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Changes in trauma-potentiated startle with treatment of posttraumatic stress disorder in combat Veterans☆

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ABSTRACT

Emotional Processing Theory proposes that habituation to trauma-related stimuli is an essential component of PTSD treatment. However, the mechanisms underlying treatment-related habituation are not well understood. We examined one psychophysiological measure that holds potential for elucidating the biological processes involved in treatment response: trauma-potentiated startle response. Seventeen OEF/OIF combat Veterans participated in the study and completed three assessments using a trauma-potentiated startle paradigm over PTSD treatment. Results revealed different patterns of trauma-potentiated startle across treatment for responders and nonresponders, but no differences in within task habituation. Responders showed an increase followed by a decrease in trauma-potentiated startle, whereas nonresponders showed a relatively flat response profile. Results suggested that PTSD patients who engage with emotional content as demonstrated by greater startle reactivity may be more likely to respond to PTSD treatment. Furthermore, trauma-potentiated startle shows promise as an objective measure of psychophysiological responses involved in PTSD recovery.

Clinical practice guidelines for posttraumatic stress disorder (PTSD) strongly support prolonged exposure (PE) therapy as a first-line treatment (IOM, 2007; VA/DOD, 2010). Several PTSD treatment meta-analyses support the efficacy of exposure-based psychotherapy for producing clinically meaningful reductions in PTSD symptoms and improvement in mental health (Bradley, Greene, Russ, Dutra, & Westen, 2005; Sherman, 1998; Steenkamp & Litz, 2013). Exposure-based psychotherapy for PTSD has also been shown to improve patients' interpersonal and emotion regulation skills (Cloitre, Koenen, Cohen, & Han, 2002), as well as to reduce comorbid guilt, anger, depression, and anxiety (Cahill, Rauch, Hembree, & Foa, 2003; Foa et al., 2005; Rauch et al., 2009; Sherman, 1998) Furthermore, patients who received PE have demonstrated improved social functioning and reduced negative health perceptions (Rauch et al., 2009). Biological changes have also been demonstrated in patients with PTSD who participated in exposure-based psychotherapy (Gerardi, Cukor, Difede, Rizzo, & Rothbaum, 2010). As such, exposure-based psychotherapy for PTSD appears to result in meaningful changes across multiple symptom and biological domains.

Whereas Emotional Processing Theory (Foa & Kozak, 1986) proposes that PE engages patients in exposure processes that promote habituation to trauma-related stimuli, and potentially extinction of fear conditioned responses (Norrholm & Jovanovic, 2010), the mechanisms involved in this process are not well understood. Few studies have examined whether PE actually achieves the predicted extinction and habituation processes (Jaycox, Foa, & Morral, 1998; Van Minnen & Hagenaars, 2002). Even fewer studies have examined whether the magnitude of change in these processes is related to treatment response (Rauch, Foa, Furr, & Filip, 2004). To date, studies of habituation/extinction processes in PE have focused on patients' ratings of their subjective distress (Subjective Units of Distress; SUDS). However, psychophysiological measures can provide

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additional, and more objective, insight into habituation/extinction processes and related underlying biological changes not easily assessed via self-report indices.

The acoustic startle response is manifested in the reflexive contraction of skeletal, facial, and neck muscles in humans and animals (Koch, 1999; Lang, Bradley, & Cuthbert, 1990). Acoustic startle of the *orbicularis oculi* muscles that results in reflexive eyelid closure has been extensively studied using auditory probes, (e.g., 108 dB white noise; see Norrholm et al., 2011). The acoustic startle response is well-suited for studying the acquisition and extinction of fear due to its direct links to the amygdala (Davis, Walker, Miles, & Grillon, 2010; Walker, Toufexis, & Davis, 2003) and sympathetic nervous system, which helps prepare an organism for fight or flight (Koch, 1999). Furthermore, patient report of exaggerated startle response is considered a hallmark symptom of PTSD (APA, 2013) thought to exemplify the hyperarousal experienced by and observed among patients. Researchers have offered different explanations for exaggerated startle in PTSD (Pole, 2007), and it remains unclear whether it represents a premorbid vulnerability or reflects a development or psychopathological process resulting from exposure to one or more traumatic events.

Fear-potentiated startle (FPS) paradigms examine relative increases in the startle reflex during exposure to a cue associated with an aversive stimulus (e.g., shock), as compared with startle responses elicited to neutral cues. Previous studies of FPS in PTSD patients have shown increased startle to anxiety-provoking aspects of the experimental context (Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1998; Grillon et al., 2009; Morgan, Grillon, Southwick, Davis, & Charney, 1995) as well as a heightened response during fear expression (i.e., "fear load" during the acquisition and extinction of fear-potentiated startle in the presence of reinforced conditioned stimuli (Norrholm et al., 2011, 2013)). However, research on PTSD patients' startle responses to cues that are specifically related to their traumas is limited. To better understand psychophysiological responses to trauma memories and related stimuli in this population, it may be informative to examine startle responses in the presence of trauma-relevant cues. Whereas the trauma cues may not represent the exact nature of the specific trauma experienced by the individual, it is plausible that general combat-related stimuli could elicit substantial anxiety and arousal among patients whose traumas are combat-related (Maren, Phan, & Liberzon, 2013). Furthermore, understanding how startle responses among patients with PTSD change over the course of PTSD treatment is not well understood.

Recent research suggests that exaggerated startle in patients with PTSD can be modified with treatment. One study found that female assault survivors with PTSD who responded to Cognitive Processing Therapy (CPT) showed a significant reduction in their acoustic startle response at post-treatment compared to treatment nonresponders (Griffin, Resick, & Galovski, 2012). Despite these encouraging results, replication with larger samples is necessary to confirm the reliability of this effect.

In the present study, we investigated whether PTSD treatment would promote reduced hyperarousal associated with sympathetic nervous system arousal, as evidenced by attenuation in trauma-relevant, cue-potentiated, acoustic startle responses among combat Veterans. To this end, we compared acoustic startle responses in the context of trauma-relevant cues among PTSD treatment responders versus nonresponders in Veterans from Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF, respectively). Responders were defined as Veterans who evidenced a 50% reduction on the Clinician-Administered PTSD Scale scores, (CAPS; Blake, Weathers, Nagy, & Kaloupek, 1995) from pre to post-treatment, while nonresponders had less than 50% symptom reduction. This conservative measure of treatment response was used in order to increase the likelihood to detect differences between the groups. The present study was part of a broader study that examined the efficacy of PE compared to a control treatment (Present Centered Therapy; PCT) for OEF/OIF Veterans with PTSD. We expected treatment responders to show larger reductions in acoustic startle potentiated by trauma-related stimuli, across the course of the treatment, compared to treatment nonresponders.

1. Methods

1.1. Participants

Thirty-six OEF/OIF Veterans with PTSD of at least three months duration were recruited from an outpatient PTSD clinic within the VA Ann Arbor Healthcare System (VAAAHS). A standard intake evaluation using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and the CAPS was used to determine diagnostic eligibility for the study. PTSD clinic providers with specialty mental health training at the Master's degree level or higher completed all assessments. Individuals were excluded from participating if they had: (1) elevated risk of self-harm requiring immediate, focused intervention; (2) unmanaged psychosis or bipolar disorder; (3) alcohol or substance dependence in the past 3 months; (4) employment requiring night-shifts; (5) changes to psychoactive medications in the past 4 weeks; or (6) medications that may alter HPA axis indices. Eligible Veterans who consented to participate were randomly assigned to receive up to twelve, 80-min sessions of PE or PCT. The protocol was approved by the VA Ann Arbor Healthcare System Human Subjects Committee.

Among 36 Veterans who were eligible for the study, 26 completed treatment. To be included in the final analysis, participants had to have complete data for all three assessments (i.e., pre, mid, post). Among the 26 participants who completed the treatment, four did not complete all three assessments and five had startle data from one or more of the assessments that could not be scored. The final sample consisted of 17 participants (16 male) with an age range of 24–45 years (M = 32.82, SD = 7). Seven (41%) were married, two (12%) remarried, four (23.5%) divorced and four (23.5%) never married. One (6%) identified as Asian, 5 (28%) as black, and 11 (64%) as white. Eight participants received PE, and 9 received PCT.

1.2. Procedure

Participants completed major assessments at pre-, mid-, and post-treatment. Assessments lasted approximately 3 h and consisted of an interview, symptom-based questionnaires, psychophysiological assessment, and salivary cortisol collection (Rauch, King, Rothbaum, Smith, & Liberzon, 2011). The startle paradigm was presented as part of a longer psychophysiological assessment protocol. EMG was used to index the startle eyeblink reflex using two 5-mm Ag/AgCl electrodes filled with electrolyte gel placed on the right *orbicularis oculi* muscle. Electrode placement was consistent with published startle guidelines (Blumenthal et al., 2005); one was placed 1 cm below the pupil, another was placed 1 cm below the lateral canthus, and the ground was placed over the mastoid process.

Participants were seated approximately 36″ in front of a 19″ LCD computer monitor where they viewed study stimuli. The visual and auditory features of the sequences were presented on the computer screen via SuperLab 4.0 for Windows (Cedrus Corp., San Pedro, CA). Startle eyeblink responses were acquired using the EMG 100c module of the BIOPAC MP150 psychophysiological recording system (Biopac Systems, Inc., Camino Goleta, CA) with Acqknowledge data collection software version 4.2.0 for Windows (1995–2011). Startle eyeblink data were sampled at 1000 kHz, amplified by a