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Posttraumatic Stress Disorder and Impaired Autonomic Modulation in Male Twins

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Abstract

Background—Posttraumatic stress disorder (PTSD) has been linked to increased morbidity. An inflexibility of the autonomic nervous system may be the underlying mechanism. We aimed to assess whether PTSD and combat trauma exposure are associated with lower heart rate variability (HRV), a measure of autonomic function and a predictor of death.

Methods—We measured HRV by power spectral analysis on 24-hour ambulatory ECG in 459 middle-aged veteran male twins. Combat trauma was assessed with the combat exposure scale, and current and remitted PTSD with the Structured Clinical Interview for Psychiatric Disorders. Mixed-effects regression models were used to test associations of PTSD and HRV between and within twin pairs.

Results—Of all twins, 211 had combat exposure, 31 had current PTSD, and 43 had remitted PTSD. Current PTSD was inversely associated with very-low frequency (VLF) and low frequency (LF) HRV both in individual twins and within 20 pairs discordant for current PTSD. Twins with current PTSD had a 49% lower LF HRV than their brothers without PTSD ($p < 0.001$). Remitted PTSD was not associated with HRV. Results were robust to adjustment for depression and other risk factors. Combat exposure was inversely associated with most HRV frequencies, but this association mostly diminished after adjustment for current PTSD.

Conclusion—In middle-aged veteran men, combat exposure and current PTSD are associated with measures of autonomic inflexibility previously shown to have prognostic significance. The

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negative health impact of combat exposure on autonomic function is mediated largely through PTSD and may reverse with remission of PTSD.

Keywords

Autonomic nervous system; heart rate variability; posttraumatic stress disorder; military combat trauma; mental stress; heart disease

Introduction

Military combat is associated with increased morbidity and mortality in veterans after return from service, although the mechanisms are not clear (1). Posttraumatic stress disorder (PTSD), a disabling psychiatric condition characterized by a persistent maladaptive reaction resulting from exposure to severe psychological stress, is common in combat veterans. The lifetime prevalence in Vietnam veterans is 15 to 19% (2–6), and possibly higher among military personnel of the Iraq and Afghanistan conflicts (7, 8). In the United States general population, it is about 8% (9–12).

Recent studies have suggested a link between PTSD and the risk of ischemic heart disease incidence and mortality (13). A commonly endorsed explanation for this association is possible “wear and tear” of the cardiovascular system due to repeated sympathetic nervous system (SNS) stimulation and parasympathetic nervous system (PNS) withdrawal caused by trauma-reminiscent stimuli in everyday life (14, 15). Over time, these repeated insults may lead to increased risk for a variety of chronic somatic conditions including cardiovascular disease (16, 17).

Heart rate variability (HRV), a measure of beat-to-beat heart rate fluctuations over time (18), is a useful indicator of autonomic function and a strong independent predictor of mortality (19). Thus far, PTSD and some other anxiety disorders have been associated with lower respiratory sinus arrhythmia and baroreflex sensitivity, suggesting impaired autonomic modulation (20–24). However, PTSD has also been related to increased 24-hour low frequency HRV (25). With these previous conflicting data, larger studies with careful consideration of potential confounders are needed (26). Genetic predisposition, which is substantial for both PTSD and HRV (27, 28), as well as the early environmental and developmental factors, could also confound this association (29).

Building upon these prior studies, we sought to examine the associations amongst combat trauma, PTSD, and long-term measures of HRV assessed by means of 24-hour electrocardiographic recordings in a large, well-characterized study of middle-aged veteran twins. We were able to adjust for a comprehensive set of potential confounding factors such as other psychiatric diagnoses and behavioral/cardiovascular risk factors. Taking advantage of the twin design, we were also able to account for genetic and early environmental influences. We hypothesized that combat exposure and PTSD are both associated with lower HRV, and that the association of combat exposure with HRV occurs primarily through PTSD. Furthermore, we hypothesized that these associations are independent of possible genetic and early environmental confounders, as well as cardiovascular risk factors and depression.

Methods and Materials

Subjects

The Emory Twin Studies (ETS) includes samples recruited in two companion studies: the Twins Heart Study (THS) and the Stress and Vascular Evaluation in Twins (SAVEIT) as

described previously (30, 31). Their purpose was to elucidate the role of depression and PTSD on subclinical cardiovascular disease. Because of the similarity in protocols, these two samples were combined. Both projects recruited middle-aged male monozygotic (MZ) and dizygotic (DZ) twin pairs from the Vietnam Era Twin (VET) Registry (32) who were born between 1946 and 1956 and were discordant for major depression or PTSD, or unaffected (control). Pairs of twins were examined at the same time 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 assessment, 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. Both studies were approved by the Emory Institutional Review Board, and all twins signed an informed consent.

Measurement of Heart Rate Variability

Twins wore an ambulatory ECG (Holter) monitor (GE Marquette SEER digital system) 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 published methodology as previously described (30, 33). The heart rate spectrum was computed using a fast Fourier transform (FFT) with a Parzen window. Because long-term autonomic function was the goal of this study, the FFT was performed on the 24-hour R-R interval file. The power spectrum was integrated over four discrete frequency bands: ultra low frequency (ULF) <0.0033 Hz; very low frequency (VLF) 0.0033 to <0.04 Hz; low frequency (LF) 0.04 to <0.15 Hz; and high frequency (HF) 0.15 to <0.40 Hz.(34) These frequency bands integrate heart rate fluctuations in response to many physiological stimuli. These include, among others, circadian patterns and physical activity (ULF), influences of the renin-angiotensin-aldosterone system (VLF), baroreceptor activity (LF), and respiration (HF). (18, 35, 36). Other than HF HRV, which is almost exclusively influenced by the PNS, both SNS and PNS together affect the other frequency bands. Total power (TP), incorporating the full spectrum <0.40 Hz, was also measured. Twins whose recordings showed >20% interpolation or <18 recorded hours were excluded from the analysis.

Assessment of PTSD, Depression, and Combat Trauma

We administered the Structured Clinical Interview for DSM IV (SCID) (37) to classify twins based on a lifetime history and current PTSD. Remitted PTSD was defined as having a lifetime but not current, diagnosis of PTSD. The SCID also provided a diagnosis of other psychiatric disorders, including major depression, a lifetime history of alcohol and of drug abuse or dependence, as well as generalized anxiety disorder and panic disorder. The Clinician-Administered PTSD Scale (CAPS) was also administered to the SAVEIT subgroup to assess PTSD symptom severity, therefore it was available in approximately 36% of the sample (38). Combat exposure was assessed with the Combat Exposure Scale (CES), a validated 7-question survey instrument (score range 0–28) (39).

Other Measurements

A medical history and a physical exam were obtained by a research nurse or physician assistant. Abdominal and hip circumferences were measured to derive the waist to hip ratio (WHR). Hypertension was defined by a measured systolic blood pressure > 140 mm Hg or current treatment with anti-hypertensive medications. Diabetes mellitus was defined as having a fasting glucose level > 126 mg/dl or current treatment with anti-diabetic medications. Venous blood samples were drawn for the measurement of glucose and lipid

profile after an overnight fast. Glucose was measured on the Beckman CX7 chemistry autoanalyzer. Direct high-density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol 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 that documented physical activity at work, during sports and non-sports activities (40). The global physical activity score was used in the analysis. Cigarette smoking was classified into current, never, or past smoker. Wine, beer, liquor, coffee, tea, and soda consumption were measured in drinks per day. A history of coronary heart disease was defined as a previous diagnosis of myocardial infarction or previous coronary revascularization procedures. Detailed information on current use of medications was also collected.

Statistical Analysis

Generalized estimating equations (GEE) were used to account for clustering within twin pairs in all analyses. Baseline characteristic differences were compared amongst twins with no PTSD, current PTSD, and remitted PTSD, using both linear (for continuous variables) and log (for binary variables) analysis of variance testing. The maximum pair-wise Z scores comparing no PTSD, current PTSD, and remitted PTSD were reported for each characteristic. The association between combat exposure and PTSD status (current, remitted, or neither) with HRV was first examined by analyzing twins as separate individuals. Each frequency spectra of HRV was log-transformed so that it could be analyzed as a normally distributed outcome variable. Combat exposure and the CAPS PTSD symptom severity scores were analyzed primarily as continuous variables; in order to assess a dose-response relationship, additional analyses were performed with CAPS and CES as 3-level ordinal variables, where the first category was zero (which included about half of the sample, or first 2 quartiles), and the remaining two categories corresponded approximately to the third and fourth quartile. Current PTSD was analyzed as a mediator of the association between combat exposure and HRV by evaluating the change in β coefficient that occurred after adding it to the multivariable model. The Sobel's Z-test was performed to test the statistical significance of PTSD as a mediator between combat exposure and HRV (41).

Multivariate Modeling

GEE models were used with log-transformed HRV as the dependent variable. Potential confounding factors to be included in multivariate analysis were carefully chosen a-priori as those factors that might potentially be related to both HRV and PTSD. These included age, hypertension, diabetes mellitus, LDL cholesterol, current and past smoking, and physical activity. Additional covariates were evaluated for possible confounding, including lifetime history of major depression, use of anti-depressants, aspirin, statins, beta-blockers, angiotensin converting enzyme inhibitors, anxiolytic drugs, body mass index, waist hip ratio, drug abuse history, alcohol abuse history, HDL cholesterol, and history of coronary heart disease. Of these variables, a history of major depression, use of anti-depressants, body mass index, and a history of drug abuse were found to cause >5% change on the effect size of PTSD on HRV, and were added to the model. The same covariates were used in the models of combat exposure (CES) and PTSD symptom severity (CAPS). Models that examined remitted PTSD additionally adjusted for current PTSD. Analyses were repeated in a subgroup of twins free from coronary heart disease. Other anxiety disorders, including generalized anxiety disorder and panic disorder, were added to the models separately as a sensitivity analysis because of their known association with reduced HRV (20).

Within Pair Analysis

We performed within-pair analyses that examined differences in HRV between twins that were discordant for PTSD. This analysis inherently controls for demographic, shared

familial, and early environmental influences; in addition, daily activities, season and other environmental factors during the ambulatory ECG recording are controlled in this analysis since co-twins were examined at the same time and under nearly identical conditions. We fitted GEE models adapted for twin research (42), which allow for examination of HRV effects within and between twin pairs as a function of 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. (42) A similar analysis was done for combat exposure (CES), as well as for PTSD severity (CAPS) as continuous measures. In such cases, discordance was measured on a continuous scale as the difference in score between brothers, and all pairs with differences greater than 0 were considered discordant.

Genetic Influences

In addition to sharing early environment, MZ twins share 100% of their genes, while 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) (41). If, on the other hand, within-pair associations are similar in MZ and DZ twin pairs, then genes may not be considered as a confounder in the association. To statistically measure the difference in effect between MZ and DZ, we tested for the interaction of the within-pair effect with zygosity.

Results

Baseline Characteristics

Of the 562 twins in the dataset, usable HRV data were available on 459 (80%). The mean age \pm standard deviation (SD) was 55.5 ± 3.1 years, 46% served in South East Asia, 95% were Caucasian, and 3% were black. Forty-six percent of twins had reported some combat trauma exposure (CES>0); of these, the median CES score was 10 (interquartile range, 5–17), and all of them served in South East Asia. Seventy-four (16%) had PTSD in their lifetime; of these, 31 had current PTSD, while 43 had remitted PTSD. Thirty-five of 43 twins with remitted PTSD and 30 of 31 twins with current PTSD were exposed to military combat. The 103 twins with missing HRV data were more likely to be smokers (37% vs. 23%), but otherwise had similar characteristics as those without missing HRV data.

Twins with current and remitted PTSD were compared to those without PTSD (Table 1). Those with current or remitted PTSD were older, less likely to be employed, and more likely to smoke, to have served in Vietnam, to be taking antidepressants, and to have a history of drug and alcohol abuse, heart disease, and major depression. No remarkable difference was found amongst groups with regards to current alcohol or caffeinated beverage consumption, physical activity, cholesterol levels, body mass index, and waist-hip ratio.

PTSD and HRV

Current PTSD was associated with significantly lower HRV for all spectra except ULF in bivariate analysis (Table 2). In analyses adjusted for demographic factors, cardiovascular risk factors, physical activity, body mass index, history of substance abuse, major depression and use of antidepressants, current PTSD continued to show significant associations with VLF and LF HRV, with the largest adjusted effect size being a 39% lower LF HRV ($p<0.001$). Similar associations were found within 20 twin pairs discordant for current PTSD (Table 2), and no significant interaction between PTSD and zygosity was found. In contrast, remitted PTSD was not associated with a lower HRV. Twins with remitted PTSD actually tended to have higher HRV than twins without PTSD; this was noted both in analyses of twins as individuals and the 29 within twin pairs discordant for remitted PTSD. Figure 1

illustrates the associations of VLF, LF, and HF HRV with current and remitted PTSD within discordant twin pairs. Results were similar when analyses were limited to individuals without previous history of coronary heart disease (n=409). Generalized anxiety disorder (n=9) and panic disorder (n=5) occurred infrequently and did not significantly alter results when added to the models.

Combat Exposure and HRV

Combat exposure was reported in 84% of twins with current or remitted PTSD and 39% of twins without PTSD. In individual twins, the combat exposure score, as a continuous measurement, was significantly associated with all frequencies of HRV (Table 3). After multivariate adjustment, all frequencies except VLF and HF remained significantly associated with the combat exposure scale score. The largest effect size was seen for LF, where a 9-point (interquartile range) increase in CES score was associated with a nearly 10% adjusted decrease in LF HRV (p=0.04). Similar results were found within 132 pairs discordant for combat exposure, defined as a within-pair differences greater than 0, where twins with a higher combat exposure than their brothers showed a 13% adjusted lower LF HRV per each 9-point CES difference (p<0.01). When additionally controlling for current PTSD, however, the associations with HRV were substantially reduced (Table 3). The largest reduction in effect size was found for LF power, where adjustment for current PTSD reduced the association by over 50% (from -8.9% to -4.2%), followed by VLF, where the association was reduced by 34%. The Sobel's test confirmed that current PTSD was a statistically significant mediator of CES for both VLF (Z score = 2.16, p=0.03) and LF (Z score = 3.0, p=0.003). HRV, while mediation was not significant for the other frequency ranges. Amongst veterans not exposed to combat (n=247), service in South East Asia (n=14) was not significantly associated with HRV.

Subgroup Analysis Using Continuous Measures

In the subgroup of subjects (n=165) for whom CAPS data were available, current and lifetime CAPS (as a continuous measure) were significantly associated with VLF, LF, and HF in unadjusted models. After multivariable adjustment, the association between current CAPS and LF persisted in individual twins (p=0.049) and within 49 CAPS discordant twin pairs (p<0.01). Figure 2 illustrates the dose-response associations between increasing levels of CES and CAPS as ordinal variables and decreasing VLF, LF, and HF HRV in individual twins.

Discussion

In a large, predominantly healthy sample of middle-aged veteran men we found a robust association between current PTSD and impaired autonomic modulation measured by means of 24-hour HRV. Combat exposure was also associated with lower HRV; however, this association was mainly accounted for by current PTSD, suggesting that autonomic inflexibility in individuals exposed to combat trauma is in large part mediated by PTSD. By studying twins, who share 50–100% genes and early familial influences, we were able to show that this association was independent of genetic, familial, and sociodemographic factors. Results were also overall robust to adjustment for cardiovascular risk factors, depression, and history of substance abuse. Furthermore, we were able to demonstrate a dose-response relationship between PTSD symptom severity and HRV. In contrast, we found a mostly null association between remitted PTSD and autonomic function, suggesting possible reversibility of autonomic dysregulation after PTSD symptom resolution.

Our findings add to a growing literature linking exposure to combat trauma and PTSD with adverse health outcomes. Combat veterans suffer from higher levels of unexplained

complaints (43), and more often experience physical health problems than non-combat veterans (1). Because poor autonomic flexibility has been linked to both psychiatric conditions (26, 44) and adverse health related outcomes (19, 34), our finding of reduced autonomic flexibility in those with increasing levels of combat exposure and PTSD provide mechanistic insight to explain these previous findings. Importantly, our data show that the effects of exposure to combat trauma on autonomic function largely occur through PTSD, since we observed that the association was reduced after adjustment for current PTSD. Our study corroborates previous findings showing that combat exposure had only an indirect effect on health status, through PTSD (45).

Previous studies of HRV and PTSD have primarily focused on short-term HRV measures and have yielded conflicting results. While some studies have found an association between PTSD and respiratory sinus arrhythmia (22, 46), which is similar to HF HRV (47), others have not (26, 48). These studies were limited by small sample sizes ($n < 100$), and did not adjust, or only partially adjusted, for potential confounding factors. In our data the association between current PTSD and HF HRV was weakened in multivariable analysis, suggesting that it is confounded by other risk factors. One of the reasons behind the difference between our findings of HF HRV, and that of respiratory sinus arrhythmia in some of the previous studies, is our use of 24-hour measures, which are subject to additional variability because of changes in position (18). In contrast to HF, the association with LF and VLF HRV was robust to adjusting for potential confounding factors and was confirmed in within-pair analyses.

Based on previous studies, LF power is a reflection of baroreflex sensitivity (BRS) (49); therefore, our results could imply reduced BRS in individuals with current PTSD. These findings are consistent with a reported association between mental stress and reduced BRS (49). Additionally, reduced BRS may explain the lack of a significant heart rate response to acute stress found in people with PTSD (22). Both reduced BRS and reduced 24-hour ambulatory LF HRV power are associated with mortality and have important prognostic significance after myocardial infarction (50, 51). According to Porges' polyvagal theory, reduced LF frequency HRV may also suggest vagal insufficiency that arises from defects in the dorsal motor nucleus (15). This is consistent with other studies showing impaired vagal modulation as assessed by low short-term respiratory sinus arrhythmia in subjects with PTSD and other anxiety disorders (20). While some studies have reported higher short-term normalized LF (which differs from 24-hour LF power) in PTSD, our finding of lower 24-hour LF HRV is consistent with Porges' polyvagal theory (20).

VLF power, a long-term frequency measure of HRV, was also significantly lower in twins with PTSD in our study. VLF is a strong prognostic indicator in patients with myocardial infarction (52), and is thought to measure slow autonomic adjustments to changes in vasomotor tone (53). This association may imply decreased thermoregulation and increased renin-angiotensin system activity in persons with PTSD (47). In contrast, we found no consistent association between PTSD and ULF power, which is an important difference with previous research showing associations between depression and ULF HRV, and suggests a different physiologic response between PTSD and depression (44).

This study is subject to some limitations. Our sample consisted of middle-aged males, primarily Caucasian, and therefore the findings may not be generalizable to other demographic groups. The design was cross-sectional, and thus temporal order in the reported associations is difficult to discern. The number of subjects with current PTSD was relatively small, thus limiting the precision of our estimates particularly after stratification for other factors such as zygosity. Despite this, many within-pair associations were significant, thus demonstrating that, overall, our findings were quite robust.

Conclusion

In this study of male veteran twins, both combat exposure and PTSD were associated with measures of autonomic inflexibility that have clinical relevance for cardiovascular risk. Furthermore, the impact of combat exposure on HRV appeared to be mostly mediated by PTSD. Our results suggest that lack of autonomic modulation is a plausible mechanism by which combat trauma, through the development of PTSD, may influence cardiovascular health. Given the growing number of veterans with PTSD from recent wars, our findings underscore the importance of appropriate care in these at-risk individuals, as it may yield both psychiatric and cardiovascular benefits.

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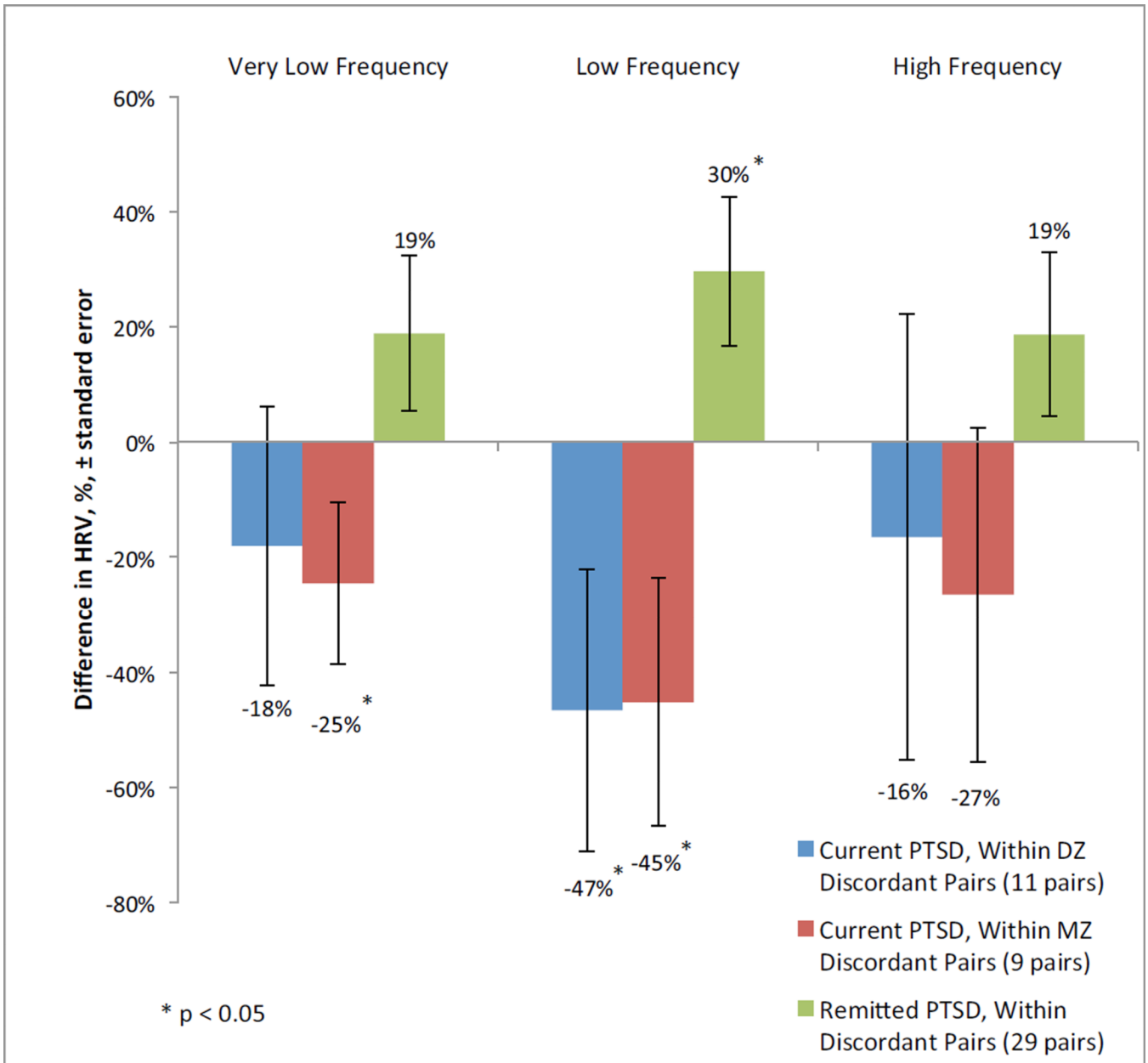


Figure 1. Adjusted Percent Difference in VLF, LF, and HF HRV Comparing Twins With and Without Current or Remitted PTSD

Note: Adjusted for age, Baecke physical activity score, current/past smoking, lifetime history of hypertension, diabetes, low density lipoprotein cholesterol, antidepressant use, lifetime history of major depression, body mass index, and history of drug abuse. When examining remitted PTSD, models additionally adjusted for current PTSD.

Abbreviations: VLF=very low frequency; LF=low frequency; HF=high frequency; MZ=monozygotic; DZ=dizygotic

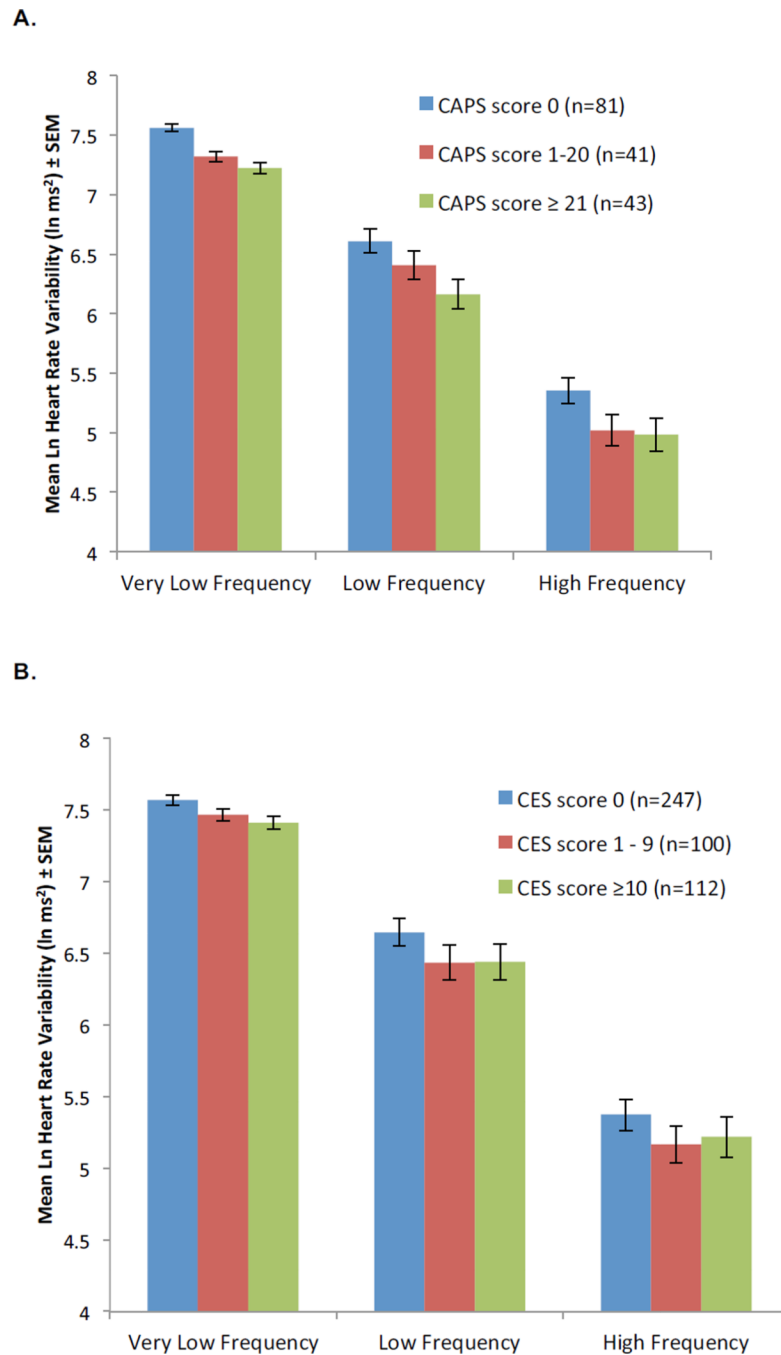


Figure 2. Mean Natural Log VLF, LF, and HF HRV, According to CAPS and CES Ordinal Categories
 Abbreviations: CAPS=Clinically Administered PTSD Scale; CES=Combat Exposure Scale;
 VLF=very low frequency; LF=low frequency; HF=high frequency; ln=natural logarithm

Table 1

Characteristics of Individuals According to PTSD History

Characteristics	No PTSD (n=385)	Current PTSD (n=31)	Remitted PTSD (n=43)	Max Z Score	P value
Age (mean years \pm SD)	55.2 \pm 3.1	57.0 \pm 1.7	57.1 \pm 2.5	2.81	0.005
Education (mean years \pm SD)	14.3 \pm 2.2	13.9 \pm 2.4	13.7 \pm 2.1	1.61	0.11
Employed (%)	77.3	45.2	65.1	4.76	<0.001
Smoking History					
Current (%)	21.3	25.8	34.9		
Past smoker (%)	43.4	48.4	41.9	2.58	0.01
Never Smoked (%)	35.3	25.8	23.2		
Alcohol, mean drinks per day \pm SD	4.6 \pm 8.4	6.1 \pm 12.3	6.6 \pm 9.4	1.27	0.2
Caffeinated drinks per day, mean \pm SD	4.7 \pm 4.7	6.3 \pm 3.6	5.3 \pm 3.1	1.99	0.046
Lifetime History of Alcohol Dependence (%)	43.3	80.6	55.8	3.12	0.002
History of Drug Dependence (%)	19.5	54.8	37.2	2.63	0.009
History of Heart Disease (%)	9.4	22.6	16.3	1.77	0.08
History of Hypertension (%)	28.7	22.6	39.5	-1.24	0.21
History of Diabetes (%)	11.4	12.9	14.0	0.88	0.38
Baecke Physical Activity Score, mean \pm SD	7.3 \pm 1.7	6.7 \pm 2.5	7.3 \pm 2.0	1.63	0.1
LDL Cholesterol (mg/dL), mean \pm SD	122 \pm 35	122 \pm 38	119 \pm 38	0.98	0.33
HDL Cholesterol (mg/dL), mean \pm SD	39 \pm 10	39.5 \pm 12.5	40 \pm 11	0.72	0.47
Antidepressant Use (%)	12.2	51.6	25.6	3.16	0.002
Beta Blocker Use (%)	13.0	12.9	18.6	0.8	0.42
BMI (kg/m ²), mean \pm SD	29.7 \pm 4.8	29.4 \pm 4.8	30.2 \pm 4.7	0.52	0.61
WHR, mean \pm SD	0.95 \pm 0.06	0.97 \pm 0.06	0.95 \pm 0.08	1.88	0.06
Lifetime History of Major Depression (%)	20.7	64.5	58.1	3.77	<0.001
History of Military Activity in Southeast Asia	38.7	96.8	74.4	3.45	<0.001
Combat Exposure Scale Score, mean \pm SD	3.3 \pm 5.7	16.9 \pm 6.6	11.8 \pm 7.4	11.04	<0.001
Heart Rate Variability, mean (ln ms ²) \pm SD*					
ln(Total Power)	9.32 \pm 0.53	9.23 \pm 0.57	9.37 \pm 0.52	1.98	0.048
ln(Ultra Low Frequency Power)	9.11 \pm 0.57	8.98 \pm 0.60	9.07 \pm 0.56	1.28	0.19

Characteristics	No PTSD (n=385)	Current PTSD (n=31)	Remitted PTSD (n=43)	Max Z Score	P value
ln(Very Low Frequency Power)	7.54 ± 0.65	7.17 ± 0.70	7.46 ± 0.57	3.09	0.002
ln(Low Frequency Power)	6.59 ± 0.81	6.05 ± 0.77	6.59 ± 0.76	4.25	<0.001
ln(High Frequency)	5.33 ± 0.91	4.96 ± 0.83	5.20 ± 0.80	2.81	0.005

Abbreviations: SD=standard deviation, IQR=interquartile range (25th percentile, 75th percentile), LDL=low density lipoprotein, HDL=high density lipoprotein, BMI=body mass index, WHR=waisthip ratio, ln=natural logarithm

Total Power <0.40 Hz; Ultra low frequency (ULF) <0.0033 Hz; Very Low frequency (VLF) 0.0033 to <0.04 Hz; low frequency (LF) 0.04 to <0.15 Hz; and high frequency (HF) 0.15 to <0.40 Hz

Table 2
Percent Difference in HRV Comparing Twins With Current PTSD to Those Without Current PTSD

Heart Rate Variability**	Individual Twins (n=459, 31 with PTSD)				PTSD Discordant Pairs (20 pairs)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	% Δ HRV	p	% Δ HRV	p	% Δ HRV	p	% Δ HRV	p
TP	-18.2%	0.05	-13.7%	0.12	-20.5%	0.03	-20.5%	0.03
ULF	-13.1%	0.20	-9.5%	0.33	-16.5%	0.15	-16.5%	0.15
VLF	-30.3%	<0.01	-21.0%	0.03	-24.2%	0.02	-24.2%	0.02
LF	-44.0%	<0.001	-39.3%	<0.001	-48.9%	<0.001	-48.9%	<0.001
HF	-28.8%	0.01	-18.4%	0.13	-26.7%	0.06	-26.7%	0.06

* Adjusted for age, Baecke physical activity score, current/past smoking, hypertension, diabetes, low density lipoprotein cholesterol, antidepressant use, lifetime history of major depression, body mass index, and history of drug abuse

[†]No significant interaction of PTSD with zygosity

Abbreviations: % Δ HRV = percentage change in heart rate variability due to post traumatic stress disorder; PTSD=posttraumatic stress disorder; TP=total power; ULF=ultra low frequency; VLF=very low frequency; LF=low frequency; HF=high frequency

** Total Power <0.40 Hz; Ultra low frequency (ULF) <0.0033 Hz; Very Low frequency (VLF) 0.0033 to <0.04 Hz; low frequency (LF) 0.04 to <0.15 Hz; and high frequency (HF) 0.15 to <0.40 Hz

Table 3

Difference in HRV for a 9 Point (Interquartile Range) Increase in CES Score

Heart Rate Variability***	Individual Twins (n=459)				CES-Discordant Pairs (132 pairs)**			
	Unadjusted		Adjusted*		Adjusted* + current PTSD		Adjusted*	
	% Δ HRV	p	% Δ HRV	p	% Δ HRV	p	% Δ HRV	p
TP	-8.6%	<0.01	-7.3%	<0.01	-6.5%	0.02	-9.2%	<0.01
ULF	-6.9%	0.02	-6.9%	0.02	-6.6%	0.03	-7.9%	0.06
VLF	-8.9%	0.01	-6.2%	0.06	-4.1%	0.21	-7.7%	0.07
LF	-13.7%	<0.01	-8.9%	0.04	-4.2%	0.37	-12.9%	<0.01
HF	-11.3%	0.01	-6.1%	0.18	-4.3%	0.35	-9.8%	0.08

* Adjusted for age, Baecke physical activity score, current/past smoking, hypertension, diabetes, low density lipoprotein cholesterol, antidepressant use, lifetime history of major depression, body mass index, and history of drug abuse

** Discordance was defined as a 1 point difference in CES score within twin pairs. Percent difference is per 9-point difference in CES within twin pairs.

Abbreviations: % Δ HRV = percentage change in heart rate variability due to 9-point increase in CES score; TP=total power; ULF=ultra low frequency; VLF=very low frequency; LF=low frequency; HF=high frequency; CES=combat exposure scale

*** Total Power <0.40 Hz; Ultra low frequency (ULF) <0.0033 Hz; Very Low frequency (VLF) 0.0033 to <0.04 Hz; low frequency (LF) 0.04 to <0.15 Hz; and high frequency (HF) 0.15 to <0.40 Hz