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Impaired Autonomic Modulation and Abnormal Circadian Variation in Male Twins with Posttraumatic Stress Disorder

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Bachelor in Science
Nankai University
2012

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Abstract

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By Lei Weng

Background: Posttraumatic stress disorder (PTSD) is associated with increased risk of developing cardiovascular disease. A core symptom of PTSD is sleep disturbance, which may lead to impaired autonomic modulation at night and downstream cardiometabolic abnormalities. We aimed to investigate nighttime and day-night differences in heart rate variability (HRV), a measure of autonomic function, in a group of veteran twins with PTSD versus without PTSD.
Methods: HRV was measured by power spectral analysis on 24-hour ambulatory electrocardiogram in 134 middle-aged veteran male twins. PTSD status was assessed with the Structured Clinical Interview for Psychiatry Disorders. We used mixed-effects regression models to analyze the association of current PTSD (symptoms within 30 days) and nighttime HRV, while adjusting for potential confounding due to cardiovascular, familial, and genetic factors through twin models that compare PTSD discordant twin brothers.
Results: Current PTSD (n=16) was associated with lower low-frequency (LF) HRV during nighttime both in individual twins and within 15 pairs discordant for current PTSD. We observed a 0.77 ln ms^2 lower LF HRV (p <.001) during nighttime in twins with current PTSD versus controls. The association persisted after adjustment for confounding factors. Patients with current PTSD also showed significantly lower high-frequency (HF) HRV and very-low-frequency (VLF) HRV during nighttime in unadjusted models, although after multivariate adjustment the associations lost significance. Twins with current PTSD exhibited a decrease in LF and HF HRV at night compared to the day (adjusted p = 0.09, p <.01), whereas for controls without current PTSD, the trends were in the opposite direction, and both HF and LF HRV increased at night.
Conclusion: Veterans with PTSD exhibited reduced LF HRV at night, which may indicate diminished parasympathetic regulation secondary to disturbed sleep. These findings suggest a possible role of sleep perturbation and autonomic dysregulation as a mechanism of increased cardiovascular risk in PTSD.

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Table of Contents

Introduction

Posttraumatic stress disorder (PTSD) is a clinical syndrome characterized by re-experiencing, avoidance, and hyperarousal reactions that persist for more than one month after exposure to a traumatic event. Violent crimes, including rape and physical assaults, combat exposure, and natural disasters constitute examples of traumatic event that can involve threat to integrity of the self or others and can be accompanied by intense fear, helplessness, or horror (1). PTSD results in poor clinical and health outcomes, as well as enormous health care utilization costs (2). Epidemiological studies indicate that in the general United States population, the lifetime prevalence of PTSD is 10%-12% in women and 5%-6% in men (3). Military combat exposure increases PTSD risk as well. The lifetime prevalence of PTSD in veterans who served in Southeast Asia during the Vietnam War is 15%-19%, and many continue to have PTSD decades after the war (4). PTSD is even more prevalent in service members from the recent Iraq and Afghanistan conflicts (5).

Recently, some studies reported a two-fold increased risk of PTSD in the development of cardiovascular disease (6). The reasons for this association are not clear, but likely explained by excess “wear and tear” due to chronic emotional stress exposure (7). In response to the trauma-reminiscent stimuli in everyday life, PTSD patients suffer from repeated sympathetic nervous system stimulation and parasympathetic nervous system withdrawal (8, 9). The dysregulation of the hypothalamic-pituitary-adrenal axis and autonomic nervous dysfunction in turn, may lead to a variety of physiological changes potentially damaging to the heart. Over time, PTSD patients may develop increased

inflammation, dysfunction of the vascular endothelium, hypercoagulability, and cardiac hyperreactivity (10).

Heart rate variability (HRV) is a measure of beat-to-beat heart rate fluctuations over time, and a noninvasive index of cardiac autonomic nervous system (sympathetic and parasympathetic) health (7, 11). Many studies have found an association between PTSD and HRV, although most of them are limited by small sample size. In most cases, higher HRV corresponds to increased capacity for autonomic modulation, and indicates improved adaptability to stressful situations and overall wellness. Low HRV is associated with higher overall mortality, specifically cardiovascular mortality (12).

In a recently published study, Shah *et. al.* reported a 40%-50% decreased 24-hour low frequency HRV in veterans with PTSD (7, 13, 14). The reasons for this are not clear, but may be in part due to disturbed sleep in PTSD. Sleep disturbance is a core feature of PTSD, as nightmares and insomnia are diagnostic symptoms (15). Recent research has indicated that 74%-90% of currently deployed and post-deployed combat veterans report poor sleep quality (16), with up to 91% of veterans with PTSD reporting sleep maintenance difficulties (17). These high sleep disturbance rates independently exacerbate daytime symptoms, and contribute to poor clinical outcomes in PTSD, such as increased severity of depression, suicidality and general psychiatric distress (18, 19). Additionally, sleep disturbance reduces parasympathetic nervous system activity during night, which may increase the risk of developing cardiovascular complications in PTSD (20).

In this study, we investigate the circadian fluctuation of HRV and it's relationship to PTSD. Specifically, we will evaluate the association between the circadian fluctuation in HRV and PTSD in a cross-sectional study of middle-age male monozygotic (MZ) and dizygotic (DZ) veteran twins from the Vietnam era. We hypothesize that the normal increase in HRV and decrease in heart rate that occurs at night is blunted in veterans with PTSD. Additionally, we hypothesize that this association persists despite adjustment for potential confounding factors, including other psychiatric diagnoses and behavioral/cardiovascular risk factors. Benefiting from the twin study design, we will also investigate for confounding from genetic (100% genetic similarity for MZ and 50% for DZ twins) and early familial/environmental factors shared by the twins, who also grew up in the same household.

Methods

Subjects

Patients were enrolled as part of the Stress and Vascular Evaluation in Twins (SAVEIT) study, which evaluated the role of psychological, behavioral, and biologic risk factors for subclinical cardiovascular disease in twins. SAVEIT recruited middle-aged male MZ and DZ twin pairs (who were raised in the same household) from the Vietnam Era Twin (VET) Registry, one of the largest twin registries in the United States (21). This primarily Caucasian group of adult males born between 1946 and 1956 was selected from the VET Registry based on their history of PTSD upon enrollment into the cohort. Both PTSD discordant pairs and randomly selected control pairs were selected. Pairs of twins across the United States were recruited to Emory University and examined simultaneously at the Emory University General Clinical Research Center. And all data collection, including ambulatory electrocardiogram (ECG) monitoring, occurred during a 24-hour admission under controlled conditions. The two twins maintained an identical schedule while in the study at Emory. Activity was limited to leisurely ambulation within the Emory facilities, and all assessments, including the ambulatory ECG monitoring, began and ended at the same time. Zygosity information by means of DNA typing was available for all twin pairs. The study was approved by the Emory Institutional Review Board and all twins signed an informed consent.

Measurement of HRV

Twins wore an ambulatory ECG monitor (Holter, GE Marquette SEER digital system, Fairfield, CT) for 24 hours and had matched recording times, schedules, and activity

levels. Activity was restricted to quiet walking around the campus, and participants were instructed to refrain from smoking and drinking alcohol or coffee during the recording. HRV data were analyzed following a published methodology (22, 23). Each tape was manually processed, edited and analyzed with customized software that used methods described in the literature (24, 25). The heart rate spectrum was computed with a fast Fourier transform with a Parzen window. Because long-term autonomic function was the goal of this study, the fast Fourier transform was performed on the 24-hour R-R interval file. The power spectrum was integrated over three discrete frequency bands: very low frequency (VLF), 0.0033 to less than 0.04Hz; low frequency (LF), 0.04 to less than 0.15 Hz; and high frequency (HF), 0.15 to less than 0.40 Hz. These frequency bands integrate heart rate fluctuations in response to many physiological stimuli. These include: influence of the renin-angiotensin-aldosterone system (VLF), baroreceptor activity (LF), and respiration (HF). Twins whose recordings showed >20% interpolation or <18 recorded hours were excluded from the analysis.

Assessment of PTSD, Depression

We administered the Structured Clinical Interview for DSM-IV (26) to classify twins on the basis of a lifetime history and current PTSD. Remitted PTSD was defined as being diagnosed as PTSD in the past but not meeting diagnostic criteria within last 30 days. The Structured Clinical Interview for DSM-IV also provided a diagnosis of other psychiatric disorders, including major depression, a lifetime history of alcohol and of drug abuse or dependence. We also administered the Beck Depression Inventory II (BDI-II) (27), a standardized scale providing a measure of depressive symptoms, with higher scores

indicating more severe depression. The Clinician Administered PTSD Scale (CAPS) was also administered to access PTSD symptom severity.

Other Measurements

A medical history and a physical examination were obtained by a research nurse or physician assistant. Abdominal and hip circumferences were measured to derive the waist/hip ratio (WHR). Hypertension was defined by a measured systolic blood pressure higher than 140 mm Hg or current treatment with antihypertensive medications. Diabetes mellitus was defined as having a fasting glucose level more than 126 mg/dL or current treatment with antidiabetic medications. Venous blood samples were drawn for the measurement of glucose and lipid profile after an overnight fast. Glucose level was measured on the Beckman CX7 chemistry autoanalyzer. Direct high-density lipoprotein and low-density lipoprotein cholesterol levels were measured with homogeneous assays (Equal Diagnostics, Exton, PA). Physical activity was assessed with a modified version of the Baecke Questionnaire of Habitual Physical Activity (used in the Atherosclerosis Risk in Communities Study (28)) that documented physical activity at work, during sports, and nonsports activities. The global physical activity score was used in the analysis. Cigarette smoking was classified into current versus never or past smoker. Wine, beer, liquor, coffee, tea and soda consumption were measured in drinks/day. A history of coronary heart disease was defined as a previous diagnosis of myocardial infarction or angina pectoris, or previous coronary revascularization procedures. Information on the current use of other medications was also collected. Baseline intelligence, measured via the Armed Forces Qualification Test, was abstracted from military records (29).

Statistical Analysis

SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina) was used for statistical analysis. Heart rate histograms were analyzed for general patterns in diurnal activity. Based on our initial qualitative analysis, we divided the 24 hours period into 3 time intervals: nighttime (11 PM-5 AM), AM awake hours (5 AM-12 PM) and PM awake hours (12 PM-11 PM). Generalized estimating equations (GEE) were used to account for clustering within twin pairs in all baseline analyses. In initial analyses for baseline characteristics, we compared means and percentages of study factors among twins with no PTSD, current PTSD, and remitted PTSD, with both linear (for continuous variable) and log (for binary variables) analysis of variance testing. The *p* value comparing baseline characteristics amongst the no PTSD, current PTSD, and remitted PTSD groups were also reported.

To examine the association between PTSD status (current, remitted, or neither) with HRV, two sets of analyses were performed: a) among individuals, in which all twins were eligible for inclusion regardless of whether their brother was available for analysis, and b) between and within twin pairs, comparing one twin brother with the other (within-pair effect) and analyzing the association among pairs of brothers (between-pair effect). The second set of analyses allow for detection of confounding by genetic and familial influences. To do this, mixed-effects regression was applied in the analysis and accounted for the twin pairs using a random effect term for each pair. We log-transformed HRV in each frequency spectra in order to analyze them as a normally distributed outcome variable. The CAPS PTSD symptom severity scores were analyzed primarily as

continuous variables to assess a dose-response relationship between PTSD symptoms and HRV. For graphical demonstration, additional analyses were performed with CAPS and as a three-level ordinal variable, where the first category was zero (which included approximately half of the sample or first 2 quartiles), and the remaining two categories corresponded approximately to the third and fourth quartile. Statistical significance was determined if $p < .05$, two-sided.

Multivariate Modeling

The GEE models were used with log-transformed HRV as the dependent variable. Potential confounding factors to be included in multivariate analysis were chosen as those factors that might potentially be related to both HRV and PTSD. These included age, education, employed status, hypertension, diabetes mellitus, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, current and past smoking, physical activity, lifetime history of major depression, beta-blockers, body mass index, WHR, drug abuse history, alcohol abuse history, and history of coronary heart disease.

A sensitivity analysis was carried out by fitting a series of sequential models that adjusted for following chosen baseline factors: unadjusted (mode l); adjusted for sociodemographics (model 2: age, education, employment); adjusted for typical risk factors (model 3: body mass index, WHR, cholesterol level, history of heart disease, hypertension and diabetes); adjusted for lifestyle factors (model 4: consumption of alcohol and caffeine, dependence of alcohol and drug, smoking); adjusted for major depression (model 5: history of depression). Each model retained all variables in previous models. Based on the results from the previous HRV analysis by Shah *et. al.* (7), the primary outcome of interest was LF HRV during night in this sensitivity analysis. We

choose model 4 as main model, because of the overlap between depression symptoms (based on Beck depression inventory, BDI) and PTSD symptoms, such as sleeping problems and concentration difficulty. The same model was used in the analysis of PTSD symptom severity (CAPS).

Within-Pair Analysis

We performed within-pair analyses that examined differences in HRV between twins that were discordant for PTSD. This analysis inherently not only controls for demographic, shared familial, and early environmental influences, but also daily activities, season, and other environmental factors during the ambulatory ECG recording are controlled in this analysis, because co-twins were examined at the same time and under nearly identical conditions. We fitted GEE models adapted for twin research (30), which allow for examination of HRV effects within and between twin pairs as a function PTSD and other possible confounders. In these models the within-pair parameter is the individual twin variation from the twin pair average. This coefficient is identical to the coefficient from a model that fits the absolute difference between the co- twins (30). A similar analysis was done for PTSD severity (CAPS) as continuous measures to assess for a possible dose-response relationship between PTSD severity and autonomic function. In such cases, discordance was measured on a continuous scale, because the difference in score between brothers and all pairs with differences greater than zero were considered discordant.

Genetic Influences

In addition to sharing early environment, MZ twins share 100% of their genes, whereas DZ twins share on average 50% of their genetic material; therefore, if a significant

within-pair association is found in DZ but not in MZ twins, this suggests genetic confounding (i.e., similar genetic influences underlie PTSD and HRV) (29). If, by contrast, within-pair associations are similar in MZ and DZ twin pairs, then genes may not be considered as a confounder in the association. To examine the genetic influence, we add a term for the interaction between zygosity and the within-pair difference in HRV to the model. If the interaction term is significant ($p < .05$), this may suggest a role for genetic factors in the association.

Results

The sample included 134 twins, of which there were 59 twin pairs (92 monozygotic and 42 dizygotic) and 16 singletons. The mean age ± SD was 57.6 ± 2.6 years. Thirty-eight twins (28%) had PTSD in their lifetime; of these, 16 had current PTSD, and 22 had remitted PTSD. Among 59 twin pairs, 15 pairs were discordant for current PTSD. Current and lifetime PTSD was also measured as continuous variable CAPS.

Baseline Characteristics

In Table 1, twins with current and remitted PTSD were compared with those without PTSD. Those with current or remitted PTSD were more likely to smoke, have a history of drug abuse and major depression. No remarkable difference was found in alcohol or caffeinated beverage consumption, physical activity, cholesterol levels, body mass index, WHR, history of heart disease, diabetes and hypertension.

Association of PTSD with HRV

Table 2 shows the results of models 1-5 for current and remitted PTSD versus controls (no history of PTSD) to predict LF HRV at night. Remitted PTSD was associated with a higher LF HRV in model 5, while current PTSD was associated with lower LF HRV in models 1-4. Table 3 expands the analysis of models 1 and 4 for HF, LF, and VLF HRV during all 3 time intervals for current PTSD versus controls without current PTSD. In model 1 (bivariate analysis), current PTSD was associated with significantly lower HRV for all spectra in all time intervals, except for the results of HF HRV, which is only significantly in time period 1 (nighttime) (Table 3). In the fully adjusted model (including covariates from model 4) that evaluated twins as individuals (not assessing for

genetic/familial confounding), current PTSD was significantly associated with VLF and LF HRV during nighttime and AM awake hours, and with HF HFV during nighttime only. The largest adjusted effect size was a 0.77 ln ms^2 lower LF HRV (p <.001) during nighttime in twins with current PTSD versus controls. When analyzing twins in groups as pairs, the similar associations were observed. When analyzing the 15 twin pairs discordant for current PTSD, a significant association was only found for the LF HRV frequency during nighttime in the unadjsted and adjusted models. No significant interaction between PTSD and zygosity was found for this relationship.

HRV Differences Between AM Awake Hours and Nighttime

We next evaluated day-night differences by comparing the nighttime HRV with the daytime HRV during the most active period of the day, the AM awake hours (8 AM-12 PM). In current PTSD patients, nighttime HRV was found to be lower than their AM daytime HRV in all frequency bands, whereas the opposite pattern was found for LF and HF HRV in control subjects without current PTSD. The difference was statistically significant (Table 4). Adjusted analysis, presented in Table 5, shows that when twins were analyzed as individuals, the association with LF HRV still remained statistically significant. The largest adjusted effect size was observed in LF HRV (p <.01), where a 0.48 ln ms^2 decrease in the night-day HRV difference was noted in the current PTSD group compared to controls. A similar and significant association was found within discordant pairs twin analysis for LF HRV in both unadjusted and adjusted models. No significant findings were noted between pairs of twins, and no significant interaction by zygosity was found.

Analysis of PTSD Symptoms as a Continuous Measure

Current and lifetime PTSD severity were measured using the Clinician-Administered PTSD Scale (CAPS) survey, which divided the veterans into groups of increasing score; 0 (n=67), 1-21 (n=31), and ≥ 22 (n=31). One-hundred and twenty-nine subjects with available CAPS data were evaluated. CAPS significantly associated with nighttime VLF, LF and HF HRV in unadjusted models (Table 6, figure 1a). After multivariable adjustment, only the association between current CAPS and LF persisted in individual twins (p <.01) and within CAPS discordant twin pairs (p = .01). Figure 1b illustrates the dose-response association between increasing levels of CAPS score and decreasing nighttime (versus daytime) VLF, LF and HF HRV in individual twins.

Discussion

In this cross-sectional study of predominantly healthy, middle-aged veteran men, we found a robust association between current PTSD and reduced nighttime LF HRV. We also found that in current PTSD, LF and HF HRV decreased at night compared to the day, whereas for controls without current PTSD, LF and HF HRV increased at night. As hypothesized, the most statistically significant results were found in the LF HRV spectrum, where the association persisted after adjustment for sociodemographics, cardiovascular risk factors, and history of substance abuse. We also showed that these associations were robust despite adjustment for genetic and familial factors as determined by our twin design, in which we compared twin brothers within pairs discordant for PTSD. Furthermore, we found a dose-response relationship between PTSD symptom severity (CAPS score) and nighttime HRV. Veterans with higher CAPS scores also showed decreased LF and HF HRV during nighttime compared to the daytime.

Our findings are consistent with previous studies such as those by Shah *et. al*., in which they found that 24 hour LF HRV was reduced in current PTSD patients (7). Our study adds to these findings by investigating abnormalities in circadian variation of HRV in PTSD patients, which may yield insight for future treatments. Our study also has important biological and clinical implications on the health of the autonomic nervous system. During nighttime, vagal tone is usually dominant and variations in heart period are largely dependent on parasympathetic modulation (31, 32). Diminished parasympathetic levels are also associated with increased susceptibility to cardiac arrhythmias and increased risk of mortality in myocardial infarction (33). According to

Porges' polyvagal theory (9), reduced LF HRV might suggest vagal insufficiency that arises from defects in the dorsal motor nucleus. This theory helps to explain the reduced parasympathetic activity during nighttime. Our results may also imply reduced BRS in individuals with current PTSD during nighttime, and are consistent with a reported association between lower BRS and with poorer sleep in women with PTSD (34, 35). Additionally, reduced BRS might signify increased risk of cardiac mortality after myocardial infarction (33).

The focus on nighttime, and the contrast between nighttime and daytime HRV are novel aspects of this study. Although no other studies have evaluated day-night differences with PTSD, similar results were shown in related studies (36, 37) of veterans with Gulf War syndrome, which showed lower HRV at night and higher HRV in the morning when compared to healthy subjects (38, 39). Although the reasons for this are likely disturbed sleep due to PTSD, other metabolic abnormalities may also be considered. For example, a similar loss of circadian variation in HRV may also occur amongst diabetic patients (38).

Patients with current PTSD also showed significantly lower HF and VLF HRV during nighttime, and although the association was not as significant as LF HRV, it persistent after adjusting for measured confounding factors, but not after additional adjustment for familial factors using the within-pair twin analysis. Lower HF HRV, as with LF HRV, indicates reduced parasympathetic modulation (31, 32). Reduced HF HRV has also been found in other studies of subjects with PTSD and generalized anxiety disorder (32, 37, 40). VLF HRV is less well-understood, but likely relate to fluctuations in renin-

angiotensin levels (41). Our findings indicate possible familial and/or genetic confounding, but additional analyses are needed in larger samples.

This study is subject to several limitations. First, our sample consisted of middle-aged and white men, and therefore the findings might not be generalizable to other demographic groups, like women. Second, the design of this study was cross-sectional, causal inferences related to the association between sleep and PTSD cannot be ascertained from the current results. Third, the number of subjects with current PTSD was relatively small, thus limiting the precision of our estimate particularly after stratification for other factors, such as zygosity. Despite this, the twin design of the study allowed us to conduct a powerful analysis by minimizing random variation through cases and controls 50-100% genetically matched, and 100% matched regarding early familial factors.

Future Directions

In this study of male veteran twins, PTSD was associated with lower LF HRV during nighttime. These findings underscore the comorbidity of PTSD with compromised neuroautonomic control and downstream increased cardiac morbidity. Given the growing number of veterans with PTSD from recent wars, our findings emphasize the importance of aggressive clinical care and prevention in these at-risk individuals, because it might yield both psychiatric and cardiovascular benefits. Future longitudinal studies should be performed to evaluate changes in HRV that occur after trauma exposure, and correlated improvement in PTSD symptoms with physiologic improvement in HRV.

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Tables

Table 1. Characteristics of Individuals According to PTSD History

Characteristics	No PTSD (n=96)	Current PTSD (n=16)	Remitted PTSD (n=22)	*p*
Age (mean yrs ± SD)	57.4±2.8	57.9±2.2	58.1±2.4	0.46
Education (mean yrs ± SD)	13.9±2.4	14.5±2.4	13.2±1.7	0.23
Employed (%)	72.9	50	68.2	0.04
Smoking History				
Current (%)	22.9	37.5	31.8	0.18
Past smoker (%)	44.8	43.8	59.1	
Never smoked (%)	32.3	18.8	9.1	
Alcohol Drinks/day, mean± SD	6.5±12.9	10.0±16.3	5.9±8.2	0.56
Caffeinated Drinks/Day, mean ± SD	5.3±3.9	5.4±3.6	5.3±3.1	0.99
Lifetime Diagnosis of Alcohol Abuse (%)	5.2	12.5	4.6	0.15
Lifetime Diagnosis of Drug Abuse (%)	38.5	68.8	54.5	0.04
History of Heart Disease (%)	10.4	12.5	22.7	0.26
History of Hypertension (%)	27.1	43.8	27.3	0.36
History of Diabetes (%)	15.6	6.3	13.6	0.22
Baecke Physical Activity Score, mean ± SD	7.2±1.5	6.9±2.5	6.9±1.8	0.80
LDL Cholesterol (mg/dL), mean± SD	120.6±34.3	122.4±36.6	118.3±38.9	0.94
HDL Cholesterol (mg/dL), mean± SD	40.2±12.1	40.3±13.2	38.5±10.2	0.83
Beta Blocker Use (%)	9.4	6.3	18.2	0.82
BMI (kg/m^2), mean± SD	30.2±5.9	27.8±3.9	29.5±3.9	0.26
WHR, mean± SD	0.96±0.06	0.95±0.06	0.94±0.10	0.51
Beck depression inventory, mean± SD	4.3±4.5	16±8.3	8.2±8.7	<.001
Lifetime History of Major Depression (%)	29.2	68.8	72.3	<.001
HRV, mean (ln ms^2) ± SD[a]				
ln(VLF power)	7.3±0.6	6.8±0.7	7.5±0.5	0.01
ln(LF power)	6.4±0.8	5.9±0.8	6.7±0.6	0.01
ln(HF power)	5.1±0.8	4.7±0.9	5.2±0.8	0.11
Heart Rate (bpm)	70.8±8.6	75.6±10.7	68.7±8.1	0.06

BMI, body mass index; HDL, high-density lipoprotein; HRV, heart rate variability; LDL, low-density lipoprotein; PTSD, posttraumatic stress disorder; WHR, waist/hip ratio; ln, natural logarithm.

[a] Very low frequency (VLF) .0033 to <.04 Hz; low frequency (LF) .04 to <.15 Hz; and high frequency (HF) .15 to <.40 Hz.

Table 2. Sensitivity Analysis for Current and Remitted PTSD versus Controls (No History of PTSD) to Predict LF HRV at Night

nighttime HRV[a], ln ms^2		Remitted PTSD		Current PTSD	
	Model	Estimate	*p*-value	Estimate	*p*-value
LF	Model 1	0.15	0.44	-0.84	<.001
	Model 2	0.23	0.23	-0.76	<.001
	Model 3	0.28	0.13	-0.77	<.001
	Model 4	0.31	0.12	-0.70	<.01
	Model 5	0.56	0.01	-0.45	0.07

Nighttime: 11 PM-5 AM
[a] low frequency (LF) .04 to <.15 Hz

Table 3. The Change Of HRV Comparing Twins with Current PTSD with Those without Current PTSD in Different Time Intervals

		Individual				Between Twins				Within Twins			
		Unadjusted		Adjusted[b]		Unadjusted		Adjusted		Unadjusted		Adjusted	
HRV[a], ln ms^2	Time	β[c]	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
VLF	Nighttime	-0.58	<.001	-0.43	0.01	-0.69	0.03	-0.68	0.03	-0.54	0.01	-0.31	0.10
	AM Awake Hours	-0.40	0.02	-0.35	0.05	-0.52	0.06	-0.51	0.05	-0.31	0.17	-0.21	0.37
	PM Awake Hours	-0.36	0.03	-0.22	0.19	-0.71	0.01	-0.68	0.01	-0.18	0.35	0.08	0.68
LF	Nighttime	-0.87	<.001	-0.77	<.001	-0.86	0.03	-1.01	0.01	-0.87	<.001	-0.65	0.01
	AM Awake Hours	-0.47	0.03	-0.48	0.03	-0.52	0.11	-0.64	0.05	-0.44	0.14	-0.34	0.25
	PM Awake Hours	-0.39	0.05	-0.27	0.17	-0.65	0.06	-0.65	0.04	-0.26	0.26	-0.03	0.91
HF	Nighttime	-0.54	0.01	-0.45	0.03	-1.15	0.01	-1.29	0.004	-0.34	0.17	-0.21	0.35
	AM Awake Hours	-0.32	0.19	-0.46	0.06	-0.78	0.04	-1.00	0.01	-0.01	0.98	-0.01	0.97
	PM Awake Hours	-0.29	0.20	-0.26	0.23	-0.75	0.05	-0.93	0.02	-0.05	0.85	0.04	0.86

No significant interaction of PTSD with zygosity.
Nighttime:11 PM-5 AM); AM Awake Hours: 5 AM-12 PM; PM Awake Hours: 12 PM-11 PM.
[a] Very low frequency (VLF) .0033 to <.04 Hz; low frequency (LF) .04 to <.15 Hz; and high frequency (HF) .15 to <.40 Hz.
[b] Adjusted for age, education, employed status, hypertension, diabetes mellitus, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, current and past smoking, physical activity, beta-blockers, body mass index, WHR, drug abuse history, alcohol abuse history, and history of coronary heart disease.
[c] β is coefficient, represents the average change in HRV due to PTSD

Table 4. Difference in HRV Between Nighttime and AM Awake periods in Veterans With and Without Current PTSD

HRV[a](Nighttime)-HRV(AM Awake periods) mean ± SD, ln ms^2	Non-PTSD	Current PTSD	*p*
VLF	-0.18±0.54	-0.42±0.49	0.10
LF	0.07±0.63	-0.44±0.75	0.01
HF	0.05±0.68	-0.36±0.90	0.04

Nighttime: 11pm-5am, AM Awake periods: 8am-12pm.

[a] Very low frequency (VLF) .0033 to <.04 Hz; low frequency (LF) .04 to <.15 Hz; and high frequency (HF) .15 to <.40 Hz.

Table 5. Regression Analysis of the Relationship of Current PTSD with the Difference in HRV Between Nighttime and AM Awake periods

HRV[a](Nighttime)-HRV(AM Awake periods)	Individual				Between Twins				Within Twins			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted		Unadjusted		Adjusted	
	β[c]	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
VLF	-0.26	0.07	-0.22	0.13	0.15	0.51	-0.16	0.49	-0.33	0.07	-0.27	0.16
LF	-0.53	<.01	-0.48	<.01	-0.40	0.15	-0.45	0.13	-0.60	<.01	-0.50	0.02
HF	-0.42	0.02	-0.33	0.09	-0.41	0.19	-0.30	0.37	-0.42	0.06	-0.35	0.14

No significant interaction of PTSD with zygosity.

Nighttime: 11pm-5am, AM Awake periods: 8am-12pm.

[a] Very low frequency (VLF) .0033 to <.04 Hz; low frequency (LF) .04 to <.15 Hz; and high frequency (HF) .15 to <.40 Hz.

[b] Adjusted for age, education, employed status, hypertension, diabetes mellitus, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, current and past smoking, physical activity, beta-blockers, body mass index, WHR, drug abuse history, alcohol abuse history, and history of coronary heart disease.

[c] β is coefficient, represents the average change in HRV due to PTSD

Table 6. The Change of Nighttime HRV Per Unit Increase in CAPS

HRV[a]_ Nighttime	Individuals				Between Twins				Within Twins[d]			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted		Unadjusted		Adjusted	
	β[c]	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
VLF	-0.008	0.01	-0.006	0.06	-0.012	0.01	-0.009	0.04	-0.005	0.09	-0.004	0.27
LF	-0.013	<.001	<.01	0.00	-0.015	<.01	-0.013	0.01	-0.012	0.00	-0.011	0.01
HF	-0.009	0.01	-0.007	0.02	-0.014	0.02	-0.014	0.04	-0.007	0.07	-0.005	0.08

Nighttime: 11pm-5am.

[a] Very low frequency (VLF) .0033 to <.04 Hz; low frequency (LF) .04 to <.15 Hz; and high frequency (HF) .15 to <.40 Hz.

[b] Adjusted for age, education, employed status, hypertension, diabetes mellitus, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, current and past smoking, physical activity, beta-blockers, body mass index, WHR, drug abuse history, alcohol abuse history, and history of coronary heart disease.

[c] β is coefficient, represents the average change in HRV due to 1 Point increase in CAPS

[d] Discordance was defined as a ≥ 1 point difference in CAPS within twin pairs.

Figures

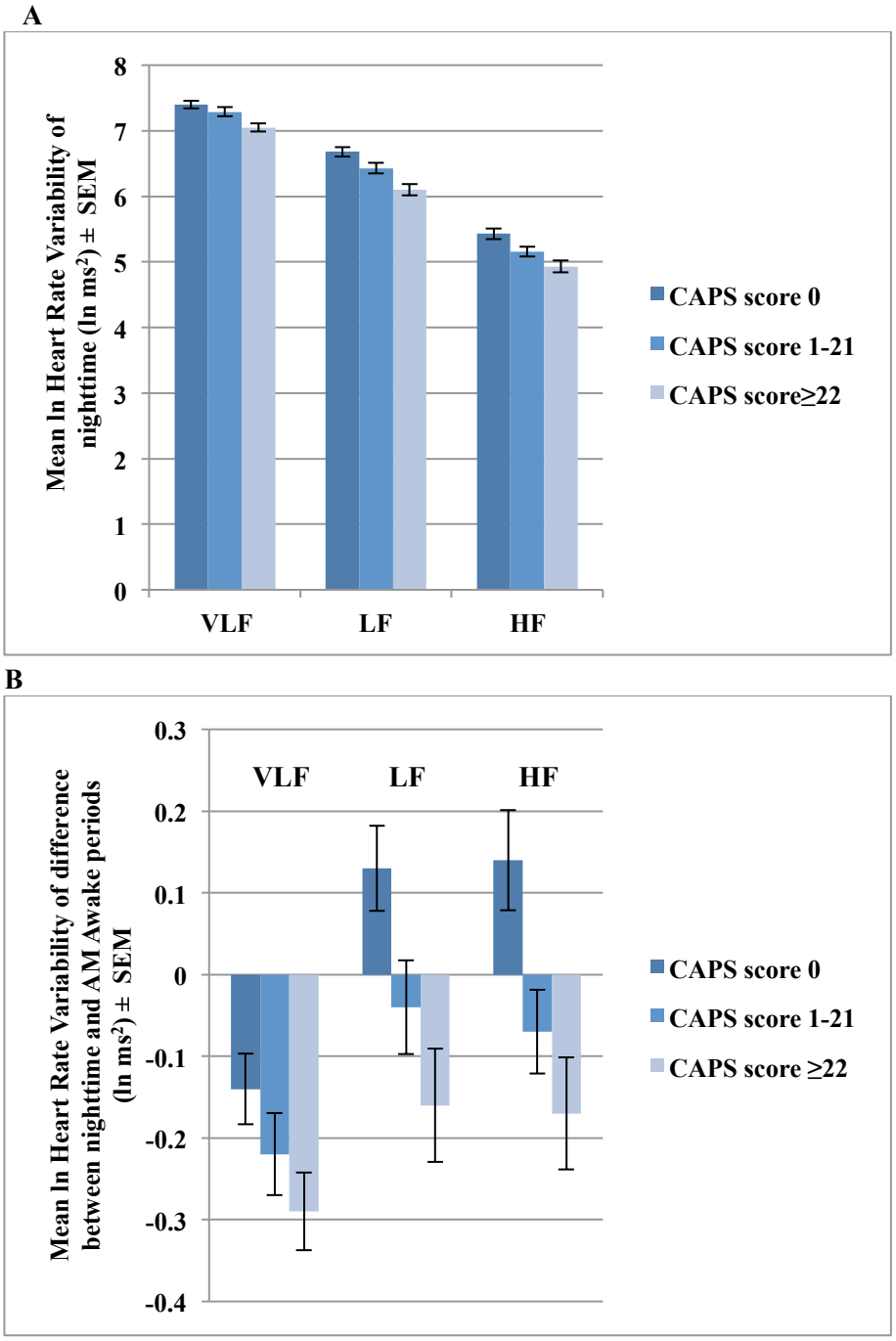

Figure 1. Mean natural log very-low frequency (VLF), low-frequency (LF), and high-frequency (HF) heart rate variability of the nighttime and of the difference between nighttime and most activated daytime, according to Clinical Administered PTSD Scale (CAPS) ordinal categories. ln= natural logarithm; PTSD, posttraumatic stress disorder.