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Increased epoch-to-epoch parasympathetic cardiac regulation in participants with posttraumatic stress disorder compared to those with panic disorder and control participants★

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ABSTRACT

Background: Research on the link between respiratory sinus arrhythmia (RSA) and posttraumatic stress disorder (PTSD) has largely focused on average levels of RSA. However, given that rapid shifts in parasympathetic tone are necessary to maintain adaptive cardiac variability, the exclusive focus on these tonic estimates provides an incomplete quantification of parasympathetic cardiac regulation.
Method: The present study is a secondary analysis of previously published data. This analysis aimed to address this limitation by examining the dynamic regulatory effect of the parasympathetic nervous system on heart rate. As such, we examined epoch-to-epoch parasympathetic cardiac regulation – operationalized as the lagged relationship between RSA and heart rate (HR) across consecutive 30-s epochs – across a single night in participants with PTSD, panic disorder (PD), comorbid PTSD and PD (PTSD + PD), and healthy controls. Electrocardiogram and respiratory signals were continuously recorded from 23 participants with PTSD, 14 with PD, 16 with PTSD + PD, and 16 control participants over a single night of sleep in a laboratory setting.
Results: No group differences in tonic RSA were observed; however, participants with PTSD only and PTSD + PD exhibited significantly greater epoch-to-epoch parasympathetic cardiac regulation over the night than those with PD only and control participants. Moreover, greater severity of hyperarousal symptoms was significantly associated with increased epoch-to-epoch parasympathetic cardiac regulation among participants with PTSD only and PTSD + PD.
Discussion: These data provide preliminary evidence for an upregulatory parasympathetic response to self-reported hyperarousal in participants with PTSD only and PTSD + PD reflected by increased epoch-to-epoch parasympathetic cardiac regulation.

1. Introduction

Posttraumatic stress disorder (PTSD) is a commonly occurring and highly disabling consequence of trauma exposure (Keane, Marshall, & Taft, 2006). In addition to its significant individual and societal cost (Kessler, 2000), epidemiological evidence indicates that PTSD also increases risk for cardiovascular morbidity and mortality (for review, see Kubzansky & Koenen, 2009). Reduced heart rate variability (HRV) has been identified as an etiological marker of cardiovascular disease (Thayer, Yamamoto, & Brosschot, 2010) and is associated with both anxiety disorders broadly and PTSD specifically (Chalmers, Quintana, Abbott, & Kemp, 2014). As such, reduced HRV has been proposed as a mechanism underlying increased cardiovascular risk in PTSD. Parasympathetic tone, mediated by efferent vagal signals to the sinoatrial node, is particularly important for maintaining adaptive cardiac variability and is thereby critical for maintaining cardiovascular health (Friedman, 2007). Thus, respiratory sinus arrhythmia (RSA) – the fluctuation in heart period resulting from the gating of vagal input during inspiration – has received considerable attention in research on PTSD and increased cardiac risk as a noninvasive index of parasympathetic tone (Berntson, Cacioppo, & Quigley, 1993). However, despite evidence for impaired tonic RSA in PTSD (Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007; Jovanovic, Norrholm, Sakoman, Esterajher, & Kozaric-Kovacic, 2009; Woodward et al., 2009), null findings have also been reported (Fisher & Woodward, 2014; Sahar, Shalev, & Porges, 2001).

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Proponents of impaired tonic RSA in PTSD argue that persistent hyperarousal symptoms promote a pattern of autonomic dysregulation characterized by sympathetic hyperactivity, parasympathetic withdrawal, and elevated heart rate (HR; Blechert et al., 2007; Jovanovic et al., 2009; Woodward et al., 2009). Blechert et al. (2007) further contend that this dysregulation pattern may be distinct to PTSD as patients with panic disorder (PD), despite exhibiting similarly elevated arousal, do not exhibit this autonomic pattern. As such, researchers have generally interpreted findings of relatively lower levels of tonic RSA – that is, the average level of RSA over a specified time period – as evidence for impaired parasympathetic cardiac regulation in PTSD. However, there are several reasons that the exclusive use of tonic RSA may provide an incomplete quantification of parasympathetic cardiac regulation in PTSD. First, studies typically estimate tonic RSA from brief recording periods at only one or two time points (Blechert et al., 2007; Jovanovic et al., 2009; Sahar et al., 2001). However, given that highly complex patterns of autonomic activity are necessary to maintain adaptive cardiac responsivity to changing environmental demands (Berntson, Cacioppo, & Quigley, 1991; Friedman, 2007; Lipsitz & Goldberger, 1992), the relative level of RSA for a given individual can be expected to shift rapidly from moment to moment. Thus, these standard estimates of RSA likely overlook these rapidly occurring shifts in parasympathetic activity underlying adaptive cardiac regulation by focusing on the average level of RSA (Gates, Gatzke-Kopp, Sandsten, & Blandon, 2015). Second, past studies have largely examined the link between tonic RSA and PTSD using data aggregated across individuals (Blechert et al., 2007; Jovanovic et al., 2009; Sahar et al., 2001; Woodward et al., 2009). Given the lack of statistical equivalence between inter- and intraindividual variability (Fisher, Medaglia, & Jeronimus, 2018; Molenaar, 2004, 2007), this aggregation likely obscures nuanced intraindividual information about parasympathetic activity. Of note, Gates et al. (2015) substantiated these former two points using a novel method for estimating moment-to-moment shifts in RSA by demonstrating how two individuals with identical tonic RSA estimates exhibited both high variability in RSA and markedly different RSA dynamics over that same time period.

Finally, expanding on the distinction between the average level of RSA and moment-to-moment variation in RSA, Fisher, Reeves, and Chi (2016)) argue that the latter can be directly measured and modeled alongside HR to examine the degree to which parasympathetic activity relates to variation in HR from moment to moment. Relative to standard RSA measures, this alternate approach instead provides a quantification of parasympathetic cardiac regulation that more closely approximates the process by which moment-to-moment changes in parasympathetic activity are expected to flexibly exert regulatory control of HR over time (Friedman, 2007). To date, however, the influence of PTSD on these nuanced moment-to-moment effects has not been previously examined. Thus, moving beyond the tonic estimates and considering novel indices of parasympathetic cardiac regulation that address their associated shortcomings may improve our understanding of parasympathetic cardiac regulation in PTSD.

Fisher and Woodward (2014) recently provided a model for examining these intraindividual moment-to-moment parasympathetic regulatory effects on the heart. Using the data drawn from the initial laboratory night of a larger multi-night in-home mattress actigraphy study (Woodward et al., 2009), these authors used dynamic factor modeling (Molenaar, 1985), a multivariate time series method, to examine physiologic instability in participants with panic disorder (PD), PTSD, comorbid PTSD and PD (PTSD + PD), and control participants. Specifically, the time series of RSA, HR, and respiration rate (RR) recorded from each participant across this night of sleep were used to estimate intraindividual structural equation models. Fisher and Woodward (2014) then isolated the autocorrelation of HR across consecutive 30-s epochs as a proxy for the average degree of cardiac stability within a given participant across the night. These authors also examined tonic estimates of HR and RSA. Of note, Woodward et al. (2009) found higher tonic RSA and HR among those with PTSD and PTSD + PD compared to those with PD and control participants when aggregating multiple nights of in-home mattress actigraphy data. Fisher and Woodward (2014) observed no group differences in these tonic estimates when aggregating data drawn from each individual across the initial night of sleep in a structured laboratory setting; nevertheless, these authors did find that participants with PD exhibited significantly less autoregressive HR stability from epoch to epoch over this initial night (Fisher & Woodward, 2014). That is, the average degree to which HR at one moment predicted HR estimates 30-s later was significantly *decreased* in PD participants compared to those with PTSD, PTSD + PD, and control participants.

Taken together, these findings both reinforce arguments for physiologic instability in PD and demonstrate the added utility of examining moment-to-moment regulatory cardiac effects above and beyond tonic effects. Moreover, the intraindividual structural equation modeling methodology employed by Fisher and Woodward could be easily extended to examine the effect of RSA on HR from moment-to-moment in PTSD. That is, the lagged regression of HR on RSA estimated in these individual models reflects the average degree to which RSA predicted HR within a given participant from epoch to epoch over the night. This parameter therefore reflects the average degree of parasympathetic downregulation of the heart across 30-s epochs over a single night rather than the tonic level of parasympathetic tone. Moreover, after extraction from individual models, this parameter can be used to examine group differences in this moment-to-moment regulatory effect.

Therefore, the present study is a secondary analysis that uses the dynamic factor models from Fisher and Woodward (2014). The purpose of this study was to move beyond the exclusive focus on tonic RSA effects and examine whether PTSD also influences moment-to-moment parasympathetic cardiac regulation. Rather than reflecting the average level of parasympathetic activity over time, we argue this latter conceptualization captures the degree to which parasympathetic activity actively downregulates HR over time within each individual. Given that moment-to-moment shifts in parasympathetic activity are necessary to maintain adaptive cardiac functioning (Berntson et al., 1991; Friedman, 2007; Lipsitz & Goldberger, 1992), these effects likely better represent how parasympathetic cardiac regulation is expected to occur. As such, we argue examination of these effects may provide added understanding of parasympathetic cardiac regulation in PTSD. Thus, in the present study, we examined moment-to-moment parasympathetic cardiac regulation in participants with PTSD only, PD only, comorbid PTSD + PD, and control participants. We were specifically interested in group differences in the average degree of intraindividual parasympathetic downregulation of HR from epoch-to-epoch over a night. To that end, we isolated the lagged relationship between RSA and HR over these consecutive 30-s epochs in intraindividual structural equation models as a proxy for this parasympathetic regulatory effect in each individual. We then used this parameter to examine group differences in the degree of epoch-to-epoch parasympathetic cardiac downregulation across the night. Given that impaired tonic RSA is associated with anxiety broadly (Chalmers et al., 2014), comparing participants with PTSD to those with PD may reveal unique features of moment-to-moment parasympathetic regulatory activity in PTSD. Further, given that existing research has generally found impaired tonic RSA in PTSD compared to those with PD and control participants (Blechert et al., 2007; Jovanovic et al., 2009; Woodward et al., 2009), we believed this would extend to impaired parasympathetic regulation of HR from moment to moment. Thus, we hypothesized that participants with PTSD would exhibit weaker moment-to-moment parasympathetic cardiac regulation compared to healthy controls and those with PD only.

Table 1
Participant characteristics by group.

	Control	PTSD	PD	PTSD + PD
Age	Mean: 36.82 *SD*: 12.54	Mean: 43.38 *SD*: 10.21	Mean: 41.49 *SD*: 8.80	Mean: 41.96 *SD*: 11.54
Sex	Male: $n = 6$ Female: $n = 10$	Male: $n = 5$ Female: $n = 18$	Male: $n = 5$ Female: $n = 9$	Male: $n = 3$ Female: $n = 13$
Education (years)	Mean: 15.93 *SD*: 4.06	Mean: 15.50 *SD*: 2.31	Mean: 14.62 *SD*: 3.25	Mean: 15.06 *SD*: 2.72
BMI	Mean: 22.65* *SD*: 1.98	Mean: 26.14 *SD*: 5.70	Mean: 25.05 *SD*: 3.10	Mean: 26.91* *SD*: 4.85
RSA	Mean: 0.22 *SD*: 0.02	Mean: 0.23 *SD*: 0.03	Mean: 0.22 *SD*: 0.03	Mean: 0.23 *SD*: 0.04
HR	Mean: 63.10 *SD*: 5.28	Mean: 63.82 *SD*: 8.02	Mean: 59.08 *SD*: 8.46	Mean: 70.33 *SD*: 9.18
RR	Mean: 15.75 *SD*: 1.79	Mean: 15.21 *SD*: 1.68	Mean: 14.93 *SD*: 1.47	Mean: 16.13 *SD*: 2.07
PSQI	Mean: 8.06 *SD*: 1.48	Mean: 11.55 *SD*: 2.81	Mean: 10.14 *SD*: 2.71	Mean: 11.00 *SD*: 1.83

Note. PTSD = posttraumatic stress disorder; PD = panic disorder; *SD* = standard deviation; BMI = body mass index; RSA = respiratory sinus arrhythmia; HR = heart rate; RR = respiration rate; PSQI = The Pittsburg Sleep Quality Index total score.

* significant difference at $p < .05$.

2. Method

2.1. Participants

The present study is a secondary analysis of previously published data (Fisher & Woodward, 2014). The 69 participants included in the original study were retained for this analysis, including 23 with PTSD, 14 with PD, 16 with comorbid PTSD + PD, and 16 control participants. Participants were largely female ($n = 50$; 72%) with an average age of 40.91 years ($SD = 10.77$) and an average of 15.28 years of education ($SD = 3.09$). Eight participants also met criteria for comorbid dysthymic disorder, including five with primary PTSD, two with primary PD, and one with comorbid PTSD + PD. Fourteen participants (20%) were currently taking selective serotonin reuptake inhibitors (SSRIs; $n = 9$) and other anti-depressant medications ($n = 5$), which they agreed to maintain at their current dosage. Table 1 summarizes participant characteristics by diagnostic group.

2.2. Procedure

All procedures were authorized by the Stanford/Veteran Affairs (VA) Palo Alto Human Research Protection Program. All participants provided written informed consent. These data were drawn from the initial night of sleep in a laboratory setting collected as a part of a larger multi-night in-home mattress actigraphy study (Woodward et al., 2009). Radio and news advertisements emphasizing distress- and anxiety-related sleep disturbance were used to recruit participants from the surrounding community. Those who responded to study advertisements were then screened over the telephone by study staff. Telephone screening excluded callers if they reported current medical illness, histories of central nervous system disease/injury, a Multivariate Apnea Prediction Index greater than 0.5, current substance abuse, and unwillingness to discontinue any current hypnotic medication. After passing the initial phone screen, participants presented to a research laboratory for structured diagnostic interviews and self-report measures. The Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV; Blake et al., 2000) and the Structured Clinical Interview for the DSM-IV (First, Spitz, Gibbon, & Williams, 2002) were used to diagnose PTSD and PD, respectively. The Mini-International Neuropsychiatric Interview was used to determine other diagnoses (Sheehan et al., 1998). Qualifying participants were invited to participate and reported to this site in the evening for screening polysomnography (PSG). Ninety-nine participants meeting screening and diagnostic criteria were invited to participate. Of these, 17 declined to present for screening PSG. Of those that underwent PSG, 10 participants were excluded for apnea/hypopnea indices greater than 10 events per hour and 3 participants were excluded for periodic limb movement arousal indices greater than 20 events per hour. These were determined by manual scoring of PSG by an expert technician. This resulted in the final sample of 69 participants. After completion of a presleep startle protocol, these participants went to sleep *ad libitium*.

2.3. Data acquisition and preparation

Electrocardiogram (ECG) was collected with electrodes at left ninth rib referenced and right subclavicular region. ECG was amplified via a Grass 78v polygraph quipped with 7P511 J AC-coupled amplifiers, analog pre-filtered to a 1–100 Hz, and sampled at 600 Hz with 16 bits of amplitude resolution via a Kiethley 3708 data acquisition circuit using custom software developed in VisualBasic. ECG was later digitally filtered to 1–100 Hz prior to R-wave detection and respiratory effort (RESP) was filtered to .1–.5 Hz prior to RR calculation. Digital filtering employed phase-invariant, time-domain, finite impulse response filters implemented in MATLAB. RESP was recorded using the Vivometrics LifeShirt system and merged with the ECG data offline employing co-recorded ECG for synchronization. For each participant, this data collection paradigm yielded continuous measures of both ECG and RESP with no missing data. Continuous ECG and RESP measures were parsed into 30-s epochs of HR, RSA, and respiration rate (RR). Whereas the average percentage of missing values across these 30-s epochs was 0.15% for HR (*minimum* = 0%, *maximum* = 5.42%) and 0.11% for RSA (*minimum* = 0%, *maximum* = 5.42%), there were no missing values for RR.

To address outliers in each individual's data, we applied multiple automated exclusion criteria to the raw interbeat intervals (IBIs), which concurrently and iteratively assessed raw signal quality and IBI range. Any local aberrant IBIs were replaced with average values with reference to the nearest six IBIs, using three on each side of the aberrant IBI within the respective 30-s epoch. Respiratory sinus arrhythmia was estimated from the .15–.40 Hz spectral band of HRV spectra. Spectra were calculated using the Welch periodogram analysis as implemented in MATLAB ("pwelch") applied to detrended, Hamming-windowed, 30-second epochs of IBIs resampled to real time at 4 Hz.

2.4. Approach to modeling epoch-to-epoch intraindividual parasympathetic cardiac regulation

To examine intraindividual epoch-to-epoch parasympathetic cardiac regulation, the present study used a structural equation modeling framework to estimate autocorrelations and time-lagged regression relationships in the time series of RSA, HR, and RR for each individual (Fisher & Woodward, 2014). Thus, for each individual, a single-indicator dynamic factor model was estimated with a zero matrix for the observed errors, an identity matrix for the factor loadings, and the variance for each variable expressed in the latent disturbances (Molenaar, 1985). This places the observed variables within a structural equation model, yielding a model with multiple concurrent dependent variables (all variables at time $t + 1$) and a shared set of predictors (all variables at time t). These multivariate time series models used a single lag structure and were constructed for each individual separately in LISREL (version 8.8). Fig. 1 displays a schematic of these intraindividual models. Further, Fig. 2 displays the distributions of the intraindividual autoregressions of RSA, HR, and RR and the lagged relationship between RSA at time t and HR at time $t + 1$ drawn from these models by diagnostic group.

The average degree of epoch-to-epoch parasympathetic cardiac regulation over the night was operationalized as the time-lagged

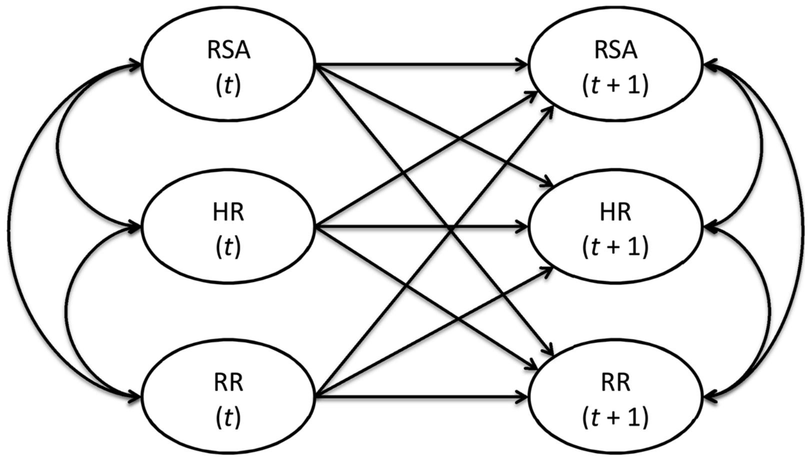

Fig. 1. Schematic representation of single-indicator dynamic factor model for each participant.

relationship between RSA at time t and HR at time $t + 1$. For a given individual, this reflects the degree to which RSA at a preceding time (time t) predicted HR at a later time (time $t + 1$) on average across consecutive 30-s epochs over the night. Standardized beta coefficients reflecting this effect were extracted from each individual model for use in multiple regression models. Given that parasympathetic signals tonically inhibit HR (Berntson et al., 1993), more negative coefficients reflected greater epoch-to-epoch parasympathetic cardiac regulation across the night.

3. Results

3.1. Preliminary baseline group differences

Complete details regarding group differences in participant characteristics, tonic RSA, tonic HR, tonic RR, sleep duration, and sleep stage percentage can be found in Fisher and Woodward (2014). As noted above, there were no significant group differences in the average level of HR, RSA, or RR across a single laboratory night in this sample. There was a baseline group difference in BMI, $F(3,65) = 3.96$, $p = .01$, whereby Scheffe's *post-hoc* tests revealed greater BMI for participants in the PTSD + PD group compared with control participants. Also, while there was a baseline group difference in subjective sleep quality at the alpha level of .001, $F(3,64) = 7.59$, $p < .001$, Scheffe's *post-hoc* tests revealed no significant differences between any groups in subjective sleep quality. No statistically significant baseline group differences in age, years of education, sleep stage percentage, or sleep duration were observed.

3.2. Effect of diagnostic group on epoch-to-epoch parasympathetic cardiac regulation

A multiple regression analysis was conducted to examine whether participants with PTSD exhibited weaker epoch-to-epoch parasympathetic cardiac regulation. SSRIs, non-SSRI anti-depressants, and sleep stage percentages (percentage of intermittent wake, slow wave, and rapid-eye-movement sleep) were included as control variables due to their known influences on vagal outflow (Rissanen, Naukkarinen, Virkkunen, Rawlings, & Linnoila, 1998; Trinder et al., 2001; Tucker et al., 1997; Yergani et al., 1991). The autocorrelation of HR from time t to time $t + 1$ (proxy for HR stability) and the correlation between RSA and HR at time t (degree of correlation between HR and RSA levels within time) were included as control variables to adjust for their potential influence on the lagged relationship between RSA at time t and HR at time $t + 1$.

Table 2 summarizes the results of this anaysis. Results indicated that participants with PTSD exhibited *increased* epoch-to-epoch parasympathetic cardiac regulation over the night than control participants (β = -.056, SE = .018, t = -3.03, p = .004, d = -.73). This effect extended to participants with comorbid PTSD and PD (β = -.067, SE = .02, t = -3.33, p = .001, d = -.80). These analyses were rerun using those with PD as the reference group. This re-analysis revealed

Fig. 2. Density plots for within-individual autoregressions of HR, RSA, RR and the cross-regression of HR at time t + 1 on RSA at time t (with group means represented by dotted lines).

Table 2
Effect of diagnostic group and control variables on epoch-to-epoch parasympathetic cardiac regulation estimates.

	β	SE	t	p	d
Intercept	0.011	0.054	0.20	0.85	0.05
PTSD	−0.056	0.018	−3.03	0.004	−0.73
PD	−0.007	0.020	−0.36	0.72	−0.09
PTSD + PD	−0.067	0.020	−3.33	0.001	−0.80
Wake %	−0.002	0.001	−1.56	0.13	−0.27
SWS %	−0.001	0.001	−0.95	0.35	−0.16
REM %	−0.001	0.001	−0.76	0.45	−0.13
SSRI	0.025	0.020	1.26	0.21	0.30
AntiD	0.023	0.025	0.92	0.36	0.22
HR_A	0.096	0.048	2.00	0.05	0.34
HR/RSA	0.063	0.031	2.05	0.05	0.35

Note. Reference group = healthy controls; PD = panic disorder; PTSD = posttraumatic stress disorder; Wake % = percentage of intermittent wake; SWS% = percentage of slow wave sleep; REM% = percentage of rapid-eye-movement sleep; SSRI = selective serotonin reuptake inhibitor; AntiD = non-SSRI antidepressant medication; HR_A = autoregression of HR; RSA/HR = correlation between RSA and HR at time *t*; Cohen's $d = t$*sqrt(2/*n*).

that those with PD did not differ significantly from control participants (β = .007, *SE* = .02, *t* = 0.36, *p* = .72, *d* = .09). However, those with PD did exhibit decreased epoch-to-epoch parasympathetic cardiac regulation relative to those with PTSD (β = -.049, *SE* = .02, *t* = -2.69, *p* = .009, *d* = -.65) and those with PTSD + PD (β = -.06, *SE* = .02, *t* = -3.10, *p* = .003, *d* = -.75).

3.3. Effect of PTSD severity on epoch-to-epoch parasympathetic cardiac regulation

To further clarify unique features of epoch-to-epoch parasympathetic cardiac regulation in PTSD, we conducted an exploratory analysis with participants with PTSD and PTSD + PD only. We specifically examined the association between the severity of each symptom cluster of PTSD (indexed by the CAPS-IV) and epoch-to-epoch parasympathetic cardiac regulation among participants with PTSD and PTSD + PD. Similar to the first model, medication use, sleep stage percentages, HR stability, and the correlation of RSA and HR at time *t* were all held as control variables due to their known influence on vagal outflow. Table 3 displays the results of this analysis. Results indicated that greater severity of hyperarousal symptoms was associated with increased epoch-to-epoch parasympathetic cardiac regulation among participants with PTSD only and PTSD + PD across the night (β = -.005, *SE* = .002, *t* = -3.05, *p* = .001, *d* = -0.69). Supplementary materials S1 presents the results from both our initial analysis and this exploratory analysis in a block-by-block fashion, beginning with the main effect for each model without control variables and ending with the results for each model displayed in Table 2 and Table 3.

Table 3
Effect of CAPS-IV criterion scores and control variables on epoch-to-epoch parasympathetic cardiac regulation estimates.

	β	SE	t	p	d
Intercept	0.081	0.084	0.97	0.34	0.22
CAPS-B	0.000	0.002	0.23	0.82	0.05
CAPS-C	0.001	0.001	1.11	0.28	0.25
CAPS-D	−0.005	0.002	−3.05	0.005	−0.69
Wake %	−0.002	0.002	−1.59	0.12	−0.36
SWS %	0.002	0.002	1.51	0.14	0.34
REM %	−0.005	0.002	−2.54	0.02	−0.58
SSRI	−0.048	0.027	−1.78	0.09	−0.40
AntiDep	0.004	0.024	0.15	0.88	0.03
HR_A	0.080	0.056	1.43	0.16	0.32
RSA/HR	0.048	0.041	1.19	0.25	0.27

Note. CAPS = Clinician-Administered PTSD Scale for DSM-IV; Wake % = percentage of intermittent wake; SWS% = percentage of slow wave sleep; REM% = percentage of rapid-eye-movement sleep; HR_A = autoregression of HR; RSA/HR = correlation between RSA and HR at time *t*; Cohen's $d = t$*sqrt(2/*n*)).

4. Discussion

The present study examined moment-to-moment parasympathetic cardiac regulation in participants with PTSD, PD, PTSD + PD, and control participants across a single night of laboratory sleep. The purpose of this study was to move beyond the exclusive use of tonic RSA estimates and examine whether PTSD also influences moment-to-moment parasympathetic cardiac regulation. This novel approach to the quantification of parasympathetic cardiac regulation more closely approximates the process by which parasympathetic activity flexibly regulates HR over time and, to the best of our knowledge, has not been previously examined in PTSD. By comparing those with PTSD to those with PD, we also aimed to identify features of moment-to-moment parasympathetic cardiac regulation unique to PTSD. Adapting methods previously used by Fisher and Woodward (2014), we used a multivariate time series methodology to isolate the lagged relationship between RSA at time *t* and HR at time *t* + 1 as a proxy for the average degree of epoch-to-epoch parasympathetic cardiac regulation for a given individual over a single night. Based on extant research (Blechert et al., 2007; Jovanovic et al., 2009; Woodward et al., 2009), we hypothesized that participants with PTSD would exhibit weaker epoch-to-epoch parasympathetic cardiac regulation compared to control participants and those with PD only. Our results instead indicated that participants with PTSD only and PTSD + PD exhibited greater moment-to-moment parasympathetic cardiac regulation than control participants and those with PD only. Moreover, results from a *post hoc* analysis indicated that greater severity of hyperarousal symptoms was associated with increased epoch-to-epoch parasympathetic cardiac regulation in participants with PTSD and PTSD + PD. As previous studies from this literature have exclusively used tonic RSA estimates (Blechert et al., 2007; Fisher & Woodward, 2014; Jovanovic et al., 2009; Sahar et al., 2001; Woodward et al., 2009), the present study represents an important extension of extant research on the link between RSA and PTSD.

These results have important implications for research on the physiologic correlates of PTSD. Cognitive models of PTSD have argued that negative trauma-related cognitions serve as maintaining factors by promoting the misperception of ongoing threat (Ehlers & Clark, 2000; Zalta & Foa, 2012). Moreover, these cognitions promote strategies that impede the processing of disconfirming information and instead reinforce these misperceptions. Those who have found evidence for low tonic RSA in PTSD have argued that a positive feedback cycle between chronic maladaptive threat-related cognition and autonomic regulation confers an ongoing state of sympathetic hyperarousal and parasympathetic withdrawal (Blechert et al., 2007; Jovanovic et al., 2009; Woodward et al., 2009). While our results provided preliminary support for the role of sympathetic hyperarousal – if only at the level of self-report – our analyses provided a paradoxical counterpoint to the extant literature. Namely, we found that the degree of sympathetic hyperarousal reported by individuals with PTSD predicted *greater* moment-to-moment parasympathetic regulatory efforts rather than moment-to-moment vagal withdrawal. These results point to the possibility that the increased epoch-to-epoch parasympathetic cardiac regulation that we observed in participants with PTSD may reflect a response to hyperarousal symptoms—an upregulation of parasympathetic control meant to counteract persistent hyperarousal and tonically elevated sympathetic activity. Future research should examine this possibility directly, while including measures of sympathetic cardiac control (such as pre-ejection period). Future studies should also examine the degree to which these findings replicate with recordings taken while awake.

Finally, our results may also point to a distinction between the physiologic correlates of PTSD and PD. As we hypothesize above, these data may point to a counteracting parasympathetic response to chronic sympathetic hyperarousal. However, despite evidence for sympathetic hyperarousal in PD (Friedman, 2007), this effect did not extend to those with PD. Whereas cognitive models argue that ongoing sympathetic hyperarousal in PTSD is driven by hypervigilance to perceived threats (Blechert et al., 2007; Ehlers & Clark, 2000; Jovanovic et al., 2009; Woodward et al., 2009), PD may instead be characterized by sensitivity to discrete physiologic cues that lead to *episodic* sympathetic hyperarousal via panic attacks (Barlow, 2004; Fisher & Woodward, 2014). Thus, while hyperarousal in PD may be maintained by vigilance toward threat cues, we argue that this process is episodic, leading to intermittent episodes of sympathetic hyperarousal — rather than the ongoing sympathetic hyperarousal in PTSD. Thus, it may be that episodic sympathetic elevations are not sufficient to elicit a counteracting parasympathetic effect. These hypotheses warrant further investigation.

There are several limitations to the present study that are important to discuss. First, the autonomic nervous system is a multidimensional system, whereby sympathetic activity may be complementary, competitive, or independent of parasympathetic activity (Berntson et al., 1991). Therefore, measuring parasympathetic tone does not necessarily account for sympathetic tone. Given that our interpretation of these results assumes sympathetic hyperactivity, the omission of a direct index of sympathetic tone is an important limitation. As such, we feel these results should be taken as preliminary and that future studies should expand our methodology by including pre-ejection period – an index of sympathetic cardiac input – to evaluate these conclusions and further characterize moment-to-moment autonomic cardiac regulation in PTSD. Second, although the examination of the downregulatory effect of RSA on HR over consecutive 30-s epochs represents an improvement upon the temporal resolution provided by standard RSA measures, this can still be viewed as temporally coarse (Fisher et al., 2016). Gates et al. (2015) recently provided a method for estimating time-varying RSA, in which a time series of second-by-second estimates of RSA are derived for each individual over a specified time period. Given that RSA dynamics are expected to be highly complex (Friedman, 2007; Lipsitz & Goldberger, 1992) and efferent parasympathetic signals operate on time-scales smaller than 1-s (Berntson et al., 1993), we contend that shorter time intervals may more precisely approximate parasympathetic cardiac effects occurring from moment-to-moment over time. Thus, future studies should further extend our methodology by incorporating estimates of these parasympathetic effects at varying time scales.

This endeavor may facilitate the identification of the optimal time scale at which alterations in these regulatory effects associated with anxiety-related pathology may be modeled and detected. Third, participants in the present study were recruited via advertisements emphasizing distress and anxiety-related sleep disturbance. Although subjectively poor sleep quality is commonly reported in PTSD and other anxiety-related pathology (Lamarche & De Koninck, 2007), these data may still represent a subsample of individuals with considerably elevated sleep disturbance, which limits the generalizability of these results. Given this limitation and the impact of sleep stage percentages on these findings, future research should endeavor to replicate these results in participants with varying levels of sleep disturbance. Lastly, as noted above, these data were drawn from a single night of sleep in a structured laboratory setting collected as a part of a larger multi-night in-home mattress actigraphy study (Woodward et al., 2009). Although no group differences in tonic RSA or HR were found over this initial night, Woodward et al. (2009) reported higher tonic HR and lower tonic RSA among those with PTSD only and PTSD + PD compared to those with PD only and healthy controls when averaging across multiple nights of data collected exclusively from in-home mattress actigraphy. Thus, the reliance on data drawn from a single night of sleep in a laboratory setting is a limitation. As such, future studies should endeavor to replicate these findings using multi-night measurements.

Finally, given that an increased parasympathetic influence was observed in both participants with PTSD only *and* comorbid PTSD and PD, future studies should use a dimensional approach to further understand the link between cardiac morbidity and mortality and patterns of anxious arousal. This is consistent with efforts to move beyond diagnostic categories and instead better understand the link between identifiable biosignatures, psychological dysfunction, and adverse outcomes in hopes of improving our ability to effectively intervene (Kozak & Cuthbert, 2016; McTeague & Lang, 2012). Despite these interpretative cautions, we believe the present study represents an important extension of extant research on parasympathetic cardiac regulation in PTSD. Specifically, these results suggest that PTSD may be uniquely associated with an upregulatory parasympathetic response to ongoing sympathetic hyperarousal. Further, these results also reinforce the added utility of examining moment-to-moment regulatory effects above and beyond tonic effects (Fisher & Woodward, 2014).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.janxdis.2019.102144.

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