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Baseline psychophysiological and cortisol reactivity as a predictor of PTSD treatment outcome in virtual reality exposure therapy

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ABSTRACT

Baseline cue-dependent physiological reactivity may serve as an objective measure of posttraumatic stress disorder (PTSD) symptoms. Additionally, prior animal model and psychological studies would suggest that subjects with greatest symptoms at baseline may have the greatest violation of expectancy to danger when undergoing exposure based psychotherapy; thus treatment approaches which enhanced the learning under these conditions would be optimal for those with maximal baseline cue-dependent reactivity. However methods to study this hypothesis objectively are lacking. Virtual reality (VR) methodologies have been successfully employed as an enhanced form of imaginal prolonged exposure therapy for the treatment of PTSD.

Our goal was to examine the predictive nature of initial psychophysiological (e.g., startle, skin conductance, heart rate) and stress hormone responses (e.g., cortisol) during presentation of VR-based combat-related stimuli on PTSD treatment outcome. Combat veterans with PTSD underwent 6 weeks of VR exposure therapy combined with either D-cycloserine (DCS), alprazolam (ALP), or placebo (PBO). In the DCS group, startle response to VR scenes prior to initiation of treatment accounted for 76% of the variance in CAPS change scores, $p < 0.001$, in that higher responses predicted greater changes in symptom severity over time. Additionally, baseline cortisol reactivity was inversely associated with treatment response in the ALP group, $p = 0.04$. We propose that baseline cue-activated physiological measures will be sensitive to predicting patients' level of response to exposure therapy, in particular in the presence of enhancement (e.g., DCS).

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1. Introduction

Clinical and empirical evidence strongly supports the use of prolonged exposure therapy as first-line intervention for reducing posttraumatic stress disorder (PTSD) symptom severity and for improving overall mental health (Bradley, Greene, Russ, Dutra, & Westen, 2005; DoD/VA PTSD Working Group, 2010; Institute of Medicine, 2007; Sherman, 1998; Steenkamp & Litz, 2013). According to the principles of Emotional Processing Theory (Foa & Kozak, 1986), prolonged exposure fosters a level of patient engagement that facilitates habituation to trauma-related cues and promotes the extinction of conditioned responses to fearful cues. Virtual reality methodologies have been successfully employed as an enhanced form of imaginal prolonged exposure therapy for the treatment of stressor-, trauma-, and anxiety-related disorders such as PTSD for more than a decade (Difede et al., 2007; Rizzo et al., 2010; Rothbaum, Hodges, Ready, Graap, & Alarcon, 2001). Virtual reality exposure (VRE) therapy is believed to foster engagement and elevate patient arousal (Robison-Andrew et al., 2014) through

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the inclusion of computer-generated simulations of trauma-related stimuli that span sensory modalities, including the ambient sights, sounds, smells, and tactile stimuli present during a traumatic event. In addition to its clinical impact, VR technology has also been used successfully to elicit robust fear reactions in patients with anxiety disorders (Diemer, Muhlberger, Pauli, & Zwanzger, 2014).

To date, the efficacy of prolonged exposure therapies, including those that are VR-based, has been largely indexed through the use of clinician-administered or self-report measures of patient symptom severity or within-session distress. More recently, psychophysiological measures have been employed as complementary assessment tools for use in traumatized populations presenting with PTSD symptoms (Costanzo et al., 2014; Griffin, Resick, & Galovski, 2012; Rabe, Dorfel, Zollner, Maercker, & Karl, 2006; Rhudy et al., 2010; Robison-Andrew et al., 2014; Rothbaum et al., 2014; Roy et al., 2013). The addition of psychophysiological indices, such as heart rate (HR), skin conductance (SC) and electromyography (EMG) responses to trauma-related cues can provide the potential prediction of treatment outcome, objective assessments of treatment outcome, and evidence of the underlying biological changes that accompany successful PTSD treatment.

Heightened psychophysiological reactivity in response to trauma cues has been observed in PTSD patients for several decades. More specifically, increased HR, SC, and startle EMG responses have repeatedly been found in chronic PTSD (Blanchard, Kolb, Gerardi, Ryan, & Pallmeyer, 1986; Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Buckley & Kaloupek, 2001; McTeague et al., 2010; Orr, Metzger, & Pitman, 2002), and have been a predictor of PTSD in acutely traumatized populations (Orr et al., 2012; Roy et al., 2013; Shalev et al., 2000). Pre- and post-treatment data suggest that exposure therapy reduces heart rate response to trauma related stimuli (Rabe et al., 2006). Similarly, EMG, HR, and SC in response to loud tones decreases after cognitive behavior therapy in those who show a positive treatment outcome (Griffin et al., 2012).

Exposure therapists have repeatedly shown that increased arousal is associated with treatment response. In fact, it is a core tenet of the theoretical underpinnings for exposure therapy in PTSD (Foa & Kozak, 1986). Many therapeutic resources and clinical supervision efforts are focused on better enabling clinicians to increase the emotional and physiological responses of clients/patients early in the exposure therapy process (Foa, 2011). Although the theory is widely supported as evidenced by clinically significant effect sizes for exposure therapy in PTSD, investigations of the specific empirical links between psychophysiological indices of patient engagement in exposure therapy and positive treatment outcomes have only recently been initiated (Price et al., 2015). There is evidence from the literature supporting a link between biological reactivity pre-treatment with positive (Foa, Riggs, Massie, & Yarczower, 1995; Rauch et al., 2015) and negative (Yehuda et al., 2009) treatment outcomes.

More recent investigations have explored acoustic startle responses to trauma-related stimuli (termed trauma-potentiated startle) within the presentation of a virtual reality environment (Costanzo et al., 2014; Robison-Andrew et al., 2014; Roy et al., 2013). Robison-Andrew et al. (2014) reported that combat veterans who responded well to prolonged exposure therapy (defined as a >50% reduction in their CAPS score over the course of treatment) showed an initial increase in trauma-potentiated startle followed by a significant decrease in startle responses to trauma-related cues compared to veterans who did not respond to treatment. As in our aforementioned previous work, we examined participants' startle response to cues specifically drawn from their collective traumatic experiences. Whereas the trauma-relevant cues depicted in the VR environment may not represent the exact nature of the index trauma experienced by the participant, it remains plausible that general combat-related stimuli produce robust arousal and psychophysiological reactivity in traumatized Veteran samples. While these physiological markers show promise as objective assessments of treatment efficacy, their predictive value has not been well studied.

Prolonged exposure therapy represents one of the most effective treatments for PTSD (group, 2010) and can be characterized as a clinical homolog of laboratory fear extinction learning (Rothbaum & Davis, 2003). D-cycloserine (DCS), an N-methyl-d-aspartate (NMDA) glutamate receptor partial agonist (Dravid et al., 2010), has improved the short- and long-term efficacy of exposure therapy when administered as a single dose just prior to treatment for several anxiety disorders (Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007; Kushner et al., 2007; Otto et al., 2010; Ressler et al., 2004; Rothbaum et al., 2014; Wilhelm et al., 2008). However, DCS has also been shown to be ineffective under specific conditions with some patient populations (e.g., cognitive behavioral therapy for social phobia Hofmann et al., 2013); for review see (Rodrigues et al., 2014). Nevertheless, acute administration of DCS has been shown to be effective at facilitating emotional learning in humans (e.g., behavioral exposure therapy Rothbaum & Davis, 2003), and fear extinction in rodent models of fear- and anxiety-based psychopathologies (e.g., Ledgerwood, Richardson, & Cranney, 2003, 2004, 2005; Richardson, Ledgerwood, & Cranney, 2004; Walker, Ressler, Lu, & Davis, 2002). Benzodiazepines, which increase g-aminobutyric acid (GABA) activity, have been used clinically to treat PTSD (Lund, Bernardy, Vaughan-Sarrazin, Alexander, & Friedman, 2013) but their effect on exposure therapies for PTSD remains largely unknown. There is evidence that the use of benzodiazepines is contraindicated for exposure therapy due to the potential to reduce engagement and arousal resulting in a lack of improvement, and, in turn, increase the likelihood of patient dropout (van Minnen, Arntz, & Keijsers, 2002; van Minnen, Harned, Zoellner, & Mills, 2012).

In addition to psychophysiological responses, alterations in stress hormones have long been a target of investigation in PTSD (Heim et al., 2000). However, findings on baseline cortisol levels have been mixed, and a recent meta-analysis based on a large number of patients and controls concluded that there are no consistent differences between PTSD and controls (Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007). A much more promising approach is measuring cortisol reactivity to a stress challenge. As part of the hypothalamic-pituitary-adrenal axis (HPA)-mediated stress hormone cascade, glucocorticoid receptors (GR) in the hypothalamus regulate cortisol release and higher GR sensitivity has been proposed as a consistent alteration in PTSD (Yehuda, 2009). To our knowledge, few studies have conducted a randomized clinical trial for PTSD with cortisol reactivity as an outcome measure. For example, one study examined treatment effects on cortisol response to a cognitive challenge and found that 12-month open label SSRI treatment reduced reactivity in women with PTSD (Vermetten et al., 2006).

In addition to the above background, it is hypothesized that subjects with the greatest within-session extinction will respond most robustly to D-cycloserine enhancement of exposure therapy (Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007; Hofmann et al., 2006; Ressler et al., 2004). How might we predict, prior to treatment, which subjects may have the most robust within-session extinction learning? Animal models have begun to suggest that prediction error may be required to explain neural plasticity in extinction learning (Delamater & Westbrook, 2014). Historically, learning theory suggests that extinction is enhanced by increased attentional salience of the conditional stimulus (Mackintosh, 1965, 1975; Pearce & Hall, 1980). Furthermore, a