 item semi-structured diagnostic interview that assessed frequency and intensity of PTSD symptoms. This measure was used in order to test the association of inter-individual differences in neural measures of reactivity and voluntary emotional regulation and current symptom severity. For each participant, the CAPS was completed with a trained professional and global severity scores calculated by combining the frequency and intensity scores. Range of possible scoring for this measure fell between 0-136 with higher scores indicative of greater severity of PTSD symptoms.

5. Combat and Non-combat Stress Exposure

In order to test for associations to combat exposure itself, scores from the CES were used as a measure of general severity of combat experiences. The CES is a seven-item measure that assesses exposure to traditional and common combat experiences, such as firing a weapon. Each of the seven items was coded dichotomously and veterans were able to self-report if they were exposed to each experience (Kean et al., 1989). In order to capture stress exposure that was either specific to combat or to other life events, participants completed the Deployment Risk and Resilience Inventory (DRRI; King et al., 2006). This measure consisted of 14 factors that together assessed a wide range of pre- and post-deployment characteristics related to stress exposure alongside a thorough assessment of military-related factors. Range of scores for each of the factors is included in Table 1. In instances where factors were initially measuring the absence of stress, these items were reverse-coded so that greater scores within each factor represented greater incidence of stress related to that experience.

C. Statistical Analyses

As a measure of initial emotional reactivity, the LPP was scored pre-instruction at a time and electrode site where the positive deflection during the viewing of negative images (e.g., on trials that would later become “maintain” and “reappraise”) was found to be maximal. At this point and location, paired *t*-tests were completed to test whether the group mean signal during the viewing of negative images differed in comparison to group mean signal during the viewing of neutral images (e.g., “look”). Following instruction, repeated measures analysis of variance (ANOVA’s) were completed to test whether the LPP amplitude during each condition (e.g.,

TABLE I

DEPLOYMENT RISK AND RESILIENCE INVENTORY (DRRI) FACTORS

Context	Factor	Construct	Sample Item	Possible Range
Combat	Feeling Unprepared[a]	Extent to which individual perceives that he or she was prepared for deployment	*"I was well trained on how to use my equipment."*	14 - 70
	Deployment-associated Stress	Exposure to events or circumstances representing war-zone pressures	*"The conditions I lived in were unsanitary."*	20 - 100
	Family and Home Concerns[a]	Worries that deployment might negatively affect other important life domains	*"While I was deployed, I was concered about losing my job while I was away."*	0 - 56
	Lack of Unit Support[a]	Amount of assstance and encouragement in the war-zone from the military in general, including leaders and other unit members	*"The commanding officer(s) in my unit were supportive of my efforts."*	12 - 60
	General Harassment	Exposure to harassment that is nonsexual but that may occur on the basis of one's biological sex or other social status	*"While I was deployed, unit leaders or other unit members treated me in an overly critical way."*	7 - 28
	Sexual Harassment	Exposure to unwanted sexual or verbal conduct sexual in nature from other unit members, commanding officers, or civilians in the war-zone	*"While I was deployed, unit leaders made crude and offensive sexual remarks directed at me."*	7 - 28
	Perceived Threat	Fear for one's safety and well-being in the war zone, especially as a response to potential exposure to circumstances of combat	*"I thought I would never survive."*	15 - 75
	Combat Stress	Exposure to stereotypical warfare experiences such as being fired upon, witnessing an injury or death, or going on special missions	*"While deployed, I went on combat patrols or missions."*	0 - 15
	Aftermath of Battle	Exposure to the consequences of combat, including observing or handling human remains, dealing with Prisoners of War (POW's) and observing devastated communities	*"I saw refugees who had lost their homes and belongings as a result of battle."*	0 - 15
	NBC Exposure	Endorsed exposures to an array of nuclear, biological, and chemical agents	*"While I was deployed, I was exposed to depleted uranium in munitions."*	0 - 40
Non-combat	Pre-deployment Stress	Exposure to traumatic events before deployment	*"Before I was deployed, I experienced the death of someone close to me."*	0 - 15
	Lack of Support during Childhood	Quality of family life in terms of cohesion	*"People in my family did things together."*	15 - 75
	Post-deployment Stress	Exposure to traumatic events after deployment	*"Since returning home, I have been left by a significant other."*	0 - 17
	Post-deployment Lack of Support[a]	Extent to which veteran received instrumental assistance upon return home	*"The reception I received when I returned from my deployment made me feel appreciated for my efforts."*	15 - 75

[a]Original DRRI factor measured extent to which veteran felt support in this factor; these items were reverse-coded for current analysis.

Table reproduced from King, L.A., King, D.W., Vogt, D.S., Knight, J., & Sampter, R.E. (2009). Deployment Risk and Resilience Inventory: A collection of measures for studying deployment-related experiences of military personnel and veterans. Military Psychology, 18(2), 89-120.

"maintain", "reappraise", and "look") changed as a function of time. Towards this, group mean signal was extracted at periods representing early (1500 – 3000 ms), middle (3000 – 4500 ms) and late (4500 – 7000 ms) phases of the task, consistent with previous research (Parvaz et al., 2012).

In order to test study hypotheses with regard to the influence of current symptoms of PTSD, exposure to combat, combat-associated stress, and non-combat-associated stress on both reactivity and regulation, independent bivariate ordinary least squares (OLS) regressions were completed. Outcome variables included the magnitude of the LPP pre-instruction in order to test predictors of initial reactivity, the difference in LPP magnitude between "maintain" and "look" conditions in order to test predictors of sustained reactivity, and the difference in LPP magnitude between "maintain" and "reappraise" conditions in order to test predictors of voluntary regulation of reactivity. Separate regressions were employed to study predictors of the LPP during sustained and voluntary regulation of reactivity at the two separate scalp locations.

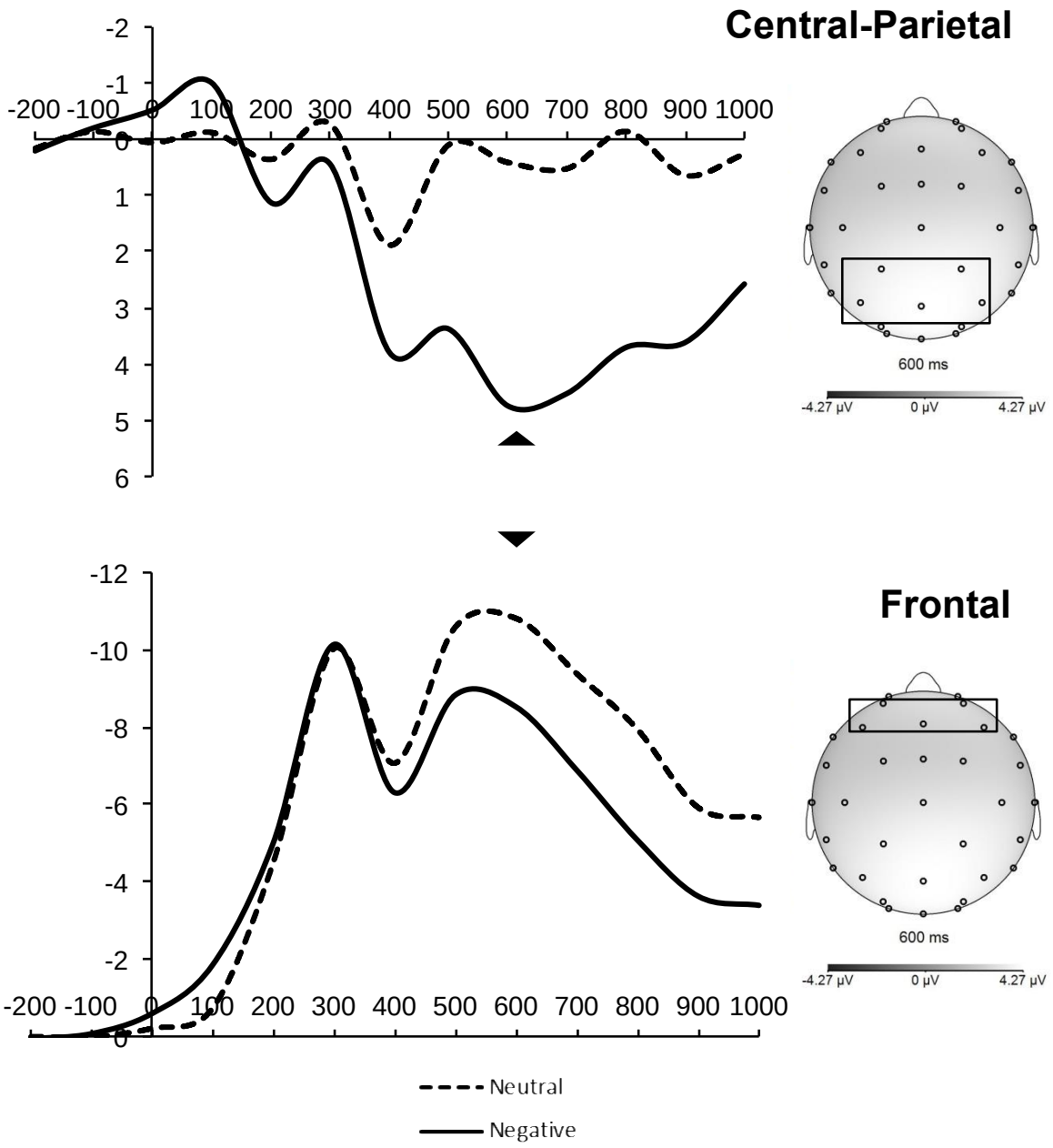
As a measure of current PTSD symptom presentation, the total CAPS score was used. Similarly, scores from CES were also regressed to study the independent effects of exposure to combat prior to examining combat-specific and non-combat-specific stressors. In order to examine independent effects of combat-specific stress, ten DRRI factors were used as predictors and regressed onto each difference wave (Table 1). Additionally, four DRRI factors that were identified as measuring non-combat related stress experienced either pre- or post-deployment were regressed as well (Table 1). As bivariate regressions were separately employed and given that a total of 16 predictors (14 DRRI variables, CAPS and CES scores) were independently tested, Bonferroni corrections were used to correct for multiple comparisons with predictors at $p < .003$ considered statistically significant.

IV. RESULTS

A. Late Positive Potential Characteristics

Characteristics of the LPP pre-instruction are depicted in Figure 3. At the central-parietal site, the LPP was observed to begin 300 ms after stimulus and found to be maximal at 600 ms. At this location, positive amplitude was greater during the viewing of negative images in comparison to neutral images ($t(108) = 3.27$, $p = .001$). At the frontal site, a positive deflection during the viewing of negative images was similarly observed but was not found to differ significantly in comparison to neutral images ($t(108) = 1.73$, $p = .087$). This result is in-line with previous research regarding the topographical location of the LPP during initial stages of emotional reactivity (Hajcak et al., 2010).

Characteristics of the LPP post-instruction are depicted in Figure 4. Results of repeated measures ANOVA's indicated that amplitude of the LPP during the "look" ($F(2, 54) = 1.07$, $p = .339$), "maintain" ($F(2, 54) = 1.39$, $p = .258$) and "reappraise" ($F(2, 54) = 3.06$, $p = .069$) conditions did not vary as a function of time at the central-parietal location. For regressions involving the difference in LPP magnitude between conditions at this location, group mean signal of each difference wave were subsequently extracted as an average across the full 1500 – 7000 ms recording time (Figure 5, Panel A). In testing LPP fluctuations at the frontal electrode site, no differences in LPP amplitude were observed across time during the look ($F(2, 54) = 2.95$, $p = .082$) or maintain ($F(2,54) = .99$, $p = .355$) conditions. However, the LPP during the reappraise condition decreased in amplitude in a linear fashion across time ($F(2, 54) = 11.66$, $p < .001$). Consistent with regressions involving changes to the LPP at the central-parietal



Note. Activation represents Late Positive Potential (LPP), plotted as differences in signal between the viewing of negative versus neutral images. Positive amplitude plotted down.

Figure 3. Late positive potential pre-instruction

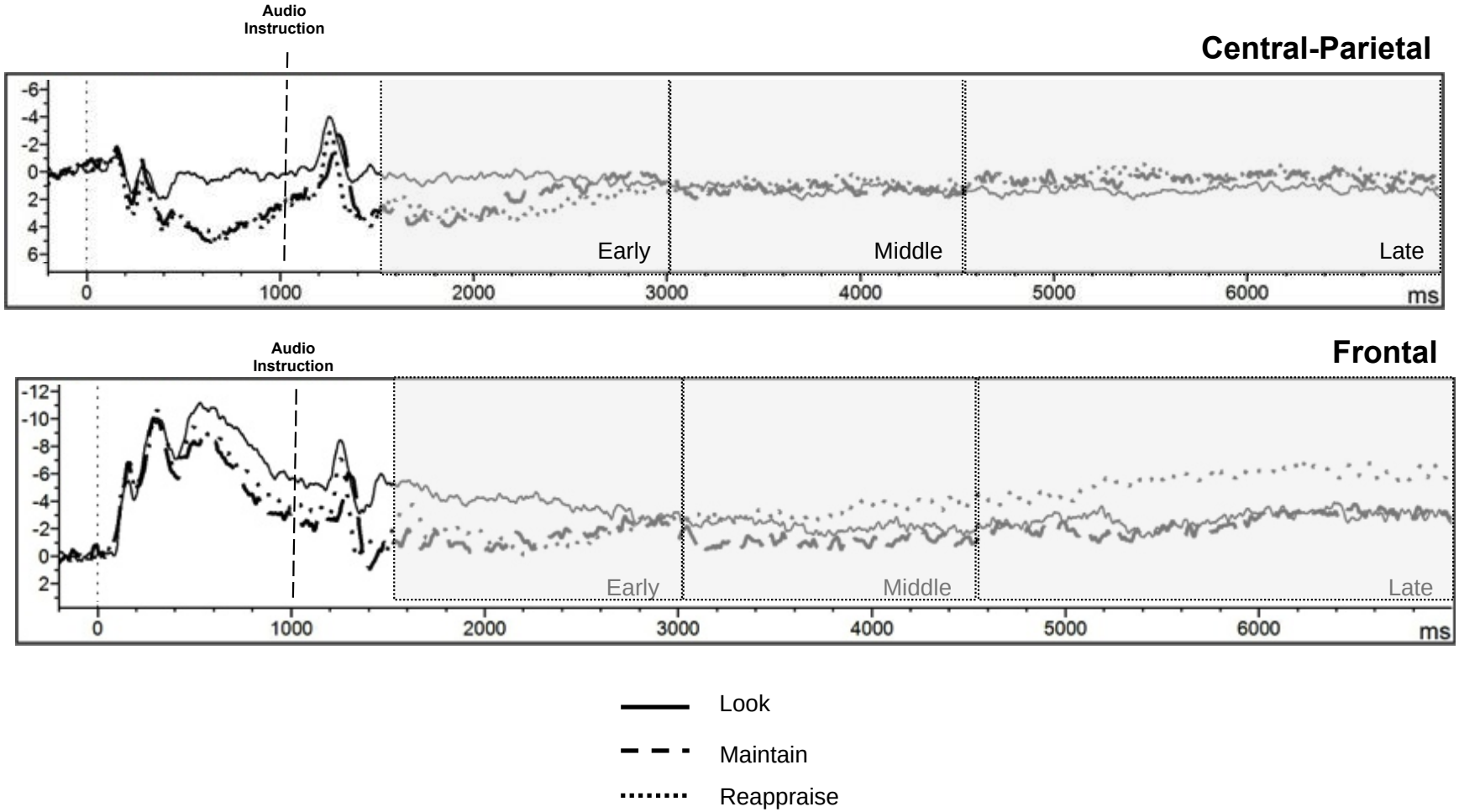


Figure 4. Group mean signal post-instruction

electrode site, regressions involving changes to the LPP during sustained reactivity at the frontal site used group mean signal of each difference wave extracted as an average across the full 1500 – 7000 ms recording time (Figure 5, Panel B). In regressions involving the difference in LPP magnitude between "maintain" and "reappraise" conditions at this location, predictors were first tested against group mean signal averaged across the full 1500 – 7000 ms recording time (Figure 5, Panel B) and, subsequently, significant predictors were re-assessed for effects at early, middle, and late phases (Figure 5, Panel C).

B. **Predictors of Late Positive Potential during Initial Emotional Reactivity**

First, the calculation of standardized residuals, standardized DFBETA's and Cook's Distance were completed for all OLS regressions in order to identify outlying or influential observations. This led to the removal of one participant who was consistently identified as a multinomial outlier and an influential data point. Subsequent analyses were completed with the remaining n = 27 participants (see Table 2 for participant demographics). Results of bivariate OLS regressions testing predictors of LPP amplitude at the central-parietal site pre-instruction are presented in Table 3. PTSD symptom severity via the inclusion of CAPS scores, severity of combat exposure via the inclusion of CES scores, combat-associated stress and non-combat associated stress all failed to predict variability in differences in LPP magnitude.

C. **Predictors of Late Positive Potential during Sustained Emotional Reactivity**

Results of bivariate OLS regressions testing predictors of differences in LPP magnitude between "maintain" and "look" conditions at the central-parietal site post-instruction are presented in Table 4. Again, PTSD symptom severity via the inclusion of CAPS scores, severity

TABLE II

VETERAN SAMPLE CHARACTERISTICS[a]

Gender (%)	
Male	96.30
Female	3.70
Ethnicity (%)	
White	88.90
African-American	3.70
Asian	3.70
Other	3.70
	M (SD)
Age	31.33 (8.38)
Education (years)	14.26 (1.99)
CAPS	38.15 (34.66)
CES	21.78 (5.44)
DRRI Variables	M (SD)
Pre-Deployment Factors	
Pre-deployment Stress	3.48 (2.50)
Lack of Support during Childhood	34.41 (11.09)
Deployment Factors	
Feeling Unprepared	35.56 (11.63)
Deployment-associated Stress	58.26 (14.63)
Family and Home Concerns	27.56 (5.56)
Lack of Unit Support	32.74 (10.46)
General Harassment	13.78 (5.71)
Sexual Harassment	8.00 (1.54)
Perceived Threat	44.04 (10.18)
Combat Stress	6.96 (4.42)
Aftermath of Battle	7.15 (5.10)
NBC Exposure	20.81 (6.53)
Post-Deployment Factors	
Post-deployment Stress	2.52 (1.99)
Post-deployment Lack of Support	35.48 (9.10)

[a] N = 27; *Note.* M = mean; SD = standard deviation; CAPS = Clinician Administered Posttraumatic stress disorder Scale; CES = Combat Exposure Scale; DRRI = Deployment Risk and Resilience Inventory; NBC = nuclear, biological, and chemical.

TABLE III

BIVARIATE REGRESSIONS FOR LATE POSITIVE POTENTIAL (LPP) PRE-INSTRUCTION AT CENTRAL-PARIETAL SITE[a]

	B	*SE*	*p*
CAPS	-0.02	0.02	.444
CES	0.04	0.10	.647
Combat-associated			
Combat Stress	0.14	0.12	.229
Deployment-associated Stress	0.001	0.05	.977
Feeling Unprepared	-0.06	0.05	.233
Family and Home Concerns	-0.06	0.10	.580
Lack of Unit Support	-0.05	0.05	.355
General Harassment	-0.13	0.09	.161
Sexual Harassment	0.34	0.36	.355
Perceived Threat	-0.06	0.06	.317
Aftermath of Battle	0.01	0.12	.913
NBC Exposure	0.12	0.09	.200
Non-combat-associated			
Pre-deployment Stress	0.07	0.20	.723
Lack of Support during Childhood	-0.02	0.05	.680
Post-deployment Stress	0.05	0.25	.843
Post-deployment Lack of Support	-0.04	0.06	.449

[a] Dependent variable is difference in group mean signal between the viewing of negative and neutral images measured in microvolts (μV) at central-parietal site (CP1, CP2, P3, P4, Pz) at 600 ms.

Note. All predictors are mean-centered; Results control for the effects of age, gender, race and years of education (beta values not shown); ms = milliseconds; CAPS = Clinician Administered PTSD Scale; CES = Combat Exposure Scale; NBC = nuclear, biological, and chemical.

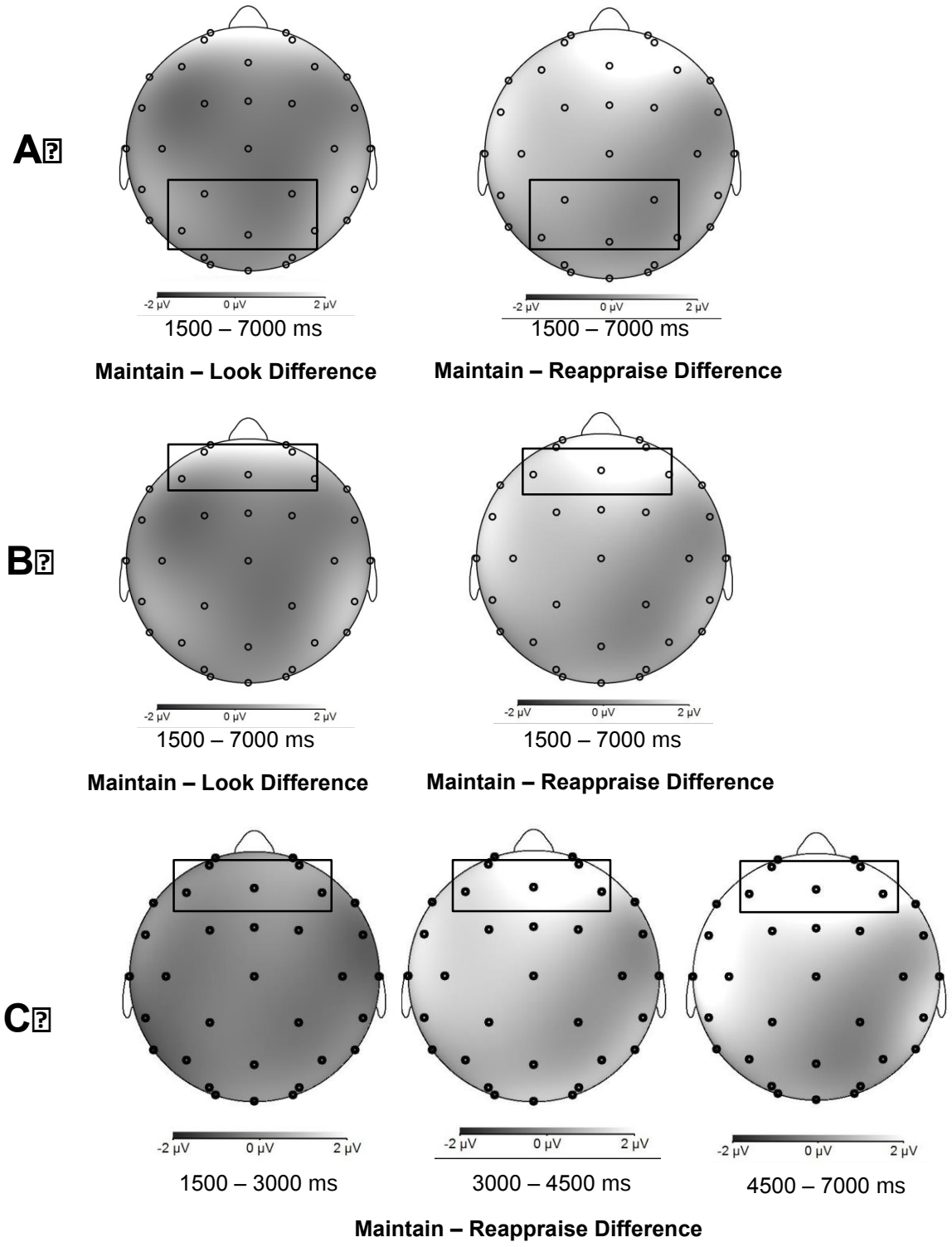
TABLE IV

BIVARIATE REGRESSIONS FOR MAINTAIN-LOOK DIFFERENCE WAVE AT CENTRAL-PARIETAL SITE[a]

	B	*SE*	*p*
CAPS	0.02	0.04	.668
CES	0.13	0.18	.475
Combat-associated			
Combat Stress	0.37	0.22	.110
Deployment-associated Stress	0.07	0.09	.443
Feeling Unprepared	-0.04	0.10	.711
Family and Home Concerns	-0.23	0.20	.252
Lack of Unit Support	-0.04	0.10	.699
General Harassment	-0.20	0.18	.280
Sexual Harassment	0.34	0.71	.633
Perceived Threat	-0.02	0.11	.854
Aftermath of Battle	-0.01	0.23	.982
NBC Exposure	0.10	0.19	.587
Non-combat-associated			
Pre-deployment Stress	0.46	0.38	.234
Lack of Support during Childhood	0.04	0.90	.671
Post-deployment Stress	-0.21	0.49	.682
Post-deployment Lack of Support	-0.10	0.11	.357

[a] Dependent variable is difference in group mean signal of the LPP between maintain and look conditions, measured in microvolts (μV) at central-parietal site (CP1, CP2, P3, P4, Pz) and averaged across 1500 - 7000 ms.

Note. All predictors are mean-centered; Results control for the effects of age, gender, race and years of education (beta values not shown); ms = milliseconds; CAPS = Clinician Administered PTSD Scale; CES = Combat Exposure Scale; NBC = nuclear, biological, and chemical.



Note. Activation represents differences in LPP amplitude between conditions

Figure 5. Group mean signal changes post-instruction from difference wave calculations

of combat exposure via the inclusion of CES scores, combat-associated stress and non-combat associated stress all failed to predict variability in differences in LPP magnitude. In examining predictors at the frontal electrode site, again no significant predictors were found (Table 5).

D. **Predictors of Late Positive Potential during Voluntary Regulation**

Results of bivariate OLS regressions testing predictors of differences in LPP magnitude between "maintain" and "reappraise" conditions at the central-parietal site post-instruction are presented in Table 6. At this location, no significant predictors were found based on pre-determined significance levels following Bonferroni correction. However, in reviewing the results of predictors of differences in LPP magnitude at the frontal electrode site (Table 7), two trend-level results emerged. First, a lack of unit support during deployment (a combat-associated stressor) did significantly predict differences in LPP amplitude between the two conditions. Results indicated that a unit increase in lack of unit support decreased the difference in amplitude between these two LPP's (B = -.39, SE = .13, p = .007), suggesting that this stressor increased the extent to which the LPP amplitudes resembled each other. In examining this relationship further, it was previously determined that this stressor did not influence the amplitude of the LPP during sustained reactivity alone (Table 5). Thus, additional independent regressions were completed between lack of unit support and LPP magnitude during the "reappraise" condition alone (e.g., "reappraise" – "look"). This effect was also examined at each of the three phases of the task given that amplitude of the LPP during this condition changed as a function of time. Results indicated that a unit increase in lack of unit support consistently increased LPP amplitude during early (B = .27, SE = .10, p = .015), middle (B = .41, SE = .14, p = .008) and late (B = .41, SE = .15, p = .011) phases of this condition (Figure 6). Results of regressions examining the effect of lack of unit support and the LPP during the "maintain"

TABLE V

BIVARIATE REGRESSIONS FOR MAINTAIN-LOOK DIFFERENCE WAVE AT FRONTAL SITE[a]

	B	*SE*	*p*
CAPS	0.01	0.04	.777
CES	-0.04	0.18	.824
Combat-associated			
Combat Stress	0.30	0.22	.186
Deployment-associated Stress	0.16	0.08	.076
Feeling Unprepared	-0.04	0.09	.681
Family and Home Concerns	-0.04	0.20	.852
Lack of Unit Support	-0.02	0.10	.841
General Harassment	-0.12	0.18	.497
Sexual Harassment	1.29	0.64	.058
Perceived Threat	0.12	0.11	.256
Aftermath of Battle	0.07	0.23	.780
NBC Exposure	0.27	0.18	.137
Non-combat-associated			
Pre-deployment Stress	0.15	0.38	.698
Lack of Support during Childhood	-0.02	0.09	.866
Post-deployment Stress	0.14	0.49	.778
Post-deployment Lack of Support	0.003	0.10	.982

[a] Dependent variable is difference in group mean signal of the LPP between maintain and look conditions, measured in microvolts (μV) at frontal site (AF3, AF4, F3, F4, Fz) and averaged across 1500 - 7000 ms.

Note. All predictors are mean-centered; Results control for the effects of age, gender, race and years of education (beta values not shown); ms = milliseconds; CAPS = Clinician Administered PTSD Scale; CES = Combat Exposure Scale; NBC = nuclear, biological, and chemical.

TABLE VI

BIVARIATE REGRESSIONS FOR MAINTAIN-REAPPRAISE DIFFERENCE WAVE AT CENTRAL-PARIETAL SITE[a]

	B	*SE*	*p*
CAPS	-0.11	0.05	.039
CES	-0.22	0.27	.429
Combat-associated			
Combat Stress	0.20	0.34	.559
Deployment-associated Stress	0.18	0.13	.167
Feeling Unprepared	-0.14	0.14	.329
Family and Home Concerns	0.03	0.30	.923
Lack of Unit Support	-0.33	0.12	.014
General Harassment	-0.41	0.25	.109
Sexual Harassment	-0.49	1.03	.642
Perceived Threat	-0.04	0.16	.799
Aftermath of Battle	-0.11	0.34	.750
NBC Exposure	-0.13	0.27	.641
Non-combat-associated			
Pre-deployment Stress	-0.80	0.53	.147
Lack of Support during Childhood	-0.08	0.13	.510
Post-deployment Stress	-0.78	0.70	.277
Post-deployment Lack of Support	-0.18	0.16	.257

[a] Dependent variable is difference in group mean signal of the LPP between maintain and look conditions, measured in microvolts (μV) at central-parietal site (CP1, CP2, P3, P4, Pz) and averaged across 1500 - 7000 ms.

Note. All predictors are mean-centered; Results control for the effects of age, gender, race and years of education (beta values not shown); ms = milliseconds; CAPS = Clinician Administered PTSD Scale; CES = Combat Exposure Scale; NBC = nuclear, biological, and chemical.

TABLE VII

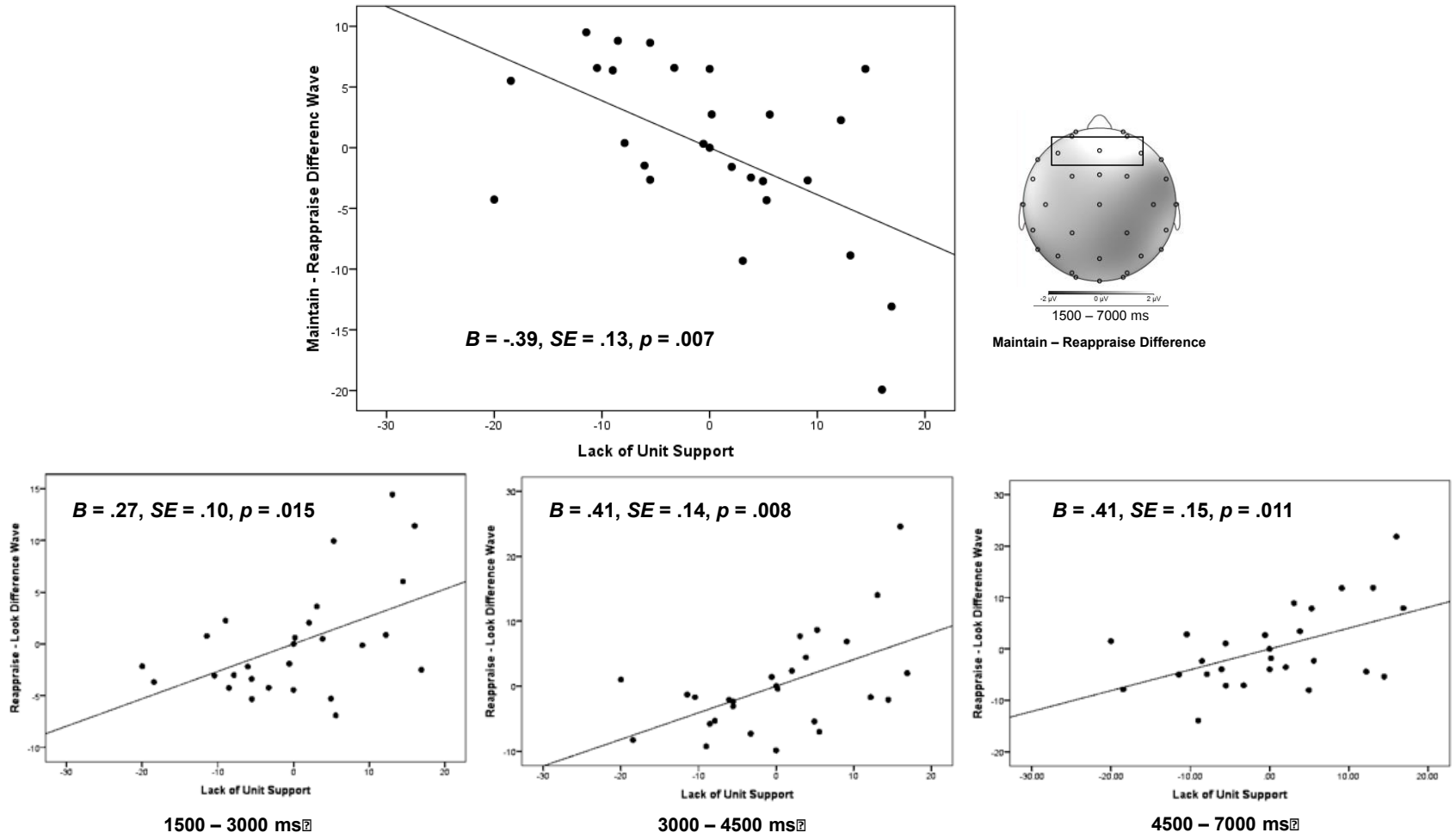
BIVARIATE REGRESSIONS FOR MAINTAIN-REAPPRAISE DIFFERENCE WAVE AT FRONTAL SITE[a]

	B	*SE*	*p*	
CAPS	-0.11	0.06	.096	
CES	-0.29	0.29	.332	
Combat-associated				
Combat Stress	0.20	0.37	.603	
Deployment-associated Stress	0.29	0.13	.043	
Feeling Unprepared	-0.13	0.15	.396	
Family and Home Concerns	0.40	0.32	.222	
Lack of Unit Support	**-0.39**	**0.13**	**.007**	*
General Harassment	-0.37	0.28	.203	
Sexual Harassment	0.83	1.13	.470	
Perceived Threat	-0.01	0.18	.940	
Aftermath of Battle	0.10	0.37	.796	
NBC Exposure	-0.12	0.30	.695	
Non-combat-associated				
Pre-deployment Stress	**-1.57**	**0.52**	**.007**	*
Lack of Support during Childhood	-0.15	0.14	.298	
Post-deployment Stress	-0.32	0.79	.696	
Post-deployment Lack of Support	-0.12	0.18	.503	

[a] Dependent variable is difference in group mean signal of the LPP between maintain and look conditions, measured in microvolts (μV) at frontal site (AF3, AF4, F3, F4, Fz) and averaged across 1500 - 7000 ms.

Note. All predictors are mean-centered; Results control for the effects of age, gender, race and years of education (beta values not shown); ms = milliseconds; CAPS = Clinician Administered PTSD Scale; CES = Combat Exposure Scale; NBC = nuclear, biological, and chemical.

* Denotes significance at $p < .01$

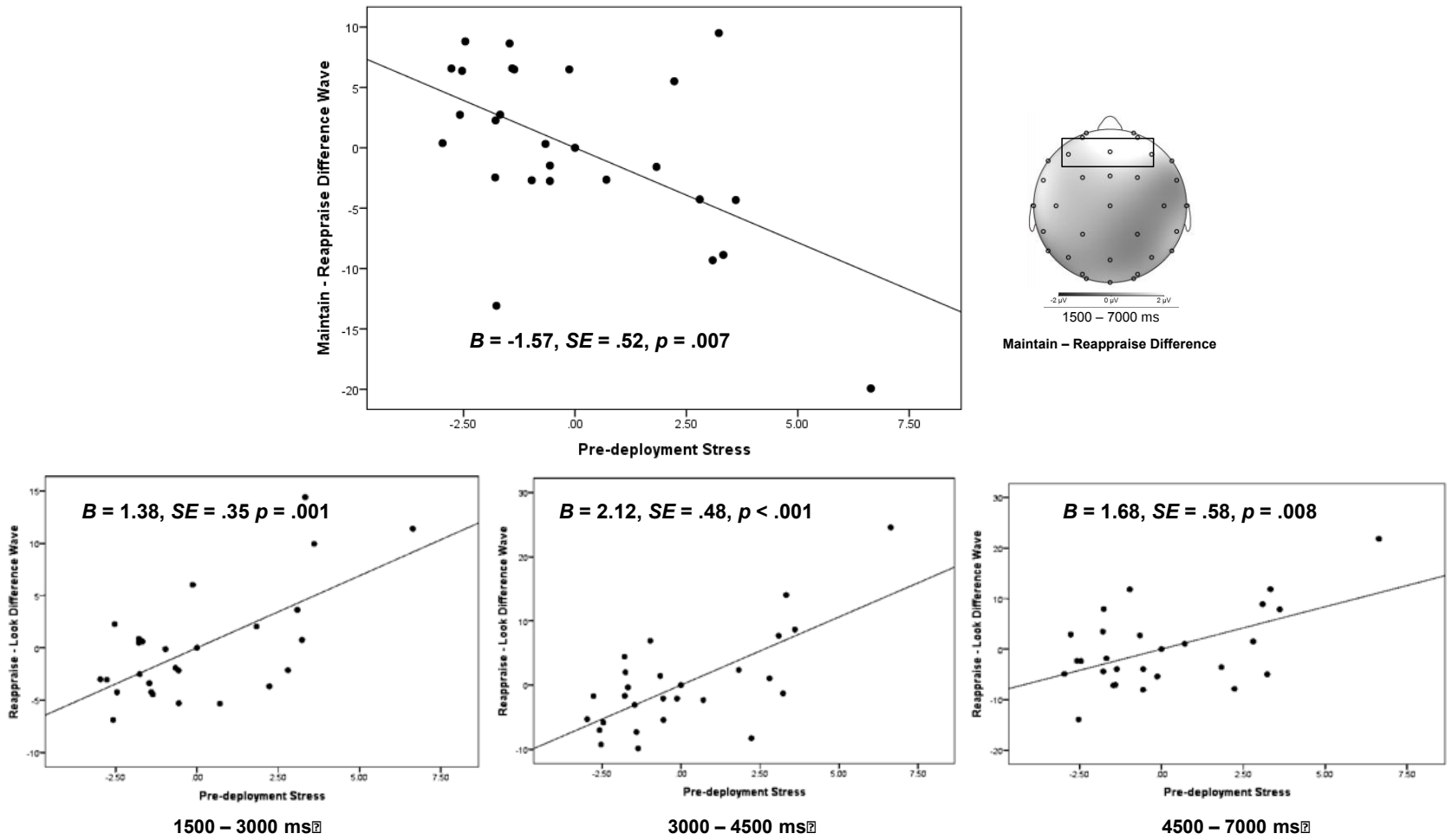


Note. All relationships control for effects of age, gender, race/ethnicity and years of education

Figure 6. Relationship between lack of unit support and maintain-reappraise difference wave at frontal electrode site

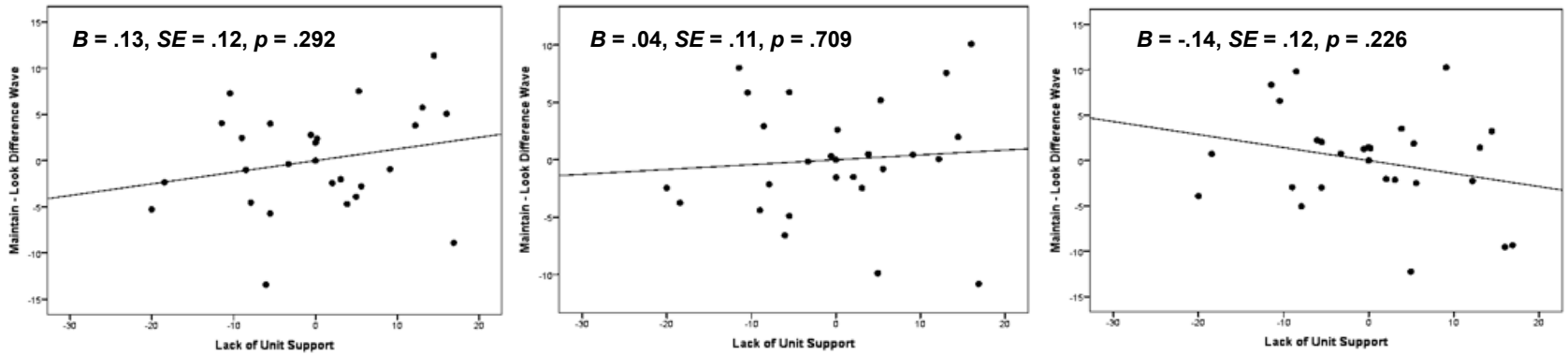
condition alone (e.g., “maintain” – “look”) at each of the three phases of the recording are presented in supplemental material (See Supplemental Material, Figure 8).

The second trend result indicated that pre-deployment stress exposure (a non-combat associated stressor) also significantly predicted differences in LPP magnitude between these two conditions (B = -1.57, SE = .52, p = .007). These results were similar to the effect of a lack of unit support, suggesting that pre-deployment stress exposure decreased the difference between the LPP amplitudes between the conditions. Again, as it was previously determined that this stressor did not influence the amplitude of the LPP during the “maintain” condition (Table 5), independent regressions were completed between pre-deployment stress and the LPP during the “reappraise” condition (e.g., “reappraise” – “look”). These results indicated that a unit increase in pre-deployment stress exposure consistently increased the LPP amplitude during early (B = 1.38, SE = .35, p = .001), middle (B = 2.12, SE = .48, p < .001), and late (B = 1.68, SE = .58, p = .008) phases (Figure 7). Results of regressions examining the effect of pre-deployment stress exposure and the LPP during the “maintain” condition alone (e.g., “maintain” – “look”) at each of the three phases of the recording are presented in supplemental material (See Supplemental Material, Figure 9).



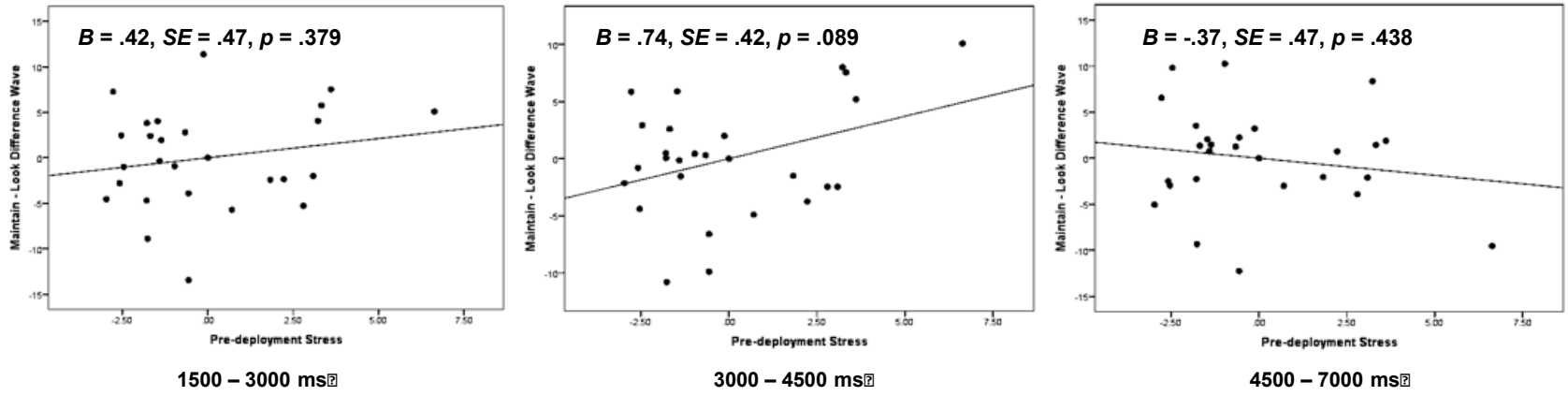
Note. All relationships control for effects of age, gender, race/ethnicity and years of education

Figure 7. Relationship between pre-deployment stress exposure and maintain-reappraise difference wave at frontal electrode site



Note. All relationships control for effects of age, gender, race/ethnicity and years of education

Figure 8. Relationship between lack of unit support and maintain-look difference wave at frontal electrode site



Note. All relationships control for effects of age, gender, race/ethnicity and years of education

Figure 9. Relationship between pre-deployment stress and maintain-look difference wave at frontal electrode site

V. DISCUSSION

A. **Group Effects**

In assessing group performance with respect to the task, the presentation of negative images in comparison to neutral image elicted an LPP prior to task instruction at a central-parietal location. This LPP began at 300 ms and obtained maximal amplitude at 600 ms, consistent with previous documentation on the temporal dynamics of the component (Cacioppo, et al., 1993; Cuthbert, et al., 2000; Foti and Hajcak, 2008; Hajcak et al., 2009; Hajcak et al., 2006; Hajcak and Nieuwenhuis, 2006; Hajcak and Olvet, 2008; MacNamara and Hajcak, 2009, 2010; Moser et al, 2006; Schupp, et al., 2000, 2003a, 2004; Weinberg and Hajcak, 2010). The LPP is again believed to represent cognitive processing specific to the processing of emotional stimuli and may, in turn, measure threat processing in light of negative imagery in the current study. As the LPP amplitude during all conditions post-instruction did not change as a function of time at the central-parietal location, yet time-effects were found at the frontal location (e.g., LPP amplitude during reappraisal steadily decreased), this finding suggests that the overall location of the LPP may have changed topographically. This finding is based on prior investigations demonstrating that cognitive reappraisal does decrease the amplitude of the LPP (Hajcak and Nieuwenhuis, 2006; Krompinger et al., 2008; Moser et al., 2006). Further, this shifting of the LPP effect forward along the midline over time is again consistent with previous literature documenting the spatial characteristics of the component (Foti et al., 2009; Hajcak et al., 2010; MacNamara et al., 2009). While previous research has reported that the reduction of the positive amplitude of the LPP during cognitive reappraisal remains during elongated processing for up to 2 seconds (Hajcak and Nieuwenhuis, 2006), the current study is the first to report that this reduction strengthens as a function of time during extended recording and when measured at a frontal scalp location.

B. **Individual Differences**

In order to study inter-individual differences in the relationship between PTSD, combat exposure, combat stress, and non-combat-associated stress with hyper-reactivity, bivariate OLS regressions were used that regressed these predictors onto LPP amplitude. Pre-instruction, as a measure of initial hyper-reactivity during the viewing of negative imagery, current symptoms of PTSD, combat exposure, combat-related stress and non-combat-related stress all failed to predict changes in the amplitude of the LPP, contrary to study hypotheses. While no other study to-date has tested the association between trauma-specific factors and characteristics of the LPP, the lack of correlation between symptoms of PTSD and the LPP is somewhat at-odds with prior work reporting that individuals with PTSD possess smaller LPP's (MacNamara et al., 2013). However, three differences in study design are noted between these investigations, which may account for differences in results.

First, this study used regression analyses to investigate PTSD symptoms as a predictor of LPP amplitude instead of investigating whether amplitude differed between individuals with high and low symptom presentation. The current study method then tested whether inter-individual differences PTSD symptoms were *related* to inter-individual differences in LPP amplitude. As is suggested by these results and confirmed elsewhere (D'Andrea et al., 2011; Herringa et al., 2013; van Wingen et al., 2011a, 2011b), no one-to-one relationship may exist with respect to hyper-reactivity and symptoms of PTSD. This point also illustrates yet another difference between the current investigation and the one employed by MacNamara et al. in that the current investigation allowed for a wider variation of "PTSD classification" using PTSD symptoms as a continuous variable instead of dichotomizing individuals into those who did and did not meet symptom criteria. Again, by using variance in PTSD symptom presentation as a

predictor, the one-to-one relationship between PTSD and hyper-reactivity was measured and found to be absent. Finally, this study controlled for years of education, which may control for other socioeconomic factors that may act as confounding variables in the relationship between hyper-reactivity and PTSD. Previous research has demonstrated that differences in education may be related to risk for PTSD diagnosis (Engelhard et al., 2006; Davis et al., 2012) or severity of PTSD symptoms (Plumb et al., 2014).

Results from regressions exploring predictors of ability to either sustain emotional reactivity or to regulate this reactivity demonstrated that no significant predictors existed when measuring the LPP at the central-parietal location. However, at the frontal electrode site, lack of unit support during deployment and incidence of pre-deployment stress both predicted that the LPP during cognitive reappraisal increased in positive amplitude. As the expected outcome of the LPP modulation during cognitive reappraisal was a decrease in the positive deflection of the component (Hajcak and Nieuwenhuis, 2006), these findings suggest that both lack of unit support (a combat-associated stressor) and pre-deployment stress (a non-combat-associated stressor) predicted inability to regulate reactivity.

The finding that lack of unit support during deployment predicted individual's inability in regulating reactivity is consistent with prior work suggesting that qualities particular to combat-exposure are influential in impairing emotional processing (Herringa et al., 2013; Karl et al., 2006; Kaufman et al., 2002; Kimble et al., 2010; van Wingen et al., 2011a, 2011b). However, this is the first study to-date to indicate that combat-specific factors may selectively impair the regulation of reactivity. Unit support in this investigation was defined broadly as the amount of assistance and encouragement that soldiers received during deployment, with support

measured in respect to fellow soldiers, commanding officers, and the military body as a whole (King et al., 2006). This definition is in-line with the study of social support in other settings, which defines itself as “information leading the subject to believe that he [she] is cared for and loved, esteemed, and a member of a network of mutual obligations” (Cobb, 1976, p. 300). The prevalence of social support in general has been shown to be effective in preventing onset of PTSD following trauma exposure (Hébert et al., 2014) and, administered during time of trauma, has been specifically associated with dampening autonomic arousal during the experience of stress itself (Eisenberger et al., 2007; Gerin et al., 1992; Hostinar et al., 2014; Lepore et al., 1993; Taylor et al., 2008; Thorsteinsson and James, 1999). Research on the neurobiology of the relationship between support and stress has demonstrated that social support may directly decrease the secretion of stress hormones during a stressful experience (De Vries et al., 1997; Kiyokawa et al., 2004; Neumann et al., 2000; Windle et al., 1997) and indirectly increase functioning of the prefrontal cortex employed during regulation of arousal (Eisenberger et al., 2007; Herman et al., 2005; Rilling et al., 2001).

The finding that a lack of support during deployment as a unique stressor is in-line with previous research involving combat-veterans that demonstrated that a lack of support *following* deployment also contributed to structural abnormalities in regions involved in emotion processing (Aupperle et al., 2013). It should be noted though that one possible interpretation for the present finding may be that low social support during deployment negatively impacts capacity to regulate emotional reactivity. However, it may also be the case that individuals who report low social support may already possess deficits in emotion regulation – a trait that may relate to and exacerbate feelings of abandonment and exclusion during deployment.

The finding that pre-deployment stress exposure predicted individual's inability in regulating reactivity is also consistent with prior work suggesting that stress exposure experienced early in life and unrelated to combat is influential in impairing emotional processing (Herringa et al., 2013; Kuo et al., 2012; Woodward et al., 2013). While related to this work, these prior investigations found association to pre-deployment stress exposure and functioning within the amygdala and ACC. In contrast and while speculative, by directly probing ability to regulate, the results from this study suggest that such trauma exposure may additionally impact brain regions involved in directed voluntary control of arousal, which is known to involve more prefrontal cortical regions (Phillips et al., 2008). Further investigations are needed, however, in order to test this association in terms of locus of dysfunction. While this is the first study to demonstrate that non-combat-associated stress exposure may impair ability to regulate reactivity, this result is in-line with a growing body of literature documenting increased risk for emotional dysregulation following early life trauma exposure (LeardMann et al., 2010; McCrory et al., 2010; Pechtel and Pizzagalli, 2011; Shonkoff et al., 2011). The pre-deployment stress exposure assessment in the present study captured stress experienced both during early development and just prior to deployment, thus the direct association to early life stress cannot be assessed. Nevertheless, these findings are consistent with research on "allostatic load". Allostatic load has been identified as the compounded effects of multiple stressors on physiological functioning that may, in turn, impair the brain's functioning within the specific domain of regulating arousal (McEwen, 1998, 2006; McEwen and Stellar, 1993; McEwen and Wingfield, 2003, Sterling and Eyer, 1988). Thus, repeated stress exposure, first outside and prior to deployment, and in combination with exposure to combat may in turn increase risk for affect dysregulation. However, it should be noted that the present study examined the correlational relationship between pre-deployment stress exposure and hyper-reactivity. Thus, while exposure to pre-deployment stress may contribute towards inability to regulate reactivity, it may also be the case that individuals who have difficulty regulating reactivity subsequently self-

report experiencing more pre-deployment stress. This last point openly considers that the causal influence within this relationship begins with the inability to regulate reactivity and its influence on the subjective report of stress exposure.

C. **Study Limitations**

It is important to note several limitations in the present study. First, the size of the current sample was relatively small and may have been underpowered. Additionally, while hyper-reactivity was measured in the present investigation via brain processes, no additional information was collected with respect to how effective participants were at either sustaining or regulating their arousal. Additional measures gathered either from the periphery or from self-report could have lent additional support to the findings that predictors selectively influenced hyper-reactivity as a physiological response. It is also important to note that while the associations between emotional reactivity and symptoms of PTSD, combat exposure, combat-stress and other lifetime exposures were explored statistically, the causal nature of these associations cannot be assumed. Further, quantification of trauma exposure depended on retrospective self-report and may be susceptible to recall bias, an established problem in studies that are unable to track participants longitudinally (Kopec et al., 1990; Schulz and Grimes, 2002). Future investigations that are able to objectively measure trauma exposure and the consequences on long-term brain functioning are needed.

D. **Study Implications**

This is the first study to-date to examine ongoing brain processes (e.g., over the course of seconds) during emotional reactivity and attempts to regulate this reactivity in individuals

exposed to combat. As a whole, findings offer three new insights with regard to characteristics of emotional hyper-reactivity following combat exposure. First, this study demonstrates that cognitive reappraisal, used as a regulation strategy to decrease reactivity, may strengthen in its effect over time. Second, the link between environmental precursors related to trauma-exposure and aberrations particular to emotional reactivity was again established, yet by way of deficits related to regulation. While many previous investigations have examined the relation between trauma and emotional reactivity, this is the first attempt to investigate these same associations with neural operations during regulation. Third, the identification of unique stressors that were found to selectively increase LPP amplitude during regulation further indicates that both combat-specific and non-combat-specific trauma may be influential in shaping emotional reactivity symptoms. This last finding is of particular interest as both stressors identified in this study fall outside the scope of more traditional work involving the influence of combat exposure itself.

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