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Altered Resting Psychophysiology and Startle Response in Croatian Combat Veterans with PTSD

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Abstract

Posttraumatic stress disorder (PTSD) is a prolonged reaction to an extremely traumatic experience. One of the core symptoms of PTSD is hyper-arousal which can be the result of an elevated activation of the autonomic nervous system. Including psychophysiological assessment methods in PTSD research can point to the neurobiological bases of the disorder. The studies of psychophysiology of PTSD to date have mostly measured reactivity. The aim of the current study was to compare resting state psychophysiology and startle reflexes in PTSD patients and controls in a sample of Croatian combat veterans. We measured heart-rate, respiratory sinus arrhythmia, skin conductance, and eyeblink muscle contraction during an acclimation period and during the presentation of startle stimuli in 45 male PTSD patients and 33 male healthy controls. We found that PTSD patient had elevated baseline heart-rate and decreased respiratory sinus arrhythmia compared to the controls. Furthermore, PTSD patients had impaired habituation to the startle probe, but there was no group difference in initial startle magnitude. There was also no group difference in skin conductance level or skin conductance response. Startle habituation and baseline heart-rate appear to offer the most reliable psychophysiological indices of PTSD. This finding replicates trends in the literature in a new population of PTSD patients.

Keywords

PTSD; psychophysiology; heart-rate; skin conductance; startle reflex

1. Introduction

Posttraumatic stress disorder (PTSD) is a prolonged reaction to an extremely traumatic experience. It is frequently difficult to make a PTSD diagnosis with absolute certainty. Due to the complicated differential diagnosis of PTSD and the fact that the diagnosis is based largely on self-report of symptoms, PTSD is not difficult to malingering. If 'secondary gain' is involved, the problem is exaggerated, which is especially present in forensic evaluations. PTSD can be isolated or comorbid with other psychiatric disorders (Kozaric-Kovacic and Borovecki, 2005a), which can also be malingered (Kozaric-Kovacic et al., 2003; Kozaric-Kovacic and Borovecki, 2005b).

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Based on the DSM-IV criterion of hyper-arousal in PTSD (APA, 1994), several investigators have examined the utility of psychophysiological recording as an aid to accurately diagnosing the disorder (see Orr et al., 2004 for recent review). Most of these studies have employed multiple psychophysiological methodologies to record cardiovascular, electrodermal, and electromyographic activity. The first two systems are under the control of the autonomic nervous system, whereas the last is under the control of the central nervous system (Cacciopo et al., 2004). The cardiovascular measurements include: (1) electrocardiograms (ECG) as a measure of both sympathetic and parasympathetic nervous system activity and (2) respiratory sinus arrhythmia (RSA) as an index of heart-rate variability or parasympathetic nervous system activity (Porges, 2007). Electrodermal activity (EDA) measures changes in sweat gland activity and these changes are measured from the skin on the fingers. Electromyographic (EMG) assessments include measuring activity from the control facial expression and eyeblink.

Early studies of the utility of physiology in assessing PTSD used combat-related stimuli to evoke arousal in Vietnam veterans with PTSD. Studies successfully discriminated veterans with or without PTSD on the basis of heart-rate responses to combat sounds (Pallmeyer et al., 1986). In studies using scripts, in which every participant describes an actual traumatic event from their combat experience (Pitman et al., 1987), PTSD patients show a greater physiological response compared to traumatized persons without PTSD. A large study of 1,461 Vietnam veterans demonstrated that physiological data offer a useful and objective, although not independent, assessment of the disorder (Keane et al., 1998).

Although exaggerated startle response was one of the earliest symptoms related to combat stress, the psychophysiological evaluation of startle in PTSD patients has not yielded consistent results; in fact, this finding is the most equivocal of all (reviewed in Orr et al., 2004). Studies of Gulf War veterans with PTSD found both self-reported (Southwick et al., 1995) and physiologically (Morgan et al., 1996) exaggerated startle compared to non-PTSD veterans. On the other hand, Vietnam veterans with PTSD did not show increased startle (Grillon et al., 1996), unless they were subjected to a threatening context (Grillon et al., 1998). Grillon (Grillon and Baas, 2003) concluded that increased baseline startle may be related to the recency of combat exposure and may decline after a few years. Several studies have examined physiological activity during startle and have found increased heart-rate (HR) and skin conductance (SC) responses, and slower skin conductance habituation in PTSD patients compared to controls (Metzger et al., 1997). The above described script-driven imagery method has been used with many different PTSD populations: World War II veterans (Orr et al., 1993), Korean War veterans (Orr et al., 1993), Vietnam War veterans (Pitman et al., 1990), Israeli War veterans (Shalev et al., 1992), and Vietnam War combat nurses (Carson et al., 2000). In all of the above studies, PTSD patients exhibit a stronger HR and SC response to scripts than non-PTSD trauma survivors.

In order to better understand the development and time course of PTSD symptomatology and the psychophysiological expression of these symptoms, it is important to examine physiological reactivity across a broad spectrum of traumatized populations. To date, traumatized populations have been studied from the victims of terrorist attacks (DiGrande et al., 2008), the Middle Eastern theater of combat (Southwick et al., 1995; Shalev et al., 1992), and the Southeast Asian theater of combat (Pitman et al., 1990). The present study is the first to examine psychophysiological responses and startle reflex in a Croatian PTSD population under resting conditions. The analysis of psychophysiological reactivity across a wide range of traumatized populations may lead to the identification of hallmark symptoms associated with specific trauma types and the tailoring of more effective treatment strategies.

2. Methods and Materials

2.1. Participants

The study included 78 male participants: 45 PTSD patients treated at the University Hospital Dubrava, Croatia, and 33 healthy controls. PTSD patients were recruited from inpatient and outpatient services of the hospital. Age and gender-matched healthy volunteers were recruited from the general population. All participants were informed of the research study and signed an informed consent form approved by the Committee for Ethical Conduct of Research, University Hospital Dubrava. The average age of the PTSD patients was 40.4 ± 5.0 years, and the age of the controls was 38.1 ± 8.9 years. The majority of the participants (89% of 78) completed high school. All PTSD patients were war veterans from the Serbo-Croatian war (1991–1995) and the PTSD was due to combat-related traumatic events. Average combat exposure was 3 years.

Inclusion criteria: Confirmed diagnosis of chronic PTSD by the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1990), Croatian version. Exclusion criteria: Current substance abuse or dependence; suicidal ideation; head injury or neurological disorder; psychotic and bipolar symptoms; hearing or visual impairment; liver or kidney disease and cardio-vascular disease.

2.2. Psychophysiological Assessment

The psychophysiological data was collected using Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA). We recorded electromyographic (EMG), electrodermal activity (EDA), and electrocardiogram (ECG) activity, and respiration. All psychophysiological data were saved to the hard drive of a Windows XP computer. All data were sampled at 1000 Hz, digitized at 16 bit A/D resolution, and amplified using the respective modules of the Biopac system. The acquired data were filtered, rectified, and smoothed in MindWare software (MindWare Technologies, Inc, Gahanna, OH) and exported for statistical analyses. The EMG signal was amplified by a gain of a 1000, rectified, and filtered with low- and high- frequency cutoffs at 28 and 500 Hz, respectively. A 60Hz notch filter was also applied. The EDA signal was amplified by $2 \mu\text{S}/\text{Volt}$ and smoothed with a rolling filter of 100 data points per block. The ECG signal was amplified by a gain of a 1000, filtered with a Hamming windowing function, and with a 60Hz notch filter.

The following dependent variables were generated from the acquired data. For EMG, we measured the magnitude of the eyeblink muscle contraction during the startle response. For EDA, we analyzed tonic skin conductance level (SCL) and skin conductance response (SCR) to the startle probe. The dependent variables for ECG included tonic heart-rate (HR in beats per minute) and heart-rate change in response to the startle probe (in interbeat-intervals, IBIs). Respiratory sinus arrhythmia (RSA) quantified by spectral analysis of the time-sampled interbeat interval series, according to the methods recommended by the SPR Committee on Heart Rate Variability (Berntson et al., 1997). Because respiratory parameters can impact RSA, we also recorded respiration as recommended by the Committee. Respiratory measures were taken to evaluate the possibility that observed experimental effects were potentially secondary to changes in respiration; however, we did not analyze respiration amplitude *per se*.

EMG activity was recorded from Ag/AgCl electrodes (Biopac EL504 pre-gelled electrodes for EMG) placed over the *orbicularis oculi* muscle. EDA was assessed using two finger electrodes (Biopac EL507 electrodes pre-gelled with isotonic paste for EDA) on the index and middle finger of the non-dominant hand. Heart-rate was recorded from electrodes (Biopac EL503 pre-gelled electrodes for ECG) placed on the chest, one 1 cm below the right

clavicle and the other below the rib cage on the left side. Respiration rate was measured via an elastic chest band placed across the sternum. All electrodes were Ag/AgCl disposable pre-gelled electrodes, but each was specific to the data being acquired (Biopac Systems, Inc). This study was a part of a larger baseline assessment study for future studies; while more stimuli were presented to the subjects, here we report on the pre- and post-startle phase of the study. Importantly, none of the stimuli used in this study were aversive and the participants were explicitly told that there would be no painful or uncomfortable events during the study. The data reported here were collected from the start of the study visit: no interviews or other psychophysiological assessments preceded the study.

2.3. Startle Procedure

The acoustic startle response (eyeblick component) was measured via EMG of the right *orbicularis oculi* muscle. Two 5 mm Ag/AgCl electrodes filled with electrolyte gel were positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus. The impedances for all subjects were less than 6 kilo-ohms. Subjects were seated and asked to look at a blank computer monitor approximately 1 m in front of them. All acoustic stimuli were delivered binaurally through headphones (Maico, TDH-39-P).

Once the electrodes were attached, the participants were seated in a chair with a computer monitor in front of them. The participants were specifically told that no aversive or threatening stimuli would be given; they were asked only to relax and look at the monitor in front of them. The session began with a three-minute acclimation phase consisting of 70-dB [A] SPL broadband noise, which continued as the background noise throughout the session. During these 3 minutes the participants was instructed to relax and sit quietly. Since this was a baseline period during which the subjects acclimated to the research environment and electrode placement, no startle probes were delivered. However, during this time, resting levels of EDA and ECG were acquired and sampled at five time points, with inter-trial intervals of 30 seconds. The acclimation phase was followed immediately by the startle phase. The startle phase consisted of seven startle probe trials, with randomized inter-trial intervals of 9–22 seconds. The startle probe (noise burst) was a 108-dB [A] SPL, 40-ms burst of broadband noise with instantaneous rise time.

2.4. Statistical Analyses

The dependent variables were the following physiological measures: Startle, Tonic Skin Conductance (SC), SC change, Tonic Heart-rate (HR), respiratory sinus arrhythmia (RSA), and HR reactivity. Startle magnitude was measured from the EMG of the *orbicularis oculi* muscle; we used the peak amplitude recorded between 20 and 200 ms after the startle probe offset. Tonic SC was averaged over 6 seconds during the 5 acclimation phase trials and for 6 seconds after the offset of the startle probes. SC change was defined as the average increase (from a 1 s pre-startle baseline) from 3 to 6 s after the startle probe offset. Tonic HR and RSA measures were averaged over 10 seconds during the acclimation trials and after each startle probe trial. HR reactivity was calculated by averaging the IBI change (from the 1 s pre-startle baseline) during the first 3 seconds after the startle probe offset.

In order to examine the effects of the startle probe on the above physiological variables we used a 2×7 mixed analysis of variance (ANOVA) with GROUP (PTSD vs. CONTROL) as the between-groups factor, and TRIAL (7 STARTLE TRIALS) as the within subject factor. Interaction effects were followed-up by one-way ANOVAs. Because we were interested in differential habituation, we also tested the polynomial contrasts over the 7 startle trials separately for the two groups. In order to avoid sphericity with the 7 trials, we used the Huynh-Feldt term of the repeated-measures ANOVA. For the tonic measures (Tonic SC and Tonic HR) we compared the last acclimation trial to the first startle trial using a 2×2 mixed

ANOVA with GROUP (PTSD vs. CONTROL) and PHASE (ACL vs. STARTLE). Alpha was set at 0.05. Effect sizes of the individual effects are reported using partial Eta square (η^2). All analyses were conducted using SPSS 13.0 for Windows (SPSS, Inc.).

3. Results

3.1. Startle Magnitude

We analyzed the peak startle amplitude using a 2×7 mixed ANOVA with GROUP (PTSD vs. CONTROL) as the between-groups factor, and TRIAL (7 STARTLE TRIALS) as the within subject factor. We found a significant main effect of TRIAL ($F(6,76)=5.24$, $p<0.001$, $\eta^2=0.06$); however, there was no GROUP difference in startle magnitude and no interaction of GROUP and TRIAL (see Figure 1). Given that we were interested in differential habituation we performed polynomial contrasts for each group separately. We found a significant linear term for the CONTROL group ($F(1,32)=9.17$, $p<0.01$, $\eta^2=0.22$), but no quadratic trend in the CONTROL group ($F(1,32)=0.32$, $p=0.57$, $\eta^2=0.01$). The PTSD patients demonstrated both a significant linear term ($F(1,44)=6.32$, $p<0.05$, $\eta^2=0.12$) and a significant quadratic term with a greater effect size ($F(1,44)=7.64$, $p<0.01$, $\eta^2=0.15$). This quadratic curve suggests that the PTSD patients had impaired habituation in that the startle magnitude to the later trials increased relative to the middle trials (see Figure 1). In order to further explore this possibility, we categorized the subjects as startle “Habitators” and “Non-Habitators”. “Habitators” were defined by having the lowest startle magnitude on the 7th trial; if the startle magnitude on the 7th startle trial was higher than any of the other trials, the subject was categorized as a “Non-Habitator”. Similar psychophysiological response curves have been observed in PTSD patients who do not show habituation (Rothbaum, B.O., personal communication). A Chi-square analysis of GROUP by HABITUATOR showed that 89% of the PTSD patients (40 of the 45) did not demonstrate normal habituation compared to 66% of the CONTROLS (22 of 33), ($\chi^2(1, N=78)=5.77$, $p=0.01$).

3.2. Electrodermal Activity

Tonic SC levels during the startle trials were analyzed using a 2×7 mixed ANOVA with GROUP (PTSD vs. CONTROL) as the between-groups factor, and TRIAL (7 STARTLE TRIALS) as the within subject factor. Again, we found a significant effect of TRIAL ($F(6,76)=16.50$, $p<0.001$, $\eta^2=0.18$), but no effect of GROUP or interaction of GROUP and TRIAL (see Figure 2). The polynomial contrasts for both groups revealed significant linear, quadratic, and cubic terms, with the effects sizes for quadratic terms indicating the best fit (CONTROLS, ($F(1,32)=20.92$, $p<0.001$, $\eta^2=0.39$), PTSD, ($F(1,44)=14.38$, $p<0.001$, $\eta^2=0.25$). As seen in Figure 2, the quadratic term describes the initial increase from trial 1 to trial 2 which reaches an asymptote at trial 4.

We also analyzed the tonic SC levels during the acclimation phase and startle phase using a 2×2 mixed ANOVA with GROUP (PTSD vs. CONTROL) as the between-groups factor, and PHASE (ACL vs. STARTLE) as the within subject factor. This comparison is depicted by the insert graph in Figure 2. We again found a significant effect of PHASE ($F(1,76)=70.16$, $p<0.001$, $\eta^2=0.48$), but no effect of GROUP or interaction of GROUP and PHASE. Tonic SC was higher during the STARTLE phase than the ACL phase for the CONTROLS ($F(1,32)=24.56$, $p<0.001$, $\eta^2=0.43$) and PTSD, ($F(1,44)=49.98$, $p<0.001$, $\eta^2=0.53$) groups.

SC change in response to the startle probes was analyzed with a 2×7 mixed ANOVA with GROUP (PTSD vs. CONTROL) as the between-groups factor, and TRIAL (7 STARTLE TRIALS) as the within subject factor. Figure 3 shows the SC change data. As with the previous analyses, we found a significant effect of TRIAL ($F(6,76)=20.68$, $p<0.001$,

$\eta^2=0.21$), but no effect of GROUP or interaction of GROUP and TRIAL. Again, the polynomial contrasts for both groups revealed significant linear, quadratic, and cubic terms. However, in this case the linear trend had the greatest effect size (CONTROLS, $(F(1,32)=30.88, p<0.001, \eta^2=0.49)$, PTSD, $(F(1,44)=32.87, p<0.001, \eta^2=0.42)$, indicating SC response habituation over trials.

3.3. Electrocardiogram Activity

Tonic HR during the startle trials was analyzed using a 2×7 mixed ANOVA with GROUP (PTSD vs. CONTROL) as the between-groups factor, and TRIAL (7 STARTLE TRIALS) as the within subject factor. Figure 4 shows the tonic HR data for GROUP and TRIAL. As opposed to the earlier analyses, we found a significant main effect of GROUP $(F(1,76)=10.81, p=0.001, \eta^2=0.12)$, but no effect of TRIAL and no interaction of GROUP by TRIAL. The PTSD patients' HR was on average 10 BPM higher than the HR of the controls. The analysis of GROUP by PHASE using a 2×2 ANOVA revealed a significant effect of GROUP $(F(1,76)=11.20, p=0.001, \eta^2=0.13)$, as well as PHASE $(F(1,76)=3.86, p=0.05, \eta^2=0.05)$, but no interaction effect of the two variables. These data are depicted in the insert graph in Figure 4. Follow-up comparisons of the PHASE within each group indicated that the PTSD patients tended to have lower HR during startle $(F(1,44)=3.36, p=0.07, \eta^2=0.07)$; there was no effect of PHASE in the CONTROL group.

Analysis of RSA during the startle trials was analyzed using the 2×7 mixed ANOVA with GROUP (PTSD vs. CONTROL) as the between-groups factor, and TRIAL (7 STARTLE TRIALS) as the within subject factor. The results mirror those of the HR data: there was a significant GROUP difference $(F(1,76)=11.23, p=0.001, \eta^2=0.13)$ with PTSD patients having lower RSA compared to the CONTROL group (see Figure 5). As with the HR there was no effect of TRIAL or TRIAL by GROUP interaction. Analyses of GROUP by PHASE showed a significant main effect of PHASE $(F(1,76)=5.06, p<0.05, \eta^2=0.06)$, as well as GROUP $(F(1,76)=18.58, p<0.001, \eta^2=0.20)$, but no interaction effect (see insert for Figure 5). Follow-up comparisons showed that only the PTSD patients had a significant increase in RSA from the ACL phase to the STARTLE phase $(F(1,76)=5.08, p<0.05, \eta^2=0.10)$.

The analysis of HR reactivity to the startle probes was analyzed using the 2×7 GROUP by TRIAL ANOVA. This analysis did not reveal any significant main effects or interaction effects. The polynomial contrasts were also not significant.

4. Discussion

The present study is the first to report physiological assessments in a Croatian sample of combat-related PTSD. This study assessed resting levels of EMG, EDA, and ECG activity as well as during startle responses to loud noises. We did not find evidence of exaggerated baseline startle response in PTSD subjects compared to controls. As mentioned above, the data in the literature are mixed in this regard (Orr et al., 2004); it appears that exaggerated startle might be limited to a shorter period post trauma (Grillon and Baas, 2003) than is the case for the Croatian veterans, who were in combat about 10 years ago. It is also possible that the exaggerated startle response is only observed in stressful contexts (Grillon et al., 1998). However, we found that PTSD patients did not habituate to the startle probe in the same way that controls did. PTSD patients showed an initial decrease in startle magnitude to the startle probes but then increased responding later in the session. A significantly higher proportion of PTSD subjects did not show linear habituation curves compared to controls. Startle habituation deficits have been reported in Israeli patients who developed PTSD after trauma—the startle deficit was seen at an assessment 4 months after trauma indicating that it developed as part of the other PTSD symptoms (Shalev et al., 2000). However, several studies that examined startle responses in PTSD found normal levels of startle habituation

(Pitman et al., 1987; 1990; Orr et al., 1993). In part, the differences between the present study and previous work from the literature are due to methodological differences. Pitman and colleagues typically use a startle probe of longer duration (500 ms) than that which we used (40 ms) and give more startle trials (15). Shalev and colleagues found that PTSD patients required more than 6 trials to habituate while the controls required less than 4 on average. Therefore, by 15 trials, all subjects may show habituation. While this may indicate that startle habituation deficits are too subtle to be clinically useful, if the difference is robust it may provide insight into other aspects of PTSD symptomatology.

The degree to which an individual habituates to the acoustic startle probe may represent a trait characteristic as has been observed in previous work on conditioned fear extinction (Norrholm et al., 2006). In the Norrholm study, psychiatrically healthy individuals were characterized as “extinguishers” or “non-extinguishers” based on the rate at which their fear-potentiated startle diminished during an extended extinction session. It is our hypothesis that, similar to fear extinction, an individual’s rate of habituation to the startle probe is influenced by both intrinsic and extrinsic factors. It was anticipated that we would observe “non-habitutors” in both the control and PTSD groups. The decreased number of “habitutors” in the PTSD group compared to the control group may reflect “non-habitutors” by trait as well as “non-habitutors” as a result of trauma exposure and the development of PTSD symptoms. The current study cannot distinguish whether impaired habituation is a pre-existing factor or a consequence of trauma exposure or PTSD.

We analyzed both tonic skin conductance level and skin conductance response to the startle probes. There were no group differences in either measure of EDA; however, tonic SC increased during the startle trials in both groups, suggesting that general arousal may have been sensitized in both groups. On the other hand, the skin conductance response to the startle probes habituated with each startle probe in all subjects. The discrepancy between EMG and SC habituation may reflect differences in how the startle reflex is modulated compared to the autonomic nervous system control of EDA, in that SC may show more rapid and sustained habituation to stimuli. As a marker of anxiety rather than arousal, startle response may be a more sensitive index of deficient habituation.

We found that heart-rate was elevated by approximately 10 beats per minute in the PTSD patients compared to controls. However, heart-rate did not appear to be affected by startle stimuli since there was no effect of phase. Neither group of subjects showed heart-rate habituation over the trials. Elevated basal heart-rate has been observed in numerous studies with PTSD patients (Buckley and Kaloupek, 2001; Hopper et al., 2006). This elevation appears to be related to the chronicity of the disorder indicating greater cardiovascular risk for PTSD patients (Buckley and Kaloupek, 2001). Respiratory sinus arrhythmia, as an index of parasympathetic activity, was lower in PTSD subjects. Furthermore, RSA increased during the startle phase in PTSD patients. While it is unclear why RSA increased in the more arousing context, these data suggest alterations in parasympathetic activity in addition to the sympathetic system hyper-arousal; alterations that contribute to cardiovascular risk (Hopper et al., 2006; Porges, 2007).

A limitation of the study was the lack of a comparison group with equivalent levels of trauma exposure but without PTSD. Thus the group differences that we observed could be due to trauma itself, rather than to the disorder. Future studies should examine healthy control samples as well as trauma exposed individuals in order to parse out the differential contribution of trauma and PTSD.

In summary, the present study found deficits in startle habituation in Croatian PTSD patients, and replicated earlier findings of elevated basal heart-rate in PTSD subjects. This

sample is unique in the literature in that the patients are young enough to be largely medically healthy, and yet have been severely traumatized 10 years ago and developed chronic PTSD. Showing consistent psychophysiological alterations associated with PTSD across diverse populations lends much support for the stability of the association of PTSD symptoms with psychophysiological biomarkers.

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Figure 1. Mean + Standard Error startle response by group and startle trial number. Solid line=PTSD, dashed line=Control.

Figure 2.

Mean + Standard Error tonic skin conductance by group and trial. Solid line=PTSD, dashed line=Control. ACL=acclimation phase, trials 1–7 startle trials.

Figure 3.
Mean + Standard Error skin conductance change by group and startle trial number. Solid line=PTSD, dashed line=Control.

Figure 4.

Mean + Standard Error tonic heart-rate by group and phase. Solid line=PTSD, dashed line=Control. ACL=acclimation phase, trials 1–7 startle trials.

Figure 5.

Mean + Standard Error respiratory sinus arrhythmia (RSA) by group and trials. The value plotted is the natural log of ms^2 . Solid line=PTSD subjects, dashed line=controls. ACL=acclimation phase, trials 1–7 startle trials.