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Neural indices of emotional reactivity and regulation predict course of PTSD symptoms in combat-exposed veterans

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ABSTRACT

After diagnosis, veterans with posttraumatic stress disorder (PTSD) display significant variability in the natural course of illness (Bonanno et al., 2012)). Cross-sectional work reveals that abnormal neural response during emotion reactivity—measured using the late positive potential (LPP)—correlates with PTSD symptom severity; however, whether the LPP during emotional reactivity and regulation predicts symptoms over time is unknown. The current study examined the LPP during emotion reactivity and regulation as predictors of PTSD symptoms over one year in OEF/OIF/OND combat-exposed veterans. At baseline, participants completed an Emotion Regulation Task (ERT) during electroencephalogram recording. The Clinician Administered PTSD Scale (CAPS) was completed at baseline (N = 86), 6-months (N = 54) and 1-year (N = 49) later. During ERT, participants viewed negative pictures; partway through they were instructed to "reappraise" (i.e., reduce negative affect/regulate) or "look" (i.e., passively react). Change in LPP during emotional reactivity (ΔLPP-E) and reappraisal (ΔLPP-R) were calculated and used in multilevel mixed modeling to predict CAPS over time. Findings demonstrated that deficiency in reappraisal (ΔLPP-R) predicted more overall symptoms over time, while greater neural responses to emotion (ΔLPP-E) and greater change in neural response as a function of reappraisal (ΔLPP-R) predicted a decline in avoidance symptoms over time. Together, results support the utility of neural markers of emotional reactivity and regulation as predictors of PTSD symptoms—and change in symptoms—across one year.

1. Introduction

After diagnosis, veterans with posttraumatic stress disorder (PTSD) display significant variability in the natural course of illness (Bonanno et al., 2012). Estimates from population-based studies involving those returning from Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) show that within the portion of veterans who exhibit at least a moderate amount of PTSD symptoms (17% of the veteran population), some (~8%) improve in these symptoms in the years following diagnosis (Bonanno et al., 2012; Bonanno and Diminich, 2013), while a nearly equal amount (~7%) experience a worsening in symptoms (Bonanno et al., 2012; Bonanno and Diminich, 2013) or live with chronically high symptoms (~2%) that remain unchanged (Bonanno et al., 2012). Although significant effort has been made to identify factors that increase risk for the initial development of PTSD immediately following combat (McAndrew et al., 2013), it is currently unknown what and how factors impact variability in symptom course in the years after exposure. That is, more research is needed to identify influential psychological, behavioral, or biological factors that characterize changes in PTSD severity over time.

Although it is not yet clear which variables fully account for changes in PTSD symptoms longitudinally (Kessler et al., 2014), variation in the extent to which individuals are impaired in their ability to regulate negative emotional experiences is a significant predictor of future symptoms (Bardeen et al., 2013; Jenness et al., 2016; Miron et al., 2014; Orcutt et al., 2014; Punamäki et al., 2015). For example, self-

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reported difficulty in using emotion regulation in the context of negative affect predicts residual PTSD symptoms 6-months after the completion of PET (Cloitre et al., 2016). Deficits in emotion regulation prior to a traumatic event also predict severity of symptoms experienced in the days (Orcutt et al., 2014), one month (Bardeen et al., 2013; Jenness et al., 2016) and eight months after trauma (Miron et al., 2014). That is, individual variability in the extent to which trauma survivors report experiencing emotion dysregulation prospectively relates to illness severity in the months that follow exposure. However, emotion dysregulation is a complex process, defined by atypical response to emotional triggers and/or deficiency in using cognitive control to alter this experience (Gross, 1998). Therefore, although subjective emotion dysregulation is promising in its relationship to PTSD outcomes, feelings of dysregulated affect may arise from one or both sub-processes (e.g., atypical response to negative stimuli and/or difficulty in using regulation). Using self-report measures, it is difficult to parse out the contributing features of emotion reactivity versus emotion dysregulation (Tracy et al., 2014).

In contrast, neural measures of emotion reactivity and regulation may be better equipped to distinguish precise aspects of emotion dysregulation. One neural measure in particular is the late positive potential (LPP), a positive-going component in the event-related potential (ERP) that occurs at centro-parietal sites beginning approximately 200 ms after stimulus onset that is larger for negative compared to neutral stimuli (Codispoti et al., 2006; Cuthbert et al., 2000; Foti et al., 2009; Schupp et al., 2000). Individual differences in the magnitude of the LPP response correlate with subjective and objective indices of arousal (Cuthbert et al., 2000). Importantly, the LPP is also sensitive to changes in reactivity during emotion regulation, as LPP magnitude *decreases* when individuals are instructed to use the strategy of cognitive reappraisal for the down-regulation of negative affect (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006; Parvaz et al., 2012). Cognitive reappraisal is the most widely-used strategy for changing negative affect (Cutuli, 2014) and alters the salience of an emotional stimulus by changing its meaning (Gross, 1998). Therefore, the LPP provides a valid measure of individual differences in both emotional reactivity and successful emotion regulation.

There is growing evidence that the LPP to negative stimuli appears to be altered in those with symptoms of PTSD or similar disorders, though direction of effects varies depending on the type of symptoms and task. For example, when assessed cross-sectionally, past research has found individual differences in distress symptoms correlate with larger LPPs in response to negative images (Lobo et al., 2014). In addition, in children exposed to a natural disaster, larger LPPs to negative images, measured prior to exposure, prospectively predicted severity of psychiatric symptoms in the six months after exposure (Kujawa et al., 2016). On the other hand, symptoms of PTSD have also been associated with smaller LPPs in response to angry faces (DiGangi et al., 2017; MacNamara et al., 2013), an association that was specific to the presence of intrusive symptoms (MacNamara et al., 2013). Thus, whether individuals with PTSD display exaggerated or reduced emotional reactivity, as measured by the LPP, may depend on the presence of specific symptom domains and may depend on stimuli type (e.g., aversive images versus fearful faces).

With regard to emotion regulation, we previously found little evidence for deficits in reducing the LPP during emotion regulation among those with PTSD (Fitzgerald et al., 2016). That is, when veterans were asked to use cognitive reappraisal in the context of negative, aversive images, they were able to reduce the LPP to a similar extent as to combat-exposed controls (Fitzgerald et al., 2016). However, individuals with PTSD were treated as a homogenous group in this work (Fitzgerald et al., 2016), although PTSD is a highly heterogeneous disorder (Galatzer-Levy and Bryant, 2013) and individuals with PTSD vary greatly in their symptom dimensions (Elklit and Shevlin, 2007; Michopoulos et al., 2015; Yufik and Simms, 2010). For instance, PTSD is characterized by symptoms spanning the avoidance of trauma-related material, emotional numbing, hyperarousaland intrusive recollections of the traumatic event (American Psychiatric Association, 2013). In the context of negative stimuli, alterations may exist either in the direction of hypervigilance and hyperarousal, and/or avoidance and distancing (Ehring and Quack, 2010; Litz et al., 2000). In addition, symptoms are labile over time within individuals (Galatzer-Levy and Bryant, 2013; Solomon and Mikulincer, 2006; Wu and Cheung, 2006; Yehuda et al., 2009), such that the most distressing symptoms for any one individual changes as a function of time (Yehuda et al., 2009). Owing to the heterogeneous nature of PTSD, there may therefore be significant individual variability in LPP response during down-regulation that depends on the presence of specific symptom dimensions. Further, all prior work on LPP and PTSD has been completed cross-sectionally and no study to-date has investigated whether the LPP as a neural marker of emotional reactivity and regulation success predicts *changes* in PTSD symptoms over time.

The aim of the current study was to measure neural markers of emotional reactivity and regulation as predictors of PTSD symptom dimensions of re-experiencing, avoidance, and hyperarousal in combat-exposed OEF/OIF/OND veterans over a one-year period. Owing to differences in findings of cross-sectional work, which provided evidence for both exaggerated and reduced LPP response to negative stimuli, we hypothesized that the LPP would be associated with severity of PTSD symptoms, but did not hypothesize directionality of these associations. Although prior work has not found strong evidence that PTSD is associated with difficulty in reducing the LPP as a function of cognitive reappraisal (Fitzgerald et al., 2016), given the prominence of emotion regulation deficits in PTSD, we hypothesized that individual differences in difficulty reducing the LPP would relate to greater symptoms over time.

2. Materials and methods

2.1. Participants and materials

A total of eighty-six veterans 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 (UIC) (Chicago, IL). Participants were eligible for study inclusion if they were discharged from active military service, between the ages of 18 and 55, and able to provide informed consent. Participants were excluded if they had a clinically significant medical or neurological condition, lifetime history of schizophrenia, or presence of an organic mental syndrome, mental retardation, or pervasive developmental disorder, or presence of suicidal or homicidal ideation. The decision to exclude older adults and individuals with significant medical conditions was made due to the high probability that concomitant drug treatments that occur frequently in these populations may exert a confound effect on electroencephalogram (EEG) testing. Exclusion of individuals with active suicidal and/or homicidal ideation was made to ensure the safety of all participants.

In addition to EEG assessment for the collection of ERPs, participants completed the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1997) to assess for Axis I psychiatric diagnoses based on Diagnostic and Statistical Manual-Fourth Edition (DSM-IV) criteria and the Clinician Administered PTSD Scale for DSM-IV (CAPS-IV; Blake et al., 1995) to record PTSD symptom severity specific to severity of re-experiencing, avoidance, and hyperarousal symptoms as measured by separate sub-scale scores. The Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) and Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) were also completed to assess for depression and anxiety severity. In addition, all participants completed a measure of severity of combat exposure assessed by the Combat Exposure Scale (CES; Keane et al., 1989).

After EEG testing and clinical questionnaires, participants were re-contacted six months and one year later to complete the CAPS, HAM-A,

and HAM-D in person at the Jesse Brown VA Medical Center. Participant retention was 63% ($N = 54$) at six months and 57% ($N = 49$) at one year. The Institutional Review Board (IRB) at the Jesse Brown VA Medical Center and its university affiliate, University of Illinois at Chicago (UIC), approved all procedures. All participants provided written consent and were monetarily compensated for their time.

2.2. Emotion regulation task

Participants completed a previously-validated Emotion Regulation Task (ERT) (Dennis and Hajcak, 2009; Fitzgerald et al., 2016; Hajcak and Nieuwenhuis, 2006; Parvaz et al., 2012) during continuous EEG recording. During ERT, participants were shown 50 negative and 50 neutral images taken from the International Affective Picture System (IAPS; Lang et al., 2008). Valence (negative: $M = 2.51 \pm 0.78$; neutral: $M = 5.02 \pm 0.44$) and arousal (negative: $M = 5.78 \pm 0.68$; neutral: $M = 3.44 \pm 0.41$) ratings were previously reported (Phan et al., 2005) (higher numbers indicate more pleasant and higher arousal ratings). Use of IAPS images as stimuli was based on prior work validating the ERT with IAPS for the study of cognitive reappraisal of negative affect (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006; Parvaz et al., 2012), and because this approach mimics prior cognitive reappraisal ERP studies involving PTSD (Fitzgerald et al., 2016). Each image was presented only once during the entirety of the task. During completion of the task, participants were seated approximately 60 cm in front of a computer screen that displayed images at 40° of visual angle horizontally and vertically. Images were shown serially for 7000 ms and grouped in blocks of negative and neutral consisting of 25 images each. During image presentation, three task conditions were used: following image onset for neutral images, an auditory instruction was given at 1000 ms to “look” (i.e., continue viewing the picture). During negative images, the instruction was “look” (i.e., view the picture without trying to change their emotional reaction) or, on half the trials, was “reappraise” (i.e., reduce negative affect by making the image appear less emotional). After picture offset, participants viewed a white fixation cross presented in the center of the screen for 1000 ms prior to the beginning of the next trial. In total, 50 “Look-Neutral”, 25 “Look-Negative”, and 25 “Reappraise” trials were used. The presentation of negative and neutral picture order was pseudorandomized across each block and, for negative image blocks, the order of “look” and “reappraise” instructions was also pseudo-randomized. In between blocks, participants were given a self-timed rest period.

Prior to the task, participants were trained in the technique of cognitive reappraisal by trained research staff (KLP, CS) in order to (1) conceptualize the depicted scenario in a less negative way (e.g., women crying outside of a church could be attending a wedding instead of a funeral); or (2) objectify the content of the pictures (e.g., a woman with facial bruises could be an actor in a movie). For training in emotional reactivity, participants were instructed to passively process the negative images they were seeing (e.g., “view the picture without trying to change their emotional reaction”). Participants performed eight practice trials with IAPS images not used in the actual task to rehearse “look” and “reappraise” instructions. During the practice session and for reappraise trials, research staff asked participants to verbalize emotion modification strategies and provided feedback to ensure participants understood task instructions and used appropriate strategies to cognitively reappraise emotional content of each images.

2.3. 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 used, based on the 10/20 system (standard 32 channel montage, as well as FCz and Iz). The voltage from each active electrode was referenced online with respect to a common mode sense (CMS) active electrode, producing a monopolar (non-differential) channel. Two electrodes were placed on the left and right mastoids, while an additional four facial electrodes were used to record the electrooculogram (EOG) generated from eye blinks and eye movements: two of these electrodes were located approximately 1 cm outside the outer edge of the right and left eyes and two electrodes were placed approximately 1 cm above and below the left eye. The EEG and EOG were low-pass filtered using a fifth order sinc filter with a half-power cutoff of 204.8 Hz and then digitized at 1024 Hz with 24 bits of resolution.

2.4. Offline data reduction and statistical analyses

Offline data processing was performed using Brain Vision Analyzer 2 software (BVA, Brain Products, Gilching, Germany). Data were re-referenced offline to the average of the two mastoids, and band-pass filtered from 0.01 to 30 Hz. Trials were segmented beginning 200 ms prior to picture onset and ending 7000 ms after picture onset for a total segment duration of 7200 ms. Following segmentation of data, eye blink and ocular corrections were made according to the method developed by Miller et al. (1988). Semi-automated artifact rejection was used to remove a voltage step of > 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of < 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-by-trial basis. Only individuals retaining 80% or more data on each electrode channel were included in analyses. Trials were averaged separately for each condition and baseline correction was performed using the 200 ms period prior to picture presentation.

For each participant, mean amplitudes in EEG activity were extracted from a central-parietal electrode pooling (Pz, P3, P4, CP1, CP2) where the LPP is maximal (Dennis and Hajcak, 2009; Fitzgerald et al., 2016; Hajcak and Olvet, 2008) during two time periods. As a measure of initial emotional reactivity prior to instruction, we calculated the negative images minus neutral images difference score in the 400–1000 ms window (ΔLPP); to measure sustained emotional reactivity post-instruction, we calculated the Look-Negative minus Look-Neutral difference score in the 1500–7000 ms window (ΔLPP-E). To measure emotion regulation success post-instruction, we calculated the Look-Negative minus Reappraise difference score in the 1500–7000 ms (ΔLPP-R). Greater ΔLPP pre-instruction and ΔLPP-E post-instruction reflected greater emotional responding, while greater ΔLPP-R denoted greater efficacy in down-regulation using the strategy of cognitive reappraisal (Moran et al., 2013).

2.5. Multilevel linear models (MLM)

PTSD symptom severity in domains of re-experiencing, avoidance, and hyperarousal symptoms, measured in CAPS sub-scales, were used as the primary dependent variables in separate 2-level multilevel linear models (MLM) to examine the slope of symptoms across time within individuals. MLM is well-suited for these aims as it allows continuous modeling of time and handles missing data by weighting slope estimates by number of observations (Goldstein, 2011). In each MLM, the ΔLPP at 400–1000 ms (pre-instruction), ΔLPP-E at 1500–7000 ms (post-instruction), and ΔLPP-R at 1500–7000 ms (post-instruction during cognitive reappraisal) were used as independent predictors. Gender and age were included in each model as covariates. All continuous predictors were grand-mean centered; time was coded as a three level variable (0 = baseline; 6 = 6-month; 12 = 12-months), and gender was effects coded (-1 = male; 1 = female).

We tested the omnibus model in a hierarchical fashion such that in the first step we only included the main effects of time, the LPP variables, and all covariates. In the second step, we tested the interaction between LPP variables and neural predictors with time. Any significant

interaction with time was followed-up using a standard simple slopes approach (Holmbeck, 2002): ± 1 standard deviation of the significant predictor was calculated and the MLM models were re-run evaluating the effect of time at high and low levels.

3. Results

3.1. Clinical characteristics

At baseline, participants ranged from 23 to 50 years of age (M = 33.47 ± 6.50); 81.40% percent were male. Average time since combat deployment and study entry was 6.22 (± 3.19) years (unknown for n = 3 participants). In individuals with more than one deployment (n = 37 [43% of the sample]), average time since first deployment and study entry was 9.86 (± 3.60) years.

In terms of diagnostic status, at baseline (N = 86) n = 38 (44%) had a primary diagnosis of PTSD, n = 13 (15%) current MDD, n = 16 (19%) past MDD, n = 7 (8%) substance abuse, and n = 1 (1%) each of generalized anxiety disorder (GAD), agoraphobia, bipolar disorder (BD), and panic disorder(PD); N = 8 (10%) did not have a primary Axis I diagnosis. At 6 months (N = 54), n = 15 (28%) had PTSD, n = 17 (31%) current MDD, n = 7 (13%) past MDD, n = 2 (4%) substance abuse, and n = 1 (2%) each of GAD, agoraphobia, and PD; n = 10 (18%) did not have a primary Axis I diagnosis. At 1 year (N = 49), n = 15 (31%) had PTSD, n = 13 (27%) had MDD, n = 3 (6%) had past MDD, n = 3 (6%) had substance abuse, n = 2 (4%) had agoraphobia and n = 1 (2%) each had GAD and PD; n = 11 (22%) did not have a primary Axis 1 diagnosis. In terms of changes to PTSD status over the study period, n = 3 (6%) of those who did not have a primary PTSD diagnosis at baseline met diagnostic criteria at a subsequent follow-up visit, while n = 7 (18%) individuals with a primary PTSD diagnosis at baseline no longer met criteria at a subsequent follow-up.

Comparing individuals who did not return for subsequent visits (e.g., either 6 months or 1 year after testing), these individuals did not differ from participants with follow-up assessments in regards to re-experiencing (t(84) = 1.32, p = 0.19), avoidance, (t(84) = 1.08, p = 0.29) or hyperarousal (t(84) = 1.74, p = 0.09) symptoms. These participants also did not differ in terms of anxiety (t(84) = 1.40, p = 0.17), depression (t(84) = 1.05, p = 0.30), age (t(84) = 0.08, p = 0.94), gender (χ^2(1) = 0.004, p = 0.95), or severity of combat exposure (t(84) = 0.98, p = 0.33).

3.2. Task effects

As a manipulation check to confirm that negative task images elicited an LPP, a paired samples t-test was completed examining differences in mean amplitude between negative and neutral images at 400–1000 ms. Here, we found a significant effect of image type, such that the LPP was larger during the viewing of negative (M = 4.20 ± 3.91) compared to neutral (M = 1.45 ± 3.63) images (t(85) = 6.92, p < 0.001). Fig. 1 depicts the ΔLPP (using a negative minus neutral difference wave) at its spatial location.

3.3. Predictors of PTSD symptoms and course of symptoms over time

Results are presented in Table 1. In our first models examining predictors of symptoms over time, there was a significant effect of time, such that re-experiencing (b = −0.23, t(106.74) = −3.25, p < 0.01), avoidance (b = −0.24, t(108.50) = −2.16, p = 0.03), and hyperarousal (b = −0.20, t(112.24) = −2.17, p = 0.03) symptoms declined over time. With regard to neural predictors, we found a significant effect of ΔLPP-R, such that smaller ΔLPP-R—reflecting less change in the LPP during cognitive reappraisal—predicted greater re-experiencing (b = −0.44, t(78.29) = −2.26, p = 0.03), avoidance (b = −0.53, t(76.84) = −2.03, p = 0.05), and hyperarousal (b = −0.43, t(79.21) = −2.21, p = 0.03) symptoms across time. There were no significant effects of the ΔLPP pre-instruction, ΔLPP-E, age or gender in predicting symptoms (p's > 0.06).

In our second models examining the interaction with time, we found a significant interaction between ΔLPP-E and time (b = 0.05, t(130.96) = 2.32, p = 0.02) and ΔLPP-R and time (b = −0.05, t(131.55) = −2.18, p = 0.03) particular to avoidance symptoms. Follow-up simple slopes analyses revealed that smaller ΔLPP-E—reflecting smaller LPP during sustained emotional experiencing—predicted a steeper decline in avoidance symptoms over time (b = −0.62, t(112.36) = −3.31, p < 0.01) and that larger ΔLPP-R—reflecting bigger change in the LPP during reappraisal—predicted a steeper decline in avoidance symptoms over time (b = −0.43, t(111.27) = −2.45, p = 0.02). There was no change in avoidance symptoms over time for relatively larger ΔLPP-E (p > 0.41) or relatively smaller ΔLPP-R (p > 0.94). In addition, there were no other significant interactions with time with other covariates or neural predictors (p's > 0.07). Results did not change significantly when severity of anxiety (e.g., HAM-A), depression (e.g., HAM-D), and combat (e.g., CES) were added as covariates in the model. Therefore, results are presented without controlling for these factors.

Figs. 2 and 3 depict the relationship between PTSD symptom changes over time and relative high versus low ΔLPP-E and relative high versus low ΔLPP-R, respectively. Groups in all cases were defined using ± 1 standard deviation.

4. Discussion

The aim of the current study was to investigate neural predictors of PTSD symptoms in the domains of re-experiencing, avoidance, and hyperarousal over a one-year period in OEF/OIF/OND veterans. Three major findings emerged from this study: first, greater difficulty in reducing the LPP using reappraisal predicted greater overall symptoms (e.g., re-experiencing, avoidance, and hyperarousal) symptoms across time; second, smaller emotional responding predicted greater decline in avoidance symptoms across time; and, third, greater reduction in the LPP using reappraisal predicted greater decline in avoidance symptoms across time.

The finding that difficulty in using cognitive reappraisal to down-regulate negative affect was also related to PTSD symptom severity over one year is consistent with prior reports that self-reported deficiency in reappraisal prospectively predicts PTSD severity in the months following trauma (Bardeen et al., 2013; Cloitre et al., 2016; Jenness et al., 2016; Miron et al., 2014; Orcutt et al., 2014). We expand this work by providing evidence that neural deficiency during reappraisal prospectively predicts severity of illness in combat-exposed veterans and up to one year. In addition, we provide evidence that the relationship between neural measures of difficulty in down-regulation is linked to all symptoms of PTSD, and is not particular to re-experiencing, avoidance, or hyperarousal. In addition, these effects remained when controlling for symptoms of anxiety and depression, suggesting that although difficulty in down-regulation is present across many disorders, it appears to be a central deficiency in PTSD (Etkin and Wager, 2007; Frewen, 2006). Nevertheless, more work is needed to decipher what sub-processes of reappraisal (e.g., initial appraisal, selection of alternative explanations and reinterpretation) are most difficult for those with PTSD given the complexity of cognitive reappraisal as a strategy. In particular, prior studies show that engaging in reappraisal attenuates the LPP beginning 700 ms post-stimulus and that this effect differs from other regulation strategies such as distraction or suppression (Paul et al., 2013). The relative delayed effect of reappraisal has been theorized to arise from the time-consuming attention processes that are needed to appraise and reappraise emotional triggers (Gross, 1998; Paul et al., 2013). At present, it is unclear which of these processes is most compromised in those with PTSD.

Previously we did not find a group difference in the LPP during cognitive reappraisal between combat-exposed veterans with and

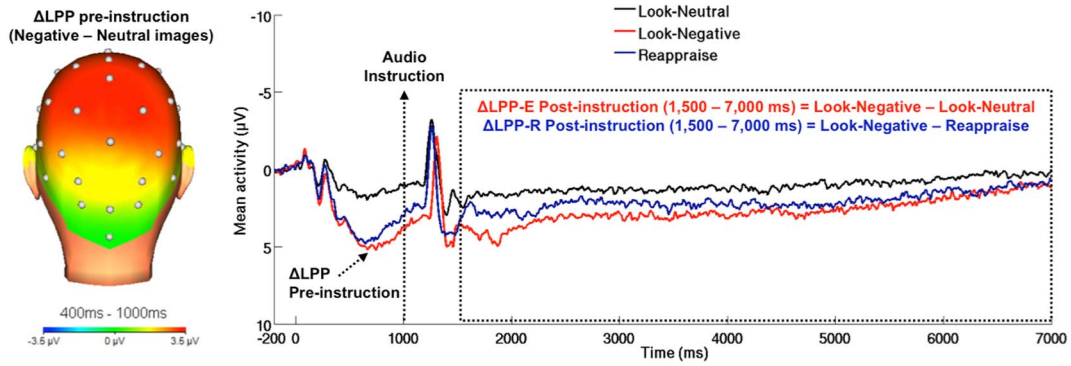

Fig. 1. Spatial location of the ΔLPP at centro-parietal sites where it was scored. Grand-averaged waveforms across the trial length (7 s) shown separately for each condition; ΔLPP-E was calculated using a Look-Negative minus Look-Neutral difference wave and ΔLPP-R was calculated using a Look-Negative minus Reappraise difference wave post-instruction. Note: Stimulus onset occurred at 0 ms, task instruction occurred at 1000 ms. Dashed boxes indicate the post-instruction time-window in which the ΔLPP-E and ΔLPP-R was analyzed. On the y-axis, positive amplitude is plotted down. LPP = late positive potential.

without PTSD (Fitzgerald et al., 2016); however, the present study differs in important ways from this earlier work. In particular, the current study tested the relationship between the LPP and more specific PTSD symptoms, each measured continuously. Therefore, the effect of down-regulation deficits may be most evident when considering more homogenous phenotypic variables, owing to variability within trauma-exposed populations in the extent to which emotion regulation is compromised. Such variability may make it more difficult to detect overall PTSD group differences, supporting the use of trans-diagnostic approaches to the study of psychopathology, in-line with the Research Domain Criteria (RDoC) initiative (Insel, 2014). This initiative emphasizes the need for measures that map onto individual differences in biological underpinnings of pathophysiology. As a consequence, individual differences in neurobiology may help uncover correlates of disease-states across a wide spectrum, while recently, emotion dysregulation has been proposed as a trans-diagnostic feature that can be studied in this fashion (Fernandez et al., 2016). In the context of those with PTSD, prior research has found substantial evidence for individual variability among trauma-exposed individuals in the extent to which they use emotion regulation (Shepherd and Wild, 2014) and are effective in down-regulation (Boden et al., 2012), including some of our prior work that demonstrated greater habitual use of reappraisal among combat-exposed veterans was related to decreased amygdala responding during the act of reappraisal (Fitzgerald et al., 2017). Further, regulatory flexibility—defined by the ability to utilize regulation strategies in varied settings—is an important individual difference factor that strongly predicts psychological health and well-being across populations (Bonanno and Burton, 2013), including resilience to trauma (Bonanno and Diminich, 2013). Together, this provides a strong case for the importance of individual differences in regulation capacity among trauma-exposed individuals, although much of the prior work on individual variability in emotion regulation is limited to physiological and self-report markers. In contrast, we demonstrate that differences in regulation capacity at the neural level also serves as an important predictor of current and future PTSD symptomatology.

With regard to predictors of course of symptoms, we found that smaller neural response and greater change in neural response during reappraisal predicted greater decline in PTSD avoidance symptoms over one-year. Therefore, the LPP in and outside the context of regulation is also a useful predictor of *changes* in avoidance symptoms in combat-exposed veterans. Noteworthy is the fact that we found that smaller ΔLPP-E and larger ΔLPP-R both predicted decline in avoidance symptoms independently when controlling for the other factor. This suggests that interventions aimed at treating avoidance symptoms in trauma

Table 1
Mixed growth models examining impact of LPP during negative emotion responding and regulation on PTSD symptoms over 1-year.

	CAPS re-experiencing					CAPS avoidance					CAPS hyperarousal				
Variable	*b*	*SE*	*t*	*β*	*p*-value	*b*	*SE*	*t*	*β*	*p*-value	*b*	*SE*	*t*	*β*	*p*-value
Step 1															
Intercept	**9.90**	**1.30**	**7.64**	**0.05**	**< 0.001*****	**14.56**	**1.73**	**8.40**	**0.06**	**< 0.001*****	**13.95**	**1.31**	**10.64**	**0.04**	**< 0.001*****
Time	**− 0.23**	**0.07**	**− 3.25**	**− 0.12**	**0.002****	**− 0.24**	**0.11**	**− 2.16**	**− 0.09**	**0.03***	**− 0.20**	**0.09**	**− 2.17**	**− 0.09**	**0.03***
Age	0.01	0.15	0.06	0.01	0.95	− 0.02	0.20	− 0.09	− 0.01	0.93	− 0.05	0.15	− 0.35	− 0.03	0.73
Gender	− 2.22	1.27	− 1.75	− 0.18	0.09	− 1.38	1.69	− 0.82	− 0.08	0.42	− 2.47	1.27	− 1.95	− 0.19	0.06
LPP	− 0.11	0.29	− 0.39	− 0.04	0.70	− 0.05	0.38	− 0.12	− 0.01	0.90	− 0.27	0.28	− 0.94	− 0.10	0.35
ΔLPP-E	0.15	0.20	0.76	0.11	0.45	0.07	0.26	0.28	0.04	0.78	− 0.04	0.20	− 0.18	− 0.02	0.86
ΔLPP-R	**− 0.44**	**0.20**	**− 2.26**	**− 0.30**	**0.03***	**− 0.53**	**0.26**	**− 2.03**	**− 0.27**	**0.05***	**− 0.43**	**0.20**	**− 2.21**	**− 0.27**	**0.03***
Step 2															
Intercept	**9.09**	**1.30**	**6.99**	**0.10**	**< 0.001*****	**13.80**	**1.71**	**8.09**	**0.10**	**< 0.001*****	**13.21**	**1.33**	**9.93**	**0.09**	**< 0.001*****
Age	0.03	0.16	0.21	0.02	0.83	− 0.002	0.21	− 0.01	0.01	0.99	− 0.04	0.16	− 0.27	− 0.02	0.79
Gender	− 2.03	1.30	− 1.6	− 0.16	0.12	− 1.20	1.71	− 0.70	− 0.1	0.48	− 2.47	1.34	− 1.85	− 0.18	0.07
LPP × Time	0.001	0.02	0.06	0.01	0.96	0.01	0.03	0.42	0.02	0.67	0.01	0.02	0.29	0.03	0.78
ΔLPP-E × Time	0.004	0.02	0.28	− 0.003	0.78	**0.05**	0.02	**2.32**	**0.13**	**0.02***	0.02	0.02	0.99	0.07	0.32
ΔLPP-R × Time	− 0.01	0.01	− 0.51	0.02	0.61	**− 0.05**	0.02	**− 2.18**	**0.07**	**0.03***	− 0.02	0.02	− 0.93	0.003	0.35

Note. Gender is effects coded (− 1 = male; 1 = female); *b* = unstandardized coefficients; *SE* = standard error of unstandardized coefficients; *β* = standardized coefficients; LPP = Late Positive Potential; ΔLPP-E = index of emotional experience; ΔLPP-ER = index of effectiveness of emotion regulation; CAPS = Clinician Administered PTSD Scale.
Bolded text indicates significant effects.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

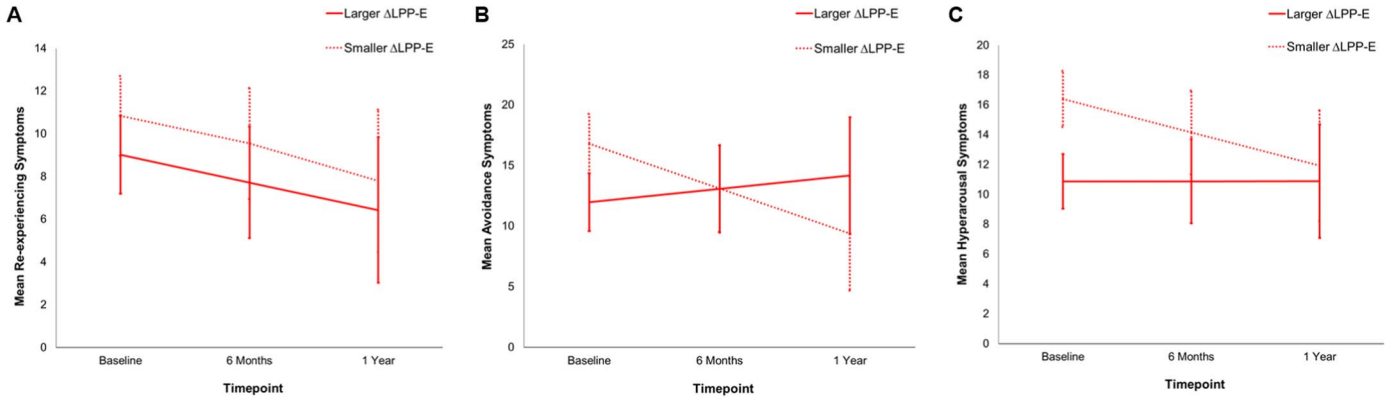

Fig. 2. (A) Changes in PTSD re-experiencing, (B) avoidance, and (C) hyperarousal symptoms over time for individuals with relative larger versus smaller ΔLPP-E. Compared to individuals with relatively larger ΔLPP-E, individuals with relatively smaller ΔLPP-E declined in avoidance symptoms over time. Note: Relative smaller versus larger ΔLPP-E defined by ± 1 standard deviation; age and gender were included as covariates in obtaining relative ΔLPP-E values; LPP = late positive potential; sample sizes were: baseline (n = 86), 6 Months (n = 54), 1 Year (n = 49.

survivors may benefit by targeting exaggerated response to negative affect and/or difficulty in down-regulation, as both interventions may be beneficial for remediation. Previous clinical work emphasizes the role that avoidance plays in the perpetuation of chronic PTSD. For instance, a reciprocal relationship exists such that avoidance predicts worse treatment outcomes, while poor outcomes predict future use of avoidance (Badour et al., 2012). Therefore, changes to avoidance symptoms over time appear to be clinically meaningful. The present research showcases the utility of neural predictors of emotional response and regulation as useful predictors specifically tied to change in avoidance symptoms long-term.

To note, prior work has found that smaller LPP responses to angry faces was related to *greater* PTSD symptoms in combat-exposed veterans when measured cross-sectionally (DiGangi et al., 2017; MacNamara et al., 2013). Disparity in terms of smaller LPPs relating to greater symptoms versus greater change in symptoms may hinge on differences in stimuli type (e.g., emotional images versus faces); smaller LPPs may be considered maladaptive in one instance, but not the other. For instance, smaller neural response to socioemotional cues like faces may signal disengagement, and therefore could be considered maladaptive. In contrast, individuals with PTSD may be reactive to threat cues that are more explicit (e.g., graphic images); therefore, smaller LPP response in this setting may be more beneficial. In addition, that smaller LPPs were specifically related to decline in avoidance hints at the possibility that specific symptom dimensions arise due to the presence of hypo- versus hyper-response to threat at the neural level. Present results therefore suggest that both patterns of abnormalities are consequential for the unfolding of different PTSD symptoms over time.

Findings should be considered in light of several limitations. First, despite demonstrating that individuals who were lost to follow-up in the current study (30%–48% for 6 month and 1 year time points, respectively) did not differ in terms of illness severity or demographics, these numbers reflect considerable attrition during study participation. More work is needed to predict symptom course in larger and more heterogeneous samples, including individuals who are at higher risk of dropping out. Second, the current study investigated changes in the course of PTSD symptoms irrespective of trauma onset and results cannot speak to the utility of the LPP as a predictor of initial symptom development immediately following deployment. Third, repeated testing may have led to bias in the measurement of PTSD symptoms over time, although decline in PTSD symptoms across participants is likely multifactorial and may also be the result of continued care in a medical setting. Fourth, although the current study used general negative imagery as the stimuli probe in-line with prior work on cognitive reappraisal in PTSD (Fitzgerald et al., 2016), results cannot generalize to the way in which the LPP in response to other types of affective stimuli (e.g., faces, trauma-specific reminders) may serve as a predictor of future symptoms. In addition, emotion dysregulation was measured in the context of negative affect and future work is needed to incorporate responses to positive stimuli as predictors of symptoms. Finally, without measuring neural markers of emotion dysregulation prior to combat, it is unclear whether emotion dysregulation is a pre-existing risk-factor for the development of the disorder, or corollary with the disease. Therefore, more work must be done to better

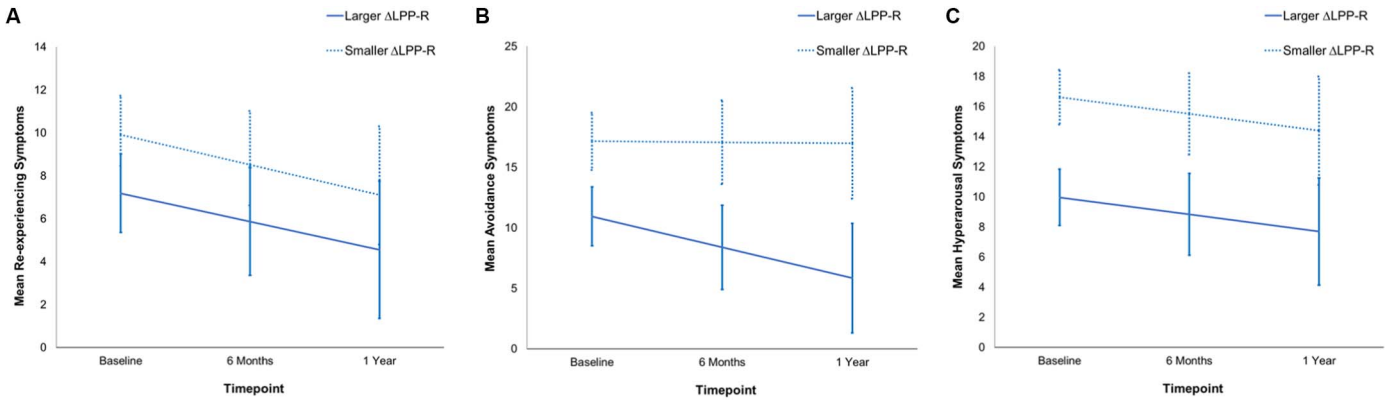

Fig. 3. (A) Changes in PTSD re-experiencing, (B) avoidance, and (C) hyperarousal symptoms over time for individuals with relative larger versus smaller ΔLPP-R. Individuals with relatively larger ΔLPP-R—reflecting greater change in the LPP during reappraisal—had less symptoms over time and, compared to individuals with smaller ΔLPP-R, experienced a decline in avoidance symptoms over time. Note: Relative larger versus smaller ΔLPP-R defined by ± 1 standard deviation; age and gender were included as covariates in obtaining relative ΔLPP-E values LPP = late positive potential; sample sizes were: baseline (n = 86), 6 Months (n = 54), 1 Year (n = 49.

understand the cause of emotion dysregulation as it relates to trauma onset (Ehring and Quack, 2010).

5. Conclusion

Findings contribute to the literature in several important ways. First, in the search of what qualifies trajectories of risk versus resilience, neurobiologically-informed predictors are relatively under-utilized; therefore, findings from this study move the field forward by demonstrating utility of neural markers using the LPP as predictors of PTSD symptom course. Second, prior work that has examined relationship between PTSD and neural functioning during negative emotional response has almost exclusively focused on neural functioning during passive emotion reactivity, ignoring the potential importance of emotion regulation. To our knowledge this is the first study to measure neural functioning during both emotion reactivity and regulation as predictors of symptom change in combat-exposed veterans. Finally, study findings are derived from a highly heterogeneous sample of veterans who are diverse in symptom profiles in the context of PTSD and other internalizing disorders, as well as age, gender, and combat severity followed for one year. Therefore, results are derived from an ecologically-valid sample for the study of the natural course of PTSD as it unfolds over time. Together, results suggest the relative importance of studying neural functioning during emotion reactivity and regulation as predictors of PTSD symptoms—and change to symptoms—across time.

Author disclosures

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