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RESEARCH ARTICLE

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Psychophysiology during exposure to trauma memories: Comparative effects of virtual reality and imaginal exposure for posttraumatic stress disorder

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Abstract

Background: This investigation involved an in-depth examination of psychophysiological responses during exposure to the trauma memory across 10 sessions among active duty soldiers with combat-related posttraumatic stress disorder (PTSD) treated by Prolonged Exposure (PE) or Virtual Reality Exposure (VRE). We compared psychophysiological changes, session-by-session, between VRE and traditional imaginal exposure.

Methods: Heart rate (HR), galvanic skin response (GSR), and peripheral skin temperature were collected every 5 min during exposure sessions with 61 combat veterans of Iraq/Afghanistan and compared to the PTSD Checklist (PCL-C) and Clinician-Administered PTSD Scale (CAPS) outcomes using multilevel modeling.

Results: Over the course of treatment, participants in the PE group had higher HR arousal compared to participants in the VRE group. With reference to GSR, in earlier sessions, participants demonstrated a within-session increase, whereas, in later sessions, participants showed a within-session habituation response. A significant interaction was found for GSR and treatment assignment for within-session change, within-person effect, predicting CAPS ($d = 0.70$) and PCL-C ($d = 0.66$) outcomes.

Conclusion: Overall, these findings suggest that exposure to traumatic memories activates arousal across sessions, with GSR being most associated with reductions in PTSD symptoms for participants in the PE group.

KEYWORDS

active duty, combat, posttraumatic stress disorder, Prolonged Exposure, psychophysiology, Virtual Reality Exposure

1 | INTRODUCTION

Prolonged Exposure (PE; Foa et al., 2019) is one of the most well-researched and efficacious treatments for posttraumatic stress disorder (PTSD), with support garnered across a range of trauma populations (Foa et al., 2018; Forbes et al., 2010; Powers et al., 2010). PE was developed according to emotional processing theory (Foa & Kozak, 1986), which postulates that the traumatic event is represented in memory as specific trauma structures. When the trauma structures are activated in daily life, they prompt distress

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that results in cognitive and behavioral avoidance as a method to reduce this distress. This avoidance prevents appropriate processing of the trauma memory and maintains the symptoms of PTSD. Exposure therapy works to decrease PTSD symptoms by countering avoidance through imaginal exposure to the trauma memory and in vivo exposure to stimuli that activate these trauma structures (Foa et al., 2019). This process is thought to facilitate inhibitory learning and reduce distress elicited by the trauma structures by creating new associations that these memories and stimuli are in fact not dangerous or intolerable (Craske et al., 2008, 2012).

Emotional engagement (i.e., elicited distress/arousal) during exposure therapy is theoretically considered to be critical to successful treatment of PTSD, as activating these trauma structures is a presumed precursor to new learning (Craske et al., 2014; Foa & Kozak, 1986). Multisensory virtual reality systems have been proposed as a potential tool for increasing activation of the trauma memory during exposure and improving outcomes (Rothbaum et al., 1995), and the addition of trauma-relevant visuals, auditory, and olfactory cues might inhibit avoidance strategies and help individuals overcome the reluctance to imagine these events in sufficient detail and affective magnitude. For instance, odor-evoked autobiographical memories elicited strong emotions and evocativeness (Herz, 2004), and a review linked olfactory cues and traumatic memories with activation of the emotional processing regions of the brain (e.g., amygdala; Daniels & Vermetten, 2016). Furthermore, a randomized controlled study of nonclinical participants found higher psychophysiological responses for virtual reality compared to script-driven imagery during stressful scenes (both conditions included auditory and olfactory stimuli; Schweizer et al., 2018). Although studies have consistently demonstrated Virtual Reality Exposure (VRE) to be an effective treatment for PTSD symptoms across populations (Difede et al., 2014; Reger et al., 2011; Rizzo et al., 2011; Rothbaum et al., 2014), research comparing VRE to traditional imaginal exposure in PE is sparse. A prior study (Reger et al., 2019), performing a secondary analysis on a subset of participants from a large-scale clinical trial (Reger et al., 2016), found no differences between PE and VRE when using ratings of subjective distress during exposure to the memory for assessing emotional engagement. However, decreased subjective distress across exposure treatments (PE and VRE), as measured by the subjective units of distress scale (SUDS), did correlate with PTSD symptom outcomes, as has been shown in prior VRE for PTSD work (Rauch et al., 2018). Nevertheless, an examination of psychophysiological processes might reveal meaningful differences in arousal between VRE and PE.

Research has consistently shown that between-session habituation, or reductions in distress during imaginal exposure over the course of exposure therapy for PTSD, is reliably related to treatment outcome, while within-session habituation, or changes in distress during a single session, is not a reliable predictor of outcome (see Cooper et al., 2017 for a review). It is unclear whether between-session habituation plays a mechanistic role, although emotional processing theory certainly posits that between-session habituation will occur over the course of treatment as trauma structures are modified (Rauch & Foa, 2006). Furthermore, research on emotional engagement and habituation in exposure therapy for PTSD has almost exclusively used self-report of SUDS, based entirely upon participants' verbal subjective ratings of distress during exposures. Given the strong evidence that subjective report of arousal does not correspond well with psychophysiological indicators of arousal (e.g., Lieberman et al., 2016; Mauss & Robinson, 2009; Mauss et al., 2005), also known as desynchrony (Grey et al., 1979; Lang, 1968; Rachman & Hodgson, 1974; Zinbarg, 1998), it is important to determine whether these more objective measures align better with treatment outcomes in exposure therapy for PTSD and serve a potential mechanistic role of physiological engagement.

Prior work has established various psychophysiological markers of arousal that can be useful in the context of studying PTSD. Elevated heart rate (HR) and galvanic skin response (GSR) have evidenced robust associations with PTSD (Pole, 2007). PTSD was associated with slower GSR habituation to startling sounds, heightened resting HR, and larger HR responses to both standardized (e.g., generic sounds of explosions) and idiosyncratic trauma cues (e.g., script-driven imagery). Clinical trials with PE and VRE have found that greater psychophysiological activation at pretreatment predicted reductions in PTSD symptoms (Norrholm et al., 2016; Wangelin & Tuerk, 2015). Furthermore, a prior study of a subsample from the Reger et al. (2016) clinical trial used a stress-test methodology in assessment appointments during which patients silently and independently focused on their trauma memory for 5 min with resting baseline and post-stressor relaxation phases (Katz et al., 2020). The study found both VRE and PE participants displayed lower GSR reactivity during 5-min trauma recall from pre- to posttreatment, but only the VRE group was significantly lower compared to the waitlist control group.

To our knowledge, this was the first examination on whether VRE increases emotional engagement (as indexed by psychophysiology) similar to that observed for traditional imaginal exposure, or if VRE results in more rapid decreases in psychophysiological arousal within and across treatment sessions. This investigation was thus initiated to begin to address this unmet need by systematically addressing the following: Aim 1—whether psychophysiological arousal during exposure to a trauma memory is greater during VRE versus PE; Aim 2—the degree to which both forms of treatment impact psychophysiological changes within and between exposure sessions; and Aim 3—whether changes in psychophysiological arousal within and between exposure sessions predict PTSD treatment outcomes.

2 | MATERIALS AND METHODS

2.1 | Participants

This sample of U.S. Army soldiers was drawn from a randomized controlled trial (Reger et al., 2016) (RCT Registration: ClinicalTrials.

gov (Greg M. Reger; identifier: NCT01193725)) that compared the efficacy of VRE to PE with a minimal attention waitlist control among personnel with PTSD from combat deployments to Iraq or Afghanistan. Participants were diagnosed with PTSD using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). Please see Reger et al. (2016) for full inclusion/exclusion criteria.

The current study included the subset of participants who received the two active treatments (PE or VRE) and remained in treatment through a minimum of three sessions, the point at which the first exposure to the trauma memory was implemented ($N = 96$). Although the psychophysiological recording was in place at the study launch, we subsequently determined that the data initially being collected was inadequate and began our collection anew with a research-grade system more suitable for our purposes. This study reports on the subsample of soldiers ($N = 61$; VRE, $n = 31$; PE, $n = 30$) whose psychophysiological data were collected with the improved equipment. The observed means at baseline showed participants excluded due to inadequate equipment did not display meaningfully different CAPS ($M = 81.25$, $SD = 16.91$) and PTSD Checklist-Civilian Version (PCL-C) total scores (Weathers et al., 1994; $M = 58.75$, $SD = 9.43$) from participants in the included sample (CAPS, $M = 76.06$, $SD = 14.83$; PCL-C, $M = 63.26$, $SD = 8.44$).

2.2 | Procedure

Although therapy included 10 sessions, each lasting 90–120 min, exposure occurred in Sessions 3 through 10. Psychotherapy was delivered consistent with the treatment manual for PE (Foa et al., 2007), with one exception; soldiers assigned to VRE used a virtual reality system during their imaginal exposure (see Rizzo et al., 2009 for a full description of the system). PTSD symptom assessments took place at baseline/pre-randomization, mid-treatment (after the 5th session), and posttreatment (after the 10th session).

2.3 | Psychophysiology measurement

The Biopac MP150 modular data acquisition system and AcqKnowledge 4.1 software (Biopac Systems Inc.) were used. HR was assessed using ECG disposable foam electrodes Biopac EL503 or EL501 attached to the right forearm and left calf, after the skin was lightly abraded with ELPREP gel. A Biopac TSD202D thermistor, attached to the most distal pad of the third finger on the right hand, measured peripheral skin temperature (SKT). GSR measurements were collected using two pre-gelled disposable Biopac EL507 Ag/AgCl electrodes attached to the most distal phalange on the palmar surface of the third and fourth fingers of the nondominant hand. Data collection and analysis procedures were consistent with established guidelines (Boucsein et al., 2012; Dawson et al., 2016).

Psychophysiological measures were continually collected during Sessions 3 through 10 when trauma memory exposure occurred, with clinicians obtaining SUDS ratings from participants every 5 min and digitally marking in the psychophysiology recordings when ratings were obtained.

2.4 | PTSD symptom measurement

2.4.1 | Clinician-Administered PTSD Scale

The CAPS (Blake et al., 1995) assesses for PTSD following the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). Symptoms are rated on frequency and intensity and summed, resulting in a total severity score. For this study, the "past week" time frame was used for all assessments. The CAPS has demonstrated good validity (Foa & Tolin, 2000) and we found acceptable internal consistencies (VRE: Cronbach's $\alpha = .806$; PE: Cronbach's $\alpha = .849$).

2.4.2 | PTSD Checklist—Civilian Version

The PCL-C (Weathers et al., 1994) is a 17-item self-report measure of PTSD symptom intensity. Participants reported how much they have been bothered by each symptom in the past month according to a 5-point scale ranging from 1 (*not at all*) to 5 (*extremely*). The PCL-C has demonstrated adequate psychometric properties among active duty military personnel (Bliese et al., 2008), and we found good internal consistencies (VRE: Cronbach's $\alpha = .827$; PE: Cronbach's $\alpha = .837$).

2.5 | Data analytic plan

Multilevel modeling (MLM) was conducted to evaluate the relations of interest. For interpretation, increases in HR (measured in beats per minute; bpm) and GSR (measured in microsiemens) indicated greater arousal, while decreases in SKT (measured in °F) denoted greater arousal. Peak arousal was defined as the highest HR or GSR value, or the lowest SKT value measured within a session. We removed extreme psychophysiological raw values based on criteria established before examining any data: HR recordings above 180 bpm and under 30 bpm, SKT recordings that exceeded 100°F, and GSR recordings with negative values (in microsiemens) due to the implausibility to have the absence of skin moisture. Room temperatures were recorded for each session and used as covariates when analyzing SKT and GSR data to minimize artifacts from the ambient temperature (Bari et al., 2018; Boucsein et al., 2012; Taub & School, 1978; Vinkers et al., 2013).

2.5.1 | Aim 1: Psychophysiological arousal between treatment groups

The first MLM analyses investigated the change in peak arousal between treatment groups across treatment sessions. Treatment session was treated as a factor variable in this model to limit assumptions about the shape of change in either treatment group. Only participants with in-session baseline recordings (time = 0 min) of HR, SKT, or GSR were included in the sessions. Baseline recordings were added as a session-level covariate to examine the difference between peak and baseline psychophysiology (i.e., arousal). Deviance likelihood ratio tests (LRTs) were used to test for an overall treatment effect on arousal.

2.5.2 | Aim 2: Psychophysiological changes within and between sessions

Longitudinal HR, SKT, and GSR measurement changes among all participants were examined using the variance in psychophysiological level (level-one) nested within treatment session (level-two) nested within each individual participant (level-three). We implemented a four-step sequential approach: baseline intercept only, random intercept only, adding fixed effects, and adding random slopes. Furthermore, we examined the shape of the change in the psychophysiological level within and between sessions through linear and quadratic trajectories. The overall best-fitted models were determined by direct comparisons of LRTs.

2.5.3 | Aim 3: Psychophysiological changes within and between sessions as predictors of PTSD outcomes

Changes in CAPS and PCL-C total scores were examined from baseline to mid-treatment and posttreatment using MLM analyses treating the assessment time point as a factor variable. Longitudinal growth curve models followed the analytics proposed by Curran and Bauer (2011). The in-session psychophysiological recordings at baseline (Session 3), mid-treatment (Sessions 4 or 5), and posttreatment (closest to Session 10) were examined to predict the CAPS and PCL-C outcome scores at baseline, mid-treatment, and posttreatment. Only participants with HR, SKT, or GSR recordings for at least two time points (baseline, mid-treatment, or posttreatment) were included in the models. The peak arousal recording at each time point was included for the between-session change variable, whereas the difference score (the difference between the peak arousal and final (end) recording) was used for the within-session change variable. The between- and within-session change variables were grand mean centered. Within-person ordinary least squares regression models were fitted to obtain the constant/intercept (between-person effect) and residuals (within-person effect) for each participant's between- and within-session change variables. In these analyses, change due to treatment is indicated if there is a meaningful within-person effect finding because this reflects a participant's movement in comparison to their overall average (between-person effect) across the time points. Then, MLM analyses using each participant's intercept and residuals for between- and within-session change were examined to predict CAPS and PCL-C outcomes, followed by examining the interaction of treatment group assignment. We applied full information maximum likelihood to deal with missing data in the growth curve models.

Cohen's *d* effect sizes were calculated by first adding both the intercept squared and residual squared MLM values, followed by taking the square root of this value, and then multiplying this value by the respective regression coefficient. MLM analyses were completed using R Studio version 3.6.3. and R version 4.0.0.

3 | RESULTS

3.1 | Descriptive statistics

Table 1 presents the demographic and baseline clinical characteristics for all participants ($N = 61$). VRE and PE participants completed a mean of 7.52 ($SD = 2.85$) and 8.90 ($SD = 2.12$) treatment sessions, respectively.

3.2 | MLM results

3.2.1 | Aim 1: Psychophysiological arousal between treatment groups

Treating treatment session as a factor, a significant effect of treatment assignment was observed on HR arousal (χ^2_{LR} (7) = 17.72, $p = .013$). Participants in the VRE group had higher HR arousal than those in the PE group at baseline Session 3 ($d = 0.87$), whereas participants in the PE group had greater increases in HR arousal compared to baseline Session 3 than those in the VRE group at Sessions 7 ($d = 0.92$), 8 ($d = 1.23$) and 10 ($d = 1.05$; see Table 2, Model a). Similar levels of SKT arousal were found across sessions between participants in the VRE and PE groups (χ^2_{LR} (7) = 1.44, $p = .984$; see Table 2, Model b). Also, no overall group difference was found for change in GSR arousal across sessions (χ^2_{LR} (7) = 4.65, $p = .703$; see Table 2, Model c).

3.2.2 | Aim 2: Psychophysiological changes within and between sessions

We first examined psychophysiological change among all participants. The HR unconditional model was based on 2570 HR measurements nested within 359 sessions nested within 61 participants.

TABLE 1 Demographic and clinical characteristics of participants at baseline by treatment group

Variable	PE (n = 30)				VRE (n = 31)			
	M	*SD*	*Min.*	*Max.*	*M*	*SD*	*Min.*	*Max.*
Age in years	30.13	6.13	21	49	30.00	6.66	21	47
CAPS (past week)	79.23	18.33	54	123	83.19	15.46	51	109
PCL-C (past month)	57.63	10.01	38	79	60.35	9.11	41	77
Variable			*n*	%			*n*	%
Male			28	93.3			29	93.5
Marital								
Not married			3	10.0			5	16.1
Married			22	73.3			16	51.6
Separated			4	13.3			5	16.1
Divorced			1	3.3			5	16.1
Education								
High school			9	30.0			10	32.3
Some college, no degree			12	40.0			17	54.8
2-year degree/Technical certificate			4	13.3			3	9.7
4-year degree			4	13.3			1	3.2
Postgraduate degree			1	3.3			0	0.0
Race/Ethnicity								
White, not Hispanic			20	66.7			23	74.2
Black, not Hispanic			1	3.3			2	6.5
Asian/Pacific Islander, not Hispanic			2	6.7			1	3.2
American Native, not Hispanic			1	3.3			0	0.0
Other, not Hispanic			1	3.3			1	3.2
Hispanic, any race			5	16.7			4	12.9
Military rank/Grade								
E-1–E-4			12	40.0			14	45.2
E-5–E-9			15	50.0			16	51.6
Officer			3	10.0			1	3.2
Prior treatment for PTSD			10	33.3			7	22.6

Note: CAPS, Clinician-Administered PTSD Scale for DSM-IV; Max., maximum; Min., minimum; PCL-C, PTSD Checklist—Civilian Version; PE, Prolonged Exposure; PTSD, posttraumatic stress disorder; VRE, Virtual Reality Exposure.

The SKT unconditional model was based on 2082 SKT measurements nested within 284 sessions nested within 53 participants. The GSR unconditional model was based on 2102 GSR measurements nested within 287 sessions nested within 53 participants. The best-fitting model for HR was a linear change within and between sessions (see Table 3, Model 4), whereas for both SKT and GSR it was a quadratic change within sessions and linear change between sessions (see Table 3, Model 5). As time increased within sessions, participant HR significantly decreased (d = 0.19; see Table 4 and Figure 1). Regarding GSR, in earlier sessions, participants demonstrated a within-session increase, whereas, in later sessions, participants showed a within-session habituation response (d = 0.36; see Table 4 and Figure 2). Conversely, as the number of sessions increased, SKT findings indicated elevated arousal during the closing minutes of exposures (d = 0.43; see Table 4 and Figure 3).

Next, we examined psychophysiological change between treatment groups. Changes in psychophysiological reductions between participants in the VRE and PE groups were analyzed using the previously fitted MLM specifications among all participants. Participants in the PE group had a stronger decrease in HR within sessions (b = −0.15, 95% CI [−0.30, −0.13e−02], df = 2,207, d = 0.26; see Figure 1). No significant group differences were found for the trajectory of GSR within (b = −0.81e−02, 95% CI [−0.16e−02, 0.79e−03], df = 1,807) or between sessions (b = 0.30, 95% CI [−0.34, 0.95], df = 276; see Figure 2). Participants in the PE group had a stronger return to baseline SKT within sessions (b = −0.34e−02, 95% CI [−0.49e−02, −0.19e−02], df = 1,790, d = 0.41; see Figure 3).

3.2.3 | Aim 3: Psychophysiological changes within and between sessions as predictors of PTSD outcomes

Across all participants, significantly lower CAPS total scores were observed with an 11.67-point reduction at mid-treatment

TABLE 2 Multilevel models of arousal for HR, SKT, and GSR by treatment group

	ΔArousal[a]								95% CI	
Ses	VRE		PE		β[b]	*SE*	*t*	*df*	*LL*	*UL*
a. Treatment Group × Session predicting HR arousal (n = 60)										
Ses3	123.5		98.0		−25.44	8.85	−2.87**	58	−42.68	−8.20
Ses4	129.9	(6.4)	104.3	(6.3)	−0.17	11.25	−0.02	240	−21.72	21.38
Ses5	119.8	(−3.7)	97.4	(−0.6)	3.13	11.86	0.26	240	−19.60	25.86
Ses6	108.0	(−15.5)	101.0	(3.0)	18.42	11.87	1.55	240	−4.32	41.16
Ses7	105.3	(−18.2)	106.7	(8.7)	26.95	12.56	2.15*	240	2.89	51.02
Ses8	100.5	(−23.0)	111.0	(13.0)	35.97	12.22	2.94**	240	12.56	59.38
Ses9	111.9	(−11.6)	100.1	(2.1)	13.65	12.32	1.11	240	−9.95	37.26
Ses10	94.8	(−28.7)	100.0	(2.0)	30.74	12.89	2.38*	240	6.04	55.43
b. Treatment Group × Session predicting SKT arousal (n = 51)[c]										
Ses3	87.5		88.1		0.55	1.30	0.43	49	−1.96	3.07
Ses4	87.7	(0.2)	88.3	(0.2)	−0.02	0.60	−0.03	195	−1.17	1.13
Ses5	87.4	(−0.1)	88.3	(0.2)	0.36	0.62	0.58	195	−0.82	1.53
Ses6	87.5	(0.0)	88.2	(0.1)	0.17	0.62	0.28	195	−1.01	1.35
Ses7	87.6	(0.1)	88.2	(0.1)	0.03	0.66	0.05	195	−1.22	1.28
Ses8	87.6	(0.1)	88.2	(0.1)	0.04	0.66	0.06	195	−1.22	1.30
Ses9	87.6	(0.1)	88.4	(0.3)	0.28	0.65	0.43	195	−0.96	1.51
Ses10	87.7	(0.2)	87.9	(−0.2)	−0.30	0.67	−0.45	195	−1.57	0.97
c. Treatment Group × Session predicting GSR arousal (n = 52)[c]										
Ses3	9.4		8.3		−1.16	1.21	−0.96	50	−3.50	1.18
Ses4	9.2	(−0.2)	9.9	(1.6)	1.77	1.10	1.61	196	−0.33	3.87
Ses5	10.4	(1.0)	9.8	(1.5)	0.48	1.14	0.42	196	−1.70	2.66
Ses6	9.2	(−0.2)	9.5	(1.2)	1.43	1.14	1.25	196	−0.74	3.59
Ses7	9.8	(0.4)	8.7	(0.4)	0.01	1.20	0.01	196	−2.28	2.30
Ses8	9.3	(−0.1)	9.1	(0.8)	0.91	1.18	0.77	196	−1.34	3.16
Ses9	8.3	(−1.1)	7.9	(−0.4)	0.67	1.20	0.56	196	−1.60	2.95
Ses10	8.1	(−1.4)	8.0	(−0.3)	1.09	1.24	0.88	196	−1.27	3.46

Note: All intercepts were allowed to vary randomly. One participant for Model a, eight participants for Model b, and seven participants for Model c were excluded because of missing baseline (time = 0 min) recordings. Two participants were excluded from Models b and c because of missing room temperature recordings.

Abbreviations: CI, confidence interval; GSR, galvanic skin response; HR, heart rate; LL, lower limit; PE, Prolonged Exposure; Ses, session; SKT, peripheral skin temperature; UL, upper limit; VRE, Virtual Reality Exposure.

[a]The values without parentheses are the peak arousals at each session and the values with parentheses are the respective session differences from the baseline (Session 3) peak arousal. In Model a, HR arousal is expressed in beats per minute. In Model b, SKT arousal is expressed in °F. In Model c, GSR arousal is expressed in microsiemens.

[b]The β values are the coefficients comparing the PE to the VRE group. For Session 3, this is the difference in baseline values. For Sessions 4–10, this is the difference in slopes from Session 3 to the other session averages between PE and VRE.

[c]In Models b and c, the room temperature was included as a session-level, fixed effect covariate.

*p < .05.

**p < .01.

(95% CI [−18.25, −5.10], df = 93, d = 0.47) and a 31.90-point reduction at posttreatment (95% CI [−38.83, −24.96], df = 93, d = 1.29). Similarly, significantly lower PCL-C total scores were found with a 7.07-point reduction at mid-treatment (95% CI [−10.18, −3.95], df = 90, d = 0.55) and a 16.87-point reduction at posttreatment (95% CI [−20.11, −13.63], df = 90, d = 1.31). In comparing the CAPS total scores between the treatment groups, the means were lower for those in the PE group by 7.80 points at mid-treatment (95% CI [−20.81, 5.22], df = 91, d = 0.32) and by 11.39 points at posttreatment (95% CI [−25.14, 2.37], df = 91, d = 0.47); however, these group differences were not significant. Consistent with the CAPS findings, there were no significant group differences for the PCL-C total scores and the means were lower for participants in the PE group by 4.25 points at mid-treatment (95% CI [−10.42, 1.92], df = 88, d = 0.33) and by 3.95 points at posttreatment (95% CI [−10.39, 2.48], df = 88, d = 0.31). These results are consistent with the larger sample findings reported by Reger et al. (2016).

TABLE 3 Fitting multilevel models for HR, SKT, and GSR using a sequential approach

Parameter	Model 1	Model 2	Model 3	Model 4[a]	Model 5	Model 6	Model 7
a. HR model comparisons (n = 61)							
Intercept	–	–	–	–	–	–	–
Time		–	–	–	–	–	–
Time^2			–		–		–
Session				–	–	–	–
Session^2						–	–
AIC	23,754	23,748	23,750	23,748	23,748	23,748	23,749
−2LL	11,873	11,869	11,869	11,867	11,865	11,865	11,863
ICC	0.39	0.39	0.39	0.39	0.39	0.39	0.39
df	4	5	6	7	9	9	12
Parameter	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5[a]**	**Model 6**	**Model 7**
b. SKT model comparisons (n = 53)							
Intercept	–	–	–	–	–	–	–
RT	–	–	–	–	–	–	–
Time		–	–	–	–	–	–
Time^2			–		–		–
Session				–	–	–	–
Session^2						–	–
AIC	11,100	10,599	10,319	10,591	10,249	10,591	10,249
−2LL	5,545	5,294	5,152	5,287	5,114	5,286	5,111
ICC	0.68	0.74	0.77	0.74	0.77	0.74	0.77
df	5	6	7	8	10	10	13
Parameter	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5[a]**	**Model 6**	**Model 7**
c. GSR model comparisons (n = 53)							
Intercept	–	–	–	–	–	–	–
RT	–	–	–	–	–	–	–
Time		–	–	–	–	–	–
Time^2			–		–		–
Session				–	–	–	–
Session^2						–	–
AIC	10,126	9,760	9,720	9,757	9,712	9,760	9,716
−2LL	5,058	4,874	4,853	4,870	4,846	4,870	4,845
ICC	0.90	0.92	0.92	0.92	0.92	0.92	0.92
df	5	6	7	8	10	10	13

Note: Time and session were grand mean centered in all models. The session growth curve between individuals and between sessions were allowed to vary randomly. Allowing the fixed effect time to vary randomly in the session did not add significantly to the models. Dashes denote the variables included in the respective models. For Models b and c, two participants were excluded because of missing room temperature recordings during exposure sessions and six participants were removed because of unusable in-session data.

Abbreviations: −2LL, −2∗log likelihood; AIC, Akaike information criterion; GSR, galvanic skin response; HR, heart rate; ICC, intraclass correlation; RT, room temperature; SKT, peripheral skin temperature.

[a]Best fitting model for the psychophysiological item based on the deviance likelihood ratio test.

TABLE 4 Multilevel models of HR, SKT, and GSR change within- and between-session

Fixed effects	β	SE	t	df	95% CI LL	95% CI UL
a. HR, linear time within-session and linear session number (n = 61)						
Intercept	87.33	1.03	85.15***	2,209	85.32	89.34
Time[a]	−0.12	0.04	−3.07**	2,209	−0.19	−0.04
Session[b]	−0.56	0.45	−1.25	6	−1.66	0.54
Time × Session[c]	−0.03	0.02	−1.55	2,209	−0.06	0.01
b. SKT, quadratic time within-session and linear session number (n = 53)[d]						
Intercept	55.05	4.73	11.63***	1,794	48.62	66.83
Time[a]	0.13	0.00	28.40***	1,794	0.12	0.13
Time^2[a]	−0.007	0.00	−17.54***	1,794	−0.007	−0.006
Session[b]	0.11	0.11	0.98	6	−0.15	0.43
Time × Session[c]	0.01	0.00	4.03***	1,794	0.004	0.01
Time^2 × Session[c]	−0.001	0.00	−8.23***	1,794	−0.002	−0.001
c. GSR, quadratic time within-session and linear session number (n = 53)[d]						
Intercept	−12.53	6.90	−1.81	1,811	−2.61	9.97
Time[a]	0.07	0.00	21.00***	1,811	0.07	0.08
Time^2[a]	−0.002	0.00	−6.66***	1,811	−0.003	−0.001
Session[b]	0.17	0.16	1.07	6	−0.22	0.57
Time × Session[c]	−0.004	0.00	−2.61**	1,811	−0.007	−0.001
Time^2 × Session[c]	−0.0003	0.00	−2.22*	1,811	−0.0006	−0.00004

Note: Time and session were grand mean centered in all models. The session growth curve between individuals and between sessions were allowed to vary randomly. Allowing the fixed effect time to vary randomly in the session did not add significantly to the models. For Models b and c, two participants were excluded because of missing room temperature recordings during exposure sessions and six participants were removed because of unusable in-session data.

Abbreviations: CI, confidence interval; GSR, galvanic skin response; HR, heart rate; LL, lower limit; SKT, peripheral skin temperature; UL, upper limit.

[a]Relationship between the psychophysiological variable change and time in session (within-session).

[b]Relationship between the psychophysiological variable change and session number (between-session).

[c]Relationship between the psychophysiological variable change, and the interaction of time in session (within-session) and session number (between-session).

[d]In Models b and c, the room temperature was included as a session-level, fixed effect covariate.

*p < .05.

**p < .01.

***p < .01.

Examining the main effects of HR, SKT, and GSR change within- and between-sessions did not predict the CAPS or PCL-C outcomes. However, the interaction of GSR and treatment assignment was significant for the within-session change variable, within-person effect, predicting both CAPS (b = −18.65, 95% CI [−32.79, −4.50], df = 65, p = .015, d = 0.70) and PCL-C (b = −9.28, 95% CI [−16.00, −2.56], df = 65, p = .011, d = 0.66) outcomes. Namely, for every one-unit increase in within-session habituation across the time points for participants in the PE group, decreases of approximately 14.94 and 8.16 points were found for the CAPS and the PCL-C total scores, respectively. See Table 5 for a full description of the marginal estimates.

4 | DISCUSSION

This secondary analysis of a randomized controlled trial exploring within- and between-session psychophysiological responses during trauma exposure via VRE versus PE for PTSD in active duty soldiers found varied patterns among the three modalities assessed. Although participants in the VRE group revealed higher levels of in-session arousal as assessed by HR during Session 3, PE overall produced greater in-session elevations in HR, most notably for Sessions 7, 8, and 10. HR revealed consistent within-session habituation, with that occurring in response to PE being most pronounced. The present finding of arousal differences for HR contrast with what we observed when analyzing arousal via subjective ratings of emotional engagement (by SUDS) collected from the same sample, wherein no significant group differences emerged between VRE and PE (Reger et al., 2019).

The finding of stronger within-session habituation for HR among participants in the PE group compared to the VRE group merits further discussion. Simulations have demonstrated the capacity for increasing arousal (Schweizer et al., 2018), which is expected in VRE's trauma-relevant visual, auditory, olfactory, and kinetic stimulations. However, when active duty soldiers are treated for PTSD via VRE they interact within an environment

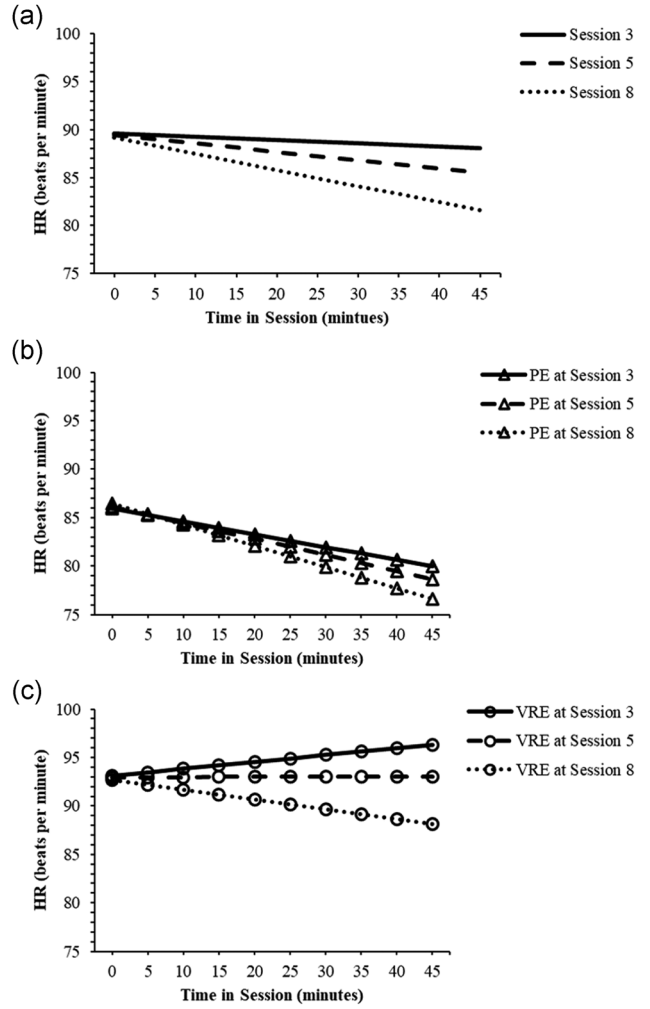

FIGURE 1 Expected heart rate (HR) linear trajectory across participants (a) and by treatment groups: Prolonged Exposure (PE) (b) and Virtual Reality Exposure (VRE) (c). Sessions 3, 5, and 8 indicate an early, average, and late session

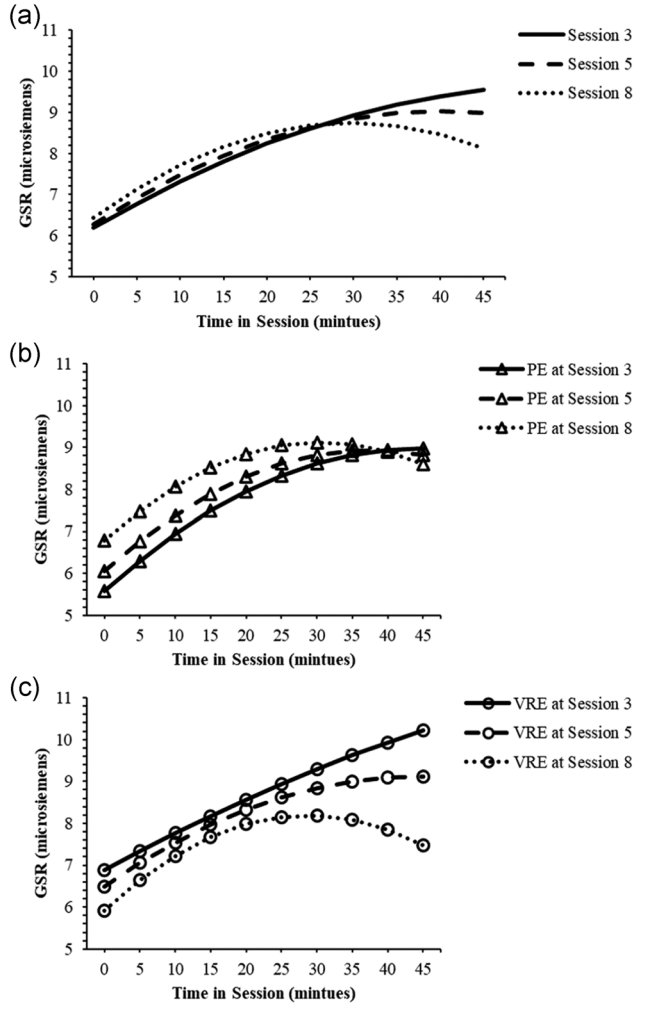

FIGURE 2 Expected galvanic skin response (GSR) quadratic trajectory across participants (a) and by treatment groups: Prolonged Exposure (PE) (b) and Virtual Reality Exposure (VRE) (c). Sessions 3, 5, and 8 indicate an early, average, and late session

where they have only partial control (walking or driving vehicles via a joystick), as a therapist controls all stimulation and effects (e.g., explosions, insurgents, gunfire, aircraft flyovers). Thus, certain elements of VRE are uncontrollable and unpredictable, which is not the case in PE. Patients often believe that PTSD-related distress is "out of their control," which can be frightening. Accordingly, clinical work aims to promote the patient's sense of control (Foa et al., 2019). As such, perhaps it is unreasonable to expect the same psychophysiological responding within and across VRE and PE sessions, as some differences in arousal may correspond with the modality of exposure.

Our findings contrast with the psychophysiological responses in veterans who received VRE or PE in the studies by Rothbaum et al. (2014) and Norrholm et al. (2016). In these studies, patients were presented with standard 2-min clips in VR head-mounted displays while recording their psychophysiological responses. The clips consisted of prerecorded VR movies that could not be adjusted; hence, after the second presentation patients would realize that the same clips were repeatedly presented. In this context, the elements of uncontrollability and unpredictability were reduced and markedly unlike what typically occurs in "live" VRE sessions. As we did not collect patient ratings of trauma fidelity for VRE, our sample may have included subgroups of patients for whom VRE may not have been an optimal fit. Future studies including patients for whom VRE fidelity to the trauma is presented in varying degrees may further illuminate treatment mechanisms.

No group differences were found when comparing arousal levels, as assessed by SKT, across the treatment. SKT increased within sessions (reflecting decreased arousal), but over time we observed a surprising growing tendency for SKT to return to session baseline values (reflecting increased arousal). Wood et al. (2008) reported a similar pattern of decreased SKT (increased arousal) at mid-treatment and posttreatment following VRE.

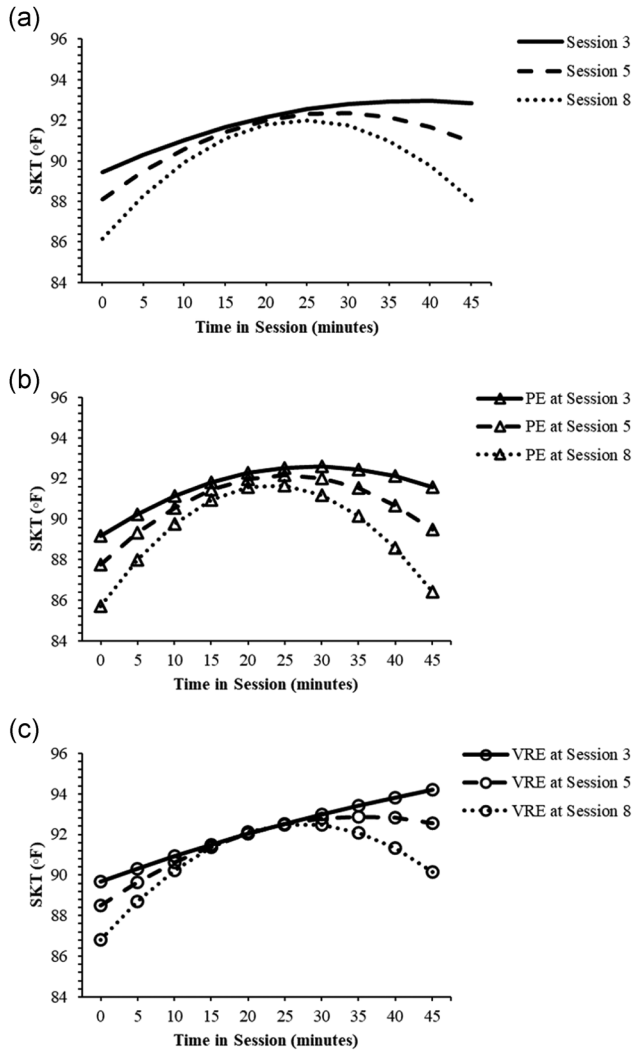

FIGURE 3 Expected peripheral skin temperature (SKT) quadratic trajectory across participants (a) and by treatment groups: Prolonged Exposure (PE) (b) and Virtual Reality Exposure (VRE) (c). Sessions 3, 5, and 8 indicate an early, average, and late session

Although few studies have examined the role of SKT for PTSD (in comparison to those for HR and GSR, e.g., Norrholm et al., 2016; Pole, 2007; Wangelin & Tuerk, 2015), we anticipated finding a U-shaped trajectory within exposure sessions based on the work of Vinkers et al. (2013). It is important to note that desynchrony among different measures of anxiety and distress, especially between psychophysiological measures, is more often the norm (Grey et al., 1979; Lang, 1968; Rachman & Hodgson, 1974; Zinbarg, 1998).

The within-session habituation observed for GSR, which strengthened as treatment progressed, is consistent with the findings of Pitman et al. (1996), who reported significant reductions during imaginal exposure. In addition, we found similar levels of peak GSR measurements across sessions and no significant group differences. GSR reactivity ran contrary to a stressor-test design of this study's sample by Katz et al. (2020), which found both VRE and PE groups displayed reductions in GSR activation from pre- to posttreatment. Disparate outcomes from different methodologies may not be surprising. Katz et al. collected GSR during assessment appointments (outside of psychotherapy) and during 5-min, silent, patient-driven imaginal trauma recalls that incorporated data from 5-min baseline and recovery phases, in comparison to the current study's examination of GSR during exposure psychotherapy.

Regarding this study's treatment outcomes, both treatment groups showed significantly lower PTSD symptoms at mid-treatment and posttreatment, which was consistent with the larger sample reported by Reger et al. (2016). Taken together, we found increased within-session habituation for GSR across sessions (within-person effect) predicted significant reductions in PTSD symptoms for participants in the PE group. Perhaps, distress tolerance or new learning was demonstrated from continued reactivity (emotional engagement) coupled with stronger recoveries from reactivity (within-session habituation) across sessions, as measured by GSR, over the course of PE. In contrast, the review by Cooper et al. (2017) reported minimal support for within-session habituation and a stronger association with lower PTSD outcomes for between-session habituation, as measured by SUDS. Should future investigations find that clinical monitoring methodologies for GSR during imaginal exposure are linked with lower PTSD symptoms, exploration of cost-effective and user-friendly sampling techniques may be indicated to support providers conducting PE. Examples of using a portable and low-cost device for recording GSR among individuals with PTSD are described by Hinrichs et al. (2017) and Post et al. (2017).

Strengths of this report include the population—active duty soldiers with PTSD, the methods—an RCT with multiple measures of psychophysiological responding session-by-session, and the novel focus—how in-session psychophysiological responses relate to each other and outcome. Also, this study incorporated the Curran and Bauer (2011) proposed analytic models, which allowed the examination of within- and between-person effects simultaneously to predict clinical outcomes. Limitations include data loss at the beginning of the study and the focus on a sample composed chiefly of male active duty soldiers, raising questions about the generality of effects. Despite artifact detection and removal procedures, the possibility of unidentified error in the psychophysiology recordings remains.

Our findings suggest that similar type comparisons between VRE and PE may yield important insights for other trauma types, such as military sexual trauma-related PTSD, that have shown successful outcomes (Khan et al., 2020; Loucks et al., 2019). The scientific and clinical yield may be further enhanced by incorporating psychophysiological measures in addition to those routinely investigated as mechanisms and indicators of change (e.g., SUDS, trauma-related beliefs, and homework compliance; Cooper et al., 2017).

TABLE 5 Marginal estimates of GSR change predicting outcomes by treatment group

	VRE				PE				
			95% CI				95% CI		
Fixed effects	Margin	*SE*	*LL*	*UL*	Margin	*SE*	*LL*	*UL*	*df*
a. GSR × Treatment Group predicting CAPS outcomes ($n = 42$)									
BSC[a] (between-person)	7.98	3.52	1.07	14.88	−7.91	3.52	−14.82	−1.01	36
BSC[b] (within-person)	6.04	3.94	−1.67	13.75	−8.76	3.94	−16.48	−1.05	65
WSC[a] (between-person)	7.14	3.97	−0.66	14.93	−6.99	3.97	−14.77	0.80	36
WSC[b]* (within-person)	19.47	6.32	7.09	31.86	−14.94	6.32	−27.33	−2.56	65
b. GSR × Treatment Group predicting PCL-C outcomes ($n = 42$)									
BSC[a] (between-person)	4.16	1.99	0.26	8.07	−4.22	1.99	−8.12	−0.31	36
BSC[b] (within-person)	3.72	2.16	−0.51	7.95	−4.54	2.16	−8.77	−0.31	65
WSC[a] (between-person)	4.02	2.24	−0.37	8.42	−3.32	2.24	−7.72	1.07	36
WSC[b]* (within-person)	9.37	3.19	3.12	15.62	−8.16	3.19	−14.41	−1.91	65

Note: Marginal estimates represent the effect of a one-unit increase in microsiemens for the between-session change and within-session change variables on CAPS or PCL-C scores across baseline, mid-treatment, and posttreatment.

Abbreviations: BSC, between-session change; CAPS, Clinician-Administered PTSD Scale for DSM-IV; CI, confidence interval; GSR, galvanic skin response; LL, lower limit; PCL-C, PTSD Checklist-Civilian Version; PE, Prolonged Exposure; UL, upper limit; VRE, Virtual Reality Exposure; WSC, within-session change.

[a]The person-specific averages for the overall peak arousal (BSC) and for the in-session difference score (the difference between peak arousal and final (end) recording; WSC) across the time points.

[b]The person-specific deviations around the person-specific averages across the time points.

*$p < .05$.

5 | CONCLUSION

The field of PTSD is plagued by reliance on self-report, even for our "clinician-completed" measures. A case has been made that psychophysiological indicators have great potential for enhancing understanding of reactivity to trauma-related stimuli before treatment and for illuminating potential mechanisms of change (e.g., Maples-Keller et al., 2019; Norrholm et al., 2016). Our session-by-session findings provide some support for this notion, but at the same time point out the complexity of conducting this type of research. The multisensory and slightly unpredictable and uncontrollable nature of VR stimuli naturally leads to different responses in the virtual environment versus a treatment narrated by the patient with eyes closed. More fine-grained analyses that concurrently address VRE and PE treatments that include multiple measurement modalities (both objective and subjective), while simultaneously controlling for fidelity differences, appear to us to have the greatest potential for enhancing understanding of therapy process as well as outcome when treating PTSD.

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CONFLICT OF INTERESTS

Dr. Reger receives royalties from Routledge. Dr. Rothbaum has funding from the Wounded Warrior Project, Department of Defense Clinical Trial Grant No. W81XWH-10-1-1045, and McCormick Foundation. Dr. Rothbaum receives royalties from Oxford University Press, Guilford, APPI, and Emory University, and received advisory board payments from Genentech, Jazz Pharmaceuticals, Nobilis Therapeutics, Sophren, Neuronetics, and Aptinyx. Dr. Rothbaum is a consultant to and owns equity in Virtually Better Inc. that creates virtual environments. However, the virtual environment tested in this study was created by Dr. Skip Rizzo and ICT at USC. The terms of these arrangements have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available to those granted access by local IRB from the corresponding author upon reasonable request.

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