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

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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 heart beats. 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 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 one 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 from diagnostic evaluations. 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 2 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]. 31 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) were 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) and 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

Correlations were explored between extinction recall indices (ERI and sERI), and age, months since index trauma, and scores of symptom scales (PCL-5 and QIDS). Pearson and Spearman's

correlations were used depending on the distribution of variables. Demographic, clinical and sleep variables were compared between sexes using student's t tests.

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 demographic variables (age or sex) and REM measures, and HF[%] was added 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 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. Significance level for hypothesis testing (α) was set at .05.

RESULTS

Association of Extinction Recall Indexes with Demographic and Clinical Measures

Across the whole sample, sERI was negatively correlated with age (r_s= -.25, p=.006), while age was not significantly correlated with ERI (r_s= .11, p=.290). There were no significant correlations between extinction recall indices and the number of months since index trauma, or PCL-5 or QIDS scores. REMD and PCL-5 score were higher in females than males [t(106)=2.45, p=.016 and t(135)=2.04, p=.043, respectively].

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 latter was included because there was a strong trend for the log transformed ERI to be significantly higher in males (t(83)=1.97, p=.052). 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 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. The latter was included because it was correlated with sERI (see above). 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, in the second model, REM-HF[%] was added to the predictors. 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, 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 with 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 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 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 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 a 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 were 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 shown to be associated with increased risk to develop 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)

Table 1. Demographic and clinical characteristics of the participants. Some of the data is displayed as mean ± standard deviation as well as range (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[ms^2]	1173.5±1068 (36.9-4620.5)
REM-HF[%]	17.5±9.0 (1.9-45.9)
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 and range (minimum - maximum).

								Model ANOVA		
Predictors	**B**	**SE**	**B**	**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**	**B**	**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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SUPPLEMENTARY MATERIAL

Inclusion and Exclusion Criteria

All participants reported experiencing a DSM-5 criterion-A traumatic event ("index trauma") in the past two years, except within the last one month. Participants were allowed with a concurrent anxiety disorder, dysthymia, Major Depressive Disorder (remitted or on case-by-case basis), or if on a stable dose of an antidepressant (≥8 weeks). Exclusion criteria included: history of chronic childhood abuse or neglect; PTSD diagnosis preceding traumatic event indexed at study interview; neurological disorder or injury; major medical disorders; psychotic, bipolar, autism spectrum or other neurodevelopmental disorders; current drug or alcohol abuse or dependence; history of sleep disorder other than insomnia or nightmare disorder; current use of hypnotic or recently adjusted psychiatric medications; shift work; and any contraindication to MRI scans.

Ambulatory PSG

Ambulatory PSG was recorded on 3 nights using the Somte-PSG ambulatory sleep monitor (Compumedics USA, Charlotte, NC, USA). Sampling rate was 256 Hz. EEG data were acquired using six EEG channels (F3, F4, C3, C4, O1, O2; positioned according to the 10-20 system). Additional electrodes were placed on bilateral mastoids, above the right and below the left eye (EOG), under the chin (EMG), and below the right clavicle and in the left fifth intercostal space (ECG). Participants returned home to sleep after being instrumented. During the acclimation/screening (first) PSG night, additional channels for pulse-oximeter, respiration transducer belts, nasal cannula and tibialis movement sensors were added to screen for obstructive sleep apnea (OSA) and Periodic Limb Movement Disorder (PLMD). No participant met criteria for clinically significant OSA or PLMD. All sleep records were scored by an experienced, registered polysomnographic technologist according to American Academy of Sleep Medicine criteria [113].

Fear conditioning, extinction learning, and extinction recall procedures

A well validated 2-day paradigm [60] was used to probe fear conditioning, extinction learning, and extinction memory 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. During each phase, images of a colored desk lamp (red, yellow, or blue) appearing in a contextual background (office for conditioning context and conference room for extinction context) served as conditioned stimuli (CS). Context images were presented for nine seconds, with three seconds with the lamp off and six seconds with the lamp on (red, yellow or blue). The unconditioned stimulus (US) was a mild (0.8-4.0 mA), 500 msec electric shock delivered to the index and middle fingers of participants' right hand using a Coulbourn

Transcutaneous Aversive Finger Stimulator (Coulbourn Instruments, Allentown, PA). Prior to entering the scanner, participants were administered increasing intensities of shock and they each selected a level that they perceived as “highly annoying but not painful” [64].

During Habituation, all six possible combinations of lamp colors and contexts were presented across six trials. During the following Fear Conditioning phase, two of the three colored lamps (CS+) were each presented 8 times paired with the US at stimulus offset, on a partial reinforcement schedule (5 out of 8 presentations were paired with US). The third lamp color, which was never paired with US (CS-), was interspersed among the CS+s for a total of 16 presentations. Fear Conditioning was followed by Extinction Learning, during which one CS+ (CS+E) was presented in the extinction context 16 times without the US along with 16 interspersed presentations of the CS-. The other CS+ remained conditioned but unextinguished (CS+U). During Extinction Recall, which took place 24 hours later, each CS+ was presented 8 times in the extinction context, with no US, along with 16 interspersed CS-.

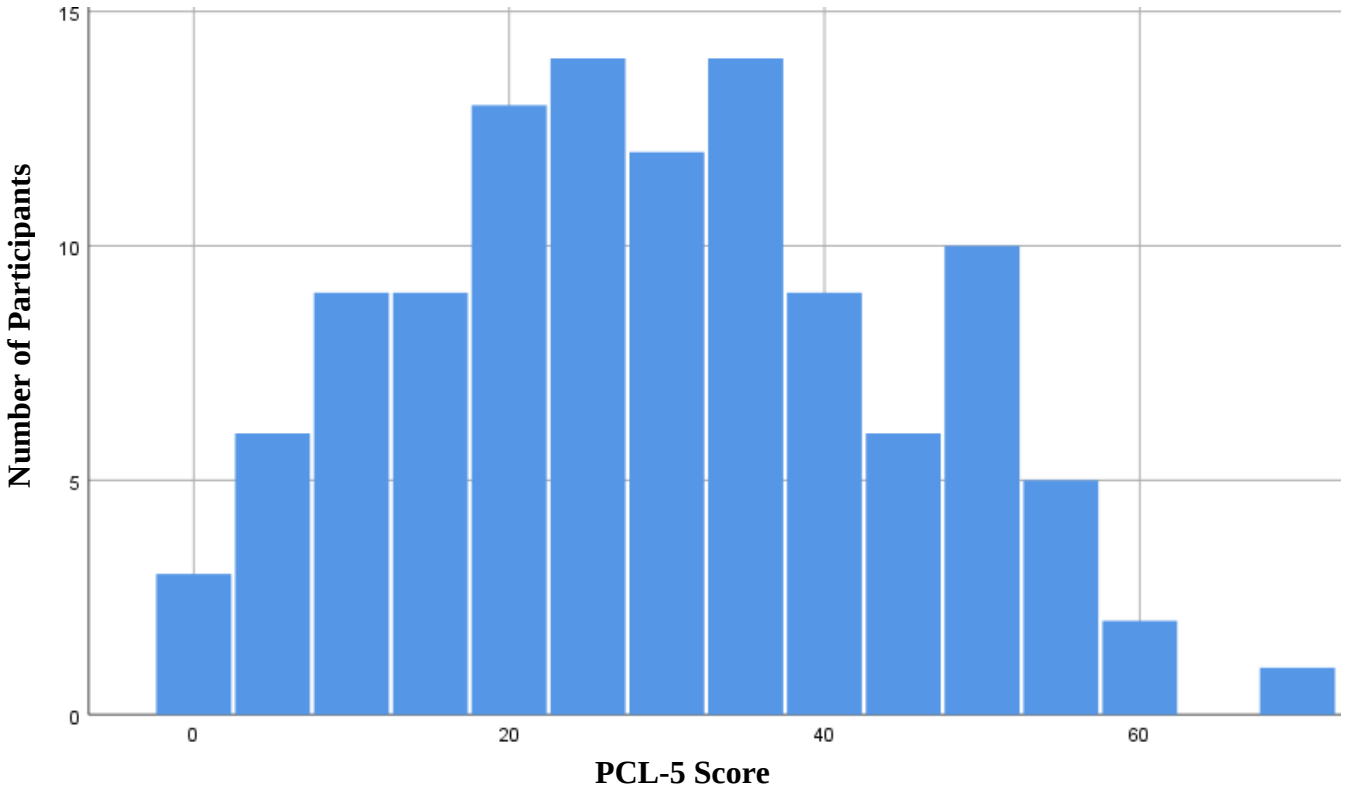

Figure S1. Distribution of PCL-5 scores in the sample.

Hierarchical Regression Analyses for ERI

Model		B	SE	β	t	p	95% CI						
1	(Constant)	1.739	0.313		5.557	<0.001	1.108	2.371					
	Sex	-0.219	0.147	-0.221	-1.483	0.145	-0.516	0.079					
	%REM	-0.022	0.012	-0.286	-1.739	0.089	-0.047	0.003					
	REMD	0.049	0.019	0.371	2.600	0.013	0.011	0.087					
	REML	-0.005	0.002	-0.410	-2.692	0.010	-0.008	-0.001					
	REMF	0.043	0.021	0.311	1.987	0.053	-0.001	0.086					
										Change		ANOVA	
									Adj. R2	ΔF	Δp	F	p
2	(Constant)	1.814	0.327		5.554	<0.001	1.155	2.473	0.159	0.697	0.409	2.507	0.037
	Sex	-0.232	0.149	-0.235	-1.560	0.126	-0.533	0.068					
	%REM	-0.020	0.013	-0.267	-1.603	0.116	-0.046	0.005					
	REMD	0.048	0.019	0.364	2.534	0.015	0.010	0.086					
	REML	-0.005	0.002	-0.408	-2.672	0.011	-0.008	-0.001					
	REMF	0.040	0.022	0.289	1.816	0.077	-0.004	0.083					
	REM-HF[ms^2]	<0.001	<0.001	-0.113	-0.835	0.409	<0.001	<0.001					

Table S1. Hierarchical regression analysis with ERI as the dependent variable. REM-HF[ms^2] is included in the second model.

Model		B	SE	β	t	p	95% CI						
1	(Constant)	1.739	0.313		5.557	<0.001	1.108	2.371					
	Sex	-0.219	0.147	-0.221	-1.483	0.145	-0.516	0.079					
	%REM	-0.022	0.012	-0.286	-1.739	0.089	-0.047	0.003					
	REMD	0.049	0.019	0.371	2.600	0.013	0.011	0.087					
	REML	-0.005	0.002	-0.410	-2.692	0.010	-0.008	-0.001					
	REMF	0.043	0.021	0.311	1.987	0.053	-0.001	0.086					
										Change		ANOVA	
									Adj. R2	ΔF	Δp	F	p
2	(Constant)	1.905	0.343		5.561	0.000	1.214	2.597	0.171	1.360	0.250	2.655	0.028
	Sex	-0.240	0.148	-0.243	-1.624	0.112	-0.539	0.058					
	%REM	-0.020	0.013	-0.262	-1.586	0.120	-0.045	0.005					
	REMD	0.048	0.019	0.365	2.563	0.014	0.010	0.086					
	REML	-0.004	0.002	-0.406	-2.681	0.010	-0.008	-0.001					
	REMF	0.039	0.022	0.285	1.811	0.077	-0.004	0.082					
	REM-RMSSD	-0.003	0.002	-0.157	-1.166	0.250	-0.007	0.002					

Table S2. Hierarchical regression analysis with ERI as the dependent variable. REM-RMSSD is included in the second model.

Hierarchical Regression Analyses for sERI

Model		B	SE	β	t	p	95% CI						
1	(Constant)	-12.638	25.774		-0.490	0.626	-64.211	38.935					
	Age	-0.218	0.738	-0.035	-0.296	0.769	-1.695	1.259					
	%REM	-0.166	0.678	-0.035	-0.245	0.807	-1.522	1.190					
	REMD	2.581	0.908	0.338	2.841	0.006	0.763	4.399					
	REML	0.009	0.091	0.013	0.102	0.919	-0.173	0.191					
	REMF	2.171	1.047	0.281	2.074	0.042	0.077	4.266					
										Change		ANOVA	
									Adj. R2	ΔF	Δp	F	p
2	(Constant)	1.750	27.139		0.064	0.949	-52.574	56.074	0.141	1.994	0.163	2.757	0.017
	Age	-0.443	0.744	-0.071	-0.595	0.554	-1.933	1.047					
	%REM	-0.107	0.671	-0.023	-0.160	0.874	-1.451	1.236					
	REMD	2.413	0.905	0.316	2.668	0.010	0.603	4.224					
	REML	0.000	0.090	0.000	0.003	0.997	-0.180	0.181					
	REMF	1.984	1.042	0.257	1.904	0.062	-0.102	4.070					
	REM-HF[ms^2]	-0.005	0.003	-0.184	-1.540	0.129	-0.012	0.002					

Table S3. Hierarchical regression analysis with sERI as the dependent variable. REM-HF[ms^2] is included in the second model.

Model		B	SE	β	t	p	95% CI						
1	(Constant)	-12.638	25.774		-0.490	0.626	-64.211	38.935					
	Age	-0.218	0.738	-0.035	-0.296	0.769	-1.695	1.259					
	%REM	-0.166	0.678	-0.035	-0.245	0.807	-1.522	1.190					
	REMD	2.581	0.908	0.338	2.841	0.006	0.763	4.399					
	REML	0.009	0.091	0.013	0.102	0.919	-0.173	0.191					
	REMF	2.171	1.047	0.281	2.074	0.042	0.077	4.266					
										Change		ANOVA	
									Adj. R2	ΔF	Δp	F	p
2	(Constant)	3.022	27.677		0.109	0.913	-52.379	58.422	0.144	2.144	0.148	2.788	0.019
	Age	-0.368	0.738	-0.059	-0.498	0.620	-1.846	1.110					
	%REM	-0.107	0.673	-0.023	-0.159	0.874	-1.453	1.240					
	REMD	2.475	0.903	0.324	2.743	0.008	0.669	4.282					
	REML	0.002	0.090	0.002	0.019	0.985	-0.179	0.182					
	REMF	2.079	1.039	0.269	2.002	0.050	0.000	4.159					
	REM-RMSSD	-0.194	0.133	-0.172	-1.464	0.148	-0.460	0.071					

Table S4. Hierarchical regression analysis with sERI as the dependent variable. REM-RMSSD is included in the second model.

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