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Predicting Post-Traumatic Stress Disorder Treatment Response Using Heart Rate Variability to Virtual Reality Environment and Modified Stroop Task: An Exploratory Study

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Abstract

Predicting treatment response can inform treatment decisions, expectations, and optimize use of mental health treatment resources. This study examined heart rate (HR), heart rate variability (HRV), and a modified Stroop task (mStroop) to predict post-traumatic stress disorder (PTSD) treatment response. We report on an observational, longitudinal study with 45 U.S. veterans in outpatient PTSD care, who had deployed to Iraq or Afghanistan. HR and HRV were collected before, during, and after virtual reality (VR) combat and civilian scenes. HRV recovery was defined as HRV after a 3-minute VR simulation minus HRV during a VR scene. mStroop threat variables included index scores for combat and general threat. Self-report data were collected at baseline and 6 months later. The outcome variable was the 17-item Clinician Administered PTSD Scale (CAPS). Controlling for baseline CAPS and number of combat experiences, the following baseline HRV recovery variables were significant predictors of 6-month CAPS: standard deviation of normal beat to beat interval (SDNN) after combat scene minus SDNN during combat scene and low-frequency (LF HRV) after civilian scene minus LF during civilian scene. HRV at rest, HR reactivity, HR recovery, and mStroop scores did not predict treatment response. In conclusion, HRV recovery variables in the context of a standardized VR stressor were significant predictors of PTSD treatment response after controlling for baseline CAPS and number of combat experiences. The direction of this relationship indicates that greater baseline HRV recovery predicts lower 6-month PTSD symptom severity. This was an exploratory study in need of replication.

Keywords: stress disorders, post-traumatic, combat disorders, heart rate variability, heart rate, attentional bias, prediction

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Introduction

Approximately 3 million service members were deployed to Iraq and Afghanistan since September 11, 2001, as part of the U.S. Operation Iraqi Freedom (OIF) and/or Operation Enduring Freedom (OEF). Approximately 2 million of these service members have become eligible for VA health care.[1] Through the third quarter of fiscal year 2015, a cumulative total of 393,139 of these service members used VA services and were diagnosed with post-traumatic stress disorder (PTSD). This subset of VA service users represents 20.0 percent of the eligible veterans and 32.2 percent of the veterans utilizing VA health care services.[1] Although the VA offers multiple trauma-focused evidence-based psychotherapies for PTSD, clinicians do not have tools to predict which patients are most likely to respond to treatment in general or match patients with specific treatments.

Predicting treatment response is a long-standing goal of mental health care,[2] including PTSD care. Models explaining the development and maintenance of PTSD emphasize physiological arousal[3] and dysfunctional information processing mechanisms, including attentional bias.[4] PTSD diagnostic criteria include increased physiological and cognitive reactivity to trauma reminders. Likewise, physiological and cognitive flexibility have been theorized as regulatory strengths[5] that promote resilience[6,7] and both are associated with decreased PTSD symptoms.[8,9] Measures of physiological and cognitive flexibility may be useful predictors of PTSD treatment response.

PTSD treatment response predictors generally fall into three categories as follows: biomarkers, cognitive markers, and self-report. A systematic review of 20 studies examining biomarkers as predictors of evidence-based PTSD psychotherapy outcomes included 9 veteran studies with the following biomarkers: neuroimaging (3 studies), serum glucocorticoids (2 studies), genetic factors (2 studies), and heart rate (HR)/electrodermal activity (2 studies).[10] Other studies found that pretreatment HR reactivity to imaginal exposure[11] or a personal trauma script[12] predicted better response to imaginal flooding therapy and prolonged exposure therapy, respectively.

Heart rate variability (HRV) is another potential biomarker related to PTSD. In a nonveteran sample of patients in substance abuse treatment with comorbid PTSD, higher baseline (at rest no stimuli) high-frequency (HF) HRV was associated with greater post-treatment PTSD symptom reduction.[13] Similarly, in a nonveteran sample, higher baseline HF predicted anxious depression treatment response to antidepressant medications.[14] HRV is generally understood as a measure of autonomic nervous system balance and flexibility, and HF HRV is positively associated with parasympathetic activity, which acts as a brake to sympathetic activity, resulting in greater emotion regulation.[15,16] In general, increased stress and PTSD symptoms are associated with lower HRV.[8]

Cognitive theories of psychopathology suggest that information-processing biases are important in the development of emotional disorders, including PTSD.[17] For example, some cognitive conceptualizations suggest that PTSD development is at least partially due to a sustained hypervigilance to threat stimuli, which perpetuates hyperarousal and other symptoms of PTSD.[18] Other evidenced-based conceptualizations suggest that attentional processing in PTSD is characterized by attentional bias variability; that is, alternatingly attending to and away from threat stimuli.[19] Presumably, this attentional bias variability reflects an impaired attentional control system, which in turn serves as a causative factor in the development and maintenance of PTSD symptoms. Regardless of the model, however, biases in attentional processes are hypothesized to be a risk factor for the maintenance of PTSD symptoms.

The following self-report variables have been reported to predict veteran PTSD treatment response: less combat exposure,[20,21] less severe depression,[22,23] less anger,[23] and less alcohol use.[23] However, in one of the largest randomized controlled medication trials in veterans with PTSD, there were no consistent self-report predictors of treatment response.[24]

In this exploratory study, we examined autonomic (HR, HRV) and attentional bias (modified Stroop task [mStroop]) measures predicting veteran PTSD treatment response after controlling for self-report variables. HR and HRV were measured at rest, during a standardized virtual reality (VR) stressor, and after the VR stressor. We hypothesized that greater autonomic and attentional processing flexibility as measured by HR, HRV, and mStroop would predict PTSD treatment response.

Materials and Methods

Design

Observational and longitudinal data were collected at baseline and 6 months from PTSD treatment-seeking veterans. The study protocol and informed consent procedures were approved by the Central Arkansas Veterans Healthcare System Internal Review Board and Research and Development Committees.

Subject eligibility

Inclusion criteria were currently receiving medication and/or counseling for PTSD at baseline; age 18 to 60; deployed to OEF or OIF; and willing to provide the name and phone number of at least one contact person, in case of difficulty locating them for follow-up assessment. Exclusion criteria were inability to don the VR headset; current diagnosis of schizophrenia; daily use of benzodiazepines except as needed for sleep; daily use of alpha-adrenergic antagonists or beta-blockers; plans to leave the area within 6 months; diagnosis of color-blindness by a physician and inability to recognize the primary colors red, blue, and green; and previous treatment with a VR-assisted intervention. The rationale for the benzodiazepine, adrenergic, or beta-blocker medication exclusion criteria was because these medications could affect participant response to simulated stressors and/or HR directly.

Recruitment and screening

Veterans were recruited from the VA outpatient mental health clinics and local National Guard and Reserve military bases by self-referral and clinician referral. A total of 101 participants completed the baseline assessment. Of these, 67.3 percent (68/101) completed the 6-month assessment.

Forty-five of these participants (45/68, 66.2 percent) had usable HRV data. Twenty-three participants (23/68, 33.8 percent) did not have usable HRV data because of equipment malfunction and/or excessive participant movement. There were no statistically significant differences in study variables between participants with usable versus nonusable HRV data, except that participants with nonusable HRV data reported higher Buss–Perry Aggression Scale scores ($p = 0.005$).

Procedure

Interview, self-report, physiological, and attentional bias data were collected during a 3- to 4-hour assessment at baseline and 6 months. Physiological and attentional bias data were collected before self-report measures in this order: at rest HR and HRV; mStroop; and HR and HRV collected before, during, and after two 3-minute VR simulations (combat and civilian scenes). The order of the combat and civilian scenes was randomized.

VR environments

Combat and civilian VR environments were developed by Virtual Reality Medical Centers. The combat scene placed participants in a military patrol walking into and through a small Iraqi market, with some distant gunfire and an explosion that resulted in people in the market taking cover. The civilian scene placed participants walking alone on the sidewalk of a U.S. city. There was an increasing number of people on the sidewalk and the sound of a car screeching to a stop, a post office mailbox closing, and glass breaking. In both VR environments, the stimulus intensity increased and then decreased and faded to black. Participants experienced 3 minutes in the first VR environment, 5 minutes of rest, 3 minutes in the second VR environment, and 5 minutes of rest.

Equipment included a Fifth Dimension Display head mount display 800-26 2D, Intersense Inertia Cube 2 for visual stimuli, and headphones for auditory stimuli. During the rest periods, the position of the VR headset eyepieces was moved up and out of view.

Measures of autonomic flexibility

HRV and HR were used to measure autonomic flexibility. HRV data collection for this study is described in more detail elsewhere.[25,26] Electrocardiogram data were used to determine the inter beat intervals (IBIs) measured in milliseconds and calculate the standard deviation of normal beat to beat interval (SDNN) and low frequency (LF, 0.04–0.15 Hz) and HF (HF, 0.15–0.4 Hz) power (ms^2). In general, both parasympathetic and sympathetic activities contribute to SDNN and LF and parasympathetic activity contributes to HF. The IBI data were cleaned and calculations for HRV indices were made using Kubios HRV analysis software version 2.0.[27] Participants requiring correction of >10 percent of IBIs were excluded from analysis. Three-minute segments were used for calculating HRV at baseline, during VR, and during the rest periods because at least 2 minutes is recommended for measuring LF.[28]

HRV measurement and analyses were conducted according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[29]

HRV recovery is increasingly used in sports physiology to indicate if an athlete has physically recovered sufficiently to continue training and prevent overtraining syndrome.[30] HRV recovery or bounce back is also consistent with the concept of resilience.[31] In the current study, HRV recovery was defined as HRV ''bouncing back'' immediately after a standardized VR stressor. HRV recovery was calculated by subtracting HRV (SDNN, HF, and LF) during the VR scene from HRV immediately following the VR scene. HRV recovery was calculated separately for the combat and civilian VR scenes.

Mean HR was measured in beats per minute for the same segments as HRV. HR reactivity was defined as the difference between HR during the VR scene minus the HR immediately before the VR scene. HR recovery was defined as the mean HR during the VR scene minus mean HR after VR scene so that recovery for HR and HRV would both result in a positive value.

Measures of attentional processing flexibility

The mStroop was utilized as a measure of attentional bias because of its robust capacity to measure attentional biases associated with processing emotional and threat-relevant stimuli. The mStroop is a variant of the original Stroop task that requires individuals to color-name trauma-relevant and trauma-irrelevant words. The mStroop used in this study is described in more detail elsewhere.[32] Briefly, participants were presented with lexical stimuli and were instructed to name the color of the words ''as quickly and as accurately'' as possible. Twelve words in three categories were used as lexical stimuli: neutral words (e.g., microwave, carpet), social threat words (e.g., pathetic, mistake), and OEF/OIF combat words (e.g., IED, firefight).

Two separate threat indices were calculated for each participant: a combat word interference index (mean combat word response time minus mean neutral word response time) and a similar general threat word interference index. Positive threat index values indicate greater attentional bias to threat-related words and negative threat index values indicate greater cognitive flexibility.

Self-report measures

The following predictors were examined: military history, PTSD, traumatic brain injury (TBI), depression, anger/aggression, and alcohol dependence. Military measures included number of deployments and level of combat exposure. The number of combat experiences was measured using the 16-item Combat Experiences Survey for any deployment period.[33] PTSD symptom severity was measured using the 17-item Clinician Administered PTSD Scale (CAPS) based on the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV).[34] The DoD Post-Deployment Health Assessment TBI items were used to assess deployment-related TBI symptoms.[35] Depression severity was measured using the Patient Health Questionnaire 9-item depression module (PHQ-9).[36] Anger/aggression was measured using the 29-item Buss–Perry aggression scale.[37] Comorbid alcohol dependence was measured using the DSM-IV version of the Mini-International

Neuropsychiatric Interview (MINI).[38] Postdeployment social support was measured using the Postdeployment Social Support from the National Center for PTSD.[39] The presence or immersion experienced during the VR environments was measured using 7 items from the Presence Questionnaire version 2.0.[40] Three items were from the sensory factor and two items each from the realism and control factors. Subjective units of distress (SUD) were collected immediately after each VR environment on a 0 = not anxious at all to 100 = extremely anxious. Additional self-report measures included the following: sociodemographic, current mental health treatment for PTSD (Yes/No), and current mental health medications.

Statistical analyses

A descriptive summary of the sample is presented in Table 1. Two-tailed Pearson bivariate correlations of predictors with baseline and 6-month CAPS are presented in Table 2. Covariates of interest for the main models were baseline variables that were correlated with 6-month CAPS $p < 0.05$ (Table 2). Covariates of interest for the secondary models were those that were correlated with 6-month CAPS $p < 0.20$ in Table 2. The PHQ-9 was used in secondary models because these analyses were focused on response to PTSD treatment. General linear model results for the main models are presented in Table 3. Covariates included baseline CAPS score and number of combat experiences (Step 1).

In Step 2, because of limited power, predictors of interest (autonomic and attentional bias measures) were added individually to the Step 1 model in separate equations (Table 3). Because HF and LF measures were (and typically are) highly skewed, they were natural log transformed. Secondary models (Step 3) analyzed the effect of other baseline predictors that were bivariately correlated with 6-month CAPS in Table 2 (e.g., PHQ-9 [$p = 0.001$], Buss–Perry aggression scale score [$p = 0.10$], deployment-related TBI [$p = 0.10$], and postdeployment support [$p = 0.10$] or known to affect HRV [e.g., age, gender, and race]).

Secondary predictors were added individually to the Step 2 models (baseline CAPS, number of combat experiences, and any significant physiological or attentional bias measures) in separate Step 3 equations. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using a 2×2 paired contingency table: positive and negative HRV recovery variables (rows) by positive and negative CAPS response (columns). Positive CAPS response is defined as the 6-month CAPS being less than the baseline CAPS.

Table 1. Baseline Characteristics of Veterans in Treatment for Post-Traumatic Stress Disorder Sample[a]

Scalar or ordinal variables	*Mean (*SD*)*
Age	35.7 (9.5)
Baseline PTSD (CAPS)	70.6 (24.1)
Baseline depression (PHQ-9 scale total)	15.2 (6.5)
Aggression (Buss–Perry scale total)	93.0 (19.6)
No. of deployments	2.0 (1.4)
No. of combat experiences	9.5 (3.6)
Postdeployment support	51.1 (12.5)
Combat scene virtual reality presence score	39.6 (7.7)
Civilian scene virtual reality presence score	39.6 (6.1)
Combat scene subjective units of distress	63.7 (32.2)
Civilian scene subjective units of distress	34.0 (26.5)
Baseline heart rate	76.7 (10.5)
Baseline SDNN, ms	30.6 (15.3)
Baseline HF, ms^2	424.1 (774.1)
Baseline LF, ms^2	636.0 (857.5)
Stroop general threat index, ms	25.2 (125.8)
Stroop combat index, ms	102.9 (166.9)
Categorical variables	N *(%)*
Gender male	41 (91.1)
Race non-Hispanic white	22 (48.9)
At least some college	32 (71.1)
Married or cohabitating	30 (66.7)
Any baseline psychotropic medication treatment	36 (80.0)
Baseline antidepressant treatment	33 (73.3)
Baseline CAPS ≥ 50	37 (82.2)
Baseline PHQ-9 ≥ 10	34 (75.6)
Alcohol dependence or abuse, current	13 (28.9)
Deployment-related TBI	26 (57.8)

[a]$N = 45$.

CAPS, Clinician Administered PTSD Scale; HF, high frequency; LF low frequency; PHQ-9, Patient Health Questionnaire, 9-item version; PTSD, posttraumatic stress disorder; *SD*, standard deviation; SDNN, standard deviation of normal beat; TBI, traumatic brain injury.

Results

Veteran participants in this sample were young, mostly male, and most with some college education (Table 1). Most participants were taking psychotropic medications (36/45, 80 percent) and of these, 33 (92 percent) were taking antidepressant medications. Most participants had baseline PTSD checklist scores ≥ 50 (37/45, 82.2 percent) and PHQ-9 scores ≥ 10 (34/45, 75.6 percent). The mean number of military deployments was two and the number of combat experiences ranged from 1 to 16. Total presence scores were very similar for combat and civilian VR environments and SUD scores were significantly higher for the combat than the civilian environment (63.7 vs. 34.0, $p < 0.001$). Compared with available norms, baseline HRV values were generally lower than reported for healthy adults.[41]

Baseline sociodemographic, clinical, military, physiological, and attentional bias measure correlations with baseline and 6-month PTSD (CAPS score) are shown in Table 2. Significant positive correlations between baseline variables and baseline PTSD (CAPS) were baseline depression (PHQ-9), aggression (Buss–Perry), number of combat experiences, deployment-related TBI, HR, and combat word interference index. Postdeployment support was significantly and inversely correlated with baseline PTSD (CAPS).

Significant positive correlations between baseline variables and 6-month PTSD (CAPS) were baseline PTSD (CAPS), depression (PHQ-9), and number of combat experiences. Significant inverse correlations were SDNN combat recovery (SDNN after combat scene minus during combat scene) and LF civilian recovery (LF after civilian scene minus civilian scene). Nonsignificant correlations with 6-month PTSD (CAPS) were baseline aggression (Buss–Perry),

Table 2. Pearson Correlation Matrix with Baseline and 6-Month Clinician Administered Post-Traumatic Stress Disorder Scale

Variable	r *with baseline PTSD (CAPS)*	p	r *with 6-month PTSD (CAPS)*	p
Age	–0.14	0.35	0.04	0.80
Gender, male	–0.02	0.88	–0.12	0.43
Race Caucasian	0.23	0.12	0.14	0.37
Any psychotropic medication	–0.06	0.70	0.09	0.57
Antidepressant medication	0.05	0.74	0.15	0.33
Alcohol dependence current	0.19	0.21	0.10	0.52
Baseline PTSD (CAPS)	—	—	0.57	<0.001
Baseline depression (PHQ-9)	0.71	<0.001	0.46	0.001
Baseline aggression (Buss–Perry)	0.50	0.001	0.25	0.10
No. of deployments	0.17	0.25	0.19	0.20
Combat experiences	0.36	0.01	0.36	0.02
Deployment-related TBI	0.31	0.04	0.25	0.10
Postdeployment support	–0.32	0.03	–0.25	0.10
Heart rate baseline	0.32	0.04	0.14	0.39
SDNN baseline	–0.16	0.29	–0.07	0.62
HF baseline	–0.03	0.85	–0.06	0.70
LF baseline	0.07	0.63	0.13	0.38
Heart rate reactivity, combat scene	0.21	0.19	0.11	0.51
Heart rate reactivity, civilian scene	–0.14	0.37	–0.07	0.67
Heart rate resilience, combat scene	0.11	0.50	0.12	0.46
Heart rate resilience, civilian scene	0.06	0.67	0.12	0.46
SDNN recovery—combat scene	–0.12	0.42	–0.32	0.03
SDNN recovery—civilian scene	0.11	0.48	–0.29	0.06
HF recovery—combat scene	–0.06	0.68	–0.12	0.43
HF recovery—civilian scene	0.05	0.76	–0.23	0.13
LF recovery—combat scene	–0.11	0.48	–0.21	0.16
LF recovery—civilian scene	–0.16	0.31	–0.38	0.01
Word Stroop General Threat Index	0.28	0.06	0.13	0.40
Word Stroop Combat Index	0.30	0.04	0.08	0.61

Note. $N = 45$. HF and LF values were natural log transformed because of skewed distribution.

deployment-related TBI, postdeployment support (all $p = 0.10$), HF civilian recovery ($p = 0.13$), LF combat recovery ($p = 0.16$) and HR reactivity, HR recovery, and mStroop index scores (all $p > 0.20$).

Multivariate general linear models were used to evaluate the effect of physiological and attentional bias measures on 6-month PTSD (CAPS), controlling for baseline PTSD (CAPS) and number of combat experiences. The variance explained by this 2-factor model was 35 percent, and the baseline CAPS was the only significant predictor ($\beta = 0.51$, $p = 0.001$); number of combat experiences was not significant ($p = 0.20$). Because of the limited sample size, HRV variables were added one at a time in separate equations to the base model in Step 2. When so added, SDNN combat recovery and LF civilian recovery were the only significant physiological predictors of 6-month PTSD, explaining an additional 10 and 7 percent of the variance, respectively (Table 3).

The effects of the other HRV recovery variables in Step 2 were not statistically significant, p's ranging from 0.050 for HF civilian recovery to 0.411 for HF combat recovery. As measured by SDNN combat recovery, HRV recovery predicted decreased PTSD over 6 months (positive response in CAPS score), PPV = 0.61, NPV = 0.33, sensitivity = 0.79, and specificity = 0.18. Similarly, as measured by LF civilian recovery, HRV recovery predicted decreased PTSD over 6 months, PPV = 0.75, NPV = 0.36, sensitivity = 0.75, and specificity = 0.23.

The HR and mStroop predictors of interest were not significant predictors, when added to the base model (Step 2).

Table 3. Models Predicting 6-Month Post-Traumatic Stress Disorder (Clinician Administered Post-Traumatic Stress Disorder Scale Score)

	Estimate	*SE*	*T*	*p*	*95% CI*
Baseline CAPS	0.45	0.13	3.35	0.002	0.178 to 0.721
No. of combat experiences	1.94	0.91	2.14	0.04	0.109 to 3.781
SDNN recovery—combat scene	–0.76	0.28	–2.70	0.01	–1.336 to –0.194
Baseline CAPS	0.51	0.14	3.76	<0.001	0.236 to 0.784
No. of combat experiences	0.81	0.92	0.88	0.38	–1.043 to 2.664
LF recovery—civilian scene	–7.19	3.17	–2.27	0.03	–13.595 to –0.784

Note. Covariates included baseline CAPS and number of combat experiences. LF values were natural log transformed. In the above models, baseline CAPS and number of combat experiences were correlated, but the variance inflation factor was <2, so both variables remained in the model.

The significance and direction of HRV results were unchanged when depression (PHQ-9), deployment-related TBI, aggression (Buss–Perry total score), age, race, or gender was added individually in separate equations (Step 3) to the HRV recovery equations reported in Table 3.

Discussion

This study reported cross-sectional and longitudinal relationships between physiological measures (HR, HRV, HRV recovery, HRV reactivity) and attentional bias measures (mStroop) and PTSD symptom severity, in veterans being treated for PTSD. While multiple predictor variables were correlated with PTSD symptoms at baseline, the most significant longitudinal predictors of 6-month PTSD (CAPS) in multivariate models were baseline PTSD (CAPS) and HRV recovery measures (SDNN combat recovery and LF civilian recovery). These HRV recovery measures explained an additional 7 to 10 percent of the variance in separate multivariate equations. These results support HRV recovery as a physiological measure predicting PTSD treatment response. Post-traumatic resilience is generally defined as the ability to bounce back from a stressor.[42] This finding is consistent with self-report resilience predicting PTSD treatment response,[43,44] and demonstrates that an objective measure of resilience also predicts treatment response.

The PPVs and NPVs reported in this exploratory study provide additional (although limited) support for the clinical relevance of HRV recovery variables predicting treatment response. Future work should consider collecting HRV recovery variables at the start of clinical trials, where the treatment provided is controlled and adherence is monitored. In addition, the characteristics of different HRV recovery thresholds could be meaningfully examined. If HRV recovery variables are found to be useful predictors of treatment response, additional HRV resilience training could then be tested as an adjunct treatment for veterans whose HRV recovery is below the identified threshold.

In addition, HRV recovery measures were significant predictors for both combat and civilian VR scenes even though SUD scores were significantly higher for the combat versus civilian scenes. This finding suggests that physiological measures can differ from self-report and that common civilian sounds and/or places may trigger or remind a veteran of a traumatic event, which is consistent with the generalized distress often reported by veterans in public during their daily civilian life. This is particularly salient for clinicians and researchers relying on subjective measures with patients in treatment for PTSD.

Baseline combat interference index was significantly correlated with baseline PTSD symptom severity, but not with or predicting 6-month PTSD. The cross-sectional relationship between attentional bias and PTSD is similar to findings from meta-analytic studies investigating the relationship between PTSD and attentional bias, particularly when using the mStroop,[45,46] and studies of general cognitive flexibility.[47] We are not aware of literature where mStroop predicts PTSD treatment response, although a small study did show that attentional bias diminishes after symptom amelioration.[48] One potential reason for the lack of a significant longitudinal effect of attentional bias on PTSD is that behavioral measures, such as the mStroop, have lower reliability relative to self-report or physiological measures, which limits predictive validity.[49]

Another explanation for the lack of a longitudinal effect is that attentional bias is a product of emotional disorders but is not a predictive or causative factor in the development or maintenance of an emotional disorder. In possible support of this latter suggestion, Henricks et al. found that interpretation bias, but not attentional bias, predicted longitudinal development of social anxiety in adolescents.[50]

The nonsignificant results for VR HR reactivity are not consistent with a report of HR reactivity to a script-driven imagery task predicting a prolonged exposure treatment response in a veteran sample.[12] Both studies used 3-minute stimulus intervals. Differences included personalized script-driven imagery versus standardized VR environments. The present study also did not control for type of PTSD treatment. These differences may explain the nonsignificant HR findings for the present study. In addition, HR has been reported to be less sensitive to acute stressors than HRV.[51]

Baseline HRV did not predict PTSD treatment response, but consistent with the literature, the baseline HRV measures were lower than those reported for control participants.[10] As expected for a treatment sample, the HRV measures reported here were also lower than for nontreatment samples of active duty Marines[52] and Army National Guard soldiers predeployment.[53]

Strengths and limitations of the study

Strengths of this study include the longitudinal study design and use of the CAPS, the gold standard measure of PTSD symptom severity.[34] Eligibility criteria were kept to a minimum, and therefore, the sample is more representative of veterans seeking VA treatment than might be included in a clinical trial. Limitations of this study include its exploratory design, use of multiple statistical tests, and setting α to 0.05. To reduce the risk of type I error, replication is needed. The sample included OEF/OIF veterans only, and so, it is unknown whether findings generalize to other populations. Type of PTSD treatment was not controlled, nor was adherence monitored, so these data do not address the question of predicting response to specific treatments. There was a large amount of unusable HRV data (33.8 percent) for this sample, which may have been due, in part, to mStroop data being collected between baseline (at rest) and VR data collection.

Conclusions

HRV recovery measures following a standardized stressor were significant predictors of PTSD treatment response. This was an exploratory study. HRV measurement and VR equipment are now more user-friendly and less expensive. Future research is needed to replicate these results in studies that control for treatment modality and treatment adherence.

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Authors' Contributions

J.M.P.: conceptualization (equal); funding acquisition (lead); methodology (equal); supervision (lead); and writing—original draft (lead). J.I.C.: conceptualization (equal);

methodology (equal); and writing—review and editing (equal). B.K.W.: conceptualization (equal) and writing—review and editing (equal). S.J.: conceptualization (supporting); data curation (lead); investigation (lead); project administration (lead); and writing—review and editing (supporting). A.R.: writing—review and editing (equal). B.H.: formal analysis (lead). M.C.W.: writing—review and editing (equal). K.D.H.: writing—review and editing (equal). M.D.W: conceptualization (equal) and writing—review and editing (equal).

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