REM Sleep Measures and REM Vagal Activity Predict Extinction Recall in Trauma-Exposed Individuals

Cagri Yuksel, MD*[1,2], Lauren Watford[1], Monami Muranaka[1], Hannah Lax[1, 4], Augustus Kram Mendelsohn[3, 4], Katelyn I. Oliver[3, 4], Caroline Daffre[3, 4], Alexis Acosta[3, 4], Abegail Vidrin[3, 4], Uriel Martinez[3, 4], Natasha Lasko[2,5], Edward F. Pace-Schott[2,3,4]

1. McLean Hospital, Belmont, MA.
2. Department of Psychiatry, Harvard Medical School, Boston, MA.
3. Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA.
4. Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA
5. Department of Psychiatry, Massachusetts General Hospital, Boston, MA

*Corresponding Author:
Cagri Yuksel, MD

McLean Hospital
AB S342
115 Mill Street, Belmont, MA. 02478
ayuksel@mgb.org

ABSTRACT

Accumulating evidence suggests that rapid eye movement sleep (REM) supports the consolidation of extinction memory. REM is disrupted in PTSD, and REM abnormalities after traumatic events increase the risk of developing PTSD. Therefore, it was hypothesized that abnormal REM in trauma-exposed individuals may pave the way for PTSD by interfering with the processing of extinction memory. In addition, PTSD patients display reduced vagal activity. Vagal activity contributes to the strengthening of memories, including fear extinction memory, and recent studies show that the role of vagus in memory processing extends to memory consolidation during sleep. Therefore, it is plausible that reduced vagal activity during sleep in trauma-exposed individuals may be an additional mechanism that impairs extinction memory consolidation. However, to date, the contribution of sleep vagal activity to the consolidation of extinction memory or any emotional memory has not been investigated. To test these hypotheses, we examined the association of extinction memory with REM characteristics and REM vagal activity (indexed as high-frequency heart rate variability; HF-HRV) in a large sample of trauma-exposed individuals (n=113). Consistent with our hypotheses, REM sleep characteristics (increased REM density and shortened REM latency) were associated with poorer physiological and explicit extinction memory. Furthermore, higher HF-HRV during REM was associated with better explicit extinction memory. These findings support the notion that disrupted REM may contribute to PTSD by impairing the consolidation of extinction memory and indicate the potential utility of interventions that target REM sleep characteristics and REM vagal activity in fear-related disorders.

INTRODUCTION

PTSD is characterized by excessive fear responses to cues associated with a traumatic event. It is hypothesized that this is due to dysfunction in fear extinction, the process whereby fear response is gradually reduced after multiple exposures to a conditioned stimulus (CS) without reinforcement [1,2]. After a traumatic event, fear extinction is achieved by repeated exposure to reminders of the traumatic event without the feared outcome. This mechanism is suggested to be the basis of exposure therapy for PTSD and other anxiety disorders [3].

Fear extinction is not simply an erasure of fear but relies on new learning and memory. While the preponderance of studies does not show impaired extinction learning in PTSD (reviewed in [4,5], accumulating evidence suggests that impaired retention of extinction memory, acquired after trauma exposure [6], may be a critical mechanism that leads to PTSD [1,6-11]. Sleep supports the consolidation of different types of memories, which stabilizes and integrates them, and enhances their retrieval [12]. Recent evidence suggests that this extends to extinction memory, with rapid eye movement sleep (REM) implicated as an important sleep stage involved in its consolidation [13]. In healthy people, more REM has been shown to be associated with better extinction recall [14-17], and REM deprivation leads to impaired extinction memory [18], suggesting the possibility of a causal role for this sleep stage. Several studies and meta-analyses find REM abnormalities in PTSD [19-21], which also have been shown to be associated with the risk of developing PTSD after trauma [22-24]. Therefore, it is postulated that sleep disruption, specifically of REM, may predispose traumatized individuals to develop PTSD symptoms by interfering with extinction memory [4,25]. Supporting this hypothesis, in a sample overlapping that of the current report, we showed that prefrontal activations during extinction recall were associated with REM density during the night before extinction recall [26]. However, much remains to be learned regarding the association between REM and extinction memory in trauma-exposed individuals. One preliminary study [27] did not find any association of REM with extinction recall in PTSD; however, the small sample size (n=13) may explain this negative finding. This study's sample was also limited to those with PTSD diagnoses and, therefore, did not provide insight into this association in individuals with subthreshold PTSD symptoms. To address this gap in knowledge, we examine here the association of REM measures on the night following extinction learning with extinction recall the following day in a large sample of trauma-exposed individuals. We hypothesized that disruptions in REM sleep would be associated with impaired extinction recall (hypothesis 1).

PTSD is characterized by abnormal autonomic nervous system function, including reduced parasympathetic nervous system (PNS) activity [28]. PNS activity can be estimated by measuring heart rate variability (HRV), the variation in the interval between successive heartbeats. Specific HRV measures in the frequency (high frequency; HF-HRV) and time (root mean square of successive differences in the R–R interval; RMSSD) domains reflect control of

heart rate by the vagus nerve, the main component of PNS outflow from the CNS [29,30]. Meta-analyses show that patients with PTSD display reduced vagal activity, as indexed by HF-HRV and RMSSD, during wakefulness [31-33], and in one study, lower baseline HF-HRV predicted the severity of later post-traumatic stress symptoms [34]. Similar to wakefulness, a small number of recent studies in sleep find reduced vagal activity in PTSD [35], including in specific sleep stages [36,37]. Additionally, in one study, HF-HRV across actigraphically measured sleep was associated with PTSD symptom severity [38].

Converging evidence indicates that vagal activity facilitates emotional processing and memory, likely via its afferents to the brainstem nuclei, which in turn modulate the activity of multiple neurotransmitter systems and relevant brain regions, including the prefrontal cortex (PFC), amygdala, and hippocampal formation, among others [39,40]. Consistent with this, high vagal tone is associated with better extinction learning in humans [41-43], and enhancing vagal activity improves extinction learning and retention of extinction memory in both rodents [44-48] and humans [49-51]. In addition, a separate line of recent studies shows that vagal activity during sleep, as indexed by HF-HRV, independently contributes to memory consolidation over and above contributions by sleep architecture and sleep-related brain oscillations [52,53]. However, no study to date has examined the role of vagal activity in the sleep-dependent consolidation of extinction memory in any population. We thus hypothesized that lower HF-HRV in REM during the night following extinction learning would independently predict lower extinction recall in trauma-exposed individuals (hypothesis 2).

METHODS

Participants

A total of 139 participants, aged between 18 and 40, were recruited from the greater Boston metropolitan area using online and posted advertisements. All participants reported experiencing a DSM-5 criterion-A traumatic event ("index trauma") in the past two years, except within the last month. Further inclusion and exclusion criteria can be found in previous publications [26,36,54], and Supplementary Materials. 26 participants were excluded from all analyses because of missing or unusable EEG or ECG data (final n=113). History of psychiatric disorders was ascertained using the Structured Clinical Interview for DSM-IV-TR for Non-Patients (SCID-I/NP) [55]. 49.6% (n=56) met diagnostic criteria for PTSD. This study followed a Research Domain Criteria (RDoC) [56] design in which dimensional rather than categorical measures were targeted, and PTSD diagnoses were established post-hoc from diagnostic evaluations, rather than by assigning subjects to PTSD and non-PTSD groups. The PTSD Checklist for DSM-5 (PCL-5) [57] was used to assess post-traumatic stress symptom severity (see **Figure S1** for its distribution in the sample). The Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR)[58] and the Pittsburg Structured Clinical Interview for Sleep Disorders (SCID-SLD) [59] were administered to evaluate depressive and sleep disorder

symptoms, respectively. Demographic and clinical characteristics of the final sample are displayed in **Table 1**. All participants provided written consent to participate in the study and were paid for their participation. All procedures were approved by the Partners Healthcare Institutional Review Board.

Procedures

Participants completed an approximately 2-week sleep assessment period during which they wore an actigraph (Actiwatch-2, Philips Respironics) and filled out a daily sleep and nightmare diary. Approximately midway through the 14-day period, they underwent a combined sleep-disorders-screening and acclimation night of ambulatory polysomnography (PSG) recording. This was followed by a "baseline" overnight PSG recording. Starting on the evening immediately after the baseline night, participants completed a 2-day fear conditioning and extinction protocol with simultaneous fMRI recordings. Between fMRI sessions, participants completed a third ("consolidation") night of ambulatory PSG. Details of the PSG methods are included in the Supplementary Methods.

Fear conditioning, extinction learning, and extinction recall

A validated 2-day paradigm [60,61] was used to probe fear conditioning and extinction during ongoing fMRI recording. This protocol consisted of 4 phases, with Habituation, Fear Conditioning, and Extinction Learning phases taking place on the first day and Extinction Recall 24 hours later. Images of a colored desk lamp (red, yellow, or blue) appearing in a conditioning and extinction-context background served as conditioned stimuli (CS). During fear conditioning, a mild electric shock was paired with the presentation of 2 differently colored lamps (CS+) but not a third color (CS-). During extinction learning, one CS+ (CS+E) but not the other (CS+U) was extinguished using presentations without any electric shock. During each phase, physiologic reactivity for each trial was indexed using skin conductance response (SCR), a measure of sympathetic activity [62]. Negative SCRs were coded as zero [63], and then all values were square root transformed. "Non-conditioners" were defined as those who exhibited less than two non-square-root transformed SCR responses to either of the two CS+s that were equal to or exceeding .05 µS during the Fear Conditioning phase [64]. Thirty-one non-conditioners were further excluded from SCR analyses based on these criteria. In addition, SCR data for 3 participants were lost.

Immediately following each phase except Habituation, participants verbally reported shock expectancy for the first and last presentations of each CS (i.e., colored light) appearing in that phase on a scale from 1 ("not expecting a shock at all") to 5 ("expecting a shock very much"). Further details of the protocol and skin conductance monitoring are provided in previous publications [16,65] and in Supplementary Materials.

Extinction Recall Variables

To examine the association of physiologically expressed and subjective extinction recall with sleep and HRV measures, we used an Extinction Retention Index (ERI) [66] and a Subjective Extinction Retention Index (sERI) [16], respectively. ERI was calculated as: [(Average of the SCRs of the first 4 CS+E presentations at Extinction Recall phase/maximum SCR to a CS+ during the Fear Conditioning phase) x 100]. Only the first 4 CS+E trials were included in this calculation in order to avoid confounding recalled extinction with new extinction learning occurring during the Extinction Recall phase. Higher ERI reflected lower extinction memory. sERI was calculated as: Expectancy to the first CS+E in Extinction Recall/mean expectancy for the last of each CS+ during Fear Conditioning × 100. Larger sERI indicated lower extinction memory. These indices were selected to align with our previous publications, acknowledging that different extinction indices may not intercorrelate [66].

Sleep Measures

The PSG data analyzed in the present study were recorded during the consolidation night. For regression analyses, we selected the REM measures that have been associated with PTSD, including %REM [20], REM density (REMD) [19], REM fragmentation (REMF) [22,67-71], and REM latency (REML) [72]. These measures were calculated as follows: Percent time spent in each sleep stage (%N1-N3, %REM) was computed as a percentage of total sleep time (TST); REML was calculated as the number of minutes occurring after sleep onset before the first REM epoch. REMD is the number of rapid eye movements per minute of REM sleep and was calculated using an automatic algorithm [73]. REMF was calculated as the average duration of REM segments [22]. REM segments were defined as continuous REM from the start of at least 1 minute of REM to the onset of at least 1 minute of non-REM or wake [22].

Heart Rate Variability

HRV was calculated in continuous ECG segments of ≥5 minutes within REM (REM-HRV) using Kubios HRV premium software (Kubios Oy, Kuopio, Finland). Prior to analysis, ECG traces were visually inspected, and artifacts were removed. Segments that did not provide reliable estimates due to excessive artifacts were excluded from the analysis. High frequency (.15-.4 Hz) absolute power (HF[ms^2]) and relative power (HF[%]), as well as RMSSD, were calculated. For frequency domain analyses, default settings of Welch's periodogram method (window width=300 seconds, 50% overlap) for fast Fourier transformation (FFT) were used. HF[%] is the relative power with respect to the total power (HF[ms^2]/total power[ms^2] × 100%). HF[%] was used as a predictor variable in the hierarchical regression analyses because this measure takes into account the inter-individual variability in the full frequency range of HRV [30], including in the low and very low-frequency bands, which have also been found to be associated with PTSD and memory [74,75].

Statistical Analyses

Associations were explored between extinction recall indices (ERI and sERI), and age, sex, months since index trauma, scores of symptom scales (PCL-5 and QIDS), and medication (antidepressants or benzodiazepines) use. For correlations, Pearson and Spearman's correlations were used depending on the distribution of variables. Student's t-tests were used for comparisons between sexes and between medication users and non-users.

We used linear regression models to test whether REM sleep variables predicted extinction recall (Hypothesis 1). For this purpose, we carried out separate analyses with ERI and sERI as dependent variables. The models included REM%, REMD, REMF, and REML as predictor variables. Because sex and age were associated with log-transformed ERI (see below) and sERI, respectively, they were also included in the respective models.

Next, hierarchical regression analyses were used to test the hypothesis that vagal activity would improve the predictions of sERI and ERI above and beyond REM sleep measures alone (Hypothesis 2). For this purpose, two models were built. Model 1 included REM measures (and sex or age), and HF[%] was added as an additional predictor in Model 2.

In all regression analyses, partial regression plots and a plot of studentized residuals against the predicted values indicated that assumptions of linear relationship were met. Variance inflation factors were within acceptable ranges (1.1-1.6), indicating that there was no multicollinearity. For ERI, the distribution histogram and P-P plot of standardized residuals showed a non-normal distribution. In addition, plotting standardized residuals and predictors revealed heteroscedasticity. Therefore, ERI was log-transformed. After transformation, normal distributions of residuals and homoscedasticity were confirmed. Residuals for sERI analyses showed normal distribution and homoscedasticity.

For all variables, outliers ± 3 standard deviations from the mean were removed. All analyses were two-tailed. The significance level for hypothesis testing (α) was set at .05.

RESULTS

Association of Extinction Recall Indexes with Demographic and Clinical Measures

Age was negatively correlated with sERI (r_s= -.25, p=.006), while it was not significantly correlated with ERI (r_s= .11, p=.290). There was a strong trend for the log-transformed ERI to be significantly higher in males (t(83)=1.97, p=.052). There were no significant correlations between extinction recall indices and the number of months since index trauma (ERI: r_s= -.003, p=.980; sERI: r_s= -.06, p=.584), or PCL-5 (ERI: r_s= -.009, p=.938; sERI: r_s=.01, p=.896) or QIDS (ERI: r_s= -.05, p=.707; sERI: r_s= -.01, p=.927) scores. Medication (antidepressants or

benzodiazepines) use was also not associated with extinction recall (ERI: t(76)=.83, p=.934; sERI: t(101)=-.31, p=.756).

Regression Analyses Predicting ERI and sERI

Measures of REM characteristics and sleep architecture are displayed in **Table 2**. The multiple regression model with log-transformed ERI as the dependent variable included REM%, REML, REMD, REMF, and sex, as predictor variables. The overall model explained a significant proportion of the variance (Adj. R^2=.14, p=.021)**,** with sex, REMD, and REML emerging as significant predictors (**Table 3**). Poorer physiological extinction recall was associated with the male sex (β=.33, p=.020), increased REMD (β=.31, p=.020), and shorter REML (β=.38, p=.007).

A similar multiple regression model with subjective extinction recall (sERI) as the dependent variable included the same REM measures, as well as age, as predictor variables. This model also explained a significant proportion of the variance (Adj. R^2=.14, p=.004). In this model, REMD was the only significant predictor (**Table 4**), and as with ERI, increased REMD was associated with poorer subjective extinction recall (β=.34, p=.002).

Hierarchical regressions with HF HRV predicting ERI and sERI

Average HRV values are displayed in **Table 2**. For the hierarchical regression analyses with log-transformed ERI as the dependent variable, REM sleep measures (REM%, REML, REMD, REMF) and sex were included in the first model. In the second model, REM-HF[%] was added to the predictors. Addition of REM-HF[%] did not lead to a significant increase in the variance accounted by the model ($\Delta R^2=1.2x10^{-4}$, p=.936), indicating that vagal activity did not contribute to the prediction of physiological extinction recall beyond REM sleep measures.

A similar hierarchical regression analysis was carried out for sERI. The first model included the same REM variables and age, and REM-HF[%] was added to the predictors in the second model. Addition of REM-HF[%] led to a significant increase in the variance accounted for by the model (ΔR^2=.06, p=.046), indicating that vagal activity contributed to the prediction of subjective extinction recall above and beyond REM sleep measures. The final model was significant (Adj. R^2=.17, p=.021), and REMD and REM-HF[%] emerged as significant predictors. Poorer subjective extinction recall was associated with higher REMD (β=.29, p=.018) and lower REM-HF[%] (β=.25, p=.009) **(Table 5)**.

For completeness, we repeated the same hierarchical regression analyses by adding other REM HRV measures (REM-HF[ms^2] or REM-RMSS) instead in the second model. In these exploratory analyses, the addition of HRV parameters did not significantly increase the variation explained. However, the effects of other REM-HRV measures on sERI, as indicated by the standardized coefficients (β), were in the same direction as REM-HF[%] (Supplementary Tables S3 and S4).

DISCUSSION

We investigated the association of REM measures with the consolidation of physiological and subjective extinction memory in a large sample of trauma-exposed individuals. Confirming our first hypothesis, we found that shorter REML and higher REMD independently predicted poorer physiological extinction recall. Similarly, poorer subjective extinction recall was predicted by high REMD. Furthermore, our second hypothesis, that higher HF HRV during REM would predict greater extinction recall above and beyond REM measures was supported for subjective extinction recall. To the best of our knowledge, this is the first study to show that features of REM are associated with the consolidation of extinction memory in trauma-exposed individuals. In addition, we show here for the first time that vagal activity during a specific sleep stage contributes to the consolidation of an emotional memory.

REM measures predicting extinction recall is in agreement with previous research in healthy individuals [13,76] and in insomnia disorder [16]. In healthy individuals, better extinction recall was associated with the presence of REM during a nap [14], higher overnight %REM [17], less fragmented REM, and increased REM theta power [16]. In addition, late-night (REM-rich) sleep but not early-night sleep benefited extinction memory [15], and selective REM, but not NREM, deprivation impaired extinction recall [18]. In contrast, among individuals with insomnia disorder [16], better extinction recall was associated with less %REM, shorter REM bouts, and longer REML. Findings are also in agreement with the general notion that REM is involved in processing emotional memories [77], although it is not backed by consistent evidence [78].

We further showed that specific REM features were independently associated with extinction recall. There is a sizable literature that implicates both REML and REMD in a variety of psychiatric disorders, including PTSD [79]. However, in PTSD, alterations in these variables are not consistently found, and the direction of change shows variability across studies, possibly due to the heterogeneity in samples and the settings in which data are collected [19,20,79]. It was also proposed that two competing processes may be at play simultaneously, REM dysregulation and the resulting pressure to achieve REM (Mellman 1997), which would explain the contradictory findings across studies (e.g., shorter or longer REML, depending on which of these processes predominate). Nonetheless, shortened REML and increased REMD have emerged as characteristics of PTSD in meta-analyses [19,20,79]. Our findings advance insight into the significance of these REM alterations and indicate that they are associated with impaired extinction memory, a mechanism that is considered central to the development of PTSD [5].

The mechanisms underlying REM alterations in PTSD and, by extension, how they might be associated with impaired extinction recall are not clear. However, it was proposed that hyperarousal, characterized by impairment in the inhibitory control of amygdala activity by the medial PFC (mPFC) with a concomitant increase in noradrenergic activity, contributes to REM dysregulation [4,80,81]. Indeed, increased REMD may be a direct manifestation of hyperarousal

in PTSD [82]. Rapid eye movements are associated with activation in the limbic and paralimbic structures [83-88], as well as heart rate surges [89] and nightmares concurrent with autonomic arousal [90]. Furthermore, in an overlapping sample, we recently showed that REMD was one of the predictors of self-reported hyperarousal symptoms in trauma-exposed individuals [36]. Therefore, our results suggest that hyperarousal during REM interferes with the consolidation of extinction memory. On the other hand, REML has been considered an indicator of REM pressure, and the shortening of REML in PTSD has been attributed to an "unmet need" due to shortening or fragmentation of REM [91]. This interpretation would suggest that a history of insufficient REM or a latent factor associated with a REM deficit may impair the consolidation of extinction memory. Although the measures that directly reflect REM length and fragmentation (%REM and REMF) were not significantly associated with extinction recall, it is plausible that arousals were not captured by these measures. Alternatively, this association may be due to an adaptive REM enhancement to facilitate emotional processing [91]. Yet another possibility is that shortened REML may reflect depression [92]. However, self-reported depressive symptoms were not correlated with REML (r_s=.05, p=.65) or ERI (r_s=.02, p=.86). Finally, a more speculative possibility is that shortened REML may disrupt the sequential organization of NREM-REM segments and thus impair memory consolidation [93-95].

Vagal activity during REM, indexed as HF HRV, was a significant predictor of subjective extinction recall. This novel finding is consistent with the role of the vagal nerve in supporting memory formation [39] and emotional regulation [96], as well as the growing body of evidence indicating that vagal activity is causally involved in fear processing [44,45,97]. Vagal activity in response to cognitive and emotional demands and vagally mediated HRV are considered to reflect the tonic inhibitory control of the amygdala by the mPFC [98,99], circuitry that is also critical for fear extinction [1]. Consistent with this, high vagal activity during wake was repeatedly shown to be associated with better fear extinction in humans [41-43,100]. Furthermore, vagal nerve stimulation (VNS) facilitated plasticity in ventromedial PFC-amygdala connectivity in rodents [44], and improved extinction learning and recall in both rodents [44-46,48,97,101-105] and humans [49-51,106]. Our results suggest that the contribution of vagal activity continues beyond extinction learning to its consolidation during sleep and supports the potential utility of interventions that can enhance sleep vagal activity in the prevention and treatment of fear-related disorders [107].

We found an association of HRV with extinction recall measured as expectancy ratings but not SCR, which is at odds with the findings in rodents [44,45]. Notably, a similar distinction has been observed in some of the previous studies in humans, which used VNS during extinction training and found an improvement in extinction learning indexed by expectancy ratings but not SCR or blink startle response [50,106]. It was proposed that vagal activity modified the hippocampus-mediated declarative aspect of extinction memory but not the amygdala-mediated "emotional load" [50,108]. However, a later study found VNS-related improvement in both expectancy ratings and startle response [49] and speculated that differential-cue conditioning,

such as that used in our study, may be the reason for this discrepancy. Further studies are needed to clarify the boundary conditions of vagally mediated extinction memory.

Our study had several limitations. First, we had to exclude a substantial number of participants because of lost or unusable sleep data. Our study employed ambulatory recordings, which allow capture of sleep characteristics in ecologically valid settings. However, lack of oversight during the recording can lead to more artifacts and data loss than in laboratory studies. Second, there is significant variability across studies in fear conditioning/extinction protocols and methods in analyzing generated data [63]. Nonetheless, we used the widely employed Milad et al. 2007 fear conditioning and extinction protocol [1], and we attempted to be consistent with our own and others' previously used metrics to index extinction recall. Third, SCR as a measure of fear response has its inherent limitations, including habituation, which can confound the extinction data. To avoid this and still remain consistent with the literature, we used only the initial trials from the Extinction Recall phase and applied range correction using the maximum SCR produced during the Conditioning phase. Fourth, a portion of our sample did not achieve physiological fear conditioning and was therefore excluded from the analysis. Nonetheless, the proportion of "non-conditioners" in our sample (49/139, 35%) was smaller than in many previous studies [109]. In addition, we found similar results with the expectancy ratings in a sample that included all the participants for whom we had the REM measures. A strength of our study is the large sample size. Many of the prior studies linking REM features to emotional processing in general and extinction, in particular, were based on small sample sizes, a limitation that reduces statistical power and can lead to Type 1 error and overestimation of effect sizes [110]. Therefore, analyses of larger samples, such as the current study, are important next steps in testing such hypotheses [111,112].

Conclusions

Abnormalities in REM have repeatedly been reported in individuals diagnosed with PTSD and have been shown to be associated with an increased risk of developing PTSD after a traumatic event. Results of this study further our insight into the role of REM disruptions and indicate that they are associated with impaired consolidation of extinction memory, a mechanism proposed to be critical in the pathogenesis of PTSD.

Age	24.0±4.8 (18-39)
Sex (%female)	69.9%
Race (%)	
American Indian or Alaskan Native	2.7%
Asian	9.8%
Black or African-American	16.8%
More than one race	6.2%
Unknown/unreported	1.8%
White	62.9%
Ethnicity	
Hispanic or Latino	9.7%
Not Hispanic or Latino	85%
Unknow/unreported	3.5%
Type of trauma	
Transportation accident	26.5%
Violent assault	19.5%
Rape or sexual assault	17.7%
Mass shooting	2.7%
Sudden loss of family or friend	4.5%
Combat incident	2.7%
Multiple or other	26.4%
Trauma Severity	
PCL-5	29.5±15.4 (0-69)
Depression Severity	
QIDS	7.4±4.4 (0-18)
Months since trauma	13.0±6.8 (1-28)
Medications	
Antidepressants	18.6%
Benzodiazepines	3.5%
Antidepressants or Benzodiazepines	19.5%
Beta-blockers	0%
Mood stabilizers	0%
Antipsychotics	0%

Table 1. Demographic and clinical characteristics of the participants. Some of the data is displayed as mean ± standard deviation (minimum - maximum).

REMD	6.6±4 (1.0-20.9)
REML	102.3±45.9 (0-238.0)
REMF	9.8±4.0 (2.8-23.4)
%N1	5.7±3.8 (0.8-27.0)
%N2	54.5±9.3 (26-81.7)
%N3	21.7±10.6 (1.7-63.3)
%REM	18.3±6.5 (2.0-35.0)
REM-HF[%]	17.5±9.0 (1.9-45.9)
REM-HF[ms^2]	1173.5±1068 (36.9-4620.5)
REM-RMSSD	54.3±26.8 (13.0-128.3)

Table 2. Sleep and HRV measures in the participants. Data is displayed as mean ± standard deviation (minimum - maximum).

								Model ANOVA		
Predictors	**B**	**SE**	**β**	**t**	**p**	**95% CI**		**Adj. R^2**	**F**	**p**
Sex	-0.33	0.14	-0.33	-2.40	**0.020**	-0.60	-0.05	0.14	2.91	**0.021**
%REM	-0.02	0.01	-0.22	-1.53	0.132	-0.04	0.01			
REMD	0.04	0.02	0.31	2.39	**0.020**	0.01	0.07			
REML	0.00	0.00	-0.38	-2.81	**0.007**	-0.01	0.00			
REMF	0.03	0.02	0.21	1.50	0.140	-0.01				

Table 3. Linear regression analysis with ERI as the dependent variable. Overall model was significant, with sex, REMD and REML emerging as significant predictors.

								Model ANOVA		
Predictors	**B**	**SE**	**β**	**t**	**p**	**95% CI**		**Adj. R^2**	**F**	**p**
Age	-0.61	0.62	-0.1	-0.98	0.329	-1.86	0.63	0.14	3.79	**0.004**
%REM	-0.01	0.61	0	-0.02	0.984	-1.22	1.2			
REMD	2.41	0.74	0.34	3.24	**0.002**	0.93	3.89			
REML	0.05	0.07	0.08	0.66	0.51	-0.1	0.19			
REMF	1.44	0.89	0.2	1.63	0.108	-0.32	3.21			

Table 4. Linear regression analysis with sERI as the dependent variable. Overall model was significant, with REMD emerging as the only significant predictor.

Model	Predictors	B	SE	β	t	p	95% CI						
1	**Age**	-0.20	0.75	-0.03	-0.27	0.788	-1.69	1.29					
	%REM	-0.18	0.68	-0.04	-0.26	0.795	-1.55	1.19					
	REMD	2.65	0.93	0.34	2.85	0.006	0.79	4.51					
	REML	0.00	0.09	0.00	0.03	0.975	-0.18	0.19					
	REMF	2.22	1.06	0.29	2.09	0.041	0.09	4.34					
										Change		**ANOVA**	
									Adj. R^2	**ΔF**	**Δp**	**F**	**p**
2	**Age**	-0.33	0.73	-0.05	-0.45	0.653	-1.79	1.13	0.17	4.17	**0.046**	3.19	**0.009**
	%REM	0.05	0.68	0.01	0.07	0.944	-1.30	1.40					
	REMD	2.42	0.91	0.31	2.66	**0.010**	0.60	4.25					
	REML	-0.02	0.09	-0.02	-0.18	0.859	-0.20	0.17					
	REMF	1.81	1.05	0.23	1.72	0.091	-0.30	3.92					
	REM-HF[%]	-0.89	0.44	-0.25	-2.04	**0.046**	-1.77	-0.02					

Table 5. Hierarchical regression analysis with sERI as the dependent variable. Addition of REM-HF[%] significantly increased the proportion of variance explained by the model.

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References

1 Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. Annu Rev Psychol. 2012;63:129-51.

2 Zuj DV, Palmer MA, Lommen MJ, Felmingham KL. The centrality of fear extinction in linking risk factors to PTSD: A narrative review. Neurosci Biobehav Rev. 2016;69:15-35.

3 Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: an inhibitory learning approach. Behav Res Ther. 2014;58:10-23.

4 Pace-Schott EF, Seo J, Bottary R. The influence of sleep on fear extinction in trauma-related disorders. Neurobiol Stress. 2023;22:100500.

5 Bottary R, Straus LD, Pace-Schott EF. The Impact of Sleep on Fear Extinction. Curr Top Behav Neurosci. 2023.

6 Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL, Pitman RK. Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. J Psychiatr Res. 2008;42(7):515-20.

7 Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009;66(12):1075-82.

8 Shvil E, Sullivan GM, Schafer S, Markowitz JC, Campeas M, Wager TD, et al. Sex differences in extinction recall in posttraumatic stress disorder: a pilot fMRI study. Neurobiol Learn Mem. 2014;113:101-8.

9 Helpman L, Marin MF, Papini S, Zhu X, Sullivan GM, Schneier F, et al. Neural changes in extinction recall following prolonged exposure treatment for PTSD: A longitudinal fMRI study. Neuroimage Clin. 2016;12:715-23.

10 Suarez-Jimenez B, Albajes-Eizagirre A, Lazarov A, Zhu X, Harrison BJ, Radua J, et al. Neural signatures of conditioning, extinction learning, and extinction recall in posttraumatic stress disorder: a meta-analysis of functional magnetic resonance imaging studies. Psychol Med. 2020;50(9):1442-51.

11 Wicking M, Steiger F, Nees F, Diener SJ, Grimm O, Ruttorf M, et al. Deficient fear extinction memory in posttraumatic stress disorder. Neurobiol Learn Mem. 2016;136:116-26.

12 Klinzing JG, Niethard N, Born J. Mechanisms of systems memory consolidation during sleep. Nat Neurosci. 2019;22(10):1598-610.

13 Davidson P, Pace-Schott E. The role of sleep in fear learning and memory. Curr Opin Psychol. 2020;34:32-36.

14 Spoormaker VI, Sturm A, Andrade KC, Schroter MS, Goya-Maldonado R, Holsboer F, et al. The neural correlates and temporal sequence of the relationship between shock exposure, disturbed sleep and impaired consolidation of fear extinction. J Psychiatr Res. 2010;44(16):1121-8.

15 Menz MM, Rihm JS, Buchel C. REM Sleep Is Causal to Successful Consolidation of Dangerous and Safety Stimuli and Reduces Return of Fear after Extinction. J Neurosci. 2016;36(7):2148-60.

16 Bottary R, Seo J, Daffre C, Gazecki S, Moore KN, Kopotiyenko K, et al. Fear extinction memory is negatively associated with REM sleep in insomnia disorder. Sleep. 2020;43(7).

17 Pace-Schott EF, Tracy LE, Rubin Z, Mollica AG, Ellenbogen JM, Bianchi MT, et al. Interactions of time of day and sleep with between-session habituation and extinction memory in young adult males. Exp Brain Res. 2014;232(5):1443-58.
18 Spoormaker VI, Schroter MS, Andrade KC, Dresler M, Kiem SA, Goya-Maldonado R, et al. Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. Hum Brain Mapp. 2012;33(10):2362-76.
19 Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44(4):660-9.
20 Zhang Y, Ren R, Sanford LD, Yang L, Zhou J, Zhang J, et al. Sleep in posttraumatic stress disorder: A systematic review and meta-analysis of polysomnographic findings. Sleep Med Rev. 2019;48:101210.
21 Richards A, Kanady JC, Neylan TC. Sleep disturbance in PTSD and other anxiety-related disorders: an updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms. Neuropsychopharmacology. 2020;45(1):55-73.
22 Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. Am J Psychiatry. 2002;159(10):1696-701.
23 Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. Biol Psychiatry. 2004;55(9):953-6.
24 Mellman TA, Pigeon WR, Nowell PD, Nolan B. Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. J Trauma Stress. 2007;20(5):893-901.
25 Colvonen PJ, Straus LD, Acheson D, Gehrman P. A Review of the Relationship Between Emotional Learning and Memory, Sleep, and PTSD. Curr Psychiatry Rep. 2019;21(1):2.
26 Seo J, Oliver KI, Daffre C, Moore KN, Gazecki S, Lasko NB, et al. Associations of sleep measures with neural activations accompanying fear conditioning and extinction learning and memory in trauma-exposed individuals. Sleep. 2022;45(3).
27 Straus LD, Norman SB, Risbrough VB, Acheson DT, Drummond SPA. REM sleep and safety signal learning in posttraumatic stress disorder: A preliminary study in military veterans. Neurobiol Stress. 2018;9:22-28.
28 Seligowski AV, Webber TK, Marvar PJ, Ressler KJ, Philip NS. Involvement of the brain-heart axis in the link between PTSD and cardiovascular disease. Depress Anxiety. 2022;39(10-11):663-74.
29 Laborde S, Mosley E, Thayer JF. Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. Front Psychol. 2017;8:213.
30 Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017;5:258.
31 Schneider M, Schwerdtfeger A. Autonomic dysfunction in posttraumatic stress disorder indexed by heart rate variability: a meta-analysis. Psychol Med. 2020;50(12):1937-48.
32 Ge F, Yuan M, Li Y, Zhang W. Posttraumatic Stress Disorder and Alterations in Resting Heart Rate Variability: A Systematic Review and Meta-Analysis. Psychiatry Investig. 2020;17(1):9-20.
33 Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. Front Psychiatry. 2014;5:80.

34 Pyne JM, Constans JI, Wiederhold MD, Gibson DP, Kimbrell T, Kramer TL, et al. Heart rate variability: Pre-deployment predictor of post-deployment PTSD symptoms. Biol Psychol. 2016;121(Pt A):91-98.
35 Kobayashi I, Lavela J, Mellman TA. Nocturnal autonomic balance and sleep in PTSD and resilience. J Trauma Stress. 2014;27(6):712-6.
36 Daffre C, Oliver KI, Nazareno JRS, Mader T, Seo J, Dominguez JP, et al. Rapid eye movement sleep parasympathetic activity predicts wake hyperarousal symptoms following a traumatic event. J Sleep Res. 2023;32(1):e13685.
37 Ulmer CS, Hall MH, Dennis PA, Beckham JC, Germain A. Posttraumatic stress disorder diagnosis is associated with reduced parasympathetic activity during sleep in US veterans and military service members of the Iraq and Afghanistan wars. Sleep. 2018;41(12).
38 Rissling MB, Dennis PA, Watkins LL, Calhoun PS, Dennis MF, Beckham JC, et al. Circadian Contrasts in Heart Rate Variability Associated With Posttraumatic Stress Disorder Symptoms in a Young Adult Cohort. J Trauma Stress. 2016;29(5):415-21.
39 McGaugh JL. Making lasting memories: remembering the significant. Proc Natl Acad Sci U S A. 2013;110 Suppl 2(Suppl 2):10402-7.
40 Broncel A, Bocian R, Klos-Wojtczak P, Kulbat-Warycha K, Konopacki J. Vagal nerve stimulation as a promising tool in the improvement of cognitive disorders. Brain Res Bull. 2020;155:37-47.
41 Pappens M, Schroijen M, Sutterlin S, Smets E, Van den Bergh O, Thayer JF, et al. Resting heart rate variability predicts safety learning and fear extinction in an interoceptive fear conditioning paradigm. PLoS One. 2014;9(9):e105054.
42 Jenness JL, Miller AB, Rosen ML, McLaughlin KA. Extinction Learning as a Potential Mechanism Linking High Vagal Tone with Lower PTSD Symptoms among Abused Youth. J Abnorm Child Psychol. 2019;47(4):659-70.
43 Wendt J, Neubert J, Koenig J, Thayer JF, Hamm AO. Resting heart rate variability is associated with inhibition of conditioned fear. Psychophysiology. 2015;52(9):1161-6.
44 Pena DF, Childs JE, Willett S, Vital A, McIntyre CK, Kroener S. Vagus nerve stimulation enhances extinction of conditioned fear and modulates plasticity in the pathway from the ventromedial prefrontal cortex to the amygdala. Front Behav Neurosci. 2014;8:327.
45 Pena DF, Engineer ND, McIntyre CK. Rapid remission of conditioned fear expression with extinction training paired with vagus nerve stimulation. Biol Psychiatry. 2013;73(11):1071-7.
46 Noble LJ, Gonzalez IJ, Meruva VB, Callahan KA, Belfort BD, Ramanathan KR, et al. Effects of vagus nerve stimulation on extinction of conditioned fear and post-traumatic stress disorder symptoms in rats. Transl Psychiatry. 2017;7(8):e1217.
47 Noble LJ, Meruva VB, Hays SA, Rennaker RL, Kilgard MP, McIntyre CK. Vagus nerve stimulation promotes generalization of conditioned fear extinction and reduces anxiety in rats. Brain Stimul. 2019;12(1):9-18.
48 Souza RR, Powers MB, Rennaker RL, McIntyre CK, Hays SA, Kilgard MP. Timing of vagus nerve stimulation during fear extinction determines efficacy in a rat model of PTSD. Sci Rep. 2022;12(1):16526.
49 Szeska C, Richter J, Wendt J, Weymar M, Hamm AO. Promoting long-term inhibition of human fear responses by non-invasive transcutaneous vagus nerve stimulation during extinction training. Sci Rep. 2020;10(1):1529.

50 Burger AM, Van Diest I, Van der Does W, Korbee JN, Waziri N, Brosschot JF, et al. The effect of transcutaneous vagus nerve stimulation on fear generalization and subsequent fear extinction. Neurobiol Learn Mem. 2019;161:192-201.
51 Burger AM, Verkuil B, Van Diest I, Van der Does W, Thayer JF, Brosschot JF. The effects of transcutaneous vagus nerve stimulation on conditioned fear extinction in humans. Neurobiol Learn Mem. 2016;132:49-56.
52 Whitehurst LN, Cellini N, McDevitt EA, Duggan KA, Mednick SC. Autonomic activity during sleep predicts memory consolidation in humans. Proc Natl Acad Sci U S A. 2016;113(26):7272-7.
53 Whitehurst LN, Subramoniam A, Krystal A, Prather AA. Links between the brain and body during sleep: implications for memory processing. Trends Neurosci. 2022;45(3):212-23.
54 Denis D, Bottary R, Cunningham TJ, Zeng S, Daffre C, Oliver KL, et al. Sleep Power Spectral Density and Spindles in PTSD and Their Relationship to Symptom Severity. Front Psychiatry. 2021;12:766647.
55 First M, Gibbon M, Spitzer R, Williams J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders–NonPatient Edition (SCID-I/NP). Biometrics Research Department, New York State Psychiatric Institute: New York, NY; 2007.
56 Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167(7):748-51.
57 Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and Initial Psychometric Evaluation. J Trauma Stress. 2015;28(6):489-98.
58 Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003;54(5):573-83.
59 Stocker RPJ, Khan H, Henry L, Germain A. Effects of Sleep Loss on Subjective Complaints and Objective Neurocognitive Performance as Measured by the Immediate Post-Concussion Assessment and Cognitive Testing. Arch Clin Neuropsychol. 2017;32(3):349-68.
60 Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry. 2007;62(5):446-54.
61 Milad MR, Furtak SC, Greenberg JL, Keshaviah A, Im JJ, Falkenstein MJ, et al. Deficits in conditioned fear extinction in obsessive-compulsive disorder and neurobiological changes in the fear circuit. JAMA Psychiatry. 2013;70(6):608-18; quiz 554.
62 Dawson ME, Schell AM, Filion DL. The electrodermal system. In: Cacioppo JT, Tassinary LG, Berntson GG, eds. Handbook of Psychophysiology. Third ed. Cambridge University Press: New York, NY; 2007.
63 Lonsdorf TB, Menz MM, Andreatta M, Fullana MA, Golkar A, Haaker J, et al. Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. Neurosci Biobehav Rev. 2017;77:247-85.

64 Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. J Abnorm Psychol. 2000;109(2):290-8.
65 Pace-Schott EF, Milad MR, Orr SP, Rauch SL, Stickgold R, Pitman RK. Sleep promotes generalization of extinction of conditioned fear. Sleep. 2009;32(1):19-26.
66 Lonsdorf TB, Merz CJ, Fullana MA. Fear Extinction Retention: Is It What We Think It Is? Biol Psychiatry. 2019;85(12):1074-82.
67 Lipinska G, Thomas KGF. Rapid eye movement fragmentation, not slow-wave sleep, predicts neutral declarative memory consolidation in posttraumatic stress disorder. J Sleep Res. 2019;28(6):e12846.
68 Saguin E, Gomez-Merino D, Sauvet F, Leger D, Chennaoui M. Sleep and PTSD in the Military Forces: A Reciprocal Relationship and a Psychiatric Approach. Brain Sci. 2021;11(10).
69 Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. Arch Gen Psychiatry. 2004;61(5):508-16.
70 Habukawa M, Uchimura N, Maeda M, Ogi K, Hiejima H, Kakuma T. Differences in rapid eye movement (REM) sleep abnormalities between posttraumatic stress disorder (PTSD) and major depressive disorder patients: REM interruption correlated with nightmare complaints in PTSD. Sleep Med. 2018;43:34-39.
71 Insana SP, Kolko DJ, Germain A. Early-life trauma is associated with rapid eye movement sleep fragmentation among military veterans. Biol Psychol. 2012;89(3):570-9.
72 Mellman TA, Kobayashi I, Lavela J, Wilson B, Hall Brown TS. A relationship between REM sleep measures and the duration of posttraumatic stress disorder in a young adult urban minority population. Sleep. 2014;37(8):1321-6.
73 Yetton BD, Niknazar M, Duggan KA, McDevitt EA, Whitehurst LN, Sattari N, et al. Automatic detection of rapid eye movements (REMs): A machine learning approach. J Neurosci Methods. 2016;259:72-82.
74 Shah AJ, Lampert R, Goldberg J, Veledar E, Bremner JD, Vaccarino V. Posttraumatic stress disorder and impaired autonomic modulation in male twins. Biol Psychiatry. 2013;73(11):1103-10.
75 Shah AJ, Su S, Veledar E, Bremner JD, Goldstein FC, Lampert R, et al. Is heart rate variability related to memory performance in middle-aged men? Psychosom Med. 2011;73(6):475-82.
76 Pace-Schott EF, Germain A, Milad MR. Effects of sleep on memory for conditioned fear and fear extinction. Psychol Bull. 2015;141(4):835-57.
77 Goldstein AN, Walker MP. The role of sleep in emotional brain function. Annu Rev Clin Psychol. 2014;10:679-708.
78 Davidson P, Jonsson P, Carlsson I, Pace-Schott E. Does Sleep Selectively Strengthen Certain Memories Over Others Based on Emotion and Perceived Future Relevance? Nat Sci Sleep. 2021;13:1257-306.
79 Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, et al. Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychol Bull. 2016;142(9):969-90.

80 Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185-95.
81 Pace-Schott EF, Germain A, Milad MR. Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. Biol Mood Anxiety Disord. 2015;5:3.
82 Barbato G. Is REM Density a Measure of Arousal during Sleep? Brain Sci. 2023;13(3).
83 Wehrle R, Kaufmann C, Wetter TC, Holsboer F, Auer DP, Pollmacher T, et al. Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods. Eur J Neurosci. 2007;25(3):863-71.
84 Ioannides AA, Corsi-Cabrera M, Fenwick PB, del Rio Portilla Y, Laskaris NA, Khurshudyan A, et al. MEG tomography of human cortex and brainstem activity in waking and REM sleep saccades. Cereb Cortex. 2004;14(1):56-72.
85 Miyauchi S, Misaki M, Kan S, Fukunaga T, Koike T. Human brain activity time-locked to rapid eye movements during REM sleep. Exp Brain Res. 2009;192(4):657-67.
86 Calvo JM, Fernandez-Guardiola A. Phasic activity of the basolateral amygdala, cingulate gyrus, and hippocampus during REM sleep in the cat. Sleep. 1984;7(3):202-10.
87 Corsi-Cabrera M, Velasco F, Del Rio-Portilla Y, Armony JL, Trejo-Martinez D, Guevara MA, et al. Human amygdala activation during rapid eye movements of rapid eye movement sleep: an intracranial study. J Sleep Res. 2016;25(5):576-82.
88 Andrillon T, Nir Y, Cirelli C, Tononi G, Fried I. Single-neuron activity and eye movements during human REM sleep and awake vision. Nat Commun. 2015;6:7884.
89 Rowe K, Moreno R, Lau TR, Wallooppillai U, Nearing BD, Kocsis B, et al. Heart rate surges during REM sleep are associated with theta rhythm and PGO activity in cats. Am J Physiol. 1999;277(3):R843-9.
90 Paul F, Alpers GW, Reinhard I, Schredl M. Nightmares do result in psychophysiological arousal: A multimeasure ambulatory assessment study. Psychophysiology. 2019;56(7):e13366.
91 Mellman TA. Psychobiology of sleep disturbances in posttraumatic stress disorder. Ann N Y Acad Sci. 1997;821:142-9.
92 Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. REM sleep dysregulation in depression: state of the art. Sleep Med Rev. 2013;17(5):377-90.
93 Giuditta A. Sleep memory processing: the sequential hypothesis. Front Syst Neurosci. 2014;8:219.
94 Cipolli C, Campana G, Campi C, Mattarozzi K, Mazzetti M, Tuozzi G, et al. Sleep and time course of consolidation of visual discrimination skills in patients with narcolepsy-cataplexy. J Sleep Res. 2009;18(2):209-20.
95 Singh D, Norman KA, Schapiro AC. A model of autonomous interactions between hippocampus and neocortex driving sleep-dependent memory consolidation. Proc Natl Acad Sci U S A. 2022;119(44):e2123432119.
96 Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61(3):201-16.
97 Alvarez-Dieppa AC, Griffin K, Cavalier S, McIntyre CK. Vagus Nerve Stimulation Enhances Extinction of Conditioned Fear in Rats and Modulates Arc Protein, CaMKII,

and GluN2B-Containing NMDA Receptors in the Basolateral Amygdala. Neural Plast. 2016;2016:4273280.
98 Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 2009;33(2):81-8.
99 Thayer JF, Ahs F, Fredrikson M, Sollers JJ, 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36(2):747-56.
100 Wendt J, Konig J, Hufenbach MC, Koenig J, Thayer JF, Hamm AO. Vagally mediated heart rate variability and safety learning: Effects of instructions and number of extinction trials. Psychophysiology. 2019;56(10):e13404.
101 Noble LJ, Chuah A, Callahan KK, Souza RR, McIntyre CK. Peripheral effects of vagus nerve stimulation on anxiety and extinction of conditioned fear in rats. Learn Mem. 2019;26(7):245-51.
102 Souza RR, Robertson NM, Pruitt DT, Gonzales PA, Hays SA, Rennaker RL, et al. Vagus nerve stimulation reverses the extinction impairments in a model of PTSD with prolonged and repeated trauma. Stress. 2019;22(4):509-20.
103 Souza RR, Robertson NM, Mathew E, Tabet MN, Bucksot JE, Pruitt DT, et al. Efficient parameters of vagus nerve stimulation to enhance extinction learning in an extinction-resistant rat model of PTSD. Prog Neuropsychopharmacol Biol Psychiatry. 2020;99:109848.
104 Souza RR, Robertson NM, McIntyre CK, Rennaker RL, Hays SA, Kilgard MP. Vagus nerve stimulation enhances fear extinction as an inverted-U function of stimulation intensity. Exp Neurol. 2021;341:113718.
105 Souza RR, Oleksiak CR, Tabet MN, Rennaker RL, Hays SA, Kilgard MP, et al. Vagus nerve stimulation promotes extinction generalization across sensory modalities. Neurobiol Learn Mem. 2021;181:107425.
106 Burger AM, Verkuil B, Fenlon H, Thijs L, Cools L, Miller HC, et al. Mixed evidence for the potential of non-invasive transcutaneous vagal nerve stimulation to improve the extinction and retention of fear. Behav Res Ther. 2017;97:64-74.
107 Noble LJ, Souza RR, McIntyre CK. Vagus nerve stimulation as a tool for enhancing extinction in exposure-based therapies. Psychopharmacology (Berl). 2019;236(1):355-67.
108 Phelps EA. Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol. 2004;14(2):198-202.
109 Alexandra Kredlow M, Orr SP, Otto MW. Who is studied in de novo fear conditioning paradigms? An examination of demographic and stimulus characteristics predicting fear learning. Int J Psychophysiol. 2018;130:21-28.
110 Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365-76.
111 Ackermann S, Hartmann F, Papassotiropoulos A, de Quervain DJ, Rasch B. No Associations between Interindividual Differences in Sleep Parameters and Episodic Memory Consolidation. Sleep. 2015;38(6):951-9.
112 Cordi MJ, Rasch B. How robust are sleep-mediated memory benefits? Curr Opin Neurobiol. 2021;67:1-7.

113 Berry RB, Gamaldo CE, Harding SM, Brooks R. The AASM Manual for the Scoring of Sleep and Associated Events: Rules,Terminology and Technical Specifications. . American Academy of Sleep Medicine: Darian, IL; 2015.