Heart Rate Response to Fear Conditioning and Virtual Reality in Subthreshold PTSD

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Abstract. Posttraumatic stress disorder (PTSD) is a significant health concern for U.S. military service members (SMs) returning from Afghanistan and Iraq. Early intervention to prevent chronic disability requires greater understanding of subthreshold PTSD symptoms, which are associated with impaired physical health, mental health, and risk for delayed onset PTSD. We report a comparison of physiologic responses for recently deployed SMs with high and low subthreshold PTSD symptoms, respectively, to a fear conditioning task and novel virtual reality paradigm (Virtual Iraq). The high symptom group demonstrated elevated heart rate (HR) response during fear conditioning. Virtual reality sequences evoked significant HR responses which predicted variance of the PTSD Checklist-Military Version self-report. Our results support the value of physiologic assessment during fear conditioning and combat-related virtual reality exposure as complementary tools in detecting subthreshold PTSD symptoms in Veterans.

Keywords. Subthreshold Posttraumatic stress disorder, Fear Conditioning, Virtual Reality, Heart Rate

Introduction

Deployment to Afghanistan or Iraq is associated with significantly higher rates of posttraumatic stress disorder (PTSD) than is seen in services members (SMs) who have not been deployed [1]. Since there is often a lag time of several months before returning SMs report significant symptoms, this affords an opportunity for an intervention such as cognitive behavioral therapy to reduce symptoms and prevent progression [2, 3], but the sheer number of deployed service members makes it impractical to intervene for all, and this requires reliable early identification of those at highest risk. The presence of subthreshold symptoms provides a surrogate means of risk stratification, since the presence of subthreshold PTSD alone is associated with significant functional impairment [4, 5], as well as elevated risk for progression to full PTSD [6-8]. The aim of this study is to begin to improve upon the power of such screens by examining the correlation between physiologic responses to both a fear

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conditioning task and combated-related virtual reality scenarios taken from Virtual Iraq with the presence of subthreshold symptoms in a recently deployed population.

Classical fear conditioning provides a model for understanding the development of PTSD. A neutral (conditioned) stimulus is paired with an aversive (unconditioned) stimulus to elicit a fear response. The subject is then primed to display a similar physiological reaction to the conditioned stimulus alone as they initially had to the unconditioned event [9]. Patients with PTSD demonstrate hyperresponsitivity to such fear conditioning paradigms, a pattern believed to be mediated by the amygdala, a brain region that is integral to fear processing. The amygdala has a particularly potent influence on heart rate (HR) [10], acting through the sympathetic nervous system hypothalamic-pituitary-adrenal axis [11].We postulate that combat-related stimuli may prove particularly effective in distinguishing those at greatest risk for combat-related PTSD. Virtual reality (VR) has been employed with some success in PTSD treatment [12-14] but physiologic responses to the VR presentation has not been previously reported as a means of PTSD risk stratification. We therefore report the heart rate response observed during fear conditioning and virtual reality exposures in a cohort of SMs within 2 months after their return from Iraq or Afghanistan. For the purposes of this analysis, we divided the SMs into two groups in accord with their PTSD Checklist-Military Version (PCL-M) score: those with high subthreshold PTSD scores (28-49) and those with low scores (below 28). We anticipated that the high symptom group would be characterized by an elevated heart rate response to both forms of physiologic stimulation.

Methods

1. Participants

The data reported was compiled from 78 SMs (11 women) with a mean age of 29.72 (SD 7.91; range 19-51) who were assessed within two months after return from a deployment to Iraq or Afghanistan. Of an initial cohort of 85 SMs, 4 were excluded because they already met criteria for PTSD (2) or Major Depressive Disorder (2) and 3 were excluded from the analysis due to recording problems with the physiologic data.

2. Data Acquisition and Analysis

Data reported was collected during the baseline assessment of a longitudinal study seeking to identify early predictors of PTSD at the National Intrepid Center of Excellence, Walter Reed National Military Medical Center (WRNMMC), Bethesda, Maryland. The study was funded by the Center for Neuroscience and Regenerative Medicine, and the design was approved by institutional review boards at WRNMMC, Uniformed Services University, and the National Institutes of Health.

All participants completed the PCL-M, a validated self-administered screen for PTSD [15]. Physiologic responses were recorded during both fear conditioning and virtual reality tasks. For fear conditioning, participants were presented with a combination of colored shapes that were paired with a 140 psi airblast to the larynx (danger cue, AX), and a different pattern of colored shapes heralding no ensuing airblast (safety cue, BX). There were 3 blocks with 12 trials (4 AX, 4 BX) in each block [16]. The second psychophysiological assessment featured three 2-minute sequences in a highly realistic Virtual Iraq environment. Two of the sequences represent a perspective from a HUMVEE in a convoy that is confronted with improvised explosive devices (IEDs) and ambushes. The third sequence involves a foot patrol that proceeds through a village marketplace where there are explosions and terrorists firing rocket-propelled grenades (Figure 1).

Figure 1. Sample scene from "Virtual Iraq"

Psychophysiologic data was recorded with Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA) sampled at 1000 Hz, digitized at 16 bit A/D resolution, and amplified. Using the Biopac Acknowledge software, the ECG signal was band pass filtered at 0.5-35 Hz and converted to heart rate in beats per minute. The data were exported to Microsoft Excel, and HR difference score for each AX and BX condition was calculated by subtracting the mean level for the 2 seconds (s) immediately preceding shape onset from the highest value among those recorded during the 6 s shape presentation interval [17]. During each VR session, mean HR values were computed during the 2 minute viewing period.

Three-way analysis of variance (ANOVA): Group (high symptom, low symptom)*Condition (AX, BX) *Time(early, middle, late) was used to examine group differences during fear conditioning. Post hoc analyses were executed using Tukey's LSD. Linear regression was performed to determine whether the PCL-M scores were predicted by the heart rate response from each period of VR.

Results

A significant Group*Condition*Time interaction was evident during the fear conditioning experiment (Figure 2), $F(2,52)=2.998$, $p=0.05$. The high symptom group had significantly greater HR responses in 2 of 3 time periods studied for both the danger (AX) and safety cues. Specifically, those with higher subthreshold symptoms reacted more strongly during the early and late periods in response to the danger cues, and during the mid and late periods in response to safety cues.

Linear regression revealed that HR across all VR sequences accounted for a significant amount of the variance in PCL-M scores $F(3,74)=3.7$, $p=0.016$, $R_2=.139$.

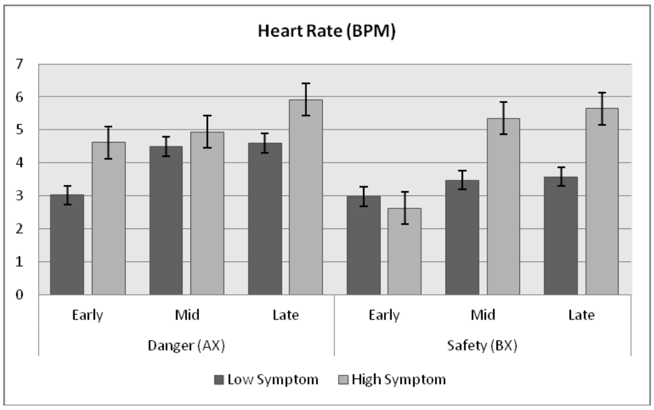

Figure 2. Significant Group*Condition*Time interaction during fear conditioning. Average HR responses during the early, middle and late time phases of fear conditioning are displayed, with standard error margins.

Discussion

Early detection of those at highest risk for PTSD may facilitate greater success in treatment intervention. Specifically, those with subthreshold PTSD symptoms represent an important population given the significant functional impairment and associated risk for delayed onset PTSD. Our results provide converging evidence of the utility of physiological measures in detecting symptoms in SMs who have recently returned from deployment.

The fear conditioning task identified significantly higher HR responses to both danger and safety cues for the high symptom group relative to the low symptom group. This is consistent with the belief that the hyperarousal features of PTSD are manifestations of sensitization and overgeneralization of the fear response [18], possibly mediated by hypoactivity in ventromedial prefrontal cortex, a brain region involved in inhibitory control, [19] along with corresponding hyperactivity in the amygdala [10]. Such a neural response may result in resistance to emotion regulation such that emotional attention is maintained at a higher level [20], which could be advantageous in situations such as deployment where threat detection is of importance. However, maintained elevation of such an increased response to emotional stimuli post-deployment could be quite counterproductive, and has in fact been documented in anxiety disorders [20] . Our findings suggest that similar patterns are evident even in those with subthreshold symptoms, consistent with prior reports that such subthreshold are associated with significant functional impairment. Our results further support efforts to intervene in those with subthreshold symptoms, and it is intuitive that such approaches should be conducted as early as possible, since delay will inevitably result in higher rates of full-blown PTSD, which can be expected to be more difficult to treat. Most notably, low intensity treatment may be effective in those with subthreshold PTSD, even though it does not necessarily successfully treat fully developed PTSD [21].

Virtual reality has proven to be a valuable option for treating behavioral disorders, including PTSD [12-14]. Our results significantly expand the scope of potential applications of VR by demonstrating that measurement of a single physiologic response explains approximately 14% of the variance in PCL-M self-report. This novel technology warrants further study in this regard to better define and validate its potential as a method for risk stratification in PTSD and other anxiety disorders.

Identification of PTSD symptoms upon return from deployment could facilitate early intervention to prevent disability. We believe that an approach that combines multiple physiologic tasks and measures is likely to prove particularly adept in the risk stratification of SMs and other populations. This can in turn engender early psychoeducation and other cognitive behavioral efforts to markedly reduce PTSD symptoms, progression to full-blown disorders, and associated functional impairment.

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