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Meta-Analysis of Heart Rate Variability as a Psychophysiological Indicator of Posttraumatic Stress Disorder

Madan L Nagpal[1], Kurt Gleichauf[1,2] and Ginsberg JP[1,3]*

[1]Shirley L Buchanan Neuroscience Laboratory, Dorn VA Medical Center, Columbia, SC, USA
[2]Department of Business Administration, University of South Carolina, Columbia, SC, USA
[3]Department of Pharmacology, Physiology, and Neuroscience, School of Medicine, University of South Carolina, Columbia, SC, USA

Abstract

Background: Posttraumatic stress disorder (PTSD) syndrome is accompanied by the changes in autonomic nervous system, and heart rate variability (HRV) parameters assess the balance of sympathetic and parasympathetic influences on heart rate. HRV is a promising psychophysiological indicator of PTSD. The aim of this meta-analysis is to provide a quantitative account of the literature findings on PTSD and co-occurring HRV parameters. We first examined the effect size of PTSD on HRV in available published studies, and we then examined the effects of PTSD treatments on various HRV parameters.

Methods: A literature search was done using three electronic databases; Pubmed, PsycINFO and Google Scholar. From each of the selected studies, we extracted study characteristics and outcomes measured. The meta-analysis was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane Handbook guidelines, using Comprehensive Meta-analysis Software, ver. 2.0. We calculated the Hedges'g effect size with 95% confidence interval (CI), statistical significance (p), and heterogeneity for each effect size estimate. We considered several variables, and for each an individual meta-analysis was performed.

Results: Meta-analysis reveals the potential utility of HRV index variables as indicators of PTSD. For high frequency (HF) power, the aggregate mean effect size of 11 studies with 379 subjects was large and negative, showing reduced HF for PTSD patients relative to controls and indicating lower vagal activity in these patients. There were also significantly decreased RMSSD values, indicating lower vagal tone in subjects with PTSD. The aggregate mean effect size of low frequency (LF) power was small, negative, and significant, indicating slightly reduced LF in PTSD patients. The LF/HF ratio was statistically significantly higher in PTSD patients. The positive LF/HF effect size indicates increase in sympatho-vagal balance under the PTSD conditions as compared with the normal conditions, and further reflects non-linearity in co-occurring shifts in LF and HF power with proportionately greater reduction in HF than LF. Heart rate (HR) was significantly elevated in PTSD patients. Lastly, there was a decrease in SDNN in the patients, indicating decrease in the variability in RR intervals and a increase in sympathetic tone. These analyses showed no significant between-study heterogeneity for any of these parameters. Very few studies have examined changes in HRV variables pre- and post-treatment; using conservative random effect modeling, a significant increase in RMSSD could be discerned, and decrease in HR was nearly significant (p 1-tailed=0.08).

Conclusion: Currently available scientific literature clearly shows that reductions HF, RMSSD and LF/HF have utility as indicators of autonomic effects of PTSD, which can be associated with impaired vagal activity. Increased LF/HF index in patients suggests non-linear decreases in both LF and HF yielding excess of sympathetic relative to vagal imbalance in PTSD patients. Data are scarce for treatment effects on HRV, but RMSSD appears to be increased.

Keywords: Posttraumatic stress; Heart rate; Heart rate variability; Meta-analysis

Introduction

Posttraumatic stress disorder (PTSD) is a com¬mon mental health problem among combat veterans. PTSD is a psychiatric condition that can develop after exposure to extremely stressful life events. It is characterized by more than 1 month of re-experiencing, avoidance, and hyper-arousal symptoms [1]. The current combat operations in Iraq and Afghanistan have resulted in a considerably large number of veterans with mental health problems. Diagnoses of mental health conditions among active duty service members due to the psychological toll of exposure to violent conflict have increased substantially, due in part to increased and improved screening methods as well as Department of Defense (DOD) efforts to reduce the stigma associated with seeking mental health treatment that in the past might have dissuaded service members from reporting mental health concerns or accessing care [2]. PTSD is not limited to veterans who experience combat trauma. PTSD is considered the fourth most common psychiatric diagnosis, affecting 10% of all men and 18% of all women [3].

Studies of psychophysiological correlates of PTSD in the past have typically involves facial electromyography (EMG; muscle contractions), heart rate (HR; cardiac activity), skin conductance (SC; sweat gland activity), systolic blood pressure (SBP; the force of blood in the circulatory system when the heart contracts), and diastolic blood pressure (DBP; the force of blood in the circulatory system when the

***Corresponding author:** Jay P Ginsberg, Shirley L. Buchanan Neuroscience Laboratory (151A), William Jennings Bryan Dorn VA Medical Center, 6439 Garners Ferry Road, Columbia, SC, 29209-1639, USA, Tel: +1 803-776-4000 ext: 6634; Fax: +1 803 695 7942; E-mail: jay.ginsberg@va.gov

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heart is at rest) [4]. Heart rate variability (HRV) is a relatively new psychophysiological measure. It is a measure of variations in beat to beat intervals recorded by electrocardiogram (ECG) or fingertip pulse plethysmograph, and it indices are operationalized by several 'time-domain' and 'frequency-domain' variables [5,6].

The 'time-domain' of HRV is often measured in terms of RR variability, where R is a point corresponding to the peak of the QRS complex of the ECG wave and RR is the interval between successive Rs. In the more general case, NN variability, or 'normal to normal', refers to any successive point or peak on the ECG wave form and is in most cases entirely equivalent to RR. Time domain variability is further expressed as SDNN (standard deviation of normal to normal intervals) and sometimes as RMSSD (the root mean square of successive RR or NN differences, where each difference is squared, summed, the results are averaged, then the square root obtained). The time domain measures such as SDNN generally reflect both sympathetic and parasympathetic activity, however RMSSD and pNN50 (the percentage of adjacent RR or NN intervals that differ by more than 50 milliseconds) are time domain variables that are strongly correlated with the high frequency (HF) frequency domain index signal (see below),and thus are more specific indicators of parasympathetic activity [7].

The 'frequency-domain' analysis, also referred to as the power spectral density analysis, separates the heart rate signal into distinct frequency bands and quantifies their relative intensity, called power. Low frequency (LF) range power (0.04-0.15 Hz) is mediated by both sympathetic and parasympathetic activity, while high frequency range power (HF) (0.15-0.4 Hz) is mediated primarily by parasympathetic activity. In the HF range, RSA is the HF component of the HRV frequency power spectrum associated with normal respiration (12-16 breaths per minute, or 0.20-0.26 Hz). The LF range was thought to be sympathetically driven, but given the lack of specificity across the entire range of the LF signal, information obtained from LF power spectra has been difficult to interpret accurately. To address this, the relationship of LF to HF power (the LF/HF ratio) has been used as an indicator of the comparative balance of the two branches of the autonomic nervous system (ANS) on cardiac activity. The ratio of LF/HF is sometimes referred to as a measure of "sympathovagal balance" [5,8]. The trend of more recent work has been to show that the upper range of the LF band (i.e. 0.08-0.15 Hz) reflects parasympathetic cardiac influence and the lower band range (0.04-0.08) is where sympathetic influence is prominent. LF and HF are sometimes normalized to total power (TP) and analyzed as normalized low frequency power: (LFn=LF/(TP-Very Low Frequency)*100) and normalized high frequency power (HFn=HF/(TP-Very Low Frequency)*100). Because the total power of the spectral signal can differ greatly from individual to individual, it has been recommended that LF and HF data be presented in values normalized to the total area under the curve [9]. Even if multiple measures are available to quantify HRV dynamic, no gold standard has been agreed upon yet. Furthermore, the complexity of the power spectrum both physiologically and mathematically has made it difficult to obtain a single number that is able to discriminate between physiologic and pathologic states [5].

The PTSD syndrome is accompanied by changes in autonomic nervous system function at two levels: basal tone and reaction to stress-related cues [10-12]. HRV as a physiological probe could contribute importantly to increasing our comprehension of the intricate sympathetic and parasympathetic systems in the autonomic hyper-arousal characterizing the PTSD patient [12]. Reduction in HRV has been associated with pathological conditions such as major depressive disorder [13] and myocardial infarction [14], in addition to its association with PTSD [12,15-18].

A meta-analysis conducted by Thayer et al. [6] on HRV and neuroimaging studies demonstrated that HRV may serve as a proxy for 'vertical integration' of the brain mechanisms that guide flexible control over behavior by peripheral physiology, and as such provides an important window into understanding stress and health. HRV may serve as an easily measured output of the neural network providing valuable information about the capacity of the organism to effectively function in a complex environment. The vagus cranial nerve is the central element of this heart-brain system. Vagally mediated HRV appears to be capable of providing information about the functioning of the heart-brain system, and therefore about integration of the neural-behavioral system. As a treatment modality, HRV biofeedback (HRVB) is a non-pharmacological technique for improvement of HRV that has been shown to effectively increase HRV and reduce the symptoms of different disorders, such as chronic pain [19,20], anxiety [21-23], depression [24,25] and PTSD [17,18]. We have previously demonstrated that HRV biofeedback (HRVB) in PTSD patients improved cardiac coherence significantly and that the increase in coherence was a possible mediator of cognitive improvement [18].

We have attempted to summarize the current scientific literature on the link of PTSD to HRV with a systematic meta-analytic review looking first at basic studies of PTSD and HRV which did not have any intervention or measures of HRV pre-post any type of intervention. Such a meta-analysis will prove useful in understanding the correlation of HRV and PTSD as an index of the change in strength of control of Parasympathetic Cardiac Deceleration in PTSD patients. We then examined the effects of interventions and or treatments considering available data from 1997 to 2012. The application of HRV analysis to PTSD patients is relatively new, the earliest studies being in the late 1990's and early 2000's. Previously published studies of HRV and PTSD describe reductions in the parasympathetic arm of the autonomic nervous system. Studies of the effects on HRV of treatments or interventions aimed at reducing PTSD have indicated that HRV power is restored.

Studies of the link between PTSD and HRV have used a variety of summary index variables to characterize the autonomic state of these patients. Earlier studies relied on Respiratory Sinus Arrhythmia (RSA), the LF/HF ratio, and RMSSD as the indices of parasympathetic influence. However, the usage and interpretation of HRV indicators was not been uniformly agreed upon. As a result, the population of available basic studies PTSD and HRV are not functionally equivalent. In addition to reporting different outcome indicators, the population of PTSD patients that has been studied is heterogeneous, with different traumatic events (e.g. war, crime, sexual assault) and demographics (e.g. sex and age). These considerations lead us to believe that the studies differed in ways that could have impacted on the results, and therefore we did not assume a common effect size of the disorder on HRV. For this reason, the more conservative random effects model, which yields smaller combined effect sizes and larger confidence intervals, was chosen for the analysis of basic studies.

When deciding on the model for the treatment intervention studies, we reasoned that the effect of interest was the change in HRV associated with changes in PTSD due to the treatment/intervention. Thus, we also included a fixed effect model for the treatment/intervention analysis because we felt that the assumption that there is one true effect size, shared by all the included studies irrespective of patient population or treatment or intervention, was a reasonable one. The studies could be

viewed as having enough in common that it makes sense to synthesize the information and the only reason the effect size varies between studies is random error.

Materials and Methods

Data sources and study selection

A literature review was conducted for studies involving PTSD and heart rate variability by using the key words;"PTSD " or "posttraumatic stress" and "heart" or "heart rate variability" or vagal or autonomic nervous system using Endnote ver. X6 software. The search included Pubmed, PsycINFO and Google Scholar databases. Other relevant articles were searched in the reference sections of each article identified from these literature searches (snowball technique). We searched for clinical trials involving PTSD and HRV on ClinicalTrials.gov and on the NIH and VA registries of grant-funded research. This systematic review and meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) by Moher et al. [26] and Cochrane Handbook guidelines by Higgins and Green [27], using Comprehensive Meta-analysis Software, ver. 2.0. If one reference reported two or three data sets (e.g.; several HRV parameters or pre-treatment and post-treatment data), then more than one study was considered. For each study, two authors using a structured form independently extracted data.

Two independent investigators (MLN and KG) read all retrieved abstracts and titles, and extracted descriptive and quantitative data. We prepared an extensive spread sheet from the extracted papers using the presence/absence of various variables related to cardiac, psychological, performance, health and treatment metrics.

We included studies that were written in English, provided data for both HRV and PTSD symptoms, and baseline measurements, as indicated in Figure 1. Studies that did not have PTSD diagnosis and HRV data were excluded. Full texts of potentially eligible studies were retrieved and screened to determine their eligibility. There were few discrepancies between the investigators, but when they did occur, were resolved by discussion including the third author (JG).

Coding of the Studies

The selected studies were coded for year of publication, PTSD diagnostic method, trauma type, age and gender, whether there was a treatment and if so, what the treatment was.

Statistical Analyses

The meta-analysis was performed according to the methods proposed by Lipsey and Wilson [28], as described by Casement and Swanson [29] using Comprehensive Meta-analysis Software, ver 2.0.

The Hedges'g effect size, which is more adequate than the Cohen's d for small sample sizes, was calculated. Hedges' g and the more commonly seen Cohen's d both are based on the difference between means divided by the standard deviation; they differ only in that Hedges' g uses the version of the standard deviation formula in which you divide by N-1, whereas Cohen's d uses the version in which you divide by N. Correlation coefficients were adjusted using a Fisher Z transformation. Then the weight for each study was calculated using its inverse variance to adjust for the sample size. A heterogeneity analysis (I^2) was performed which indicates that the variability across the effect sizes is greater than expected from sample error alone [30]. We examined random effects for the basic studies and random and fixed effects models for the treatment/intervention analysis. The random effects model is the more

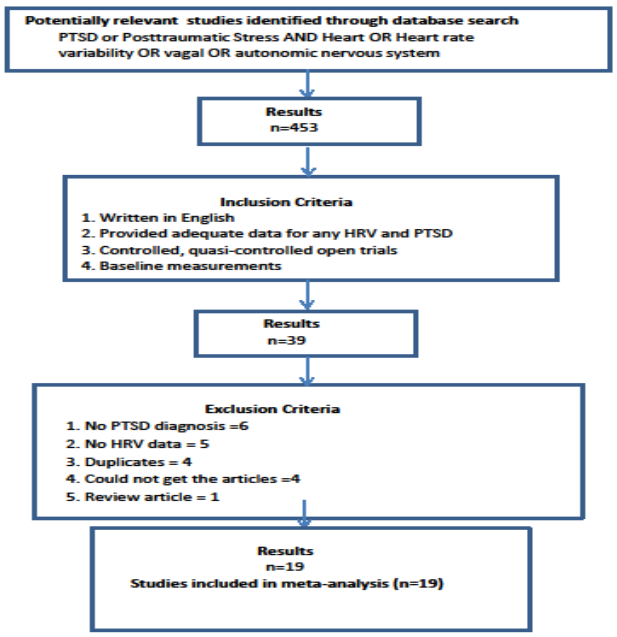

Figure 1: Flow Chart, showing the number of studies included at each step of the selection process and the reasons for it.

conservative method, and takes into account that study heterogeneity of combined effect size can vary beyond chance, thus providing more generalizable results. Similarly to a previous HRV meta-analysis [13], we considered several variables, for each of which an individual meta-analysis was performed [31-35].

Results

Excluded studies

453 articles were initially identified from the keyword search most were excluded after browsing the title and abstract as they did not have HRV variable parameters this set was reduced to 19 after applying the inclusion and exclusion criteria (Figure 1). Quality assessment revealed that the publication bias was not significant, as virtually all studies used age- and gender-matched controls, confirmed PTSD diagnosis according to standardized criteria, and all performed analyses on the whole sample

Characteristics of the Selected Studies

The selected studies had been published between 1997 to 2012. The characteristics of the studies which include trauma type, diagnostic method, subjects (n), age, gender, outcomes measured (HRV parameters), and comparison of groups (e.g. PTSD + vs. PTSD – with trauma exposure; PTSD vs. Healthy control, and PTSD+ Pre- and Post-treatment) are presented in Table 1. The study sample appears to be heterogenous, with four different trauma type populations and a dozen different HRV parameters used as outcome measures.

Quality ratings of likelihood of bias were made on the five studies of PTSD clinical treatment / intervention that were selected and which had outcome variables that could be combined and assessed for treatment effects on HRV. The quality of reports of clinical studies depends crucially on three methodological processes [45,46]: (1) Is the study described as randomized, and use an adequate procedure

Study	Trauma Type	Diagnostic	Subjects (n)	Age	Gender	Treatment	PTSD (n)	Non-PTSD / Control (n)	PTSD Post-tx (n)	Outcomes measured
Cohen et al. [12]	T	DSM-IV	18	37-40	M/F	No	9	9		%LF, %HF, LF/HF, HR
Cohen et al. [15]	W, T, A	DSM-IV	39	25-41	M/F	No	14	25		LnLF, LnHF, LF/HF, HR
Cohen et al. [31]	W,T,A	DSM-IV	32	24-56	M/F	SSRI	16	16	16	%LF, %HF, LF/HF
Frustaci et al. [32]	T	MINI ver 5.0	4	18-65	F	EMDR	4		4	RMSSD, HR
Ginsberg [33]	W	DSM-IV	28	40-70	M/F	No	16	12		HR, HRV
Ginsberg [18]	W	DSM-IV	10	27-37	M	HRVB	5	5	5	LnLF, COH
Hauschildt et al. [34]	T, V	DSM-IV	52	25-49	M/F	No	26	26		LF, HF, RMSSD, HR
Keary et al. [35]	T	DSM-IV	40	25-49	F	No	20	20		LnLF, HR
Lakusic et al. [16]	W	DSM-IV	68	41-57	M	No	34	34		LnLF, LnHF, LnSDNN, LnTP
Mellman [36]	T	DSM-IV	19	22-62	M/F	No	9	10		LF/HF(E,L,EN,LN)
Mitani [37]	T	DSM-IV(IES-R)	22	32-55	M	AT	10	12	10	LF/HF
Nishith et al. [38]	T	CAPS	5	21-41	F	PET	5		5	LF/HF,REM
Sack [39]	A, V	DSM-IV	10	26-47	M/F	EMDR	10		10	RMSSD, HR
Shaikh et al. [40]	A	DSM-IV	18	20-40	M/F	No	7	11		SDNN, MSSD
Slewa-Younan et al. [41]	W	DSM-IV	25	>25	M/F	No	12	13		LF, HF, TP, HR
Song et al. [42]	T	MMPI-PTSD	24	40-64	M/F	No	14	10		LnLF, LnHF, LnSDNN, LnTP,HR
Tan et al. [43]	T	DSM-IV	28	22-52	M/F	No	16	12		SDNN
Tan [44]	W	DSM-IV	30	25-58	M	No	20	10		SDNN
Zucker et al. [17]	T	PTS-T, DAPS	19	18-60	M/F	HRVB	19		19	SDNN

A : Accident; AT: Autogenic Training; CAPS: Clinician-Administered Ptsd Scale; COH: Coherence Coefficient; DAPS: Detailed Assessment of Posttraumatic Stress States; DSM: Diagnostic and Statistical Manual of Mental Disorders; E: early-REM period; EMDR: Eye Movement Desensitization And Reprocessing Treatment; EN: Early Non-Rem Period; HF: High Frequwency; HR: Heart Rate; HRVB: Heart Rate Variability Feedback; IES-R: Impact of Event Scale-Revised; L: Late Rem Period; LF: Low Frequency; Ln: Natural Log; LN: Late Non-Rem Period; MINI: Mini-International Neuropsychiatric Interview; MMPI-PTSD, Minnesota Multiphasic Personality Inventory-PTSD; PET: Prolonged Exposure Therapy; PNN50: Percentage of Successive Normal Inter beat Intervals Differing by at Least 50 s (correlated with HF-HRV); PTS-T, Posttraumatic Stress-Total; REM: Rapid Eye Movement; RMSSD: Root Mean Square of Successive Rhythm to Rhythm Differences; SDNN: standard Deviation of Normal to Normal Beats; SSRI: Selective Serotonin Re-Uptake Inhibitor; T: Terror Act; TP: Total Power; V: Violence; W:War

Table 1: Study design and outcomes measured in the meta-analysis.

for randomization? (2) Is there a treatment control group (placebo, treatment as usual) and is the study described as double blind? (3) Is there a description and analysis of participants who dropped out or withdrew? An accepted, objectively quantifiable scale of these factors [45], which ranged from 0 (poor quality with likelihood of bias) to 5 (good quality, with acceptable control of bias) was used. All five of the studies were rated as 0, poor quality. After consideration, we determined to carry out the meta-analysis nonetheless and at the same time report the quality ratings and make the statement that true, randomized controlled clinical trials studies of the effects of PTSD treatment on HRV are needed. The motivation to continue with the analysis was also due to the fact that our search results did not include any other clinical intervention / treatment studies.

HRV parameters in PTSD vs. Controls

Table 2 shows the effect sizes (p two-tailed) of differences between PTSD and control subjects of the sample of studies for each HRV parameter. Significant between-study heterogeneity within the study sample of each HRV parameter was present. Thus, caution must be used in evaluating the results [47], even though we have used the random effects model, a decision based on logical and clinical grounds.

Significant effect sizes showing PTSD lower than Controls were found for HF, LF, RMSSD, and SDNN. This finding for HF, RMSSD, and SDNN is consistent with the general understanding that PTSD brings with it tonic autonomic hyper-arousal. HF and RMSSD are highly correlated and both are indicators of parasympathetic cardiac influence, which is diminished by PTSD. The finding that LF is lower in PTSD is similarly interpretable if the assumption is furthermore made that LF power in individuals with PTSD is not found in the upper, parasympathetic, LF band range (0.08-0.15 Hz). However, this conjecture is speculative as data bearing on this issue were not available in the sample of studies analyzed. For HF, the aggregate mean effect size in 11 studies with 379 subjects was large and negative, showing reduced HF for PTSD patients compared to controls and suggesting lower vagal activity in these patients. For RMSSD, the aggregate mean effect size 6 studies with 264 subjects was large and negative, again showing a reduction in PTSD and showing lower vagal activity in subjects with PTSD. For LF, the aggregate mean effect size in 8 studies with 307 subjects showed a small and negative effect size, indicating reduced LF in PTSD patients. SDNN is a non-specific indicator of total HRV and in 5 studies with 173 subjects, SDNN was found to be lower in PTSD compared to controls, consistent with the other indicators of lowered vagal parasympathetic tone.

For LF/HF, the aggregate mean effect size in 10 studies with 280 subjects was significantly higher and positive, meaning that the ratio is greater in PTSD than in controls. The LF/HF ratio incorporates changes in sympathetic and parasympathetic (vagal) modulation. The high positive LF/HF effect size (PTSD greater than controls), given that both HF and LF appear to be lower in PTSD, suggests that the decrease in HF (parasympathetic) power due to PTSD is proportionately greater than the decrease in LF power. This may in part be due to the fact that HF power is typically much smaller in absolute value than LF power, and in part due to a shifting of HRV power from the upper (0.08-0.15 Hz), parasympathetic LF band range to the lower (0.04-0.08 Hz), sympathetic LF band range, with relatively little change in overall LF band power.

For HR, the aggregate mean effect size in 14 studies with 401 subjects was significantly large and positive, indicating increased heart rate for PTSD patients compared to controls. Elevated heart rate in

HRV Parameters	N Data Sets*	N PTSD Participants*	N Control Participants*	Hedge's g effect size (95% CI)	SE effect size	p effect size (2-tailed)	Heterogeneity	
							I^2	p
HF	11	186	193	-2.27 (-3.43 to -1.11)	0.592	<0.001	94.9	<0.001
LF	8	151	156	-1.72 (-3.06 to -0.36)	0.688	0.013	95.8	<0.001
LF/HF	10	131	149	2.20 (1.20 to 3.02)	0.510	<0.001	91.1	<0.001
TP	4	65	67	-0.33 (-1.04 to 0.38)	0.365	0.366	72.4	0.012
HR	14	196	205	1.29 (0.58 to 2.00)	0.640	<0.001	90.3	<0.001
RMSSD	6	121	143	-2.94 (-4.84 to -1.03)	0.972	0.002	96.7	<0.001
SDNN	5	91	82	-0.61 (-1.26 to 0.03)	0.329	0.062	74.9	0.03

HF: High Frequency; HR: Heart Rate; LF: Low Frequency; RMSSD: Root Mean Square of Successive Rhythm To Rhythm Differences; SDNN: Standard Deviation Ofnormal To Normal Beats; TP: Total Power

*More than one HRV parameter was compared in some of the individual studies, so the n of data sets and participants listed above for each comparison is greater than the sum of the individual studies

Table 2: Effect size estimates for HRV parameters for samples of PTSD compared to control samples.

PTSD is consistent with the tonic sympathetic hyper-arousal associated with PTSD, and with the findings that HR prospectively predicts PTSD (Bryant et al. [48]; Buckley et al. [49]).

Analysis of differences in total HRV power in 4 studies with 132 subjects showed no significant difference between PTSD and control groups.

Effects of PTSD treatments on HRV parameters

There are very few studies of effects of PTSD treatment on HRV variables. As shown in Table 3, five different studies with a total of 43 PTSD subjects were available to assess the aggregate mean effect size of treatment on HRV variables. Two studies that examined HRV variables, both using an HRV Biofeedback treatment, were not included in this analysis because they did not contain equivalent HRV variables and so could not be combined. Because more than one HRV parameter was measured in some of the studies, the number of data sets and PTSD participants is not a simple sum of the separate HRV parameters reported in Table 3. As was true for the meta-analysis of HRV parameters in PTSD vs. control groups, significant between-study heterogeneity was present.

Three studies examined effects of treatment on LF/HF in a total of 29 PTSD patients, and each study used a different treatment: AT (autogenic training); PET (Prolonged Exposure Therapy), and SSRI (Selective serotonin re-uptake inhibitor). The aggregate mean effect size of the three studies on LF/HF was statistically significant and positive for both the Fixed and Random effect models, indicating that LF/HF ratio decreased as a result of treatment. This finding is consistent with the meta-analysis of LF/HF in PTSD vs. controls (above, and Table 2), where lower LF/HF ratios were found in the control subjects.

Meta-analysis of RMSSD in two studies with a total of 14 patients with PTSD using EMDR did not show a statistically significant effect size with either the Fixed or Random effect model. However, both effect sizes were negative indicating increased RMSSD value, or higher vagal activity post-treatment.

Meta-analysis of HR in three studies (two EMDR, one SSRI) with a total of 28 PTSD patients revealed a positive effect size , indicating higher HR in the pre-treatment group than the post-treatment group, that was significant in the Fixed effect model and trended (p=0.08) in the more conservative Random effect model.

It should be noted that across all five studies with 43 PTSD patients, the effect size of PTSD severity, showing reduction in level of symptoms of PTSD post-treatment compared to pre-treatment levels, was large and positive.

Discussion

Our meta-analysis was informative about the diversity of parameters of HRV that have been reported in the scientific literature in association with PTSD, and emphasizes the need for standardization of reporting of variables in studies of HRV. Although source HRV data are quite simple (inter-beat intervals), cardiac tachygrams (HR over time) and power spectra (variance at each frequency or period) are quite complex. Non-linearity is increasingly known to exist in the associations between HRV variables. The mathematical complexity of HRV is due to the complexity of the underlying physiological systems (cardiac, respiratory, blood pressure) and their interactions which produce the source data. New constructs such as coherence and LF peak power are being examined for their utility in predicting outcomes, which are themselves difficult to measure constructs: behavior, emotion, and cognition.

The results of our meta-analyses reveal that many of the traditional HRV variables are significantly associated with PTSD, and these associations can be interpreted in terms of a basic and widespread model of PTSD as a disorder comprising hyper-arousal of the sympathetic nervous system. This model applies well to the observation of lower HF, RMSSD, and SDNN, and higher HR, in PTSD.

However, more work remains to be done to fully explain the association of low LF band power and high LF/HF with PTSD, given that power in the upper portion of the LF band (0.08-0.15 Hz) is derived from parasympathetic, deceleratory influences on cardiac adjustment. Studies of how power shifts within LF are associated with PTSD symptom reduction as normal sympatho-vagal balance is restored and LF band power coalesces from the lower portions of the LF band around 0.1 Hz frequency, would provide an important answer to this question.

Dissipation and restoration of the 0.1 Hz peak may also underlie the observed increase in LF/HF index in PTSD, and its reduction after PTSD treatment, but only in combination with non-linearity in transformation of power within the LF band and between the HF band. There is an abundance of literature pointing to the LF/HF ratio as a measure of "sympatho-vagal balance" [5,8,9,16,39], with LF power being sympathetic and HF being parasympathetic. But this conceptualization is oversimplified. The LF/HF ratio is limited in its usefulness as an HRV parameter because (1) the LF band is heterogeneous in its composition, with power derived both from sympathetic and parasympathetic sources, and (2) non-linearity in shifts of power between sympathetic and parasympathetic sources. The absence of differences in Total HRV power between PTSD and controls despite significant differences in component power sources is consistent with this proposition.

Our meta-analysis for HR (heart rate) showed that the aggregate

HRV parameter	Treatment method	Data sets	PTSD Participants (n)	Model	Hedge's g effect size	95% CI of effect size	SE effect size	p (1-tail)	Heterogeneity	
									I^2	p
LF/HF	AT/PET/SSRI	3	29	Fixed	1.141	0.486 to 1.795	0.334	<0.001	93.2	<0.001
				Random	2.461	-0.357 to 5.279	1.478	0.043	n/a	
RMSSD	EMDR/EMDR	2	14	Fixed	-0.475	-1.309 to 0.358	0.424	0.132	93.0	<0.001
				Random	-5.41	-16.25 to 5.43	5.53	0.164	n/a	
HR	EMDR/EMDR/SSRI	3	28	Fixed	0.794	0.251 to 1.337	0.277	0.002	89.5	<0.001
				Random	1.24	-0.496 to 2.976	0.886	0.081	n/a	
PTSD Severity*		5	43		1.382	0.717 to 2.047	0.339	<0.001	61.9	0.022

AT: Autogenic Training; PET; Prolonged Exposure Therapy; SSRI: Selective Serotonin re-uptake Inhibitor; EMDR: Eye Movement Desensitization And Reprocessing Treatment

*More than one HRV parameter was measured in some studies, so the n of data sets and PTSD participants is not a simple sum of the separate HRV parameter n's

Table 3: Effect size estimates for HRV parameters in PTSD treatment.

mean effect size was significantly large and positive, showing increased heart rate for PTSD patients than controls. A meta-analysis conducted by Pole [6] demonstrated significant effect size of PTSD on HR. HR is regulated by both the sympathetic and parasympathetic nervous system, such that increases in HR could be due to sympathetic activation, parasympathetic withdrawal, or both [4,50].

A meta-analysis conducted by Kemp et al. [13]on HRV in depression demonstrated that depression was associated with reduced HRV, and that the antidepressant treatment did not resolve reductions in HRV, despite reduction in depressive symptoms, suggesting that affective illness might have residual effects on neurophysiological systems, as proposed previously [51,52]. PTSD has been associated with reduced cardiac coherence (an indicator of heart rate variability) and deficits in early stage information processing (attention and immediate memory) in several studies [18,33,53,54].

We have reported previously [55] that conditioned HR responding (deceleration) is impaired in PTSD. Autonomic conditioning to a warning signal is reduced in PTSD+ combat veterans when the signal predicts aversive stimulation. Thus, decreased autonomic control of cardiac responding is clearly an aspect of PTSD. The autonomic conditioned response as indexed by HR reflects central nervous substrates that mediate them. A meta-analysis on HRV and neuroimaging studies identified a number of regions including the amygdala and ventro-medial prefrontal cortex, showing significant associations across studies with HRV [6].

This meta-analysis of HRV as a psychophysiological aspect of PTSD has shown that these parameters are a prominent, robust feature of the disorder. This is not surprising, since PTSD is related to failure of biological systems involved in recovery from fear and threat. A chronic, repeated activation of the autonomic nervous system could lead to sympatho-vagal imbalance, ultimately triggering PTSD syndrome [14]. We believe that these findings will pave the way for an expansion of research aimed at examining psychophysiological subtypes and regulatory processes of PTSD [4].

In view of the relatively few studies that have been carried out so far using HRV variables in PTSD, the conclusions of this meta-analysis should be regarded as exploratory and tentative. More outcome studies in this field are needed to examine the utility of HRV as a diagnostic criterion of PTSD, and how interventions used in the treatment of PTSD affect these variables. Each measure appears to have its own biological underpinning and therefore, may be uniquely informative about the pathophysiology of PTSD [4].

Limitations of this Study

Publication bias is a potential limitation for any meta-analysis. We made a very thorough search of the major, relevant scientific publication databases. For the clinical trials, we searched the registries for funded unpublished studies, even though there is evidence that publication bias has not been significantly reduced since introduction of the registries [56]. HRV is a relatively new field of study, and we do not believe that publication bias is as great a problem for our meta-analysis of the association between PTSD and HRV as is the few number of publications that fit the inclusion criteria. From our point of view, the serious problem is with the poor quality of the studies of HRV in clinical trials of treatment / interventions for PTSD. Great heterogeneity between basic studies of PTSD and HRV was observed. This fact in and of itself does not vitiate our basic premise that the link between PTSD and HRV is an important one, as we have already argued that combining these effect sizes can be logically and clinically justified. The urgent need at this time is for true, randomized clinical trials of the effects of PTSD treatments and interventions on key HRV parameters.

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