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Changes in trauma-potentiated startle, skin conductance, and heart rate within prolonged exposure therapy for PTSD in high and low treatment responders

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ABSTRACT

While exposure-based psychotherapy is recommended as a first-line treatment for posttraumatic stress disorder (PTSD) given strong evidence for its effectiveness, some patients fail to receive full benefit. Psychophysiological data may be important complementary indices for investigating variability in treatment response and changes over the course of treatment. The focus of the present investigation was to examine change in psychophysiological indices pre- to post-treatment and to investigate if changes differed for high versus low PTSD treatment responders. Participants included veterans with primary PTSD diagnoses who received a two-week intensive prolonged exposure (PE) treatment. Psychophysiological assessment included trauma-potentiated startle, heart rate, and skin conductance recordings during presentation of three standard virtual reality (VR)-based, trauma-relevant scenes presented through a head mounted display. Results indicate that 48.6% were classified as high treatment responders (≥50% reduction in PCL-5 from baseline). Trauma-potentiated startle was observed in all patients at pre-treatment, $F = 13.58$, $p < .001$, in that startle magnitude was increased during VR stimuli relative to baseline regardless of responder status. However, in high treatment responders, there was an interaction of VR with time, $F = 14.10$, $p = .001$; VR scenes did not potentiate startle post-treatment. Specifically, high treatment responders were less reactive to trauma stimuli following PE treatment. There was no effect of time in the low responder group. Heart rate reactivity data revealed a significant main effect of treatment, $F = 45.7$, $p = .035$, but no significant interaction with responder status. Skin conductance reactivity did not significantly change from pre to post-treatment. These results suggest that trauma-potentiated startle may represent an objective marker of fear- and anxiety-related symptom reduction that is sensitive to both traditional outpatient as well as intensive treatment approaches.

1. Introduction

Prolonged exposure therapy (PE) is widely considered a first-line treatment of posttraumatic stress disorder (PTSD; American Psychological Association (APA, 2017; VA/DOD, 2010) due to substantial evidence of self-reported and clinician-rated symptom reduction across dozens of clinical trials (Cusack et al., 2016; Lee et al., 2016; Watts et al., 2013). Despite reports of large treatment effect sizes, accumulating evidence suggests that approximately one-third to one-half of patients who start PE do not demonstrate clinically meaningful symptom change (Steenkamp, Litz, Hoge, & Marmar, 2015). While some of this is due to patients not completing treatment or not fully engaging the exposures while in treatment, other factors are also likely at play. Further research is needed to identify predictors and mechanisms of change to better understand variability in treatment response (Van Minnen, Arntz, & Keijsers, 2002) and improve outcomes for suboptimal responders. Identification of clinical features that robustly relate to treatment response has proven difficult to date.

One strategy to improve PE is to identify the mechanisms by which it works and then, using this knowledge, re-organize or augment PE to better target the underlying mechanism(s) (Kazdin, 2007; Rauch & Liberzon, 2017). Mechanism research benefits from conceptualizing psychopathology in terms of transdiagnostic systems of functioning. In recent years, the National Institute of Mental Health's Research Domain

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Criteria (RDoC) project has focused research on dimensions of functioning at various units of analyses (from genes to neural circuits to observable behavior; Cuthbert, 2014). Potentiation of the acoustic startle reflex is identified as a psychophysiological unit of analysis within the RDoC domain of Negative Valence Systems. However, many clinical trials exclusively rely upon subjective reports of distress and symptom severity and, as such, limit our understanding of treatment response from a psychophysiological perspective. According to Emotional Processing Theory (Foa & Kozak, 1986), exposure requires emotional engagement and appropriate activation of fear networks to facilitate extinction of conditioned fear. As such, increased arousal and emotional engagement are important targets of this treatment, suggesting that psychophysiological data may provide an important and objective assessment of processes relevant to treatment outcome (Norrholm et al., 2016). While emotional engagement and subsequent habituation to trauma-relevant stimuli and extinction of conditioned fear are proposed as mechanisms of PE, few studies have investigated how these processes relate to treatment response, and most have focused on subjective ratings of distress during PE exposures (i.e., Subjective Units of Distress or SUDS; Wolpe, 1958). Psychophysiological measures can provide an objective assessment of arousal and emotional engagement. Additionally, previous research suggests that psychophysiological data and subjective ratings often demonstrate discordance (e.g., Maples-Keller et al., 2017) indicating that psychophysiological data may provide unique information regarding treatment mechanisms and outcome.

To that end, the present study investigates psychophysiological indices, including trauma-potentiated startle, heart rate reactivity, and skin conductance response across PE treatment for PTSD. Trauma-potentiated startle is assessed via electromyographic recordings of the *orbicularis oculi* muscle that mediates eyeblink responses to acoustic stimuli and has been associated with treatment outcome in cognitive behavioral therapy (Karl, Malta, Alexander, & Blanchard, 2004), virtual reality-based exposure therapy (Norrholm et al., 2016), and PE and present centered therapy (Robison-Andrew et al., 2014). In a small trial, significant reduction in startle responses was seen for PTSD patients who received cognitive behavioral therapy or supportive therapy compared to wait-list controls (Karl et al., 2004). Two recent studies have shown that the effect of PE is related to changes in trauma-potentiated startle. First, Rothbaum et al. (2014) assessed trauma-potentiated startle pre- and post-treatment in combat veterans receiving virtual reality PE for PTSD who were assigned to three medication conditions: d-cycloserine, alprazolam, or placebo. Those receiving d-cycloserine demonstrated a significant change in startle response from baseline to post-treatment. In the same sample, greater trauma potentiated startle prior to treatment predicted better response to treatment across groups (Norrholm et al., 2016). Second, Robison-Andrew et al. (2014) assessed trauma-potentiated startle in a sample of combat Veterans assigned to either PE or present-centered therapy. High treatment responders demonstrated increasing trauma-potentiated startle from pre- to mid-treatment and decreasing trauma-potentiated startle from mid- to post-treatment. Patients with smaller treatment gains demonstrated a flat pattern with no significant changes to trauma-potentiated startle. Change in heart rate reactivity across cognitive behavioral treatment for PTSD has been shown to relate to treatment outcome (Rabe, Dörfel, Zöllner, Maercker, & Karl, 2006). In a sample of Vietnam veterans with chronic PTSD in imaginal flooding therapy, heart rate activation during the first flooding session was associated with reduction in intrusive memories over the course of treatment (Pitman et al., 1996). PE has also shown decreased heart rate and skin conductance reactivity to a script-driven imagery task across treatment (Wangelin & Tuerk, 2015). Further, individuals with greater trauma-cued HR reactivity at baseline showed greater symptom reductions (Wangelin & Tuerk, 2015).

Psychophysiological data may be important sources of complementary, objective indices for investigating variability in treatment response and changes over the course of treatment and previous research has not yet characterized these processes. Understanding biological mechanisms of treatment response can help elucidate why some individuals respond more slowly and/or fail to receive full benefit. It may also inform efforts to improve treatment efficacy and personalize medicine. In the present study, we investigate the change in trauma-potentiated startle, heart rate reactivity, and skin conductance response from pre- to post-treatment and investigate if changes differed for high versus low treatment responders in a sample of military veterans receiving intensive PE treatment for PTSD. Consistent with previous research, it is hypothesized that high treatment responders will demonstrate increased startle at baseline and greater reductions across the course of treatment (Norrholm et al., 2016; Robison-Andrew et al., 2014; Rothbaum et al., 2014).

2. Method

2.1. Participants

Participants in the present study were 189 post-9/11 veterans or military servicemembers with PTSD who were referred for a two-week intensive outpatient program (IOP) and who provided consent to participate in research. Useable psychophysiological data were available for 103 participants for heart rate, 79 for skin conductance, and 68 for startle response. Participants with and without psychophysiological data were compared with regard to demographics, including gender and race. No significant differences emerged across pre and post-treatment startle, skin conductance, or heart rate for gender or race. Participants with and without physiological data were compared with regard to clinical measures, including PTSD and depression symptoms. Participants with and without pre-treatment heart rate, post-treatment heart rate, pre-treatment skin conductance, and post-treatment skin conductance data did not significantly differ with regard to baseline PTSD or depression symptoms. Participants without startle data did differ on baseline PTSD indicating higher pre-treatment symptoms ($t = 2.91$, $p < .01$) but did not differ with regard to baseline depression symptoms. Variability in the number of available cases for each psychophysiological modality was due to unforeseen hardware and/or software malfunctions, errors during data collection, or low response rates. Referrals were from multiple sources including the Wounded Warrior Project, federal and private mental health providers, and self-referral. Participants were 69.2% male and 30.8% female, ranged in age from 24 to 70 ($M = 42.30$; $SD = 9.68$), and were ethnically diverse (Caucasian: 56.2%, Black: 32.3%, Hispanic: 13.4%). All patients underwent an intake process involving psychosocial interview, structured interview of PTSD symptoms with the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013), assessment of comorbid diagnoses with the Mini International Neuropsychiatric Interview (Sheehan et al., 2015), and review of medical records. All participants were diagnosed with primary PTSD. Exclusionary criteria for entrance into treatment program include unmanaged psychosis or bipolar disorder, severe alcohol or substance abuse or dependence, and acute suicidality requiring a higher level of care.

2.2. Measures

2.2.1. Clinician-administered PTSD scale for DSM-5 (CAPS-5)

The CAPS-5 (Weathers et al., 2013) is a structured clinician-administered measure that assesses the presence and severity of PTSD per DSM-5 criteria. All the DSM-5 symptoms of PTSD are assessed and rated on a scale from 0 (Absent) to 4 (Extremely Severe), with clear anchors provided to clinicians to assist with accurate ratings. The CAPS-5 has strong interrater reliability ($ICC = .91$), internal consistency ($\alpha = .88$), test-retest reliability ($ICC = .78$), and convergent validity with the PCL-5 ($r = .66$) and the previous version of the CAPS, the CAPS-IV ($r = .83$) (Weathers et al., 2018). In the present study, the CAPS-5 was

administered by postdoctoral or licensed clinical psychologists and had adequate internal consistency (α = .77).

2.2.2. PTSD checklist for DSM-5 (PCL-5)

The PCL-5 (Weathers et al., 2013) is a 20-item self-report measure of DSM-5 PTSD symptoms. Scores on the PCL range from 0 to 80, with higher scores indicating higher symptom severity, and a cutoff of 33 indicating clinical levels of PTSD symptoms (Weathers et al., 2013). The PCL-5 is psychometrically sound, with strong internal consistency (α = .94), test-retest reliability, and convergent and discriminant validity (Blevins, Weathers, Davis, Witte, & Domino, 2015). In the present study, the PCL-5 demonstrated strong internal consistency (α = .94).

2.2.3. Patient health questionnaire-9 (PHQ-9)

The PHQ-9 (Kroenke, Spitzer, & Williams, 2001) is a 9-item self-report measure of depressive symptoms. The PHQ-9 screens for major depression, with a score of 10 or above indicative of a possible major depressive episode, and it provides a measure of severity of these symptoms. The PHQ-9 has adequate internal consistency (α = .74), strong convergent and discriminant validity, and good responsiveness to change (Titov et al., 2011). In the present study, the PHQ-9 had good internal consistency (α = .86).

2.3. Treatment

All participants in the present study underwent a two-week IOP for PTSD at Emory Healthcare Veterans Program (EHVP) that specializes in trauma-focused treatment for veterans and military servicemembers (Yasinski, Sherrill, Maples-Keller, Rauch, & Rothbaum, 2017). While exposure-based therapy is effective and recommended as a first-line treatment for PTSD (American Psychological Association, 2017; VA/DOD, 2010), drop-out rates are unfortunately high, particularly among recent veterans and service members (Kehle-Forbes, Meis, Spoont, & Polusny, 2016). Empirical evidence suggests that fewer days between sessions is associated with improved outcomes in PTSD treatment (Gutner, Suvak, Sloan, & Resick, 2016). Data for depression and anxiety disorder treatment suggest that massed treatments may be associated with faster rates of clinical improvement (Cuijpers, Huibers, Ebert, Koole, & Andersson, 2013; Storch et al., 2008) and a previous case study has demonstrated good outcome for this two week massed PE approach (Blount, Cigrang, Foa, Ford, & Peterson, 2014). EHVP IOP aims to improve treatment engagement, decrease avoidance, and decrease drop-out rates. Results from EHVP IOP indicate large improvements in PTSD and depression symptoms comparable to those found in standard outpatient PE, and drop-out is notably lower (4% versus typical rates of 30–45%; Yasinski et al., 2017). Patient satisfaction is also high; 95% of patient report overall satisfaction with the program and 84% report that treatment improved their clinical concerns (Yasinski et al., 2017).

EHVP utilizes a mixed group and individual approach adapted from Prolonged Exposure (PE) therapy (Foa, Hembree, & Rothbaum, 2007; Smith et al., 2015), involving daily 90-minute individual imaginal exposure sessions (i.e., repeated revisiting of trauma memories) and daily 120-minute group *in vivo* exposure sessions (i.e., repeatedly confronting previously avoided trauma-related stimuli). During IOP treatment, participants were assigned daily out-of-session practice exercises, involving *in vivo* exposures and listening to audio recordings of imaginal sessions. Imaginal and in-vivo exposure exercises are focused on facilitating extinction of fear responses via corrective learning and generating adaptive cognitions related to self, world, and others. In order to increase positive coping concurrent with PTSD symptom reduction, participants received multiple additional services, including wellness services (yoga, acupuncture), enhanced case management, recreational activities, family treatment, medication management, and sleep intervention. For a more extensive review of EHVP IOP treatment procedures, see Yasinski et al. (2017).

2.4. Psychophysiological reactivity to trauma-related VR-based cues

Participants underwent a psychophysiological assessment procedure at pre-treatment (first day of the IOP, prior to any individual therapy sessions) and post-treatment (last day of the IOP, following all individual therapy sessions). This assessment included measures of acoustic startle response, heart rate reactivity, and skin conductance response. Psychophysiological data were collected using the Biopac M150 Data Acquisition System (Biopac Systems, Inc., Goleta, CA) similar to previously published methods from this group (Norrholm et al., 2016). Scenes were displayed with a head mounted eMagin Z800 3D Visor. Participants wore headphones that administered audio stimuli binaurally.

2.4.1. Trauma-potentiated startle

Acoustic startle response was assessed while participants viewed three virtual reality (VR) trauma-relevant scenes presented through a head mounted display (Rothbaum et al., 2014). This procedure was conducted at pre- and post-treatment; participants viewed a set of three standardized VR clips involving scenes commonly experienced by OEF/OIF military servicemembers. Each VR scene was two minutes separated by presentation of a 30 s blank blue screen. The scenes involved taking the perspective of a servicemember encountering explosions and other hazards while sitting at a gun turret, sitting inside the cabin of a Humvee, and walking through an Iraqi marketplace. Thirty-second neutral blank blue screens (termed “Blue Square” as a control stimulus) were shown between each VR scene. Five startle probes were delivered during each of the three VR scenes and the neutral blue squares for a total of 25 startle probes were administered. The startle trials were averaged across scenes and the two neural blocks.

Acoustic white noise bursts of 40 ms at 108 dB were presented at times the ambient noise of the VR environment was absent or minimal, and EMG startle response (i.e., peak amplitude 20–200 ms following onset of the acoustic burst) was assessed in response. EMG activity of the *orbicularis oculi* muscle was measured using two 5-mm Ag/AgCl electrodes, with one electrode placed 1 cm below the pupil and one electrode placed 1 cm below the lateral canthus of the right eye. EMG responses were sampled at 1000 Hz, amplified, and filtered using Biopac before export to Mindware software (Mindware Technologies, Gahanna, OH) for further analysis. The EMG signal was acquired with a gain of 5000, and according to guidelines for human startle measurement (Blumenthal et al., 2005), was bandpass filtered at 28 and 500 Hz.

2.4.2. Heart rate

During the psychophysiological reactivity paradigm, ECG data were collected with two 5-mm Ag/AgCl electrodes placed on the upper right torso and left wrist using the ECG module of the Biopac MP150. Heart rate was based on R-peaks detected from ECG; data were analyzed as average HR in beats per minute during 30-s intervals of the VR and neutral blank blue screen segments of the startle paradigm. The 30-s bins during VR were compared to the 30-s neutral blue screen.

2.4.3. Skin conductance level

Skin conductance level (SCL) was measured concurrently with the other psychophysiological indices during the VR-based reactivity task. Two 5-mm Ag/AgCl electrodes were placed on the middle fingers of the non-dominant hand and collected using the galvanic skin response (GSR) module of the Biopac MP150. Data were analyzed as average SCL during 30-s intervals of the VR and blank screen segments of the psychophysiological reactivity paradigm.

For each of the psychophysiological indices measured, signal quality was confirmed according to previously published methods (Weingast, Haas, & Norrholm, 2018). Artifactual data or missing data were excluded from analyses where necessary.

Table 1
Baseline self-reported and clinician-rated PTSD symptoms and self-reported depression symptoms in overall sample and high and low responder groups.

	Low responders	High responders	t	p	Total
Pre-treatment					
PCL-5	51.56 (15.88)	48.98 (15.11)	1.09	.28	49.97 (15.58)
CAPS-5 severity	35.40 (12.46)	34.63 (11.89)	.41	.68	35.31 (11.97)
CAPS-5 symptom count	12.82 (5.17)	12.81 (5.04)	.01	.99	12.98 (5.02)
PHQ-9	16.89 (5.73)	15.94 (5.29)	1.12	.26	16.42 (5.53)
Post-treatment					
PCL-5	40.77 (16.77)	12.30 (8.27)	14.88	> .01	27.60 (19.60)
PHQ-9	12.81 (6.19)	5.83 (4.45)	9.05	> .01	9.60 (6.40)

Note. PCL-5 = PTSD Checklist for DSM-5; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; PHQ-9 = Patient Health Questionnaire-9.

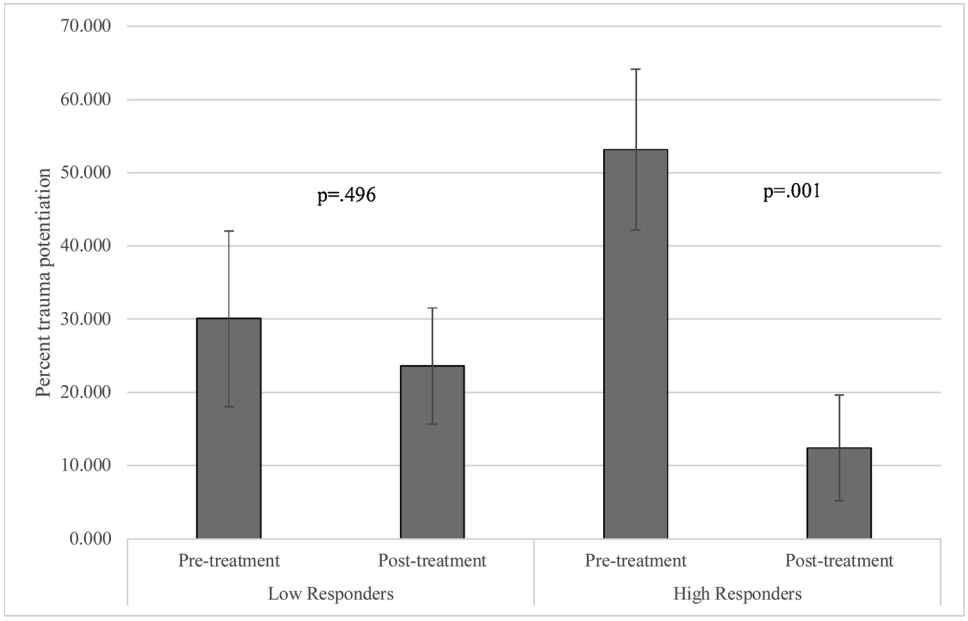

Fig. 1. Percent trauma potentiation at pre and post-treatment in high and low responders.
Percent trauma potentiated startle (VR startle-blue square startle/blue square startle*100) assessed and pre and post-treatment. Results indicate a significant interaction with time and responder group (F = 14.09, p = .001) indicating that the high responder group demonstrate a significant decrease in trauma potentiated startle from pre to post-treatment. There was no significant interaction for low-responders (F = .47, p = .496) indicating there low-responders did not demonstrate a significant decrease from pre to post-treatment.

3. Results

3.1. High versus low treatment responders

High and low responders were defined based on whether or not they demonstrated a 50% or greater reduction in PCL-5 symptoms from baseline to posttreatment consistent with Robison-Andrew et al. (2014). Results indicate that 48.6% were classified as high treatment responders. Differences in baseline symptoms for responder groups were investigated; total sample descriptive and results from group comparisons are presented in Table 1. High and low treatment responders did not differ on baseline PCL-5 symptom severity, CAPS-5 symptom severity, CAPS-5 symptom count, or PHQ-9 symptom severity (p = .28, .68, .99, and .26, respectively). Post-treatment descriptive data for PCL-5 and PHQ-9 for high and low responders and overall sample are also provided in Table 1. As expected, the high responder group demonstrated significantly lower levels of PTSD and depression symptoms compared to the low responder group (t = 14.88 and 9.05, respectively).

3.2. Trauma potentiated startle

To examine differences in trauma-potentiated startle following treatment in high and low responders, we conducted a repeated measures ANOVA with group (high and low responder) as the between-subjects factor, and time (pre- and post-treatment assessment) and stimulus (neutral blue square versus trauma-relevant cues) as within-subject factors. Pre- and post- FPS data were available for 68 participants. There was a main effect of stimulus indicating that trauma potentiated startle was observed in all patients regardless of responder status, in that startle magnitude was increased during VR stimuli relative to blue square (F = 13.53, p < .001). There was a significant three-way interaction of group, time, and stimulus (F = 6.875, p = .01). As such, degree of trauma potentiation in high and low responders across treatment was investigated.

Percent trauma potentiation was calculated to derive an index of startle reactivity that accounts for participant variability of baseline startle using the formula: (([startle magnitude to the VR-related cues] – [startle magnitude to the neutral blue square cue])/[startle magnitude to the neutral blue square cue]) × 100. A repeated measures ANOVA with group (high and low responders) as the between-subjects factors and pre-treatment percent trauma potentiation and post-treatment percent trauma potentiation as the within-subjects factors identified a main effect of treatment (F = 10.36, p = .002) and a significant interaction between treatment and responder group (F = 5.465, p = .023).

The effect of time in each of the two responder groups was subsequently investigated. An ANOVA with pre-treatment percent trauma potentiation and post-treatment percent trauma potentiation as the within-subjects factors in the high and low responder groups revealed a significant main effect of time (F = 14.10, p = .001) in the high responder group, indicating that trauma-potentiated startle significantly decreased at post-treatment compared to pre-treatment. For the low responders, there was no significant main effect of time (F = .48, p = .50), indicating that trauma-potentiated startle was not significantly different at post-treatment compared to pre-treatment. Mean

percent trauma potentiation at pre and post-treatment for the high and low responder groups is presented in Fig. 1. Differences for high and low responders in pre and post-treatment percent trauma potentiation were compared; results indicate no significant between group differences (p = .16 and p = .30, respectively).

3.3. Heart rate

To examine differences in heart rate following treatment in high and low responders, we conducted a repeated measures ANOVA with group (high and low responder) as the between-subjects factor, and time (pre and post-treatment assessment) and stimulus (blue square versus trauma-relevant cues) as within-subject factors. Pre and post-treatment heart rate data were available for 103 participants. Mean heart rate during the initial 30 s epochs within each condition was used as a dependent measure. A significant interaction was identified between time and stimulus (F = 4.57; p = .04). Difference scores for pre and post-treatment were created via subtracting mean heart rate to the 30-s interval of neutral blue square stimulus from heart rate to the initial 30-s interval of the VR scenes. A repeated measures ANOVA with heart rate difference scores at pre and post-treatment as within-subjects factors and high and low responders as between-subjects factors identified a significant effect of treatment (F = 4.57, p = .035; Fig. 2) indicating a significant decrease over the course of treatment; a significant interaction between time and responder group was not identified (F = .56, p = .46). Differences for high and low responders in pre and post-treatment heart rate difference scores were compared; results indicate no significant between group differences (p = .42 and p = .96, respectively).

3.4. Skin conductance

To examine differences in skin conductance before and after treatment in high and low responders, we conducted a repeated measures ANOVA with group (high and low responder) as the between-subjects factor, and time (pre and post-treatment assessment) and stimulus (neutral blue square versus trauma-relevant cues) as within-subject factors. Pre- and post-treatment skin conductance data were available for 79 participants. Results indicated a main effect of stimulus (neutral blue square versus VR-based trauma relevant cues: F = 4.34, p = .04). Difference scores were created by subtracting skin conductance level during the 30-s blue square from the skin conductance level during the initial 30-s interval of the VR scene. A repeated measures ANOVA with skin conductance difference scores at pre and post-treatment as within-subjects factors and high and low responders as between-subjects factors did not identify a significant main effect of time or an interaction between time and responder group (Fig. 3). Differences for high and low responders in pre and post-treatment skin conductance difference scores were compared; results indicate no significant between group differences (p = .33 and .73, respectively).

4. Discussion

While exposure-based psychotherapy for PTSD has strong evidence for its effectiveness, some fail to receive full benefit (Steenkamp et al., 2015) indicating the need for further research investigating treatment processes that can help identify likely low-responders to inform personalized treatment matching or augmentation strategies. PE requires emotional engagement and appropriate activation of fear networks to facilitate extinction of conditioned fear (Foa & Kozak, 1986) suggesting psychophysiological data may provide an important and objective assessment of processes relevant to treatment outcome. The focus of the present study was to investigate changes in trauma-potentiated startle response, heart rate reactivity, and skin conductance response over the course of PE treatment for PTSD, and how these changes differed for high and low treatment responders.

The present study used the same criteria for high treatment responders used in Robison-Andrew and colleagues investigation (i.e., 50% or greater reduction in PTSD symptoms; 2014), and results in the present study identified a similar number of patients as high treatment responders as this study (47.1% and 48.6%, respectively; Robison-Andrew et al., 2014). Both studies found that high and low responder groups did not significantly differ on PTSD or depression symptoms at baseline (Robison-Andrew et al., 2014). The extant literature illustrates the ongoing difficulty in identifying a baseline symptom measure that reliably predicts PTSD treatment response (e.g., Van Minnen et al., 2002), providing a compelling rationale for investigating psychophysiological methods in order to understand variability in treatment response.

Robison-Andrew et al. (2014) reported that low responders demonstrated a relatively flat response profile, in general, whereas high responders showed an initial increase following by a decrease in trauma-potentiated startle over the assessment time period. In the present study, trauma potentiated startle was observed in all patients, indicating that they exhibited increased startle reactivity to trauma-relevant cues compared to neutral cues. However, a significant interaction with responder group and time was identified further indicating that the VR scenes did not continue to potentiate startle responses when assessed at post-treatment for the high responder group. Consistent with previous findings (Robison-Andrew et al., 2014), the low responders demonstrated a relatively flat profile in which they did not demonstrate a significant change in trauma-potentiated startle from the

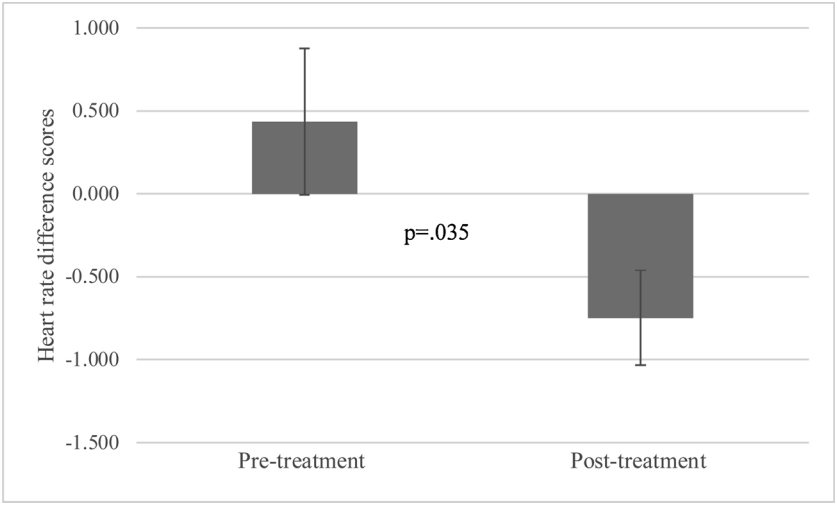

Fig. 2. Heart rate difference scores at pre and post-treatment. Heart rate difference scores (VR HR-Blue square HR) at pre and post-treatment demonstrated a significant effect of treatment (F = 4.57, p = .035); a significant interaction between time and responder group was not identified (F = .56, p = .46) suggesting that heart rate reactivity significantly decreased from pre to post-treatment, but high and low responders did not differ significantly.

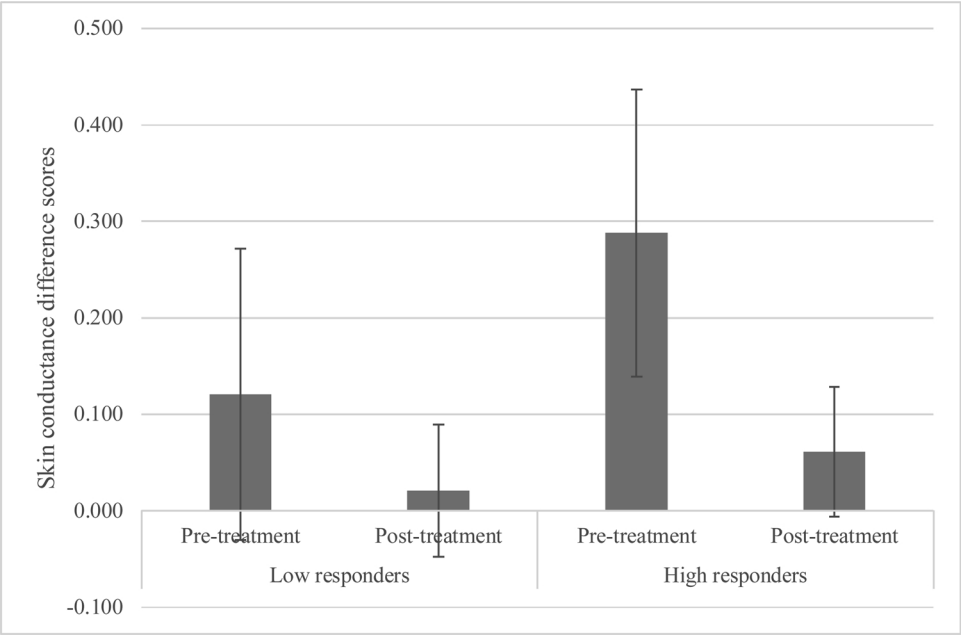

Fig. 3. Skin conductance difference scores at pre and post-treatment.
Skin conductance difference scores (VR SC-Blue square SC) did not identify a significant main effect of time ($F = 2.02$; $p = 0.16$) or interaction between time and responder group ($F = .30$, $p = 0.58$) indicating that overall skin conductance reactivity did not significantly change from pre to post-treatment and responder groups did not differ significantly in change across treatment.

pre- to post-treatment time points. A previous study using the same methodology from our group found that higher trauma-potentiated startle at baseline predicted better treatment outcomes in virtual reality-based PE treatment (Norrholm et al., 2016). In the present study, between group differences were not significant at pre-treatment, however there was a trend towards larger pre-treatment potentiated startle responses in the high responder group. A similar non-significant trend was present for the skin conductance data, to a lesser degree. This pattern is consistent with the previous study finding that higher startle responses at pre-treatment was associated with greater symptom change over time (Norrholm et al., 2016). This suggests that heightened baseline psychophysiological reactivity and increased engagement with trauma stimuli may relate to positive treatment response in exposure-based therapy for PTSD, suggesting a fruitful area for future clinical research.

Results indicate that high PE responders demonstrate a significant decrease in trauma-potentiated startle over the course of treatment. The present results extend previous findings in that change in trauma-potentiated startle patterns suggest that low responders don't experience significant changes in startle over the course of PE, whereas high responders are less reactive to trauma stimuli following treatment. It is also possible that the trend towards higher reactivity at baseline in high responders is contributing towards this pattern. These results suggest that increased psychophysiological reactivity to trauma cues is associated with improved treatment response, consistent with theoretical models of PE indicating that ability to activate fear response and emotionally engage in exposures in order to facilitate extinction learning is an important element of this treatment (Rauch & Liberzon, 2017; Weingast et al., 2018).

In the present study, heart rate demonstrated a main effect of time, indicating that across all patients, PE treatment was associated with reductions in heart rate reactivity to trauma cues. This is consistent with previous research demonstrating reductions in heart rate reactivity to a script-driven imagery task over the time course of PE treatment for PTSD (Wangelin & Tuerk, 2015), suggesting trauma potentiated startle and heart rate may represent important objective markers of treatment response to be considered within psychotherapy. However, results did not identify a significant interaction with responder group, indicating that the low and high responders did not demonstrate significantly different patterns of heart rate reactivity across PE treatment. There was no significant main effect of time or interaction between time and responder group with skin conductance measures, indicating that reactivity within this psychophysiological index did not significantly change over the course of PE treatment and did not significantly differ in high and low responders. This is inconsistent with previous findings showing reduced skin conductance reactivity across an imaginal PE treatment regimen (Wangelin & Tuerk, 2015), an inconsistency that may be related to differences in trauma cue task (script-driven imagery task versus virtual reality trauma cues) or may be due to the low response group still showing significant improvement as the average percent PTSD symptom change was 16.6% in the low responders group in the present study.

One notable limitation of the present study is the lack of a no-treatment or comparison treatment control arm. Although previous work has shown similar results across exposure-based PTSD psychotherapies (e.g., Robison-Andrew et al., 2014), future research should investigate these associations in comparison treatment or no treatment control groups to investigate the generalizability to other forms of PTSD treatment. An additional limitation of the present study is missing data due to unforeseen hardware and/or software malfunctions, data collections errors, and low response rates. However, even with missing data, the sample size for the smallest dataset, i.e. startle ($n = 68$), had significant power to detect treatment effects in high responders. While the sample is fairly diverse with regard to gender and racial demographics, future research should also determine the generalizability of the current findings to non-combat trauma PTSD populations. Another notable difference between the current study and previous studies is the schedule of PE treatment being daily for two weeks.

Broadly, these results are consistent with previous research indicating the importance of considering psychophysiological processes with regard to PTSD treatment outcomes (Norrholm et al., 2016; Rauch et al., 2015; Wangelin & Tuerk, 2015). In the present study, we observed significant trauma cue-evoked increases in acoustic startle, heart rate, and skin conductance responses at pre-treatment indicating that these methods effectively measure psychophysiological reactivity within this paradigm. Trauma potentiated startle and skin conductance responses were significantly reduced across the time course of PE treatment in the overall sample; however, only trauma potentiated startle differentiated high and low responder groups in that low responders demonstrated a relatively flat pattern with no significant changes whereas the high responder group demonstrated significant

reduction such that VR scenes no longer potentiated startle in this group significantly after treatment.

These results suggest that being able to engage in emotional content relevant to trauma stimuli is related to successful treatment outcome, consistent with a foundation of PE in extinction learning principles. Trauma potentiated startle may be more sensitive to treatment effects in a manner that is related to the more direct neural connections between expression of potentiated startle and underlying amygdala functioning whereas heart rate and skin conductance more likely assess distal downstream central nervous system effects. These findings are consistent with previous studies indicating potential differences across psychophysiological indices and psychotherapy (e.g., Maples-Keller et al., 2017) and highlights the importance of considering multiple indices. The results of the present study suggest that high PE treatment response is associated with less startle-based reactivity following treatment completion, consistent with theoretical models of PE suggesting that initial ability to engage emotionally with trauma relevant stimuli is important to facilitate fear extinction processes leading to reduced conditioned fear response. Investigation of mechanisms of PE can inform personalized treatment approaches including potential treatment augmentation efforts aimed at patients who may be unlikely to receive full benefit. These results suggest that trauma-potentiated startle may represent an objective marker of fear- and anxiety-related symptom reduction that is sensitive to both short- and long-term treatment approaches.

Disclosure statement

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