Original Investigation

Association of Predeployment Heart Rate Variability With Risk of Postdeployment Posttraumatic Stress Disorder in Active-Duty Marines

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IMPORTANCE Disrupted autonomic nervous system functioning as measured by heart rate variability (HRV) has been associated with posttraumatic stress disorder (PTSD). It is not clear, however, whether reduced HRV before trauma exposure contributes to the risk for development of PTSD.

OBJECTIVE To examine whether HRV before combat deployment is associated with increased risk of a PTSD diagnosis after deployment when accounting for deployment-related combat exposure.

DESIGN, SETTING, AND PARTICIPANTS Between July 14, 2008, and May 24, 2012, active-duty Marines were assessed 1 to 2 months before a combat deployment and again 4 to 6 months after their return. The first phase of the Marine Resiliency Study (MRS-I) included 1415 male Marines, 59 of whom developed PTSD after deployment. Participants in the second phase of the Marine Resiliency Study (MRS-II) included 745 male Marines, 25 of whom developed PTSD after deployment. Analysis was conducted from November 25, 2013, to April 16, 2015.

MAIN OUTCOMES AND MEASURES Predeployment HRV was measured via finger photoplethysmography during a 5-minute period of rest. Frequency-domain measures of HRV were generated. Diagnosis of PTSD was determined using the Clinician-Administered PTSD Scale.

RESULTS After accounting for deployment-related combat exposure, lower HRV before deployment as measured by an increased low-frequency (LF) to high-frequency (HF) ratio of HRV was associated with risk of PTSD diagnosis after deployment (combined MRS-I and MRS-II cohort meta-analysis odds ratio, 1.47; 95% CI, 1.10-1.98; P = .01). The prevalence of postdeployment PTSD was higher in participants with high predeployment LF:HF ratios (15.8% [6 of 38 participants]) compared with participants who did not have high LF:HF ratios (3.7% [78 of 2122 participants]).

CONCLUSIONS AND RELEVANCE This prospective longitudinal study provides initial and modest evidence that an altered state of autonomic nervous system functioning contributes to PTSD vulnerability, taking into account other key risk factors. If these findings are replicated, interventions that change autonomic nervous system function may open novel opportunities for prevention and treatment of PTSD.

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Corresponding Author: Arpi Minassian, PhD, Department of Psychiatry, University of California, San Diego, 200 W Arbor Dr, Mail Code 8620, San Diego, CA 92103 (aminassian@ucsd.edu). osttraumatic stress disorder (PTSD) is, historically and currently, a significant public health problem in individuals deployed to war. Lifetime prevalence of the disorder is approximately 19% in Vietnam-era combat veterans¹ and 13% to 15% in US military servicemembers serving in this era's conflicts in Iraq and Afghanistan²,³ compared with the 8% general prevalence rate of PTSD in the United States.⁴ These differences in prevalence rates may be in part attributable to variations in the disorder's diagnostic criteria or how it is assessed. Regardless, psychological and functional consequences of PTSD can be devastating (eg, high suicide rates⁵ and long-term disability with substantial impairment in functioning⁶). Furthermore, PTSD is associated with several adverse health consequences.^{7,8}

Heart rate variability (HRV) is the quantitative assessment of variation in heartbeat intervals and is a sensitive index of autonomic nervous system (ANS) function. 9 Heart rate is modulated by both the parasympathetic and sympathetic branches of the ANS via influences on the sinoatrial node pacemaker.¹⁰ The consistent findings of reduced HRV in PTSD suggest autonomic inflexibility due to sympathetic overactivity and/or parasympathetic insufficiency, 11-13 potentially mediated by the presence or worsening of the cardiovascular problems that are common in the disorder.14 It is unclear whether autonomic inflexibility is simply reduced during active PTSD symptoms or whether abnormalities can also be detected in individuals who are at risk for PTSD. In other words, does diminished HRV before trauma increase the likelihood of stress disorder symptoms after trauma? Low parasympathetic control of sympathetic output could reflect an at-risk state for development of stress disorders via reduced cortical modulation of ANS responses to stress15,16 or, alternatively, could be a traitlike phenomenon associated with decreased resilience to stress. Some evidence17 suggests that diminished HRV immediately after trauma can predict development of PTSD; however, to our knowledge, HRV before trauma has not been tested. Identifying biology-based markers of PTSD susceptibility will enable delineation of mechanisms that confer susceptibility to the longterm effects of trauma and inform preventive strategies.

To this end, we tested the hypothesis that HRV before trauma is associated with the development of PTSD in a large group of Marines and Sailors after their return from deployment to a combat zone. Active-duty Marines in the Marine Resiliency Study (MRS), previously described by our group, 13,18-20 were evaluated for HRV and PTSD symptoms before and after deployment. We¹⁹ reported a cross-sectional association before deployment between reduced HRV and PTSD in the MRS cohort. In the present study, we tested our hypothesis that low HRV is a risk factor for PTSD, predicting that Marines and Sailors who developed PTSD after deployment would exhibit low HRV before deployment.

Methods

Participants

Participants were active-duty US Marines and Sailors tested approximately 1 month before deployment to Iraq or Afghani-

stan as part of the first phase of the MRS (MRS-I), a prospective longitudinal study to examine markers of risk and resilience to combat stress. The participants were reassessed approximately 3 and 6 months after return from deployment. The 6-month time frame was the focus of the present study in an effort to assess the prolonged PTSD syndrome. Four infantry battalions were tested between July 14, 2008, and May 24, 2012, at 1 of 2 bases in Southern California. 18 Additional data from a smaller cohort (drawn from the second phase of the MRS [MRS-II]) were analyzed separately owing to assessment time differences (assessments 1 week before deployment and 4-5 months after deployment, with the final evaluation occurring October 10, 2013). Studies were approved by the institutional review boards of the Veteran's Administration San Diego Healthcare System; the University of California, San Diego; and the Naval Health Research Center. All participants provided voluntary written informed consent. Data analysis was conducted between November 25, 2013, and April 16, 2015.

All active-duty Marines planning to deploy with their units were considered for study inclusion. Women were not included since female Marines were not part of infantry battalions at the time of testing.

Procedure

All participants from whom blood samples were drawn received a nominal financial compensation. The predeployment test battery included a comprehensive evaluation of demographic information, history, and current symptoms with respect to military service; drug, alcohol, and tobacco use; psychiatric conditions; head injuries; and psychological trauma. Blood samples were used to determine genetic-based ancestry information (eMethods in the Supplement). The postdeployment test battery was similar in duration and included reevaluation of symptoms and psychological adjustment as well as deployment-related occurrence of traumatic brain injury.

To measure HRV, participants were seated in quiet rooms and a finger photoplethysmograph ([PPG] Pasco Scientific) was placed on the nail of the right fifth finger. The PPG is an optical technique used to detect beat-to-beat blood volume changes in microvascular tissue and was sampled at 1000 Hz (eMethods in the Supplement). We elected to use a 5-minute at-rest PPG reading because this method offers cost-effectiveness, rapid implementation, and feasibility for screening large numbers of people compared with electrocardiogram protocols. However, PPG is limited in that it cannot accurately detect respiration rate and the time frame is not adequate to measure very low frequency components of the spectral band.

Outcome Measurements

The PPG data were processed to generate HRV variables using our group's published methods.¹⁹ Frequency-domain HRV measures were generated per the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.²² The low-frequency (LF) and high-frequency (HF) components and the LF:HF ratio were examined (eMethods in the Supplement).

The Clinician-Administered PTSD Scale (CAPS) 23 was used to determine the presence of a PTSD diagnosis at the prede-

ployment and postdeployment (6-month) visits. The CAPS is a structured interview and is considered the criterion standard for ascertainment of a PTSD diagnosis using *DSM-IV* criteria. Using CAPS responses, we categorized participants as either not meeting or meeting criteria for PTSD at each of the 2 time points. Criteria were derived from the *DSM-IV*: at least 1 B symptom (traumatic event is persistently reexperienced), 3 C symptoms (persistent avoidance of trauma-associated stimuli and numbing of general responsiveness), and 2 D symptoms (persistent arousal symptoms). Because we used a *DSM-5* diagnosis approach with the CAPS, there was not a quantitative criterion for a minimum CAPS score. The range of CAPS scores for participants who met criteria for PTSD was 28 to 96; the mean (SD) score was 61.91 (16.07).

Statistical Analysis

The LF, HF, and LF:HF ratio were positively skewed and natural log transformations were generated; such transformations are widely used in HRV research. ^{12,13,24-27} After transformation, outliers greater than 3 SDs from the mean were excluded from subsequent data analyses, ²⁸ and data were reinspected for normal distribution.

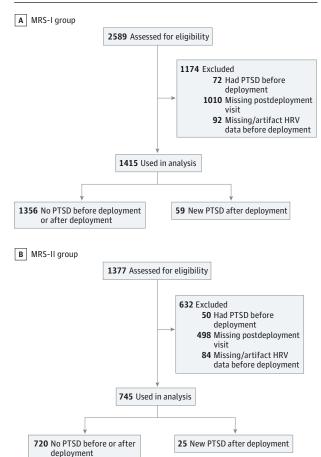
To assess the relationship between HRV before deployment and PTSD at the postdeployment visit, multivariate logistic regressions were conducted for each of the 3 HRV variables for the MRS-I and MRS-II cohorts. The outcome variable was a comparison of participants who did not meet criteria for PTSD either before or after deployment with participants who did not meet PTSD criteria before deployment but fulfilled diagnostic criteria for the disorder after deployment. A summary measure of combat exposure and deployment-related stressors was included as a covariate in the regression model since this factor is the strongest causal predictor of combatrelated PTSD. This factor was derived from the Deployment Risk and Resilience Inventory (DRRI).²⁹ Four DRRI subscales were combined into 1 composite score to measure deployment stressors: Combat Experiences, Aftermath of Battle, Deployment Concerns About Life and Family Disruptions, and the Difficulty Living and Working Environments (eMethods in the Supplement).

The MRS-I and MRS-II analyses were next subjected to a fixed-effect meta-analysis to generate an overall effect size. Power to detect a significant effect was calculated using the a priori power analysis method within the logistic regression module of G*Power, version 3.1.9.³⁰

To determine whether HRV remained significant in the regression model when accounting for other variables that have been closely associated with HRV and/or PTSD in our ¹⁹ and others' ^{11-13,31} findings, the HRV variable that achieved significance in the primary regressions was reassessed in an additional multivariate logistic regression controlling for the following covariates: age, ancestry, battalion, CAPS total scores at the predeployment visit, deployment-related traumatic brain injury as defined by a self-report of a new head injury sustained during deployment that was accompanied by either a loss of consciousness or altered mental status, and DRRI scores.

Post hoc correlations between HRV variables and clinical variables were conducted using Pearson *R* correlation coeffi-

Figure 1. Marine Resiliency Study (MRS)-I and MRS-II Participant Flow Diagrams



HRV indicates heart rate variability; PTSD, posttraumatic stress disorder.

cients. A substantial proportion of participants (464 of 2160 [21.5%]) had a CAPS total score of zero at the postdeployment visit. Those participants' data were not included in the correlational analysis.

Significance levels were set at P < .02 (χ^2 analysis) for the primary regressions to account for multiple comparisons (3 HRV variables). Significance levels for the follow-up regression using the single HRV variable were set at P < .05. Effect sizes were calculated when relevant (eg, odds ratios [ORs] for regression analyses). Statistical analyses were conducted with SPSS, version 20 (SPSS Inc), and R, version 2.15.3 (R Foundation for Statistical Computing).

Results

The overall demographic composition of Marines and Sailors in the MRS has been reported. ^{18-20,32} Overall, the analyses suggested that lower HRV at the predeployment visit, as measured by higher values of the LF:HF ratio, was associated with increased risk of a PTSD diagnosis at the postdeployment visit. Participants with high LF:HF ratios at the predeployment visit

Table 1. Demographic and Descriptive Information for Participants in the MRS

Characteristic	MRS Phase	Mean (SD) [No.]	Statistical Value		
MRS-I, No.		1415			
MRS-II, No.		745			
Age, y	I	22.4 (3.5)	Mann-Whitney = 487 320.50; P = .002		
	II	21.9 (2.8)			
Ancestry, No. (%)	l	European American, 903 (63.8) African American, 83 (5.9) Hispanic/Native American, 253 (17.9) Asian/other, 176 (12.4)	$\chi^2 = 1.80; P = .62$		
	II	European American, 479 (64.3) African American, 39 (5.2) Hispanic/Native American, 145 (19.5) Asian/other, 82 (11.0)			
Prior deployment, No. (%)	I	570 (40.3)	$\chi^2 = 21.76; P < .001$		
	II	379 (50.9)			
Time in the military before deployment, mo	I	31.6 (35.1)	Mann-Whitney =		
	II	29.4 (25.5)	522 321.50; P = .61		
AUDIT total score before deployment	I	7.4 (6.6)	Mann-Whitney =		
	II	6.9 (5.5)	520 056.50; P = .92		
Hours since caffeine use	I	6.4 (6.3) [799]	Mann-Whitney =		
before deployment ^a	II	7.8 (7.2) [457]	164 654.00; P = .004		
Hours since nicotine use	I	3.1 (3.8) [654]	Mann-Whitney = 113 119.50; <i>P</i> < .001		
before deployment ^a	II	4.0 (4.5) [396]			
CAPS total score					
Before deployment	I	13.0 (12.0)	Mann-Whitney =		
	II	11.1 (10.8)	480 851.50; P < .001		
After deployment	I	14.6 (16.4)	Mann-Whitney =		
	II	15.3 (15.7)	503 461.00; P = .05		
Sustained TBI during	I	274 (19.4)	$\chi^2 = 0.07; P = .82$		
deployment, No. (%)	II	148 (19.9)			
DRRI composite imputed	I	-0.09 (0.79)	Mann-Whitney = 481 285.00; P < .001		
score after deployment ^b	II	0.01 (0.77)			

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CAPS, Clinician-Administered PTSD Scale; DRRI, Deployment Risk and Resilience Inventory, MRS, Marine Resiliency Study; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

Table 2. Parameter Estimates for Multivariate Logistic Regressions Including the LF:HF Ratio in Predicting PTSD After Deployment

	MRS-I ^a			MRS-II ^b			Meta-analysis		
Characteristic	OR (95% CI)	Wald χ^2	P Value	OR (95% CI)	Wald χ^2	P Value	OR (95% CI)	Wald χ^2	P Value
DRRI after deployment	2.95 (2.15-4.09)	43.39	<.001	2.55 (1.50-4.43)	11.59	.001	2.84 (2.15-3.74)	54.75	<.001
LF:HF ratio ^c	1.63 (1.14-2.34)	7.07	.008	1.20 (0.72-2.03)	0.45	.50	1.47 (1.10-1.98)	6.60	.01

Abbreviations: DRRI, Deployment Risk and Resilience Inventory; LF:HF, low-frequency to high-frequency ratio; MRS, Marine Resiliency Study; OR, odds ratio; PTSD, posttraumatic stress disorder.

had a higher prevalence of PTSD after deployment than did participants with low predeployment LF:HF ratios. Figure 1 presents the flow of participants in both cohorts. Of the 1415 participants in MRS-I, 1356 individuals (95.8%) who had valid HRV data at the predeployment visit and also attended the 6-month postdeployment visit did not meet PTSD criteria at either visit, and 59 participants did not meet criteria for PTSD before deployment but met the criteria after being deployed (4.2% prevalence of postdeployment PTSD). In the MRS-II cohort of 745 participants, 720 individuals (96.6%) did not meet PTSD criteria at either visit, and 25 participants met the criteria for PTSD after deployment (3.4% prevalence of postdeployment PTSD).

Demographic, military service, and clinical data comparing MRS-I and MRS-II are found in **Table 1**. Compared with MRS-I participants, those of the MRS-II cohort were younger, with lower predeployment CAPS scores, a higher prevalence of prior deployment, more time elapsed since the use of nicotine and caffeine, and a higher self-report of deployment-related stress (higher DRRI scores).

In MRS-I participants, the log-transformed LF:HF ratio was significantly associated with membership in the PTSD group such that higher LF:HF ratios at the predeployment visit were associated with new PTSD cases after deployment (OR, 1.63; 95% CI, 1.14-2.34; P=.008) (Table 2) (analyses of shrinkage and

^a Calculated only in participants who self-reported use of this substance within 24 hours.

^b Imputed composite score as described in the eMethods in the Supplement.

^a The MRS-I cohort included 1356 participants without PTSD before and after deployment and 59 individuals with PTSD after deployment.

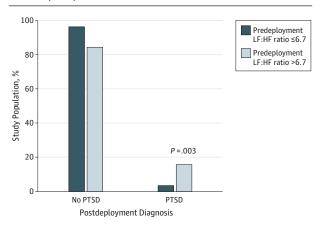
^b The MRS-II cohort included 720 participants without PTSD before and after deployment and 25 individuals with PTSD after deployment.

^c The LF:HF ratio was log transformed.

performance of the regression model are in the eMethods in the Supplement). Neither the log-transformed LF (OR, 1.28; 95% CI, 0.92-1.73; P = .21) nor HF (OR, 0.91; 95% CI, 0.68-1.15; P = .54) achieved statistical significance in the logistic regressions.

Regression with the log-transformed LF:HF ratio was repeated in MRS-II participants. In that analysis, the LF:HF ratio was not statistically significant (OR, 1.20; 95% CI, 0.72-2.03; P=.50) (Table 2). Power to detect a significant effect in the MRS-II cohort was then calculated. Parameters used were the observed OR (1.63) of the LF:HF ratio in MRS-I, observed mean (SD) of the LF:HF ratio in MRS-I (0.36 [0.77]), no correlation between the LF:HF ratio and other covariates, and a 5% probability of PTSD under the null hypothesis of no effect of the LF:HF ratio. Power calculations suggested that 964 participants would have been required in MRS-II to achieve 80%

Figure 2. Percentage of Marine Resiliency Study Participants With Low (n=2122) vs High (n=38) Predeployment Low-Frequency to High-Frequency (LF:HF) Ratios and Postdeployment Posttraumatic Stress Disorder (PTSD)



The LF:HF ratios were back transformed from natural log transformations. Ratios greater than 6.7 represent values greater than 2 SDs from the grand mean; χ^2 analysis was used.

power to detect an effect of the magnitude observed in MRS-I at P=.05. However, a meta-analysis of the weighted β values for the LF:HF ratio regression from both the MRS-I (OR, 1.63; 95% CI, 1.14-2.34) and MRS-II (OR, 1.20; 95% CI, 0.72-2.03) samples indicated that the LF:HF ratio was a statistically significant predictor of PTSD (OR, 1.47; 95% CI, 1.10-1.98; z=2.57; P=.01) (Table 2). **Figure 2** illustrates that the prevalence of postdeployment PTSD was higher in MRS-I and MRS-II participants with high (>2 SDs above the mean) predeployment LF:HF ratios (15.8% [6 of 38 participants]) compared with participants who did not have high LF:HF ratios (3.7% [78 of 2122 participants]).

When all covariates were accounted for in the multivariate logistic regression analyses for MRS-I participants, the log-transformed LF:HF ratio retained statistical significance as a predictor of PTSD group (OR, 1.57; 95% CI, 1.04-2.37; P = .03). Parameter estimates of this regression are reported in **Table 3**.

The multivariate regression model with the log-transformed LF:HF ratio was repeated in MRS-II participants. The LF:HF ratio was not statistically significant, but the meta-analysis of weighted β values for the MRS-I and MRS-II groups indicated that the LF:HF ratio was a statistically significant predictor of PTSD development (OR, 1.42; 95% CI, 1.02-1.98; z=2.05; P=.04) (Table 3). Additional exploratory multivariate logistic regressions with the LF:HF ratio and each covariate in predicting PTSD in MRS-I and MRS-II participants are presented in the eTable in the Supplement.

Although some correlations between predeployment log-transformed LF and HF and postdeployment CAPS scores reached or approached statistical significance owing to the large sample size, the variance in symptom severity predicted by HRV was low (LF correlations with total CAPS: Pearson r=-0.06, P=.03; CAPS Avoidance-Numbing: Pearson r=-0.07, P=.02; and CAPS Arousal: Pearson r=-0.07, P=.02; HF correlations with CAPS Avoidance-Numbing: Pearson r=-0.08, P=.01 and CAPS Arousal: Pearson r=-0.06, P=.04). Post hoc correlations between HRV and other variables are presented in the eMaterial in the Supplement.

Table 3. Parameter Estimates for Multivariate Logistic Regressions Including the LF:HF Ratio and Additional Covariates in Predicting PTSD After Deployment

	MRS-I ^a			MRS-II ^b			Meta-analysis		
Characteristics	OR (95% CI)	Wald χ^2	P Value	OR (95% CI)	Wald χ^2	P Value	OR (95% CI)	Wald χ ²	P Value
Deployment-related TBI	2.92 (1.42-6.03)	8.47	.004	4.67 (1.92-11.40)	11.48	.001	3.52 (2.01-6.17)	19.30	<.001
DRRI after deployment	2.37 (1.41-3.99)	10.53	.001	1.82 (0.99-3.32)	3.77	.05	2.12 (1.43-3.14)	13.87	.001
LF:HF ratio ^c	1.57 (1.04-2.37)	4.52	.03	1.18 (0.67-2.06)	0.33	.57	1.42 (1.02-1.98)	4.21	.04
Predeployment CAPS score	1.04 (1.02-1.06)	15.01	<.001	1.05 (1.02-1.08)	9.49	.002	1.05 (1.03-1.06)	24.40	<.001
Ancestry ^d	NA	2.16	.54		1.67	.64	NA	NA	NA
Battalion ^d	NA	2.04	.56	0.80 (0.32-1.99)	0.23	.63	NA	NA	NA
Age	0.95 (0.43-1.07)	0.63	.43	0.92 (0.76-1.13)	0.63	.43	0.94 (0.85-1.05)	1.18	.28

Abbreviations: CAPS, Clinician-Administered PTSD Scale, DRRI, Deployment Risk and Resilience Inventory; LF:HF, low-frequency to high-frequency ratio; MRS, Marine Resiliency Study; NA, not applicable; OR, odds ratio; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

^a The MRS-I cohort included 1237 participants without PTSD before and after deployment and 44 individuals with PTSD after deployment. Some MRS-I participants were missing a full set of data for all covariates.

^b The MRS-II cohort included 720 participants without PTSD before and after deployment and 25 individuals with PTSD after deployment.

^c The LF:HF ratio was log transformed.

 $^{^{\}rm d}$ These variables included multiple levels (except for the MRS-II battalion, with 2 levels), and the significance levels refer to an overall effect.

Discussion

Previous cross-sectional studies 11-13,19,31 repeatedly showed that lower HRV, thought to reflect inflexibility in the ANS response, is associated with PTSD. To our knowledge, the present study is the first large-scale report of a modest association between HRV before a potentially traumatic circumstance (in this case, combat exposure) and subsequent development of PTSD. The association was not observed when examining HRV variables that putatively isolate sympathetic and parasympathetic components, in contrast to previous findings of an association between lower predeployment HF and predeployment PTSD in this MRS sample. 19 Although those results suggested that, in this cohort of Marines, existing or chronic PTSD was most strongly associated with reduced parasympathetic activity, our present findings imply a role for pretrauma sympathetic activation (relative to parasympathetic activity) in influencing future vulnerability to significant trauma symptoms after combat exposure-related deployment. We did not observe meaningful correlations between HRV measures and symptom severity. Heart rate variability may not necessarily be associated with incremental changes in the severity of PTSD symptoms but may be a factor in or a harbinger for the development of the full syndrome and its associated adverse functional consequences.

The origin of the lower HRV observed in participants who eventually developed PTSD is unknown. A recent twin study¹³ suggested that lower HRV is not found in the unaffected twin of veterans with PTSD and that low HRV is normalized with remission of PTSD symptoms. Taken together with the present results, low HRV may reflect an at-risk state rather than a trait. Low HRV may reflect the effects of environmental factors, perhaps recent, that increase PTSD risk. For example, a heightened stress response may contribute to the low HRV observed in the group that eventually developed PTSD since sensitivity to anxiety has been suggested as a PTSD vulnerability factor.33 Deployment history was similar across groups, and this factor has not been strongly associated with HRV in past studies. 13 Nevertheless, it is possible that the PTSD risk group was exposed to more intense combat in previous deployments, or they may have experienced other adverse events that rendered them at greater risk for eventual development of PTSD. The results suggest that exposure to a combat-related deployment may not substantially affect ANS function for all military personnel; rather, there may be individuals who are particularly vulnerable to the serious psychological consequences of trauma. Resilience and vulnerability to PTSD are complex and multifactorial phenomena³⁴ that include genetic inheritance risk factors, ^{35,36} preexisting cognitive and psychological features, ³⁷ lifetime trauma exposure especially early in childhood, ³⁸ and perhaps also perturbations in ANS regulation. A recent review¹⁶ posits that lower HRV may constitute a vulnerability factor for development of PTSD, perhaps because disrupted ANS function reflects perturbed cognitive and inhibitory control of stress response systems. Disruption in the neuroendocrine system that governs the stress response, the hypothalamic-pituitaryadrenal axis, may influence trauma vulnerability. The ANS is thought to play a role in the regulation of stress responses via inhibition of the hypothalamic-pituitary-adrenal axis by the vagus. ³⁹ Thus, relatively increased sympathetic activation may reflect insufficient inhibition of the hypothalamic-pituitary-adrenal axis, leading to dysregulation of stress hormones and disruption of a normal stress response, which may ultimately contribute to vulnerability to PTSD following a traumatic event. Assuming that low HRV is associated with core mechanisms of PTSD risk and is not an epiphenomenon, an intriguing issue is whether PTSD risk can be decreased via methods intended to improve ANS function, such as biofeedback⁴⁰ and other interventions. ^{41,42} For example, there is a promising role for mindfulness-based interventions, particularly meditation, in increasing HRV. ⁴³⁻⁴⁵

The present study's restriction to a young male group of US military personnel limits its generalizability to other PTSD populations. As our group 19 has previously suggested, the association between ANS function and trauma symptoms probably depends on the population and context of the traumatic event. Furthermore, the LF:HF ratio, although widely used, has been criticized for not always reflecting a robust and specific measure of sympathetic to parasympathetic balance, 46 particularly in situations when respiration is not accounted for, as in the present study (eg, respiratory sinus arrhythmia^{47,48}). The assessment of many Marines in short time frames rendered a brief PPG recording to be the most practical method compared with longer recordings using electrocardiographic Holter monitors plus respiratory bands. Thus, we could not assess to what extent breathing rates may have moderated HRV. No significant association was observed between postdeployment PTSD and other predeployment HRV indices (ie, the LF and HF components); a small sample size for the PTSD group certainly may have reduced the power to detect these potential associations. The MRS-I and MRS-II cohorts were somewhat heterogeneous (Table 1 and Figure 1), which is why we conducted a meta-analysis instead of simply combining the $2\,$ cohorts. Although the LF:HF ratio showed a similar effect size in MRS-II, it did not reach statistical significance in that cohort, likely owing to low power. Finally, in contrast to studies using 24-hour Holter monitoring recordings, 11,13 we did not observe a linear relationship between predeployment HRV and postdeployment PTSD symptoms. Previous studies^{11,13} demonstrated cross-sectional-not longitudinal-correlations between HRV indices and PTSD symptoms. In the present study, a 5-minute HRV sample may have been insufficient to adequately capture an association between this relatively nonspecific physiologic measure and PTSD symptoms obtained more than 1 year later. Integrated analyses of HRV with other risk factors in this cohort (eg, markers of inflammation, fear processing, and traumatic brain injury) will help to elucidate the relative usefulness of this marker for predicting PTSD risk in active-duty military members. 18,20,32,49

Conclusions

This investigation provides initial longitudinal evidence that ANS function may contribute to vulnerability and resilience

to PTSD along with known risk factors, such as combat exposure and preexisting stress and trauma symptoms. If supported, this association sheds additional light on the in-

terplay between complex biological systems and the psychological and functional consequences of trauma and may provide new opportunities for prevention.

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 $\label{eq:constraint} \textit{Acquisition, analysis, or interpretation of data:} \ \textit{All authors.}$

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