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Heart Rate Variability Characteristics in a Large Group of Active-Duty Marines and Relationship to Posttraumatic Stress

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Objective: Heart rate variability (HRV), thought to reflect autonomic nervous system function, is lowered under conditions such as posttraumatic stress disorder (PTSD). The potential confounding effects of traumatic brain injury (TBI) and depression in the relationship between HRV and PTSD have not been elucidated in a large cohort of military service members. Here we describe HRV associations with stress disorder symptoms in a large study of Marines while accounting for well-known covariates of HRV and PTSD including TBI and depression. **Methods:** Four battalions of male active-duty Marines ($n = 2430$) were assessed 1 to 2 months before a combat deployment. HRV was measured during a 5-minute rest. Depression and PTSD were assessed using the Beck Depression Inventory and Clinician-Administered PTSD Scale, respectively. **Results:** When adjusting for covariates, including TBI, regression analyses showed that lower levels of high-frequency HRV were associated with a diagnosis of PTSD ($\beta = -0.20$, $p = .035$). Depression and PTSD severity were correlated ($r = 0.49$, $p < .001$); however, participants with PTSD but relatively low depression scores exhibited reduced high frequency compared with controls ($p = .012$). Marines with deployment experience ($n = 1254$) had lower HRV than did those with no experience ($p = .033$). **Conclusions:** This cross-sectional analysis of a large cohort supports associations between PTSD and reduced HRV when accounting for TBI and depression symptoms. Future postdeployment assessments will be used to determine whether predeployment HRV can predict vulnerability and resilience to the serious psychological and physiological consequences of combat exposure.
Key words: sympathetic nervous system, PTSD, vagal tone, combat, depression, parasympathetic.

ANS = autonomic nervous system; **BDI** = Beck Depression Inventory; **BMI** = body mass index; **CAPS** = Clinician-Administered PTSD Scale; **HF** = high-frequency index; **HR** = heart rate; **HRV** = heart rate variability; **LF** = low-frequency index; **MRS** = Marine Resiliency Study; **OEF** = Operation Enduring Freedom; **OIF** = Operation Iraqi Freedom; **PPG** = photoplethysmograph; **PTSD** = posttraumatic stress disorder; **SSRI** = selective serotonin reuptake inhibitor; **TBI** = traumatic brain injury; **VLF** = very low frequency index.

INTRODUCTION

Heart rate variability (HRV), the quantitative assessment of variation in heartbeat intervals, can be used to detect alterations in autonomic nervous system (ANS) function (1). Heart rate is in part determined by influences on the sinoatrial node pacemaker, which is modulated by both the parasympathetic and sympathetic branches of the ANS (2). Spectral analysis of interbeat intervals is used to derive the high-frequency (HF) peak of HRV, which is thought to reflect parasympathetic or vagal tone, although controversy about the sensitivity and specificity of widely used HRV measures exists (3,4).

HRV and regulation of the ANS have been suggested to be useful in understanding cardiovascular and other health risks (4,5). Decreased HRV has been associated with pathophysiology, psychopathology, and increased mortality (2,6). Previous studies have reported lower HRV in psychiatric disorders such as schizophrenia, depression, bipolar disorder, panic disorder (7–10), and posttraumatic stress disorder (PTSD) (11–13). Accurate assessment of HRV can be done in a rapid (5-minute) period (14) using relatively nonobtrusive instrumentation; thus, this physiological index has been used to study populations that may be at high risk for disrupted ANS functioning and the associated health complications.

One such high-risk group is represented by US military service members who are deployed to combat situations such as Operation Enduring Freedom (OEF; Afghanistan post-2001), Operation Iraqi Freedom (OIF), or Operation New Dawn. Since the onset of these conflicts, the prevalence of PTSD in returning veterans has been reported at 13% to 15% (15,16). Prior studies have shown an association between PTSD and lower HRV (8,11–13). PTSD is strongly associated with the occurrence of a traumatic brain injury (TBI) in OEF/OIF war veterans (17); furthermore, TBI in and of itself has been related to lower HRV (18). Thus, an unanswered question is whether HRV is associated with PTSD even when TBI is accounted for, in a population at elevated risk for both TBI and PTSD. Depression is also an important factor in understanding the relationship between trauma and HRV, as illustrated by several studies on civilian trauma survivors (19,20). Unknown, however, is the potential role of depressive symptoms in influencing the relationship between HRV and PTSD in military service members who are at high risk for both psychiatric conditions. Military personnel may constitute a unique population with respect to trauma and autonomic function because of a number of factors including prevalence of TBI, physical fitness, repeated exposure to severe combat-related trauma, and other features distinct to military service members.

The current study's objective was two-fold: a) assess the relationship between PTSD and HRV in a large group of active-duty Marines while accounting for important covariates of PTSD and HRV such as TBI and depression and (2) introduce the methodology used to assess HRV in this large participant group and assess the influence of potential covariates such as age (21,22), ancestry (23), and use of nicotine (24) and caffeine (25,26). This latter goal is in the service of studying HRV changes in the longitudinal portion of this study, that is, after these service members return from deployment. The quantification of ancestry

TABLE 1. Cohort Sizes for HRV Data Collected in Active-Duty Marines Before Deployment to OIF/OEF/OND

	No. Eligible Participants in a Cohort	Participants With Sufficient Artifact-Free HRV Data, n (%)
Cohort 1	315	298 (94.6)
Cohort 2	721	699 (96.9)
Cohort 3	670	603 (90.1)
Cohort 4	886	830 (93.7)
Total	2592	2430 (93.8)

HRV = heart rate variability; OIF = Operation Iraqi Freedom; OEF = Operation Enduring Freedom; OND = Operation New Dawn.

using genetic markers versus relying on participant self-report is a novel approach to replicating previous associations between HRV and ethnicity (23).

We hypothesized that lower HRV as quantified by the HF component would be associated with a PTSD diagnosis even when TBI was accounted for. We further hypothesized, based on previous findings in civilian trauma survivors (20), that the co-occurrence of depressive symptoms and PTSD would result in lower HRV than PTSD alone.

METHODS
Participants

Participants were active-duty Marines who were tested approximately 1 month before deployment to OEF, OIF, or Operation New Dawn as part of the Marine Resiliency Study (MRS), a prospective longitudinal study whose objective is to examine markers of risk and resilience to effects of combat stress in active-duty Marines. Four unique Infantry battalions (cohorts) of Marines were tested between July 2008 and August 2010 at one of two bases: Marine Corps Air Ground Combat Center in Twenty-nine Palms, CA (Cohorts 1, 2, and 3) and Camp Pendleton, CA (Cohort 4). See Table 1 for individual cohort sizes. This study was approved by the institutional review boards of the Veteran's Administration San Diego Health System, the University of California San Diego, and the Naval Health Research Center.

All active-duty Marines who were planning to deploy with their units were considered for inclusion into the study. Women were not included because female Marines were not part of infantry battalions at the time of data collection. Because the US Marine Corps maintains specific guidelines that prohibit the severely mentally ill (i.e., schizophrenia, psychotic disorder, and bipolar disorder) from active-duty service, Marines with these preexisting mental illness conditions were not included in the study.

The overall demographic composition of Marines in the MRS has been previously reported (27). Age, ancestry, and other covariate data for the participants are found in Table 2. More than half (64.8%) of the participants reported graduating high school or receiving a GED, 32.1% reported some college or a college degree, and 0.4% reported a masters or doctoral-level degree. Also, 61.8% of participants reported their marital status as never married, 36.1% reported being married, and 2.1% reported being separated or divorced. More than half of the participants (68.3%) had a junior enlisted rank (E1-E3), 28.9% were noncommissioned officers (E4-E9), and 2.6% were commissioned or warrant officers. Participants reported an average (standard deviation) of 36.2 (34.6) months of military service. Less than half of the participants (48.2%) reported at least one prior deployment.

Procedure

All participating Marines provided voluntary written informed consent. Marines were informed about confidentiality relating to research data, and research records were rigorously protected. The entire MRS test battery was approximately 4 hours in duration and included a comprehensive evaluation

TABLE 2. Demographic and Descriptive Information for Participants in Each Cohort

	Cohort 1 ($n = 298$)	Cohort 2 ($n = 699$)	Cohort 3 ($n = 603$)	Cohort 4 ($n = 830$)	Total ($n = 2430$)
Age, y	21.9 (3.1)	22.4 (3.4)	23.2 (3.7)	23.1 (3.7)	22.8 (3.5)
Ancestry, %					
European American	62.8	66.5	60.7	58.4	61.9
African American	3.7	4.7	6.5	7.5	6.0
Native American/Mexican	19.1	15.5	17.2	19.8	17.9
Asian/Other	14.4	13.2	15.6	14.3	14.3
Body mass index, kg/m^2	26.8 (3.4)	27.3 (3.0)	28.1 (3.4)	27.8 (3.3)	27.6 (3.2)
With a history of TBI, n (%)	188 (63.1)	422 (60.3)	326 (54.1)	413 (49.8)	1349 (55.5)
Hours since nicotine use[a]	$n = 133$; 4.0 (4.5)	$n = 371$; 3.3 (4.2)	$n = 284$; 2.7 (3.1)	$n = 390$; 2.6 (3.3)	$n = 1178$; 3.0 (3.7)
Hours since caffeine use[a]	$n = 189$; 7.6 (6.7)	$n = 460$; 6.6 (6.3)	$n = 293$; 6.1 (2.7)	$n = 419$; 5.0 (5.6)	$n = 1361$; 6.1 (6.1)
AUDIT (alcohol use) total score	8.2 (6.3)	8.4 (7.4)	7.6 (6.7)	6.9 (6.3)	7.7 (6.8)
Participant using psychotropic medications, n (%)	7 (2.3)	12 (1.7)	7 (1.2)	4 (0.5)	30 (1.2)
BDI (depression) total score	7.5 (8.3)	8.5 (8.8)	6.2 (7.3)	5.2 (6.5)	6.7 (7.8)
CAPS (PTSD) total score	16.9 (16.8)	16.8 (15.6)	14.6 (15.8)	13.2 (14.6)	15.0 (15.5)
Participants with PTSD, n (%)	14 (4.7)	41 (5.9)	36 (6.0)	29 (3.5)	120 (5.0)
Participants with a prior deployment, n (%)	161 (54)	386 (55.2)	281 (46.5)	426 (51.3)	1254 (51.7)

History of TBI = self-reported history of a head injury accompanied by either loss of consciousness or altered mental status; AUDIT = Alcohol Use Disorders Identification Test; BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD Scale; PTSD = posttraumatic stress disorder.
PTSD diagnosis was determined by meeting the full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria as assessed by the CAPS. Values in the table are means (standard deviations), unless specified otherwise.
[a] Calculated only in participants who self-reported use of this substance within 24 hours.

of demographic information, history, and current symptoms with respect to military service, drug, alcohol and tobacco use, psychiatric conditions, head injuries, and psychological trauma (27). Height and weight were measured, and blood samples were taken for genetic association studies.

For the assessment of HRV, participants were seated in quiet rooms. A finger photoplethysmograph (PPG; Pasco Scientific, Roseville, CA) was placed on the nail of the right fifth finger which rested on a desk. PPG is an optical technique used to detect beat-to-beat blood volume changes, for example, as a result of pulse, in microvascular tissue. Fluctuations in the blood volume of the finger are directly related to the activity of the heart; thus, the interval between peaks in the PPG signal, known as the PP interval, is considered a reasonably accurate reflection of the R-R interval (28). PPG has been shown to be a sensitive and reliable peripheral instrument for the capture of cardiac activity (29); for example, it is highly correlated with waveforms from simultaneous electrocardiogram (ECG) recordings (30,31). Frequency and time-domain measures of HRV derived from PPG were not significantly different from those derived by a simultaneous two-lead ECG recording (28). PPG was sampled at the rate of 1000 Hz. Using an oscilloscope display and amplification of the PPG signal (San Diego Instruments), the examiner ensured that the PPG was adequately capturing the heart beat waveforms without cutting off the peak of the R wave. The position of the PPG was adjusted until a visually clear heartbeat signal was obtained, and each Marine was asked to keep his hand relatively motionless during the 5-minute recording. Participants were asked to sit comfortably and direct their attention to a computer monitor where they were entertained with simple visual puzzles (e.g., locating hidden images in a photograph). The images were selected to be neutral and minimally affectively arousing or stress inducing (e.g., dolphins and frogs). They were told that they did not need to memorize anything and that they would not be tested on the images afterward. The purpose of the hidden image task was to maximize the likelihood that participants remained stationary, awake, and alert for the duration of the recording. The images changed every 60 seconds (thus, outside the bandwidth for both low-frequency (LF) and HF ranges—see below), and the order of presentation of the images was the same for all participants. The 5-minute HRV recording session was simultaneous with the 5-minute acclimation period, which is standardly used immediately before a session of eyeblink startle and prepulse inhibition measurement (32,33). Thus, during the 5-minute PPG recording session, participants wore headphones that delivered continuous broadband noise at a decibel level of 70 dB, which is a standard level for an acclimation period before an eyeblink startle session. Participants were also prepared for electromyography of the orbicularis oculi muscle recordings via the placement of two skin electrodes near the left eye for the purpose of subsequently assessing the eyeblink startle response and sensorimotor inhibition after the heart rate recordings presented here were completed (electromyography data will be reported elsewhere). Only the constant 70-dB background noise was delivered during the 5-minute HRV recording.

Data Processing

Data files (one file per 5-minute session) from the PPG were extracted and processed through a multistep procedure to generate HRV variables:

1. The systolic peaks of the PPG signal were identified and a tachogram representing intervals between heartbeats (the PP interval) was generated by measuring the time difference between successive peaks.
2. Tachograms were processed by the HRV analysis module of VivoSense 1.0 (Vivonoetics, 2011), which can process multiple files in an automated batch process format. See Supplemental Digital Content 1, http://links.lww.com/PSYMED/A120, for details of processing and derivation of HRV measures.
3. After the batch process, trained scorers (V.R., A.M.) visually inspected each file in accordance with the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology that automated HRV analyses should be followed by visual inspection and manual correction. Additional corrections were required in approximately 8% to 10% of files, and each corrected file was reprocessed to generate HRV variables.
4. Files for which the software determined that there was insufficient artifact-free data to accurately calculate frequency-domain variables were excluded from further HRV analysis. Typically, this occurred when there was

prominent motion artifact throughout the 5-minute session. Table 1 displays the percentages of sufficient artifact-free HRV data in each cohort.

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 (14) and included (definitions and physiological correlates can be found in Refs. (3,14) and specified citations):

1. HR: heart rate in beats per minute over the 5-minute session; a time-domain measure;
2. SDNN: standard deviation of the R-R intervals in milliseconds; a time-domain measure influenced by both sympathetic and parasympathetic activity;
3. RMSSD: root mean square successive differences between R-R intervals; a time-domain measure primarily influenced by parasympathetic activity;
4. VLF: absolute power of the very low frequency (<0.04 Hz) band in milliseconds squared; a frequency-domain measure whose physiological correlates are not well understood;
5. LF: absolute power of the LF (0.04–0.15 Hz) band in milliseconds squared; a frequency-domain measure thought to reflect sympathetic activity and some parasympathetic activity (34,35);
6. HF: absolute power of the HF (0.15-0.4 Hz) band in milliseconds squared; a frequency-domain measure thought to reflect primarily parasympathetic activity (34,35);
7. LFnorm: LF power in normalized units calculated by LF/(total power − VLF); a frequency-domain measure (LFnorm reflects the percentage of total power that is accounted for by LF which reflects both sympathetic and parasympathetic activity);
8. HFnorm: HF power in normalized units calculated by HF/(total power − VLF); a frequency-domain measure (HFnorm is thought to reflect percentage of total power that is accounted for by HF which reflects primarily parasympathetic activity); and
9. LF/HF ratio: ratio of LF over HF; a frequency-domain measure. Higher ratios have been proposed to reflect more sympathetic relative to parasympathetic activity (36). It is important to note, however, that use of the LF/HF ratio as a robust measure of sympathetic to parasympathetic balance has come under substantial scrutiny. Eckberg (4) provides a review of the evidence that parasympathetic contributions to LF are significant and that HF may not reflect parasympathetic function when respiration is not controlled.

Of these nine variables, the LF/HF ratio and the transformed values for SDNN, RMSSD, LF, and HF were used in further analysis. Heart rate was not used because, in relation to the other measures, is not a direct index of HRV. The LF/HF ratio is a widely used index that is the ratio of LFnorm and HFnorm; thus, these latter variables were not further analyzed. Guidelines on the selection of appropriate epochs for assessing HRV suggest that a 5-minute recording window is sufficient to derive LF and HF as well as time-domain indices such as SDNN and RMSSD, but accurate assessment of VLF likely requires at least a 50-minute recording window (3,14). Thus, VLF was not included in subsequent analyses.

Variables studied in relationship to HRV were as follows: age in years, ancestry, hours since last nicotine use (for participants who reported using nicotine within 24 hours), hours since last caffeine use (for participants who reported using caffeine within 24 hours), body mass index (BMI) in kilograms per meter squared, history of TBI as defined by a self-report of head injury that was accompanied by either a loss of consciousness or altered mental status, and current use of psychotropic medications (Table 2). This latter category was defined broadly as the current use of one or more of the following classes of medications: antidepressants, benzodiazepines, sleep aids, mood stabilizers, prescription stimulants, or antipsychotic medications. Beck Depression Inventory-II (BDI) (37) scores and the Clinician-Administered PTSD Scale (CAPS) (38) scores were also assessed in relation to HRV. The CAPS is a clinician-administered structured interview and is considered the gold standard for assessment of PTSD symptoms and ascertainment of a PTSD diagnosis using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (see below).

Ancestry was determined using genetic information as described in Ref. (39). In brief, genotypes of 1783 ancestry-informative markers were used to determine a participant's ancestry at the continental level for the seven

TABLE 3. Descriptive Information for Heart Rate Variability Variables in the Entire Sample (n = 2430)

	Heart Rate	SDNN	RMSSD	VLF	LF	HF	LFnorm	HFnorm	LF/HF Ratio
Mean (SD)	67.1 (10.2)	64.1 (26.9)	58.9 (34.5)	2380.2 (2470.9)	5144.1 (5467.4)	4153.8 (5074.4)	0.56 (0.17)	0.41 (0.16)	1.9 (1.7)

SD = standard deviation; SDNN = standard deviation of the R-R intervals in milliseconds; RMSSD = root mean square successive differences between R-R intervals; VLF = absolute power of the very low frequency (<0.04 Hz) band in milliseconds squared; LF, absolute power of the low frequency (0.04-0.15 Hz) band in milliseconds squared; HF = absolute power of the high frequency (0.15-0.4 Hz) band in milliseconds squared; LFnorm = LF power in normalized units calculated by LF/(total power − VLF); HFnorm = HF power in normalized units calculated by HF/(total power − VLF); LF/HF ratio = ratio of LF over HF.
Heart rate is in beats/min. For a given variable in a given cohort, a range of 0 to 9 participants were moved due to outlier scores, for an average 0.34% removed due to outlier scores.

geographic regions Africa, Middle East, Europe, Central/South Asia, East Asia, Americas, and Oceania. Ancestry estimates were determined using STRUCTURE v2.3.2.1. (40) at K = 7, including prior population information of the Human Genome Diversity Project reference set (41). Based on these ancestry estimates, MRS participants with HRV data were placed into four groups: participants with more than 95% European ancestry were grouped with European Americans (n = 1503); participants with more than 5% African ancestry and less than 5% each Native American, Central Asian, East Asian, and Oceanic ancestry as African Americans (n = 145); participants with more than 5% Native American and less than 10% African, and less than 5% each Central Asian, East Asian, and Oceanic ancestry as Hispanic and Native Americans (n = 434); and all others, including 43 East Asians with more than 95% East Asian ancestry as Others (n = 348).

Statistical Analysis

Frequency and descriptive statistics were generated for each HRV measure (Table 3). In cases where a variable showed significant skew, transformations were applied per the recommendations of Tabachnick and Fidel (42). Natural log transformations of frequency-domain measures such as LF, HF, and the LF/HF ratio are widely used (11,13,21,43–45). After the transformation of the appropriate variables, outliers defined as greater than 3 standard deviations from the mean were excluded from subsequent data analyses (Table 3). SDNN and RMSSD showed a moderate positive skew, and square root transformations of these variables were generated (42). LF, HF, and the LF/HF ratio showed a substantial positive skew, and natural log transformations were generated. After the log transformations, distributions were inspected and skew was assessed. The log-transformed HRV values were normally distributed. Distributions of HRV were relatively similar across the four cohorts (although differences in mean HRV measures were observed between cohorts; see Table 4 and below).

A high proportion of Marines had BDI and CAPS scores of zero (22.3% for BDI, 15.7% for CAPS); hence categorical variables were created for BDI and CAPS scores. For the BDI, three categories were generated: BDI scores of 0, BDI scores between 1 and 19 suggesting minimal/mild depression, and BDI scores of 20 or greater suggesting moderate/severe depression. For the CAPS, Marines were categorized as having no symptoms of PTSD, meeting the partial criteria for PTSD, or meeting the full criteria for PTSD. Full criteria are derived from the DSM-IV diagnosis for PTSD and require the following: at least one B symptom (the traumatic event is persistently reexperienced), three C symptoms (persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness), and two D symptoms (persistent symptoms of increased arousal). Participants were deemed to have met the partial criteria for PTSD if they did not meet the full criteria but did endorse a) at least one B symptom, two C symptoms, *and* two D symptoms, or b) at least one B symptom, three C symptoms, *or* two D symptoms.

To assess the relationship between HRV and PTSD after accounting for important covariates, a single multinomial logistic regression was conducted with PTSD category (comparing no PTSD to partial PTSD and full PTSD) as the outcome variable and HRV and TBI history as predictors, as well as age, cohort, and ancestry, because these variables were shown to have significant and consistent associations with HRV (see Table 4). A regression approach was chosen to account for multiple covariates while preserving power, and PTSD category was chosen as the outcome with the hope that this approach could most sensitively detect potential HRV changes associated with different severity

levels of PTSD. Cases with no PTSD were used as the reference category. As above, a large proportion of zero CAPS scores precluded the use of CAPS scores as a continuous measure of PTSD severity. To minimize multicollinearity among the highly intercorrelated HRV variables, one HRV index, log-transformed HF, was entered as a predictor. The assumptions of the model were tested with goodness-of-fit Pearson and deviance χ tests. Significance values were both p > .100, indicating that the data were consistent with model assumptions.

To assess whether there was a PTSD-by-depression interaction on HRV, a two-way analysis of variance (ANOVA) was conducted with PTSD category (no PTSD versus full or partial PTSD) and BDI category (no or minimal/mild depression versus moderate/severe depression) as the independent variables and log-transformed HF as the dependent variable.

To provide simple descriptive statistics across diagnostic groups, HRV differences with respect to presence or absence of a DSM-IV diagnosis of PTSD as defined by the CAPS were assessed using an independent-sample t test, and HRV differences between the three BDI categories (no depression, minimal/mild, and moderate/severe) were assessed using a univariate ANOVA.

Relationships between HRV and symptoms scores as well as the continuous variables of age, BMI, hours since nicotine use, hours since caffeine use, and scores on the Alcohol Use Disorders Identification Test (46) were assessed with Pearson R correlation coefficients. HRV differences with respect to presence or absence of a TBI and history and presence or absence of psychotropic medication usage were analyzed using independent-sample t tests. HRV differences between cohorts and ancestry categories were analyzed using ANOVA. HRV differences between those with a deployment history and those without a deployment history were analyzed using analysis of covariance, with age as a covariate and PTSD group as a factor. It should be noted that cohort membership had significant associations with both HRV variables and outcome measures of interest (BDI, CAPS); hence, our descriptive statistics are presented by cohort. The four cohorts were tested during four different periods, and uncontrolled factors such as season, differences in training, and differences in specific deployment destination may have occurred. To account for this potential variance, cohort was consistently kept as a factor in our statistical models.

Significance levels were set at p < .050, and Cohen d and partial eta squared (η_p^2) effect sizes were calculated when relevant. Statistical analyses were conducted with PASW/SPSS 18.

RESULTS
Description of HRV

The range of the HRV measures (Table 3) were generally consistent with HRV values reported in a recent review of 44 short-recording HRV studies (47), with the exception of values of VLF, LF and HF, which are substantially higher in the current population than what has been previously reported.

Relationship of HRV to Depression and PTSD

Across all four cohorts, 1678 (69%) participants were categorized as having minimal to mild depression, whereas 189 (7.8%) participants were categorized as having moderate to severe depression. The ANOVA yielded no significant

TABLE 4. Relationship of Heart Rate Variability Variables to Demographic and Other Factors

	SDNN	RMSSD	LF	HF	LF/HF Ratio
Cohort	$F_{(3,2419)} = 45.68$***, $\eta_p^2 = 0.054$; Cohort 1 > Cohorts 3 and 4 > Cohort 2	$F_{(3,2411)} = 34.65$***, $\eta_p^2 = 0.041$; Cohort 1 > Cohorts 3 and 4 > Cohort 2	$F_{(3,2408)} = 25.59$***, $\eta_p^2 = 0.031$; Cohort 1 > Cohorts 3 and 4 > Cohort 2	$F_{(3,2414)} = 15.56$***, $\eta_p^2 = 0.019$; Cohort 1 > Cohorts 3 and 4 > Cohort 2	$F_{(3,2419)} = 2.06$, $\eta_p^2 = 0.003$; Cohort 1 > Cohort 3[c]
Age, y	Pearson $r = -0.11$***	Pearson $r = -0.12$***	Pearson $r = -0.11$***	Pearson $r = -0.16$***	Pearson $r = 0.09$***
Ancestry	$F_{(3,2419)} = 2.54$*, $\eta_p^2 = 0.003$; white > African American, Asian/other	$F_{(3,2411)} = 0.37$, $\eta_p^2 = 0.000$	$F_{(3,2408)} = 8.48$***, $\eta_p^2 = 0.010$; white > African American, Native American/Mexican, Asian/other	$F_{(3,2414)} = 1.74$, $\eta_p^2 = 0.002$; white > Asian/other[c]	$F_{(3,2419)} = 7.10$***, $\eta_p^2 = 0.009$; white > African American, Native American/Mexican, Asian/other
Body mass index, kg/m²	Pearson $r = -0.04$	Pearson $r = 0.01$	Pearson $r = -0.07$**	Pearson $r = -0.01$	Pearson $r = -0.08$***
History of TBI	$t_{(2413)} = 0.03$, $d = 0.001$	$t_{(2405)} = 0.44$, $d = 0.02$	$t_{(2402)} = 0.17$, $d = 0.01$	$t_{(2408)} = 1.91$, $d = 0.08$	$t_{(2413)} = 2.44$*, $d = 0.10$; TBI history > no TBI
Hours since nicotine use[a]	Pearson $r = 0.10$***	Pearson $r = 0.09$**	Pearson $r = 0.09$**	Pearson $r = 0.07$*	Pearson $r = -0.01$
Hours since caffeine use[a]	Pearson $r = 0.05$	Pearson $r = 0.03$	Pearson $r = 0.02$	Pearson $r = 0.02$	Pearson $r = 0.01$
AUDIT total score	Pearson $r = 0.01$	Pearson $r = 0.02$	Pearson $r = -0.01$	Pearson $r = 0.01$	Pearson $r = -0.01$
Use of psychotropic medications	$t_{(2422)} = 1.50$; med $d = 0.28$; med users > nonusers	$t_{(2412)} = 1.28$, $d = 0.24$; med users > nonusers	$t_{(2409)} = 2.03$*, $d = 0.38$; med users > nonusers	$t_{(2415)} = 1.47$, $d = 0.27$; med users > nonusers	$t_{(2420)} = 0.17$, $d = 0.03$
History of a deployment[b]	$F_{(1,2407)} = 2.52$, $\eta_p^2 = 0.001$	$F_{(1,2399)} = 2.95$, $\eta_p^2 = 0.001$	$F_{(1,2396)} = 2.02$, $\eta_p^2 = 0.001$	$F_{(1,2402)} = 5.13$*, $\eta_p^2 = 0.002$; prior < no prior	$F_{(1,2407)} = 0.45$, $\eta_p^2 < 0.001$

History of TBI = self-reported history of a head injury accompanied by either loss of consciousness or altered mental status; AUDIT = Alcohol Use Disorders Identification Test; SDNN = standard deviation of the R-R intervals in milliseconds; RMSSD = root mean square successive differences between R-R intervals; LF = absolute power of the low frequency (0.04-0.15 Hz) band in milliseconds squared; HF = absolute power of the high frequency (0.15-0.4 Hz) band in milliseconds squared; LF/HF ratio = ratio of LF over HF; η_p^2 = partial eta squared. d = Cohen d effect size. SDNN and RMSSD were square root transformed. VLF, LF, HF, and the LF/HF ratio were natural log transformed. Direction of findings is reported if statistical significance is reached in either the overall test or planned comparisons, or at least a small effect size is achieved.

* $p < .050$, ** $p < .010$, *** $p < .001$.
[a] Calculated only in participants who self-reported use of this substance within 24 hours.
[b] Analyses of covariance for history of deployment were conducted with age as a covariate and PTSD group (no PTSD versus partial PTSD versus full PTSD) as a factor.
[c] Overall analysis of variance did not achieve statistical significance, but this planned comparison was significant at $p < .05$.

TABLE 5. Parameter Estimates for the HF Index in the Multinomial Logistic Regression Predicting no PTSD diagnosis (n = 2115) Versus Partial PTSD Diagnosis (n = 195) Versus Full PTSD Diagnosis (n = 120)

PTSD Group	B	Standard Error	Wald χ^2	df	Significance	Exp (B) Odds Ratio	95% CI Lower for Exp (B)	95% CI Upper for Exp (B)
Partial PTSD	−0.16	0.08	4.44	1	.035	0.85	0.94	1.02
Full PTSD	−0.20	0.09	4.44	1	.035	0.82	0.67	0.99

HF = high frequency; PTSD = posttraumatic stress disorder; CI = confidence interval.
The following covariates were first entered into the model: age, ancestry, cohort, and history of TBI. HF values were log transformed. PTSD groups were determined by the CAPS. Partial PTSD = did not meet full criteria and had one of two CAPS profiles: a) at least one B symptom, two C symptoms, and two D symptoms, or b) at least one B symptom, three C symptoms, or two D symptoms. Full PTSD = at least one B symptom, three C symptoms, and two D symptoms.

differences or trends among the three BDI categories on any of the HRV measures.

Across all four cohorts, 120 Marines (4.9%) were categorized as meeting the full criteria for PTSD, whereas 195 Marines (8.0%) were categorized as meeting the partial PTSD criteria. The multinomial logistic regression with PTSD category as the outcome and HRV, TBI group, and other covariates as predictors was statistically significant (χ^2 = 77.7, p < .001, pseudo-R^2 = 0.03). HRV reached statistical significance in its association with partial PTSD and full PTSD (Table 5) such that log-transformed HF values were lower in individuals with partial and full PTSD compared with individuals without PTSD. As a confirmatory post hoc analysis, an ordinal regression was conducted with PTSD category (no PTSD, partial PTSD, full PTSD) as the ordinal outcome. The proportional odds assumption was met (test of parallel lines: χ^2 = 11.8, p < .100). The model was statistically significant (χ^2 = 65.5, p < .001), and again, HF was statistically significant in its association with PTSD (ordered log-odds estimate = −0.18, p = .004) when other covariates were also in the model.

The two-way ANOVA with the PTSD group and depression group as independent variables and log-transformed HF as the dependent variable indicated no significant PTSD-by-depression interaction ($F(1,2387)$ = 0.18, not significant [ns], η_p^2 < 0.001) or a main effect of depression group ($F(1,2397)$ = 0.05, ns, η_p^2 < 0.001). Figure 1A displays back-transformed HF means comparing participants with no PTSD and no depression, participants with depression but no PTSD, participants with full or partial PTSD and depression, and participants with full or partial PTSD but no depression. The main effect of the PTSD group did not reach statistical significance ($F(1,2397)$ = 2.55, p = .111, η_p^2 = 0.001), but post hoc comparisons of the four groups indicated that the PTSD-only group had significantly lower HF than did the group without PTSD and depression (p = .012).

Follow-up Pearson correlations within full and partial PTSD cases indicated that HF was not significantly associated with any specific symptom CAPS symptom domains (reexperiencing: r = −0.02, ns; avoidance: r = −0.001, ns; or arousal: r = 0.02, ns). A Pearson correlation also indicated that total CAPS scores were significantly positively correlated with BDI scores (r = 0.54, p < .001), even when participants with BDI and CAPS scores of zero were excluded from the correlation (n = 1655, r = 0.49, p < .001).

The 120 participants across all four cohorts who met the full diagnostic criteria for PTSD were compared with participants without full or partial PTSD (n = 2115) on the selected HRV

measures using independent-sample t tests. Levene tests for equality of variances were nonsignificant for all five HRV measures. Marines with PTSD had significantly lower RMSSD ($t(2210)$ = 2.2, p = .027, d = 0.21), lower LF ($t(2207)$ = 2.6, p = .010, d = 0.24), and lower HF ($t(2213)$ = 2.5, p = .013, d = 0.23) than did study participants without full or partial PTSD. The LF/HF ratio did not significantly differ among the two groups ($t(2217)$ = 0.82, ns, d = 0.08), nor did SDNN ($t(2218)$ = 1.7, p = .087, d = 0.16).

Relationship of HRV Variables to Covariates

The relationship between at least one of the selected HRV measures and the following variables reached statistical significance: cohort, age, ancestry, hours since nicotine use, BMI, history of TBI, psychotropic medication use, and history of deployments (Table 4). Because cohort had significant associations with many HRV variables, we consistently kept it in as a factor in our subsequent regression models. Variables associated with lower HRV included older age, nonwhite ancestry,
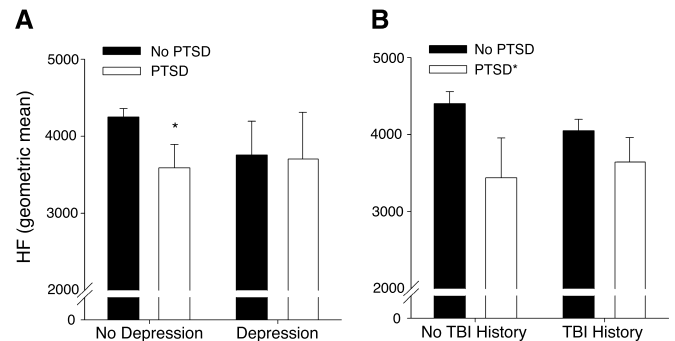

Figure 1. Mean high-frequency index in Marines with and without PTSD and depression or TBI, all cohorts combined. Note: Error bars are standard errors of the mean. Values in figure are back-transformed absolute HF means. A, * p < .050, PTSD only versus no PTSD/no depression in post hoc comparison with transformed HF values as the dependent variable. Sample sizes are as follows: no PTSD and no depression, n = 1965; PTSD only, n = 248; depression only, n = 124; and PTSD and depression, n = 64. PTSD refers to partial or full PTSD cases as determined by the CAPS. Depression refers to moderate/severe depression as determined by the BDI. B, * p < .050, main effect of PTSD versus no PTSD in ANOVA with transformed HF values as the dependent variable. Sample sizes are as follows: no PTSD and no TBI history, n = 981; PTSD and no TBI history, n = 87; no PTSD and TBI history, n = 1113; and PTSD and TBI history, n = 228. History of TBI refers to self-reported history of a head injury accompanied by either loss of consciousness or altered mental status. HF = high frequency; PTSD = posttraumatic stress disorder; TBI = traumatic brain injury; CAPS = Clinician-Administered PTSD Scale; BDI = Beck Depression Inventory; ANOVA = analysis of variance.
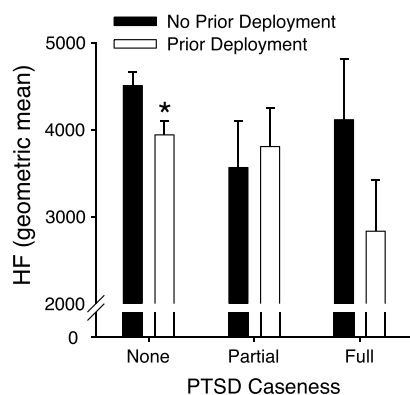
Figure 2. Mean HF index for no history of deployments versus deployment history in Marines with no PTSD, partial PTSD, and full PTSD, all cohorts combined. Note: Errors bars are standard errors of the mean. Values in figure are back-transformed absolute HF means. *$p < .050$ versus no PTSD/no prior deployment group using ANCOVA with transformed HF values as the dependent variable and age as a covariate. Sample sizes are as follows: no PTSD and no prior deployment, $n = 1031$; no PTSD and prior deployment, $n = 1063$; partial PTSD and no prior deployment, $n = 80$; partial PTSD and prior deployment, $n = 116$; full PTSD and no prior deployment, $n = 51$; and full PTSD and prior deployment, $n = 68$. See Results for details. HF = high frequency; PTSD = posttraumatic stress disorder; ANCOVA = analysis of covariance.

BMI, recency of nicotine use, and TBI history. Figure 1B displays back-transformed HF means of participants with no PTSD versus those with partial or full PTSD with and without a TBI history. There were small effect sizes for HRV differences between participants who were taking psychotropic medications and those who were not, such that psychotropic medication users had, on average, higher HRV. Finally, when age was used as a covariate, Marines with a history of deployment had significantly lower HF than did those without a deployment history. Although the deployment history-by-PTSD-group interaction was not statistically significant ($F(2,2402 = 0.72$, ns), planned comparisons indicated that HF was significantly lower in previously deployed participants without PTSD versus participants without PTSD who did not have a previous deployment ($p = .033$). This difference did not reach statistical significance in those with partial PTSD or full PTSD (Fig. 2). It is detailed in Figure 2 that the sample sizes for the comparisons in the partial and full PTSD groups were substantially smaller than those for the no PTSD comparisons. Figure 2 displays back-transformed HF means for Marines with and without a deployment history delineated by PTSD groups and adjusted for age.

DISCUSSION

We have described a relatively nonobtrusive and rapid methodology to assess, process, and analyze HRV in a large population of military service members who, because of their eventual deployment to combat zones, are at risk for developing stress-related conditions. Furthermore, we have tested the relationship between HRV and PTSD while accounting for a history of TBI and depression symptoms. TBI is highly prevalent in military service members of the recent conflicts in the Middle East, and the presence of TBI and PTSD together has been identified as the signature injury of these wars (48). The overlap between TBI and PTSD in military service members is further exemplified by

the recent observation that deployment-related TBI is a strong predictor of deployment-related PTSD (49). Furthermore, there are known effects of head injuries on HRV (albeit not strongly observed in our study; see below). Despite this knowledge, no study on PTSD and HRV in a military population has controlled for TBI history. The current results suggest that, even when a TBI history is accounted for, lower HRV is significantly associated with PTSD.

Depressive symptoms, however, were not related to HRV in this sample, and contrary to our hypothesis, the co-occurrence of PTSD and depressive symptoms was not associated with lower HRV than either condition alone, although PTSD symptom severity and depressive symptom severity were highly related. Rather, the group with PTSD in the absence of moderate or severe depressive symptoms had the lowest HRV. This finding is in contrast to what has been previously observed. Studies in nonmilitary trauma survivors suggest that a trauma history and depression interact in their influence on autonomic arousal; for example, the presence of depression with a trauma history was associated with lower respiratory sinus arrhythmia than either condition alone in women with a history of trauma related to crime, natural disaster, or assault (19). In a study of survivors of Hurricane Katrina, depression was more strongly associated with lower HRV than was PTSD (20), a finding in notable contrast to the current results. Although depression was not related to lower HRV in the current study, a history of deployment was, even in Marines without a PTSD diagnosis, reminiscent of a recent report of an association between combat exposure and decreased HRV (13). Thus, the relationships among depressive symptoms, trauma symptoms, and ANS function may vary depending on the population of trauma survivors and is highly dependent on the nature and context of the traumatic event.

Several factors could explain the absence of a relationship between depressive symptoms and HRV, one of which is the inherent limitation of a self-report instrument. Furthermore, our classification of BDI scores into just three categories, although necessary to achieve adequate sizes of groups, may have been too coarse to detect more subtle HRV differences. Lastly but importantly, the BDI is sensitive in capturing the severity of acute depressive symptoms but is less informative about the chronicity of depression. Most findings relating depression to HRV have been conducted on individuals with a chronic depression condition (7,19). Nevertheless, the current findings suggest that there remains a high co-occurrence of symptoms of depression with posttraumatic symptoms, which is an immediate public health concern in active-duty military personnel. The causal directions of these relationships have not been well elucidated.

Marines with a history of TBI with associated altered mental status or loss of consciousness demonstrated lower HRV, but the effect size for this finding was very small. The proportion of Marines reporting a previous TBI was relatively high (55.5%) but was consistent with the published characteristics of this cohort of Marines (27). Many of these cases are likely mild head injuries, given that either altered mental status or loss of consciousness was sufficient to identify a TBI. It is also important to note that participants were asked about a history of any head

injury, not solely those related to prior military deployments, which likely accounted for the high percentage of TBIs in this sample as compared with other studies (17). Head injury has been associated with alterations in the regulation of the cardiac system and lower HRV (18,50,51). Interestingly and potentially relevant to the current findings, HRV abnormalities in athletes with a recent concussion were only observed during an exercise session but not at rest (52). The severity of a TBI and time elapsed since the injury are also likely to be important factors in the normalization of HRV (51).

Other factors that were associated with HRV and are relevant to consider in future analyses with these cohorts included age, ancestry, BMI, and nicotine use. The relationship between age and HRV has been widely observed. The genetic determination of ancestry underscores previous observations that genetic factors are thought to contribute to a substantial proportion of the variance (13%-23%) in HRV, albeit less so than the combined influence of nongenetic variables such as age, sex, and environmental factors (53). BMI was only weakly related to one HRV measure, the HF index. BMI is known to be a relatively less reliable index of fat accumulation in athletes with high muscle mass (54). Active-duty Marines readying for deployment to a combat zone fall into this category. The high fitness levels and relative youth of these participants may also account for the higher values of HRV observed in this study compared with other published reports. Recent use of nicotine was related to lower HRV, supporting previous work indicating that nicotine use may alter autonomic functioning (24).

Mechanisms underlying lower HRV in PTSD have been postulated to reflect reduced vagal or parasympathetic tone (14). Diminished parasympathetic tone may accompany changes in amygdala and medial prefrontal cortex activation, brain regions that have been implicated in PTSD and are thought to underlie fear and threat responses (55,56). Changes in LF and HF have been associated with altered connectivity between the aforementioned brain regions and structures such as the anterior cingulate and insula that are implicated in orienting attention and vigilance (56,57). In any interpretation of findings related to LF, HF, and the LF/HF ratio, however, it is important to consider the following caveat. There has traditionally been an overreliance on these indices as being direct reflections of sympathetic/vagal balance. As Eckberg (4) reviews, parasympathetic contributions to LF are significant, changes in HF may not always be explained by changes in parasympathetic activity, and under certain conditions, sympathetic and parasympathetic changes occur in parallel to one another and not reciprocally. Thus, caution should be used in making firm conclusions about the physiological underpinnings of sympathetic versus parasympathetic functioning in the absence of rigorous experimental controls.

Other limitations of this study include a restricted age range and a lack of female participants, limiting the generalizability of our findings to a relatively young, athletic group of males. This sample is, we would argue, highly representative of US service members currently at greatest risk for combat-related PTSD. Another limitation is that there were small but significant differences ($\eta_p^2 = 0.003$-0.054) between cohorts in HRV and other demographic variables that may have been due to chance or may have been attributable to a number of random factors such as differences in season of testing, individual battalion demographics, and physical training courses leading up to or before the data collection. The relationship between HRV measures and PTSD caseness, however, was robust enough to be significant even when controlling for cohort. Several potential experimental factors that can affect HRV are relevant to mention. First, participants were asked to attend to video images of hidden pictures. Previous studies have reported cardiac deceleration during reaction time and response inhibition tests (see Ref. (58) for a summary). Although participants in this study were told that they would not be required to respond to the visual images, the paradigm could arguably represent a cognitive challenge that affected HRV. We cannot entirely rule out that cognitive activity may have affected HRV, which would be a consistent phenomenon across all participants in the study. Second, no measure of respiration was obtained during HRV assessment, which is a notable limitation because changes in breathing rates are directly related to respiratory sinus arrhythmia (3) and can also be associated with different mood states, for example, higher respiratory rates in anxious patients (59). The collection of large sample sizes of Marines in short time frames rendered PPG a practical rapid method as opposed to use of ECG Holter monitors plus respiratory band application and recordings. Thus, we were not able to assess to what extent breathing rates in participants with PTSD may have moderated HRV. A final limitation is that this study is cross sectional; however, prospective analysis of these cohorts upon return from deployment and after onset of PTSD symptoms is ongoing.

In conclusion, we have described our methodology for the collection and analysis of short-term HRV in a large population of Marines readying for deployment. Lower HRV was observed in participants with full or partial PTSD diagnoses at the predeployment MRS time frame, even when TBI history was accounted for. Previous deployments were associated with lower HRV, whereas depression was not, but depression was more strongly related to PTSD than it was to HRV. Future longitudinal analyses of these military service members will include the consideration of the HRV factors and covariates elucidated here. The ultimate aim of this research is to uncover whether ANS functions can predict who is vulnerable and who is resilient, or whether ANS functions emerge in tandem with mental health effects of combat exposure.

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