Autonomic and Respiratory Characteristics of Posttraumatic Stress Disorder and Panic Disorder

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Objective: Posttraumatic stress disorder (PTSD) and panic disorder (PD) are two anxiety disorders with prominent psychophysiological symptoms. The PTSD criterion of persistent hyperarousal suggests autonomic dysregulation, and the disorder has been associated with elevated heart rate. In contrast, PD has been associated with respiratory abnormalities such as low end-tidal \( P_{\text{CO}_2} \). An integrated analysis of automatic and respiratory function in a direct comparison of these anxiety disorders is currently lacking.

Methods: Electrodermal, cardiovascular, and respiratory psychophysiology was examined in 23 PTSD patients, 26 PD patients, and 32 healthy individuals at baseline and during threat of shock. Results: At baseline, the PTSD patients, in contrast to the other two groups, were characterized by attenuated parasympathetic and elevated sympathetic control, as evidenced by low respiratory sinus arrhythmia (a measure of cardiac vagal control) and high electrodermal activity. They also displayed elevated heart rate and cardiovascular sympathetic activation in comparison with healthy controls. PD patients exhibited lower \( P_{\text{CO}_2} \) (hypocapnia) and higher cardiovascular sympathetic activation compared with healthy controls. PTSD patients, but not PD patients, sighed more frequently than controls. During the threat of shock phase, the PTSD group demonstrated blunted electrodermal responses.

Conclusions: Persistent hyperarousal symptoms in PTSD seem to be due to high sympathetic activity coupled with low parasympathetic cardiac control. Respiratory abnormalities were also present in PTSD. Several psychophysiological measures exhibited group-comparison effect sizes in the order of 1.0, supporting their potential for enhancing differential diagnosis and possibly suggesting utility as endophenotypes in genetic studies of anxiety disorders. Key words: posttraumatic stress disorder, panic disorder, respiratory sinus arrhythmia, sympathetic nervous system, parasympathetic nervous system, end-tidal \( P_{\text{CO}_2} \).

INTRODUCTION

Physical symptoms play a role in the diagnosis of all anxiety disorders, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1). In posttraumatic stress disorder (PTSD) and panic disorder (PD), physical symptoms can become central concerns for patients. Intense psychophysiological symptoms are reported during panic attacks by PD patients, whereas similar symptoms are reported by PTSD patients when they re-experience traumatic events.

However, despite partial diagnostic overlap and a high comorbidity (2), the two disorders may differ in their underlying physiology: whereas elevated resting heart rate (HR) has frequently been found in PTSD (3), the respiratory system seems to be dysregulated in PD (4–10). In addition, although some aspects of psychophysiological dysregulation might be evident during baseline (e.g., the persistent hyperarousal symptoms in PTSD, suggesting a dispositional, or persistent, autonomic dysregulation), others might only be revealed during psychological stress (situational dysregulation, possibly predominating in PD).

The research literature on psychophysiological functioning in PD and PTSD has yielded numerous inconsistencies (11,12). One reason for this could be the focus of most studies on a small number of physiological measures. This approach does not account for the complexity of possible interactions, e.g., between sympathetic and parasympathetic branches of the autonomic nervous system or autonomic relations to the respiratory system (13). These particular systems may be dysregulated in PD and PTSD. A comprehensive assessment of multiple systems and their relationships thus promises to provide a more complete characterization of these disorders.

Research has recently turned to specific cardiac autonomic indices regulating HR: the recognition that HR is primarily under parasympathetic control during most conditions of daily life, especially during resting phases (14), has stimulated the assessment of HR variability (HRV) measures, especially respiratory sinus arrhythmia (RSA). RSA is characterized by the rhythmic oscillation of HR related to phase of breathing and is associated with vagal efferent effects on the heart. Consequently, it is often used as a noninvasive index of parasympathetic control of HR (15).

Cohen et al. (16) measured several HRV indices in patients with PTSD, PD, and healthy controls (HC). The laboratory task comprised a baseline and a recall phase during which the PTSD, the PD, and the HC groups respectively recalled either a traumatic event, a panic attack, or a stressful life episode. During baseline, lower RSA values and higher HR were found in both patient groups compared with the HC. However, only

**CSI** = cardiovascular sympathetic index; **CVT** = cardiac vagal tone; **ESI** = electrodermal sympathetic index; **HR** = heart rate; **HP** = heart period; **RSA** = respiratory sinus arrhythmia; **NS-SCR** = number of nonspecific skin conductance fluctuations; **HRV** = heart rate variability; **SCL** = skin conductance level; **Pco2** = end-tidal partial pressure of expired \( \text{CO}_2 \); **PDS** = Posttraumatic Diagnostic Scale; **PTSD** = posttraumatic stress disorder; **PD** = panic disorder; **STAI** = State-Trait Anxiety Inventory; **BDI** = Beck Depression Inventory; **SCRamp** = amplitude of nonspecific skin conductance responses; **ECG** = electrocardiogram; **lnHF** = high-frequency power of HP variability; **lnLF** = low-frequency power of HP variability; **lnVLF** = very low-frequency power of HP variability; **MANOVA** = multivariate analysis of variance; **HC** = healthy controls.

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the PD and the HC groups showed increased HR during recall, suggesting blunted cardiac responses in the PTSD group. However, the study by Cohen and associates (16) had two limitations. First, the group-specific nature of the recall task raised some doubt about whether the degree of stress was equivalent for all groups. In the present study, in addition to baseline assessment, a threat of shock task was used to assess stress reactivity. This standard laboratory task, during which an unpredictable shock is announced but not presented, reliably induces a defensive physiological activation (17,18) and might represent a task with greater commonality for the two disorders than the recall task used by Cohen’s group (16). A second limitation of Cohen et al. is the confinement on parasympathetic and putative sympathetic indicators from the HRV spectrum. Sympathetic indices from other physiological systems (e.g., the electrodermal system) and other psychophysiological indicators (e.g., the respiratory system) have not been assessed. We now review additional evidence regarding cardiovascular, electrodermal, and respiratory dysregulation in PTSD and PD.

With respect to the cardiovascular system, PTSD has frequently been found to be associated with elevated resting HR and HR responses to experimental protocols (3), the findings in PD being more inconsistent (19). Attenuated baseline RSA has frequently (16,20), although not invariably, been found in PTSD (21). The findings on vagal tone deficits in PD can be characterized as inconsistent (6,16,19,22,23).

Regarding the electrodermal system, primarily controlled by the sympathetic nervous system, elevated electrodermal baseline levels and heightened responses have been reported both in PTSD and PD patients (6,24), making the electrodermal system a promising candidate for psychophysiological differentiation from the HC group.

The respiratory system has long played a hypothetical etiological role in PD. Both the suffocation false alarm theory (6,25) and the hyperventilation theory (26) argue that respiratory dysregulation is a core feature of PD. A number of studies have found evidence for respiratory irregularities, such as frequent sighing (7,9,10) or lowered end-tidal partial pressure of expired CO₂ (PETO) in PD (4–7). In PTSD, however, respiration has been rarely studied; so far, most laboratory investigations have only measured respiratory rates and have found no differences between PTSD patients and HC (21).

In summary, evidence for sympathetic, parasympathetic, and respiratory abnormalities in PD and PTSD exists, but findings are largely based on studies focusing on only one physiological system or only one disorder at a time. The current study was designed to delineate psychophysiological differences between PTSD patients, PD patients, and HC participants by examining various measures of cardiovascular, electrodermal, and respiratory functioning during baseline and threat of shock, i.e., psychological stress. To account for the complexity of cardiorespiratory and sympathetic-parasympathetic interactions, special care was given to the estimation of RSA as a vagal index. Based on the evidence described, we expected to find 1) elevated HR and lowered RSA in PTSD patients, 2) lowered PCO₂ and increased sigh frequency in PD patients, and 3) heightened electrodermal and cardiovascular activation in both patient groups in comparison with HC. We additionally explored whether these differences would represent dispositional variations (parallel elevated levels among anxiety groups during baseline and threat of shock task), or situational reactions to stress (i.e., differences in reactivity to the threat of shock phase).

METHOD

Participants

The experimental groups consisted of 23 PTSD patients, 26 PD patients (with or without agoraphobia), and 32 healthy individuals who had never qualified for a psychiatric disorder and who were matched to the patient groups on age, gender, and education. The diagnosis was assessed by clinical psychologists trained in using the F-DIPS (Diagnostic Interview for Mental Disorders—Research Revision) (27), a well-validated structured interview for diagnosing DSM-IV disorders. It is a modified German version of the Anxiety Disorder Interview Schedule for DSM-IV—Lifetime version (28). Trauma types in the PTSD group included accidents (traffic and work-related; n = 8); physical or sexual violence (n = 7); war-related trauma (imprisonment, torture; n = 3); natural disasters (n = 2); and other trauma (n = 3). The average duration of the PTSD diagnosis was 5.8 years (standard deviation (SD) = 8.8; range = 2 months to 27 years). The following secondary disorders were diagnosed in the PTSD/PD groups: agoraphobia (1/20), major depression (8/4), social phobia (3/3), pain disorder (3/0), generalized anxiety disorder (3/4), other disorders (2/3). None of the PTSD patients had a diagnosis of PD and vice versa.

Exclusion criteria, assessed by self-report, included the following: lifetime history of psychosis, bipolar disorder, drug abuse or dependence, a medical history of conditions that might affect the physiological systems under study (e.g., angina, myocardial infarction, asthma), and the use of medication with strong autonomic effects such as benzodiazepines, β blockers, sympathomimetic drugs, antipsychotics, or tricyclic antidepressants. Of the included PTSD/PD patients, 6/4 took analgesic drugs and 1/4 took selective serotonin noradrenalin reuptake inhibitors; however, medication did not alter the pattern of results. Participants were told to abstain from alcohol or recreational drugs 24 hours before testing. They were referred to us by collaborating mental health institutions or they responded to advertisements in the local media.

Psychometric assessment of the study groups included the German versions of the State-Trait Anxiety Inventory (STAI) (29), the Beck Depression Inventory (BDI) (30), the Anxiety Sensitivity Index (ASI) (31), and the Mobility Inventory (MI)—a scale assessing agoraphobic avoidance (32). Only the PTSD patients completed the Posttraumatic Diagnostic Scale (PDS) (33) because the questions referred to the traumatic event. All questionnaires demonstrated good internal consistency (Cronbach’s α = 0.73–0.95) and satisfactory stability (29–34). The study was approved by the local ethics committee for medical research, and participants gave written consent before participating. Each participant received a reimbursement of 90 CHF (approximately 70 USD). The data collection period extended from February 2005 to April 2006.

Procedure

One week after the diagnostic interview and an independent laboratory session, participants returned to the laboratory for the present investigation. The 30-minute protocol was conducted in a temperature- and sound-controlled 4 × 2.5 m room, electronically connected to an adjoining room where the experimental apparatus was located. Participants were seated in a comfortable armchair and all physiological electrodes were attached. For the next 20 minutes, participants completed psychometric questionnaires and a calibration procedure for the respiration belts. The baseline period commenced with written instructions asking participants to sit quietly for 5 minutes with their eyes open. Then, the experimenter attached the shock electrodes to the participant’s wrist and, in a dial up procedure, adjusted the electric stimulus.
to an intensity the participant described as being “unpleasant and demanding some effort to tolerate.” After the experimenter had left the room, the threat of shock phase commenced with the instructions that two pictures would be shown on the screen in random order and that one of them could occasionally be accompanied by the shock. For the following 5 minutes, two inkblot pictures repeatedly appeared on the screen (six presentations each); however, no electric stimulation occurred. After the threat of shock phase, two different paradigms were conducted (35,36). Finally, the experimenter removed all electrodes, and debriefed participants. Participants received a remuneration of about 70 USD.

**Physiological Measures**

Placement of electrodes/sensors, data recording, and data reduction followed the conventions established for psychophysiological research and published guidelines. Physiological channels were A/D converted (400 Hz), and simultaneously streamed to disk and displayed on a PC monitor (Biopac MP150 system, Biopac Systems, Inc., Goleta, California). Offline, all channels were manually edited to reject movement or electronic artifacts, or ectopic beats in the electrocardiogram (ECG) using an integrated suite of biosignal analysis programs (37).

**Electrodermal Measures**

Electrodermal activity was recorded from the middle phalanx of the index and middle finger of the left hand using 11-mm inner diameter Ag/AgCl electrodes filled with isotonic electrode paste (TD-246, Med Associates, Inc., St. Albans, Vermont). Three parameters were calculated: skin conductance level (SCL), number of nonspecific skin conductance fluctuations (NS-SCR, number of deflections from a zero-slope baseline exceeding 0.02 μS), and SCR_{amp} (amplitude of NS-SCRs). The electrodermal system is innervated primarily by the sympathetic nervous system (38).

**Cardiovascular Measures**

From the ECG lead II, heart period (HP) was calculated as the interval in milliseconds between successive R-waves. For statistical and physiological reasons, HP was used in all analyses (39), but for ease of interpretation, HP was often converted to HR. High-frequency (lnHF or RSA), low-frequency (lnLF), and very-low frequency (lnVLF) powers of HP variability were computed as the natural logarithms of the summed power spectral density between 0.15 and 0.4 Hz, 0.05 and 0.15 Hz, and 0.0033 and 0.05 Hz, respectively. We also calculated a HP-normalized index of RSA (Hayano index, or RSA_{norm}), which has been shown to reflect vagal control independently of sympathetic influences (40,41).

\[
\text{RSA norm} \% = 100 \cdot (\text{lnHF power})^{1/2} / \text{(mean RR interval)} \quad (41)
\]

Additionally, several studies, based on autonomic blockade findings, seriously call into question the accuracy of RSA as an index of individual differences in cardiac vagal tone (CVT) (13,42–44). Grossman and Kollai (42) also demonstrated that multivariate estimation of individual differences in CVT, using both RSA and HP as joint predictors, was far superior to RSA alone. We, therefore, applied regression weights from that study to estimate individual differences in CVT.

Three measures were calculated beat-by-beat from the ECG and the finger pulse waveform measured by a plethysmographic sensor (N-1000, Nellcor, Hayward, California): a) T-wave amplitude, calculated in reference to the isoelectric ECG baseline; b) pulse wave transit time, as time between steepest upstroke and ECG R-wave; and c) pulse wave amplitude, as peak minus trough. All three measures primarily reflect sympathetic activity (45–47). To obtain more representative and reliable indices of sympathetic cardiovascular and electrodermal activation, as well as to reduce the number of statistical tests, the three measures were combined by means of z-transformation (between individuals) and averaging (within individuals) to form a cardiovascular sympathetic index (CSI). The CSI was scored inversely because the three measures are inversely related to sympathetic activation. SCL, NS-SCRs, and SCR_{amp} were combined in the same way to form an electrodermal sympathetic index (ESI).
interaction was not significant, thus reactivity in the three groups was similar, $F(12,138) = 1.33, p = .203, \eta^2 = 10.4\%$.

Table 2 provides the results of the ANOVAs for single measures. At baseline, groups differed significantly on all primary measures. Post hoc tests indicated that PTSD patients had higher ESI and lower RSA scores compared with both comparison groups. PTSD patients also showed elevated HR (attenuated HP) and sighed more frequently compared with HC. Both PD patients and PTSD patients had lower $P_{CO_2}$ compared with HC; however, the difference was significant for the PD group only (although the PTSD-HC difference tended toward significance, $p = .08$, and the PTSD-PD difference was not significant). Both patient groups demonstrated higher cardiovascular sympathetic activity as indicated by the CSI compared with the HC group. During the threat of shock phase, significant differences were only found for ESI, with reduced electrodermal reactivity in the PTSD group compared with the other two groups. Because the two patient groups differed significantly on the BDI, correlations between the BDI score and the primary measures at baseline and during threat were calculated. Significant correlations were found with RSA at baseline ($r = -.313, p = .006$) and ESI during threat ($r = -.276, p = .014$). All other correlations were not significant.

**Adjustments of RSA During Baseline**

Research has demonstrated that RSA is affected by a multitude of factors (48,49), including respiratory rate, tidal volume, and $P_{CO_2}$ as well as subject characteristics like age and gender. We attempted to control subject characteristics by matching and respiratory rate, tidal volume, and $P_{CO_2}$ by using them as covariates in three analyses of covariance (ANCOVA) on baseline RSA values. In all three ANCOVAs, the covariates did not reach significance, $F < 2.45, p > .115$. The Group factor remained significant in all three analyses, $F > 3.90, p < .023$, with more attenuated RSA in the PTSD than in the other groups.

In addition, autonomic blockade studies suggest that HP should be considered in addition to RSA in the calculation of a measure of vagal control (41,42). When RSA was normalized for HP as suggested by Hayano et al. (41), values were lower in the PTSD group (mean = 2.08, SD = 0.86) compared with the PD group (mean = 2.80, SD = 0.99), and the control group (mean = 2.85, SD = 1.4), $F(2,74) = 3.42, p = .038$ (no difference between the latter two groups).

Similarly, when an “individual differences” index of CVT was calculated jointly using HP and RSA (42), the group effect was highly significant ($F(2,74) = 5.52, p = .006$), once again with more attenuated CVT in the PTSD group (mean = 153 ms, SD = 81.1) than in PD group (mean = 215 ms, SD = 126) and the HC group (mean = 254 ms, SD = 116).

**Analyzes of Secondary Measures**

Of the secondary measures, only ribcage contribution to tidal volume passed the 0.01 significance criterion, with PTSD patients showing less thoracic and more abdominal breathing than the other groups. Again, no group differences in reactivity reached significance.

**Diagnostic Separation**

Figure 1 displays effect sizes for the three pairwise group contrasts for primary measures at baseline. ESI and HP dominate in the group contrast for PTSD versus HC. CSI and $P_{CO_2}$ primarily distinguished PD and HC groups. Importantly, the two patient groups were discriminated by ESI and RSA measures. A predictive discriminant analysis was computed using the baseline values on the six primary measures as predictors of group membership. This analysis yielded an overall correct classification in 64.2% of cases, which is about twice the level expected by chance. When reactivity scores were included as predictors, this value increased slightly to 70.4%.

**DISCUSSION**

This is the first study, to our knowledge, to provide an integrated analysis of sympathetic, parasympathetic, and respiratory psychophysiology in PTSD and PD patients and HC. Importantly, patient groups did not differ on state anxiety, which is a prerequisite for assigning differences between the

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**TABLE 1. Demographic and Psychometric Values for the Study Groups**

<table>
<thead>
<tr>
<th></th>
<th>PTSD Group</th>
<th>PD Group</th>
<th>HC Group</th>
<th>Statistic</th>
<th>Post Hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$ in sample</td>
<td>23</td>
<td>26</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% female</td>
<td>65.2</td>
<td>76.9</td>
<td>71.8</td>
<td>$\chi^2(2,81) = 0.82, p = .66$</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.78 ± 11.3</td>
<td>39.4 ± 10.7</td>
<td>42.1 ± 8.47</td>
<td>$F(2,80) = 0.60, p = .55$</td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.95 ± 2.13</td>
<td>10.2 ± 2.23</td>
<td>11.1 ± 2.04</td>
<td>$F(2,79) = 1.36, p = .26$</td>
<td></td>
</tr>
<tr>
<td>PDS</td>
<td>30.9 ± 10.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI-State</td>
<td>50.14 ± 7.99</td>
<td>48.2 ± 11.5</td>
<td>37.0 ± 8.56</td>
<td>$F(2,79) = 16.8, p &lt; .001$</td>
<td>PTSD = PD &gt; HC</td>
</tr>
<tr>
<td>STAI-Trait</td>
<td>55.65 ± 9.77</td>
<td>50.0 ± 11.0</td>
<td>32.9 ± 8.80</td>
<td>$F(2,80) = 43.5, p &lt; .001$</td>
<td>PTSD = PD &gt; HC</td>
</tr>
<tr>
<td>BDI</td>
<td>25.61 ± 10.7</td>
<td>13.0 ± 8.32</td>
<td>4.40 ± 4.57</td>
<td>$F(2,80) = 51.0, p &lt; .001$</td>
<td>PTSD &gt; PD &gt; HC</td>
</tr>
<tr>
<td>ASI</td>
<td>30.04 ± 16.1</td>
<td>31.2 ± 12.1</td>
<td>7.26 ± 4.57</td>
<td>$F(2,80) = 45.0, p &lt; .001$</td>
<td>PTSD = PD &gt; HC</td>
</tr>
<tr>
<td>MI</td>
<td>2.20 ± 0.61</td>
<td>2.27 ± 0.81</td>
<td>1.25 ± 0.45</td>
<td>$F(2,76) = 24.4, p &lt; .001$</td>
<td>PTSD = PD &gt; HC</td>
</tr>
</tbody>
</table>

PTSD = posttraumatic stress disorder; PD = panic disorder; HC = healthy control group; SD = standard deviation; PDS = Posttraumatic Diagnostic Scale; STAI = State/Trait, Spielberger State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; ASI = Anxiety Sensitivity Inventory; MI = Mobility Inventory.

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**TABLE 2. Results of the ANOVAs for Single Measures**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Statistic</th>
<th>Post Hoc</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>$F(2,80) = 43.5, p &lt; .001$</td>
<td>PTSD &gt; PD &gt; HC</td>
</tr>
<tr>
<td>Education (years)</td>
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<td></td>
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<tr>
<td>PDS</td>
<td></td>
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</table>
TABLE 2. Mean ± Standard Deviation (SD) for Selected Primary and Secondary Measures at Baseline and for Reactivity Scores

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>Reactivity</th>
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<tr>
<td></td>
<td>PTSD</td>
<td>PD</td>
<td>HC</td>
<td>ANOVA</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>f, p, Post Hoc</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>f, p, Post Hoc</td>
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<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>f, p, Post Hoc</td>
</tr>
</tbody>
</table>

- **Primary measures (α = 0.05)**
  - **HP (ms)**
    - PTSD: 762 ± 92.5, PD: 823 ± 140, HC: 868 ± 125
    - Means and standard deviations for the measures included in the composite scores CSI and ESI are listed for comparison purposes.
  - **RSA (ln ms²)**
    - PTSD: 5.36 ± 0.88, PD: 6.13 ± 0.89, HC: 6.16 ± 1.17
    - ANOVA: PTSD < HC
  - **PCO₂ (torr)**
    - PTSD: 36.2 ± 2.64, PD: 35.1 ± 4.87, HC: 38.2 ± 2.50
    - ANOVA: PTSD < HC
  - **Sigh rate (number/min)**
    - PTSD: 0.50 ± 0.51, PD: 0.35 ± 0.48, HC: 0.21 ± 0.29
    - ANOVA: PTSD < HC
  - **CSI (z-scores)**
    - PTSD: 0.14 ± 0.54, PD: 0.23 ± 0.57, HC: 0.27 ± 0.71
    - ANOVA: PTSD < HC
  - **Pulse wave amplitude (units)**
    - PTSD: 3.22 ± 2.22, PD: 2.31 ± 1.98, HC: 3.57 ± 2.65
    - ANOVA: PTSD < HC
  - **Pulse wave transit time (ms)**
    - PTSD: 355 ± 34.4, PD: 354 ± 33.1, HC: 371 ± 34.2
    - ANOVA: PTSD < HC
  - **T-wave amplitude (mV)**
    - PTSD: 0.2 ± 0.12, PD: 0.23 ± 0.14, HC: 0.29 ± 0.17
    - ANOVA: PTSD < HC
  - **ESI (z-scores)**
    - PTSD: 9.41 ± 3.9, PD: 6.24 ± 2.37, HC: 6.05 ± 2.07
    - ANOVA: PTSD < HC
  - **SCL (µV)**
    - PTSD: 0.19 ± 0.1, PD: 0.14 ± 0.1, HC: 0.11 ± 0.1
    - ANOVA: PTSD < HC
  - **SCR (µV)**
    - PTSD: 3.91 ± 2.87, PD: 2.73 ± 2.7, HC: 1.99 ± 1.62
    - ANOVA: PTSD < HC
  - **Secondary measures (α = 0.01)**
    - **Ribcage contribution (%)**
      - PTSD: 58.9 ± 13.1, PD: 63.8 ± 9.21, HC: 69.8 ± 12.2, ANOVA: PTSD < HC
      - ANOVA: PTSD < HC

- **Reactivity**
  - **Means and standard deviations for the measures included in the composite scores CSI and ESI are listed for comparison purposes.**
clinical groups to their diagnosis rather than to state anxiety present in the laboratory. The pattern of results indicates that PTSD and PD patients were characterized by specific autonomic and respiratory differences, particularly at baseline. Despite overall robust physiological reactivity to the threat of shock paradigm, groups differed only on one measure of reactivity: the PTSD group showed reduced electrodermal responding to the psychological stressor, although this may reactivity: the PTSD group showed reduced electrodermal activity in comparison with HC. Importantly, elevated electrodermal arousal and attenuated RSA were specific to the PTSD group: despite similar elevated levels of state anxiety, PD patients did not show these features.

In contrast, PD patients did not show a distinct autonomic pattern. Although they demonstrated higher cardiovascular sympathetic activity than HC, they did not differ significantly from the PTSD group. In contrast to the findings of Cohen et al. (16), we found no differences between PD patients and HC on RSA. However, our results are in line with other previous reports of comparable RSA values in PD patients and HC (6,23).

Different conceptualizations have been proposed to explain the functional psychobiological significance of RSA and vagal activity in relationship to broad classes of behavior and higher-order processes (22,51). RSA can reflect variations in CVT, phasic vagal influence on HR, peripheral sympathetic-parasympathetic interactions, and/or respiratory variations (13). Therefore, we carefully considered these issues in our methods and controlled for subject characteristics that could influence RSA. To our knowledge, this is the first study in anxiety patients that has accounted for possible confounds in RSA as a measure of individual difference in cardiac vagal control (42) and controlled for the respiratory influences on RSA (13,49). Our findings suggest that respiratory variations were not responsible for RSA differences between groups, and elevated HR confirmed cardiac autonomic effects on PTSD patients. Additionally, the joint RSA and HP index of CVT, previously shown to be highly related to gold standard pharmacological estimates \( r = .9 \), provided the most significant evidence of profoundly attenuated vagal control among PTSD patients at baseline (42).

The elevated cardiovascular and electrodermal activity among PTSD patients is also consistent in suggesting particularly high levels of sympathetic activity in this clinical group. Thus, sympathetic hyperarousal and profound parasympathetic withdrawal may be characteristic of PTSD and may contribute to a failure to downregulate from the state of hyperarousal caused by the trauma.

Our findings also demonstrate the importance of examining both autonomic branches in relationship to anxiety. Previous investigations only examining vagal indices may unduly exaggerate the importance of parasympathetic mechanisms in specific disorders. It may be the double burden of sympathetic hyperarousal accompanied by an absence of cardiac vagal restraint that may be responsible for the cardiovascular morbidity found in epidemiological studies of anxiety (52).

### Respiratory Dysregulation

Two theories emphasize a respiratory abnormality in PD patients: the hyperventilation theory (26) and the suffocation false alarm theory (25). The hypocapnia of about 3 torr found in our PD patients is consistent with both theories and previous research (3,16,20). Sahar et al. (21) did not find lower baseline RSA in PTSD patients versus controls. However, they only studied male patients and had a small sample size. In the present study, PTSD patients also showed elevated electrodermal and cardiovascular sympathetic arousal in comparison with HC. Importantly, elevated electrodermal arousal and attenuated RSA were specific to the PTSD group: despite similar elevated levels of state anxiety, PD patients did not show these features.

Figure 1. Effect sizes (Cohen’s d) for the three group contrasts during baseline for all primary measures. ESI = electrodermal sympathetic index (sum of standardized skin conductance level, amplitude and number of nonspecific skin conductance fluctuations); HP = heart period; RSA = respiratory sinus arrhythmia; pCO₂ = end-tidal partial pressure of expired CO₂; CSI = cardiovascular sympathetic index (sum of standardized T-wave amplitude, pulse wave transit time and pulse wave amplitude); PTSD = posttraumatic stress disorder; PD = panic disorder; HC = healthy control group. 1 Interpretation of effect sizes according to Cohen (58).

### Autonomic Dysregulation

RSA was attenuated and HR was elevated during baseline in PTSD, compared with HC. This is in line with our expectations and previous research (3,16,20). Sahar et al. (21) did not find lower baseline RSA in PTSD patients versus controls.
ous research (4–7). However, the PTSD group also showed abnormal breathing patterns (high sigh rate, more abdominal breathing, and only slightly less hypocapnia than the PD group). This calls into question the claim for specificity of respiratory dysregulation in PD and stresses the importance of including respiratory measures in the study of anxiety disorders, in general.

Contrary to our expectations and prior findings, PD patients did not show elevated sigh rates. The fact that our previous studies (7,8) used a longer period of quiet sitting gives rise to the question whether the 5 minutes used here were too short. However, sigh rates did not increase or decrease markedly across time in these studies, so 5 minutes should have been sufficient to detect this feature. More likely, sample characteristics might explain this inconsistency, because marked respiratory dysregulation has frequently been found only in a subgroup of PD patients (the respiratory subtype) (53).

The finding of more abdominal breathing in PTSD patients during baseline, in comparison with HC, is surprising, because clinical lore presumes that anxious patients often engage in tense and predominantly chest breathing. However, given the exploratory nature of this analysis, replication of this finding is necessary before drawing any conclusions.

Psychophysiological Assessment: Implication for Diagnosis and Genetic Studies

Based on baseline scores on the primary measures, group membership was correctly predicted for about two thirds of study participants. The classification slightly improved when reactivity scores were included. This prediction can be considered as fairly accurate, even when compared with studies using disorder-specific symptom-provocation paradigms (12). This is likely due to the comprehensive assessment of relevant physiological systems in the present study and emphasizes the value of such a broad approach. The results of the current study support the possibility that psychophysiological assessment might, in the future, aid the diagnostic diagnosis of PTSD and PD as an adjunct to diagnostic interviews. In cases of ambiguous interview information or comorbidity of PTSD and PD, psychophysiological information may provide supplemental information (11). In a medical setting, the 5-minute measurement of ECG (which permits HR and RSA calculations) as well as possibly PCO₂ and electrodermal activity is feasible without much burden on patients.

Related to the issue of diagnostic separation is the search for disorder-specific genes, which remain to be located, despite findings of considerable heritability in PD and PTSD (54,55). Recently, the concept of psychophysiological endophenotypes was introduced (56). An endophenotype can be seen as a measurable component along the pathway between the phenotypic expression of a disorder and its genetic basis and can therefore aid gene-finding strategies (57). The present study identified two measures (ESI and RSA) that showed reliable and specific associations to PTSD and might therefore be explored as psychophysiological endophenotypes in future genetic studies. Similarly, research investigating the neural concomitants of RSA is likely to advance the knowledge underlying mechanisms of vagal functioning (22).

Limitations and Conclusions

This study has several limitations. First, except for blunted electrodermal responding in PTSD patients, no group differences were found during the threat of shock phase. This nonspecific stress-task was chosen to achieve comparable mental stress in both anxiety disorder groups, with the aim of discriminating their psychophysiological profiles. When focusing on one disorder only (PD or PTSD), disorder-specific stress paradigms (e.g., respiratory challenges or trauma scripts, respectively) may reveal more group differences in stress-reactivity than the present paradigm. Similarly, other nonspecific stressors (for example, an arithmetic task) could have produced different results.

Second, we found negative correlations between depression severity as measured by the BDI and the RSA and ESI indices. Because the PTSD group scored higher on the BDI than the other groups, comorbid depression may have influenced some results. Subsequent studies should investigate nondepressed PTSD patients or use a depressed clinical control group.

Finally, the substantially elevated state anxiety levels of both PTSD and PD groups versus HC at baseline may suggest expectancy effects regarding the threat of shock phase or a hypersensitivity to a broad range of unfamiliar and/or challenging situations. Thus, it is possible that physiological patterns of anxiety patients are normal under conditions perceived as secure and safe. We must be careful in distinguishing between possible dispositional and situational characteristics when making inferences from experimental studies. Only studies employing psychophysiological ambulatory monitoring can definitively determine whether anxiety patients resemble healthy controls at rest in a naturalistic setting (for example, at home).

To conclude, this study supports the idea of autonomic dysregulation in PTSD. Elevated sympathetic activity (as indicated by both electrodermal and cardiac measures) and profound cardiac vagal withdrawal may represent psychophysiological markers for PTSD and may predict long-term cardiovascular risk (52). Hypocapnia once again characterized PD patients, but elevated frequency of sighing was unexpectedly only found among the PTSD group, who also showed depressed levels of PCO₂, compared with HC. The latter findings call into question suggestions that PD is related to unique central respiratory abnormalities. Finally, it may be worthwhile to explore the utility of these physiological parameters as supplemental diagnostic criteria or even as indices of endophenotypes in more genetically oriented investigations.

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REFERENCES


