REM disruption 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 heart rate variability) in a large sample of trauma-exposed individuals (n=113). Consistent with our hypotheses, REM disruption was associated with poorer physiological and explicit extinction memory. Furthermore, higher vagal activity during REM was associated with better explicit extinction memory, and physiological extinction memory in males. These findings support the notion that abnormal 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 (Milad and Quirk 2012; Zuj et al. 2016). 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 (Craske et al. 2014).

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 (Bottary et al. 2023; Pace-Schott et al. 2023), accumulating evidence suggests that impaired retention of extinction memory, acquired after trauma exposure (Milad et al. 2008), may be a critical mechanism that leads to PTSD (Helpman et al. 2016; Milad et al. 2008; Milad et al. 2009; Milad and Quirk 2012; Shvil et al. 2014; Suarez-Jimenez et al. 2020; Wicking et al. 2016). Sleep supports the consolidation of different types of memories, which stabilizes and integrates them, and enhances their retrieval (Klinzing et al. 2019). 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 (Davidson and Pace-Schott 2020). In healthy people, more REM has been shown to be associated with better extinction recall (Bottary et al. 2020; Menz et al. 2016; Pace-Schott et al. 2014; Spoormaker et al. 2010), and REM deprivation leads to impaired extinction memory (Spoormaker et al. 2012), suggesting the possibility of a causal role for this sleep stage. Several studies and meta-analyses find REM abnormalities in PTSD (Kobayashi et al. 2007; Richards et al. 2020; Zhang et al. 2019), which also have been shown to be associated with the risk of developing PTSD after trauma (Mellman et al. 2002; Mellman et al. 2004; Mellman et al. 2007). Therefore, it is postulated that sleep disruption, specifically of REM, may predispose traumatized individuals to develop PTSD symptoms by interfering with extinction memory (Colvonen et al. 2019; Pace-Schott et al. 2023). 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 (Seo et al. 2022). However, much remains to be learned regarding the association between REM and extinction memory in trauma-exposed individuals. One preliminary study (Straus et al. 2018) 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 (Seligowski et al. 2022). 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 (Laborde et al. 2017; Shaffer and Ginsberg 2017). Meta-analyses show that patients with PTSD display reduced vagal activity, as indexed by HF-HRV and RMSSD, during wakefulness (Chalmers et al. 2014; Ge et al. 2020; Schneider and Schwerdtfeger 2020), and in one study, lower baseline HF-HRV predicted the severity of later post-traumatic stress symptoms (Pyne et al. 2016). Similar to wakefulness, a small number of recent studies in sleep find reduced vagal activity in PTSD (Kobayashi et al. 2014), including in specific sleep stages (Daffre et al. 2023; Ulmer et al. 2018). Additionally, in one study, HF-HRV across actigraphically measured sleep was associated with PTSD symptom severity (Rissling et al. 2016).

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 (Broncel et al. 2020; McGaugh 2013). Consistent with this, high vagal tone is associated with better extinction learning in humans (Jenness et al. 2019; Pappens et al. 2014; Wendt et al. 2015), and enhancing vagal activity improves extinction learning and retention of extinction memory in both rodents (Noble et al. 2017; NobleMeruva et al. 2019; Pena et al. 2014; Pena et al. 2013; Souza et al. 2022) and humans (Burger et al. 2019; Burger et al. 2016; Szeska et al. 2020). 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 neural oscillations (Whitehurst et al. 2016; Whitehurst et al. 2022). However, to date, no study 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). If this hypothesis is supported, it would further underscore vagal activity as a promising target for enhancing extinction memory through readily accessible interventions (Jung et al. 2024; Siepmann et al. 2022) in the aftermath of trauma exposure.

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 (Daffre et al. 2023; Denis et al. 2021; Seo et al. 2022) and Supplementary Materials. Twenty-six participants were excluded from all analyses because of missing or unusable EEG or ECG data (final n=113). Psychiatric history was ascertained using the Structured Clinical Interview for DSM-IV-TR for Non-Patients (SCID-I/NP) (First et al. 2007). The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; (Weathers et al. 2018)) was used to assess post-traumatic stress symptom severity (see **Figure S1** for its distribution in the sample). This study followed a Research Domain Criteria (RDoC) (Insel et al. 2010) 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. 49.6% (n=56) of participants met diagnostic criteria for PTSD. The Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) (Rush et al. 2003), and the Pittsburg Structured Clinical Interview for Sleep Disorders (SCID-SLD) (Stocker et al. 2017) were administered to evaluate depressive and sleep disorder symptoms, respectively. Demographic and clinical characteristics of the final sample are displayed in **Table S1**. 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 in the evening immediately after the baseline night, participants completed a 2-day fear conditioning and extinction protocol with simultaneous fMRI recordings (Milad et al. 2013). 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 (Milad et al. 2013; Milad et al. 2007) 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 (Dawson et al. 2007). Negative SCRs were coded as zero (Lonsdorf et al. 2017), 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 (Orr et al. 2000). Thirty-one non-conditioners were further excluded from SCR analyses based on these criteria. In addition, SCR data for 3 participants were lost. Differential SCR (SCRd) was calculated by subtracting from the SCR to each CS+ the SCR from its closest temporally corresponding CS- to adjust for nonspecific reactivity to the nonreinforced CS- (Bottary et al. 2020; Lonsdorf et al. 2019).

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"). Expectancy ratings for 7 participants were not included in the analyses, because they did not complete the experiment or because of missing data. Further details of the protocol and skin conductance monitoring are provided in previous publications (Bottary et al. 2020; Pace-Schott et al. 2009) 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 a Differential Extinction Retention Index (dERI) (Lonsdorf et al. 2019) and a Subjective Extinction Retention Index (sERI) (Bottary et al. 2020), respectively. dERI was calculated as: [(Average of the SCRds of the first 4 CS+E presentations at Extinction Recall phase/maximum SCRd to the "to-be" CS+E during the Fear Conditioning phase) x 100] (Lonsdorf et al. 2019). Only the first 4 CS+E trials from the Extinction Recall phase were included in this calculation in order to avoid confounding recalled extinction with new extinction learning. Higher dERI 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.

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 (Zhang et al. 2019), REM density (REMD) (Kobayashi et al. 2007), REM latency (REML) (Mellman et al. 2014), and REM fragmentation (REMF) (Breslau et al. 2004;

Habukawa et al. 2018; Insana et al. 2012; Lipinska and Thomas 2019; Mellman et al. 2002; Saguin et al. 2021). Percent time spent in each sleep stage (%N1-N3, %REM) was computed as a percentage of total sleep time (TST). REMD is the number of rapid eye movements per minute of REM sleep and was calculated using an automatic algorithm (Yetton et al. 2016). REML was calculated as the number of minutes occurring after sleep onset before the first REM epoch. REMF was calculated as the average duration of REM segments (Mellman et al. 2002). 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 (Mellman et al. 2002).

Heart Rate Variability

HRV was calculated in continuous ECG segments of ≥5 minutes within REM using Kubios HRV premium software (Kubios Oy, Kuopio, Finland). Prior to analysis, ECG traces were visually inspected for physiological and technical artifacts (Laborde et al. 2017). Misplaced or ectopic beats were manually corrected if possible. Very low to low, or occasionally medium, filter was applied, if necessary, after correction (https://www.kubios.com/hrv-preprocessing/). Segments that did not provide reliable estimates due to excessive artifacts were removed. Twenty-three participants were excluded because of artifacts, not having ≥5 minute REM segments, or because their records were missing. High frequency (HF; .15-.4 Hz) absolute power (HF[ms^2]) was used as a predictor variable in the primary analyses because it was shown to be associated with sleep-dependent memory processing (Whitehurst et al. 2016). We also carried out the same analyses with RMSSD, another measure of vagal activity (Shaffer and Ginsberg 2017). For frequency domain analyses, autoregressive method was used, with model order set at 16 (Laborde et al. 2017). Data was transformed by their natural logarithm (Laborde et al. 2017).

Statistical Analyses

Associations were explored between extinction recall indices (dERI and sERI), and age, sex, months since index trauma, scores of symptom scales (CAPS-5 and QIDS), and medication use as a binary variable. 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 (dERI and sERI; Hypothesis 1). The models included %REM, REMD, REML, and REMF as predictor variables. Sex and medication use were also included as predictors as these factors have been shown to modulate fear extinction and its retention (Bouton et al. 1990; Gunduz-Cinar et al. 2016; Milad et al. 2006).

Next, hierarchical regression analyses were used to test the hypothesis that vagal activity would improve the predictions of dERI and sERI above and beyond REM sleep measures alone

(Hypothesis 2). For this purpose, two models were built. Model 1 included sex, medication use and REM measures. HF[ms^2] was added as an additional predictor in Model 2. Because missing HF[ms^2] data further limited the number of participants that could be included in the analysis, only REM variables that were significant predictors in the regression analysis that tested Hypothesis 1 were included. Results for the models that included all REM variables and RMSSD instead of HF[ms2] were also reported for completeness.

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 (1.1-1.4), indicating that there was no confounding multicollinearity. For dERI, 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, dERI was log-transformed. After transformation, normal distributions of residuals and homoscedasticity were confirmed.

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 inversely correlated with sERI (r_s= -.27, p=.006), while it was not significantly correlated with dERI (r_s= .12, p=.305). There were no differences between sexes in dERI or sERI (t(76)=.233, p=.817 and t(104)=.116, p=.250, respectively). There were no significant correlations between either extinction recall index and the number of months since index trauma (dERI: r_s= -.03, p=.796; sERI: r_s= -.04, p=.659), or CAPS-5 (dERI: r_s= .11, p=.333; sERI: r_s=-.02, p=.831) or QIDS (dERI: r_s= .13, p=.350; sERI: r_s= -.04, p=.692) scores.

Regression Analyses Predicting dERI and sERI

Measures of REM characteristics and sleep architecture are displayed in **Table 1**. The multiple regression model with dERI as the dependent variable included sex, medication use, %REM, REMD, REML, and REMF as predictor variables (N=67). The overall model explained a significant proportion of the variance (Adj. R^2=.14, p=.021)**,** with sex, **%**REM**,** REMD, and REML emerging as significant predictors (**Table 2; Figure S2**). Poorer physiological extinction recall was associated with the male sex (B[SE]=-.71[.34], p=.041), less time in REM sleep (%REM; B[SE]=-.06[.03], p=.018), increased REMD (B[SE]=.14[.05], p=.009), and shorter REML (B[SE]=-.01[.003], p=.002).

A similar multiple regression model for sERI was carried out (N=94). In our sample, age was associated with sERI (see Results), therefore it was also included in the model. This model also

explained a significant proportion of the variance (Adj. R^2=.09, p=.031). In this model, REMD was the only significant predictor (**Table 3; Figure S3**), and as with dERI, increased REMD was associated with poorer subjective extinction recall (B[SE]=2.80[.94], p=.004).

Hierarchical regressions with HF HRV predicting dERI and sERI

Average HRV values are displayed in **Table 1**. For the hierarchical regression analyses with dERI as the dependent variable (N=61), sex, medication use, and REM sleep measures (%REM, REMD, and REML) were included in the first model. HF[ms2] was included as an additional predictor in the second model. Visual inspection of the data suggested that the association of HF[ms^2] with dERI might be different between sexes. Therefore a sex × HF[ms^2] interaction was also added to the second model. The final model was significant (Adj. R^2=.17, p=.018; **Table 4**). There was a trend for an increase in the variance accounted for by the second model (ΔR^2=.08, p=.074). HF[ms^2] and the sex × HF[ms^2] interaction were significant predictors (B[SE]=-.42[.20], p=.042 and B[SE]=.65[.29], p=.030, respectively. We therefore probed this interaction by examining the simple slopes, which showed that the effect of HF[ms^2] on dERI was significant for males (B[SE]=-.42[.20], p=.042) but not for females (B[SE]=.23[.21], p=.263), and the effects were different between sexes (p=.031).

A similar hierarchical regression analysis was carried out for sERI (N=85). The first model included age, sex, medication use, and REMD. HF[ms^2] was added to the predictors in the second model. Addition of HF[ms^2] led to a significant increase in the variance accounted for by the model (ΔR^2=.06, p=.018), 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=.13, p=.006), and medication use, REMD, and HF[ms^2] emerged as significant predictors. Poorer subjective extinction recall was associated with not using medications (B[SE]=-18.81[8.19], p=.024), higher REMD (B[SE]=2.64[.95], p=.007), and lower HF[ms^2] (B[SE]=-7.05[2.92], p=.018) (**Table 5, Figure S3)**.

For completeness, we repeated the same hierarchical regression analyses by adding all REM variables. The results were similar (**Tables S2 and S3).** Using RMSSD instead of HF[ms^2] also did not change the results **(Tables S4 and S5).**

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 less time spent in REM sleep, shorter REML, and higher REMD independently predicted poorer physiological extinction recall. Similarly, poorer subjective extinction recall was predicted by higher 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 and partially supported for physiological 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 (Davidson and Pace-Schott 2020; Pace-Schott et al. 2015a) and in insomnia disorder (Bottary et al. 2020). In healthy individuals, better extinction recall was associated with the presence of REM during a nap (Spoormaker et al. 2010), higher overnight %REM (Pace-Schott et al. 2014), less fragmented REM, and increased REM theta power (Bottary et al. 2020). In addition, late-night (REM-rich) sleep but not early-night sleep benefited extinction memory (Menz et al. 2016), and selective REM, but not NREM, deprivation impaired extinction recall (Spoormaker et al. 2012). In contrast, among individuals with insomnia disorder (Bottary et al. 2020), 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 (Goldstein and Walker 2014), although this assertion is not consistently supported by experimental evidence (Davidson et al. 2021).

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 (Baglioni et al. 2016). However, in PTSD, alterations in these variables are not consistently found, and the direction of change showed variability across studies, possibly due to the heterogeneity in samples and the settings in which data were collected (Baglioni et al. 2016; Kobayashi et al. 2007; Zhang et al. 2019). 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 (Baglioni et al. 2016; Kobayashi et al. 2007; Zhang et al. 2019). 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 (Bottary et al. 2023).

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 (Cabrera et al. 2024; Germain et al. 2008; Pace-Schott et al. 2015b; Pace-Schott et al. 2023). Indeed, increased REMD may be a direct manifestation of hyperarousal in PTSD (Barbato 2023). Rapid eye movements are associated with activation in the limbic and

paralimbic structures (Andrillon et al. 2015; Calvo and Fernandez-Guardiola 1984; Corsi-Cabrera et al. 2016; Ioannides et al. 2004; Miyauchi et al. 2009; Wehrle et al. 2007), as well as heart rate surges (Rowe et al. 1999) and nightmares concurrent with autonomic arousal (Paul et al. 2019). Furthermore, in an overlapping sample, we recently showed that REMD was one of the predictors of self-reported hyperarousal symptoms in trauma-exposed individuals (Daffre et al. 2023). Therefore, our results suggest that hyperarousal during REM interferes with the consolidation of extinction memory. REML has been considered an indicator of REM pressure, and the shortening of REML in PTSD has been attributed to an "unmet need" (Mellman 1997). 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. Alternatively, this association may be due to an adaptive REM enhancement to facilitate emotional processing (Mellman 1997). Yet another possibility is that shortened REML may reflect depression (Palagini et al. 2013). However, self-reported depressive symptoms were not correlated with REML (r_s=.05, p=.65) or dERI (r_s=.02, p=.86).

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 (McGaugh 2013) and emotional regulation (Thayer and Lane 2000), as well as the growing body of evidence indicating that vagal activity is causally involved in fear processing (Alvarez-Dieppa et al. 2016; Pena et al. 2014; Pena et al. 2013). 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 (Thayer et al. 2012; Thayer and Lane 2009), circuitry that is also critical for fear extinction (Milad and Quirk 2012). Consistent with this, high vagal activity during wake was repeatedly shown to be associated with better fear extinction in humans (Jenness et al. 2019; Pappens et al. 2014; Wendt et al. 2019; Wendt et al. 2015). Furthermore, vagal nerve stimulation (VNS) facilitated plasticity in ventromedial PFC-amygdala connectivity in rodents (Pena et al. 2014), and improved extinction learning and recall in both rodents (Alvarez-Dieppa et al. 2016; NobleChuah et al. 2019; Noble et al. 2017; Pena et al. 2014; Pena et al. 2013; SouzaOleksiak et al. 2021; Souza et al. 2022; Souza et al. 2020; SouzaRobertson et al. 2021; Souza et al. 2019) and humans (Burger et al. 2019; Burger et al. 2017; Burger et al. 2016; Szeska et al. 2020). 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 (NobleSouza et al. 2019). The association of HRV with physiological extinction recall in males should be treated as a preliminary finding, because of the small number of male participants in our sample (N=34). Nevertheless, if replicated, it would be in line with prior research suggesting that sex modulates fear extinction (Milad et al. 2006; Milad et al. 2010; Shvil et al. 2014; Velasco et al. 2019) and its processing during sleep (Schenker et al. 2022).

Our study had several limitations. We had to exclude a substantial number of participants because of lost or unusable sleep data. Lack of oversight during ambulatory recordings can lead to more artifacts than in laboratory studies. Second, there is significant variability across studies in fear conditioning/extinction protocols and methods in analyzing generated data (Lonsdorf et al. 2017). Nonetheless, we used the widely employed Milad et al. 2007 fear conditioning and extinction protocol (Milad and Quirk 2012), and we attempted to be consistent with our own and others' previously used metrics to index extinction recall. Third, 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 (Alexandra Kredlow et al. 2018). In addition, we found similar results with the expectancy ratings. A strength of our study is the large sample size. Many of the prior studies linking REM features to emotional processing and extinction were based on small sample sizes, a limitation that reduces statistical power and can lead to Type 1 error and overestimation of effect sizes (Button et al. 2013).

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.

REMD	5.1±3.1 (.62-13.0)
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)
HF[ms^2]	1198.0±1069.5 (39.2-4788.6)
RMSSD	54.3±26.8 (13.0-128.3)

Table 1. Sleep and HRV measures in the participants. Data is displayed as mean ± standard deviation (minimum - maximum). HF[ms^2]: Absolute power of high frequency heart rate variability; %N1-REM: Proportion of the sleep stage to the total sleep time; REMD: REM density; REMF: REM fragmentation; REML: REM latency; RMSSD: Root mean square of successive differences.

									ANOVA	
Predictors	**B**	**SE**	**β**	**t**	**p**	**95% CI**		**Adj. R^2**	**F**	**p**
Sex	-.714	.341	-.279	-2.092	**.041**	-1.397	-.031	.135	2.716	**.021**
Medications	.113	.372	.038	.304	.762	-.630	.856			
%REM	-.061	.025	-.326	-2.427	**.018**	-.111	-.011			
REMD	.141	.052	.365	2.701	**.009**	.036	.245			
REML	-.011	.003	-.421	-3.167	**.002**	-.018	-.004			
REMF	.036	.031	.153	1.155	.253	-.026	.098			

Table 2. Linear regression analysis for physiological extinction recall (dERI; N=67). Sex, %REM, REMD and REML were significant predictors. Note that smaller dERI denotes better extinction recall. %REM: Proportion of REM sleep to the total sleep time; REMD: REM density; REMF: REM fragmentation; REML: REM latency.

									ANOVA	
Predictors	**B**	**SE**	**β**	**t**	**p**	**95% CI**		**Adj. R^2**	**F**	**p**
Age	-.512	.629	-.084	-.814	.418	-1.763	.739	.092	2.345	**.031**
Sex	-2.903	6.842	-.046	-.424	.672	-16.503	10.698			
Medications	-12.574	7.632	-.175	-1.648	.103	-27.747	2.598			
%REM	.238	.527	.052	.452	.653	-.810	1.286			
REMD	2.801	.936	.331	2.994	**.004**	.942	4.661			
REML	.087	.072	.136	1.209	.230	-.056	.229			
REMF	.528	.653	.090	.808	.421	-.771	1.827			

Table 3. Linear regression analysis for subjective extinction recall (sERI; N=94). REMD was the only significant predictor. Note that smaller sERI denotes better extinction recall. %REM: Proportion of REM sleep to the total sleep time; REMD: REM density; REMF: REM fragmentation; REML: REM latency.

Model	Predictors	B	SE	β	t	p	95% CI						
1	**Sex**	-.531	.345	-.213	-1.539	.130	-1.221	.160					
	Medications	.017	.386	.006	.045	.964	-.757	.791					
	%REM	-.043	.025	-.234	-1.763	.083	-.093	.006					
	REMD	.143	.053	.379	2.718	.009	.037	.248					
	REML	-.008	.003	-.323	-2.481	.016	-.015	-.002					
									Change			**ANOV**	
									ΔF	**p**	**Adj. R^2**	**F**	**p**
2	**Sex**	-.591	.338	-.237	-1.750	.086	-1.269	.086	2.738	0.074	0.165	2.700	**0.0**
	Medications	.143	.385	.048	.370	.713	-.630	.915					
	%REM	-.051	.024	-.275	-2.113	.039	-.100	-.003					
	REMD	.156	.052	.414	2.976	**.004**	.051	.261					
	REML	-.010	.003	-.397	-3.021	**.004**	-.017	-.003					
	HF[ms^2]	-.416	.199	-.358	-2.089	**.042**	-.816	-.016					
	HF[ms^2]×Sex	.651	.293	.401	2.223	**.030**	.064	1.238					

Table 4. Hierarchical regression analysis for physiological extinction recall (dERI; N=61). HF[ms^2] and HF[ms^2]×Sex interaction were significant predictors. Note that smaller dERI denotes better extinction recall. HF[ms^2]: Absolute power of high frequency heart rate variability; %REM: Proportion of REM sleep to the total sleep time; REMD: REM density; REML: REM latency.

Model	Predictors	B	SE	β	t	p	95% CI						
1	**Age**	-.506	.630	-.085	-.803	.424	-1.761	.748					
	Sex	-.224	7.153	-.004	-.031	.975	-14.458	14.010					
	Medications	-14.982	8.278	-.203	-1.810	.074	-31.456	1.492					
	REMD	2.917	.970	.348	3.006	.004	.986	4.849					
									Change			**ANOVA**	
									ΔF	**p**	**Adj. R^2**	**F**	**p**
2	**Age**	-.678	.616	-.114	-1.100	.274	-1.905	.549	5.834	**0.018**	0.133	3.566	**0.0**
	Sex	.830	6.960	.013	.119	.905	-13.022	14.683					
	Medications	-18.809	8.194	-.255	-2.296	**.024**	-35.118	-2.500					
	REMD	2.638	.950	.314	2.778	**.007**	.748	4.528					
	HF[ms^2]	-7.048	2.918	-.255	-2.415	**.018**	-12.857	-1.240					

Table 5. Hierarchical regression analysis for subjective extinction recall (sERI; N=85). Addition of HF[ms^2] significantly increased the proportion of variance explained by the model. Note that smaller sERI denotes better extinction recall. HF[ms2]: Absolute power of high frequency heart rate variability; REMD: REM density.

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References

Ackermann S, Hartmann F, Papassotiropoulos A, de Quervain DJ and Rasch B (2015) No Associations between Interindividual Differences in Sleep Parameters and Episodic Memory Consolidation. *Sleep* **38**(6)**,** 951-959. https://doi.org/10.5665/sleep.4748.

Alexandra Kredlow M, Orr SP and Otto MW (2018) Who is studied in de novo fear conditioning paradigms? An examination of demographic and stimulus characteristics predicting fear learning. *Int J Psychophysiol* **130,** 21-28. https://doi.org/10.1016/j.ijpsycho.2018.05.008.

Alvarez-Dieppa AC, Griffin K, Cavalier S and McIntyre CK (2016) 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,** 4273280. https://doi.org/10.1155/2016/4273280.

Andrillon T, Nir Y, Cirelli C, Tononi G and Fried I (2015) Single-neuron activity and eye movements during human REM sleep and awake vision. *Nat Commun* **6,** 7884. https://doi.org/10.1038/ncomms8884.

Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, Reynolds CF and Riemann D (2016) Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychol Bull* **142**(9)**,** 969-990. https://doi.org/10.1037/bul0000053.

Barbato G (2023) Is REM Density a Measure of Arousal during Sleep? *Brain Sci* **13**(3). https://doi.org/10.3390/brainsci13030378.

Bottary R, Seo J, Daffre C, Gazecki S, Moore KN, Kopotiyenko K, Dominguez JP, Gannon K, Lasko NB, Roth B, Milad MR and Pace-Schott EF (2020) Fear extinction memory is negatively associated with REM sleep in insomnia disorder. *Sleep* **43**(7). https://doi.org/10.1093/sleep/zsaa007.

Bottary R, Straus LD and Pace-Schott EF (2023) The Impact of Sleep on Fear Extinction. *Curr Top Behav Neurosci*. https://doi.org/10.1007/7854_2023_431.

Bouton ME, Kenney FA and Rosengard C (1990) State-dependent fear extinction with two benzodiazepine tranquilizers. *Behav Neurosci* **104**(1)**,** 44-55. https://doi.org/10.1037//0735-7044.104.1.44.

Breslau N, Roth T, Burduvali E, Kapke A, Schultz L and Roehrs T (2004) Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. *Arch Gen Psychiatry* **61**(5)**,** 508-516. https://doi.org/10.1001/archpsyc.61.5.508.

Broncel A, Bocian R, Klos-Wojtczak P, Kulbat-Warycha K and Konopacki J (2020) Vagal nerve stimulation as a promising tool in the improvement of cognitive disorders. *Brain Res Bull* **155,** 37-47. https://doi.org/10.1016/j.brainresbull.2019.11.011.

Burger AM, Van Diest I, Van der Does W, Korbee JN, Waziri N, Brosschot JF and Verkuil B (2019) The effect of transcutaneous vagus nerve stimulation on fear generalization and subsequent fear extinction. *Neurobiol Learn Mem* **161,** 192-201. https://doi.org/10.1016/j.nlm.2019.04.006.

Burger AM, Verkuil B, Fenlon H, Thijs L, Cools L, Miller HC, Vervliet B and Van Diest I (2017) Mixed evidence for the potential of non-invasive transcutaneous vagal nerve stimulation to improve the extinction and retention of fear. *Behav Res Ther* **97,** 64-74. https://doi.org/10.1016/j.brat.2017.07.005.

Burger AM, Verkuil B, Van Diest I, Van der Does W, Thayer JF and Brosschot JF (2016) The effects of transcutaneous vagus nerve stimulation on conditioned fear extinction in humans. *Neurobiol Learn Mem* **132,** 49-56. https://doi.org/10.1016/j.nlm.2016.05.007.

Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES and Munafo MR (2013) Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci* **14**(5)**,** 365-376. https://doi.org/10.1038/nrn3475.

Cabrera Y, Koymans KJ, Poe GR, Kessels HW, Van Someren EJW and Wassing R (2024) Overnight neuronal plasticity and adaptation to emotional distress. *Nat Rev Neurosci* **25**(4)**,** 253-271. https://doi.org/10.1038/s41583-024-00799-w.

Calvo JM and Fernandez-Guardiola A (1984) Phasic activity of the basolateral amygdala, cingulate gyrus, and hippocampus during REM sleep in the cat. *Sleep* **7**(3)**,** 202-210. https://doi.org/10.1093/sleep/7.3.202.

Chalmers JA, Quintana DS, Abbott MJ and Kemp AH (2014) Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. *Front Psychiatry* **5,** 80. https://doi.org/10.3389/fpsyt.2014.00080.

Cipolli C, Campana G, Campi C, Mattarozzi K, Mazzetti M, Tuozzi G, Vandi S, Vignatelli L and Plazzi G (2009) Sleep and time course of consolidation of visual discrimination skills in patients with narcolepsy-cataplexy. *J Sleep Res* **18**(2)**,** 209-220. https://doi.org/10.1111/j.1365-2869.2008.00712.x.

Colvonen PJ, Straus LD, Acheson D and Gehrman P (2019) A Review of the Relationship Between Emotional Learning and Memory, Sleep, and PTSD. *Curr Psychiatry Rep* **21**(1)**,** 2. https://doi.org/10.1007/s11920-019-0987-2.

Cordi MJ and Rasch B (2021) How robust are sleep-mediated memory benefits? *Curr Opin Neurobiol* **67,** 1-7. https://doi.org/10.1016/j.conb.2020.06.002.

Corsi-Cabrera M, Velasco F, Del Rio-Portilla Y, Armony JL, Trejo-Martinez D, Guevara MA and Velasco AL (2016) Human amygdala activation during rapid eye movements of rapid eye movement sleep: an intracranial study. *J Sleep Res* **25**(5)**,** 576-582. https://doi.org/10.1111/jsr.12415.

Craske MG, Treanor M, Conway CC, Zbozinek T and Vervliet B (2014) Maximizing exposure therapy: an inhibitory learning approach. *Behav Res Ther* **58,** 10-23. https://doi.org/10.1016/j.brat.2014.04.006.

Daffre C, Oliver KI, Nazareno JRS, Mader T, Seo J, Dominguez JP, Gannon K, Lasko NB, Orr SP and Pace-Schott EF (2023) Rapid eye movement sleep parasympathetic activity predicts wake hyperarousal symptoms following a traumatic event. *J Sleep Res* **32**(1)**,** e13685. https://doi.org/10.1111/jsr.13685.

Davidson P, Jonsson P, Carlsson I and Pace-Schott E (2021) Does Sleep Selectively Strengthen Certain Memories Over Others Based on Emotion and Perceived Future Relevance? *Nat Sci Sleep* **13,** 1257-1306. https://doi.org/10.2147/NSS.S286701.

Davidson P and Pace-Schott E (2020) The role of sleep in fear learning and memory. *Curr Opin Psychol* **34,** 32-36. https://doi.org/10.1016/j.copsyc.2019.08.016.

Dawson ME, Schell AM and Filion DL (2007) *The electrodermal system. In: Cacioppo JT, Tassinary LG, Berntson GG, eds. Handbook of Psychophysiology*, Third edn. New York, NY: Cambridge University Press.

Denis D, Bottary R, Cunningham TJ, Zeng S, Daffre C, Oliver KL, Moore K, Gazecki S, Kram Mendelsohn A, Martinez U, Gannon K, Lasko NB and Pace-Schott EF (2021) Sleep Power Spectral Density and Spindles in PTSD and Their Relationship to Symptom Severity. *Front Psychiatry* **12,** 766647. https://doi.org/10.3389/fpsyt.2021.766647.

First M, Gibbon M, Spitzer R and Williams J (2007) *Structured Clinical Interview for DSM-IV-TR Axis I Disorders–NonPatient Edition (SCID-I/NP).* New York, NY: Biometrics Research Department, New York State Psychiatric Institute.

Ge F, Yuan M, Li Y and Zhang W (2020) Posttraumatic Stress Disorder and Alterations in Resting Heart Rate Variability: A Systematic Review and Meta-Analysis. *Psychiatry Investig* **17**(1)**,** 9-20. https://doi.org/10.30773/pi.2019.0112.

Germain A, Buysse DJ and Nofzinger E (2008) Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. *Sleep Med Rev* **12**(3)**,** 185-195. https://doi.org/10.1016/j.smrv.2007.09.003.

Giuditta A (2014) Sleep memory processing: the sequential hypothesis. *Front Syst Neurosci* **8,** 219. https://doi.org/10.3389/fnsys.2014.00219.

Goldstein AN and Walker MP (2014) The role of sleep in emotional brain function. *Annu Rev Clin Psychol* **10,** 679-708. https://doi.org/10.1146/annurev-clinpsy-032813-153716.

Gunduz-Cinar O, Flynn S, Brockway E, Kaugars K, Baldi R, Ramikie TS, Cinar R, Kunos G, Patel S and Holmes A (2016) Fluoxetine Facilitates Fear Extinction Through Amygdala Endocannabinoids. *Neuropsychopharmacology* **41**(6)**,** 1598-1609. https://doi.org/10.1038/npp.2015.318.

Habukawa M, Uchimura N, Maeda M, Ogi K, Hiejima H and Kakuma T (2018) 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* **43,** 34-39. https://doi.org/10.1016/j.sleep.2017.10.012.

Helpman L, Marin MF, Papini S, Zhu X, Sullivan GM, Schneier F, Neria M, Shvil E, Malaga Aragon MJ, Markowitz JC, Lindquist MA, Wager T, Milad M and Neria Y (2016) Neural changes in extinction recall following prolonged exposure treatment for PTSD: A longitudinal fMRI study. *Neuroimage Clin* **12,** 715-723. https://doi.org/10.1016/j.nicl.2016.10.007.

Insana SP, Kolko DJ and Germain A (2012) Early-life trauma is associated with rapid eye movement sleep fragmentation among military veterans. *Biol Psychol* **89**(3)**,** 570-579. https://doi.org/10.1016/j.biopsycho.2012.01.001.

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C and Wang P (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* **167**(7)**,** 748-751. https://doi.org/10.1176/appi.ajp.2010.09091379.

Ioannides AA, Corsi-Cabrera M, Fenwick PB, del Rio Portilla Y, Laskaris NA, Khurshudyan A, Theofilou D, Shibata T, Uchida S, Nakabayashi T and Kostopoulos GK (2004) MEG tomography of human cortex and brainstem activity in waking and REM sleep saccades. *Cereb Cortex* **14**(1)**,** 56-72. https://doi.org/10.1093/cercor/bhg091.

Jenness JL, Miller AB, Rosen ML and McLaughlin KA (2019) Extinction Learning as a Potential Mechanism Linking High Vagal Tone with Lower PTSD Symptoms among Abused Youth. *J Abnorm Child Psychol* **47**(4)**,** 659-670. https://doi.org/10.1007/s10802-018-0464-0.

Jung B, Yang C and Lee SH (2024) Vagus Nerves Stimulation: Clinical Implication and Practical Issue as a Neuropsychiatric Treatment. *Clin Psychopharmacol Neurosci* **22**(1)**,** 13-22. https://doi.org/10.9758/cpn.23.1101.

Klinzing JG, Niethard N and Born J (2019) Mechanisms of systems memory consolidation during sleep. *Nat Neurosci* **22**(10)**,** 1598-1610. https://doi.org/10.1038/s41593-019-0467-3.

Kobayashi I, Boarts JM and Delahanty DL (2007) Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. *Psychophysiology* **44**(4)**,** 660-669. https://doi.org/10.1111/j.1469-8986.2007.537.x.

Kobayashi I, Lavela J and Mellman TA (2014) Nocturnal autonomic balance and sleep in PTSD and resilience. *J Trauma Stress* **27**(6)**,** 712-716. https://doi.org/10.1002/jts.21973.

Laborde S, Mosley E and Thayer JF (2017) Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Front Psychol* **8,** 213. https://doi.org/10.3389/fpsyg.2017.00213.

Lipinska G and Thomas KGF (2019) Rapid eye movement fragmentation, not slow-wave sleep, predicts neutral declarative memory consolidation in posttraumatic stress disorder. *J Sleep Res* **28**(6)**,** e12846. https://doi.org/10.1111/jsr.12846.

Lonsdorf TB, Menz MM, Andreatta M, Fullana MA, Golkar A, Haaker J, Heitland I, Hermann A, Kuhn M, Kruse O, Meir Drexler S, Meulders A, Nees F, Pittig A, Richter J, Romer S, Shiban Y, Schmitz A, Straube B, Vervliet B, Wendt J, Baas JMP and Merz CJ (2017) 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* **77,** 247-285. https://doi.org/10.1016/j.neubiorev.2017.02.026.

Lonsdorf TB, Merz CJ and Fullana MA (2019) Fear Extinction Retention: Is It What We Think It Is? *Biol Psychiatry* **85**(12)**,** 1074-1082. https://doi.org/10.1016/j.biopsych.2019.02.011.

McGaugh JL (2013) Making lasting memories: remembering the significant. *Proc Natl Acad Sci U S A* **110 Suppl 2**(Suppl 2)**,** 10402-10407. https://doi.org/10.1073/pnas.1301209110.

Mellman TA (1997) Psychobiology of sleep disturbances in posttraumatic stress disorder. *Ann N Y Acad Sci* **821,** 142-149. https://doi.org/10.1111/j.1749-6632.1997.tb48275.x.

Mellman TA, Bustamante V, Fins AI, Pigeon WR and Nolan B (2002) REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry* **159**(10)**,** 1696-1701. https://doi.org/10.1176/appi.ajp.159.10.1696.

Mellman TA, Knorr BR, Pigeon WR, Leiter JC and Akay M (2004) Heart rate variability during sleep and the early development of posttraumatic stress disorder. *Biol Psychiatry* **55**(9)**,** 953-956. https://doi.org/10.1016/j.biopsych.2003.12.018.

Mellman TA, Kobayashi I, Lavela J, Wilson B and Hall Brown TS (2014) A relationship between REM sleep measures and the duration of posttraumatic stress disorder in a young adult urban minority population. *Sleep* **37**(8)**,** 1321-1326. https://doi.org/10.5665/sleep.3922.

Mellman TA, Pigeon WR, Nowell PD and Nolan B (2007) Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. *J Trauma Stress* **20**(5)**,** 893-901. https://doi.org/10.1002/jts.20246.

Menz MM, Rihm JS and Buchel C (2016) REM Sleep Is Causal to Successful Consolidation of Dangerous and Safety Stimuli and Reduces Return of Fear after Extinction. *J Neurosci* **36**(7)**,** 2148-2160. https://doi.org/10.1523/JNEUROSCI.3083-15.2016.

Milad MR, Furtak SC, Greenberg JL, Keshaviah A, Im JJ, Falkenstein MJ, Jenike M, Rauch SL and Wilhelm S (2013) Deficits in conditioned fear extinction in obsessive-compulsive disorder and neurobiological changes in the fear circuit. *JAMA Psychiatry* **70**(6)**,** 608-618; quiz 554. https://doi.org/10.1001/jamapsychiatry.2013.914.

Milad MR, Goldstein JM, Orr SP, Wedig MM, Klibanski A, Pitman RK and Rauch SL (2006) Fear conditioning and extinction: influence of sex and menstrual cycle in healthy humans. *Behav Neurosci* **120**(6)**,** 1196-1203. https://doi.org/10.1037/0735-7044.120.5.1196.

Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL and Pitman RK (2008) Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *J Psychiatr Res* **42**(7)**,** 515-520. https://doi.org/10.1016/j.jpsychires.2008.01.017.

Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP and Rauch SL (2009) Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol Psychiatry* **66**(12)**,** 1075-1082. https://doi.org/10.1016/j.biopsych.2009.06.026.

Milad MR and Quirk GJ (2012) Fear extinction as a model for translational neuroscience: ten years of progress. *Annu Rev Psychol* **63,** 129-151. https://doi.org/10.1146/annurev.psych.121208.131631.

Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ and Rauch SL (2007) Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry* **62**(5)**,** 446-454. https://doi.org/10.1016/j.biopsych.2006.10.011.

Milad MR, Zeidan MA, Contero A, Pitman RK, Klibanski A, Rauch SL and Goldstein JM (2010) The influence of gonadal hormones on conditioned fear extinction in healthy humans. *Neuroscience* **168**(3)**,** 652-658. https://doi.org/10.1016/j.neuroscience.2010.04.030.

Miyauchi S, Misaki M, Kan S, Fukunaga T and Koike T (2009) Human brain activity time-locked to rapid eye movements during REM sleep. *Exp Brain Res* **192**(4)**,** 657-667. https://doi.org/10.1007/s00221-008-1579-2.

Noble LJ, Chuah A, Callahan KK, Souza RR and McIntyre CK (2019) Peripheral effects of vagus nerve stimulation on anxiety and extinction of conditioned fear in rats. *Learn Mem* **26**(7)**,** 245-251. https://doi.org/10.1101/lm.048447.118.

Noble LJ, Gonzalez IJ, Meruva VB, Callahan KA, Belfort BD, Ramanathan KR, Meyers E, Kilgard MP, Rennaker RL and McIntyre CK (2017) Effects of vagus nerve stimulation on extinction of conditioned fear and post-traumatic stress disorder symptoms in rats. *Transl Psychiatry* **7**(8)**,** e1217. https://doi.org/10.1038/tp.2017.191.

Noble LJ, Meruva VB, Hays SA, Rennaker RL, Kilgard MP and McIntyre CK (2019) Vagus nerve stimulation promotes generalization of conditioned fear extinction and reduces anxiety in rats. *Brain Stimul* **12**(1)**,** 9-18. https://doi.org/10.1016/j.brs.2018.09.013.

Noble LJ, Souza RR and McIntyre CK (2019) Vagus nerve stimulation as a tool for enhancing extinction in exposure-based therapies. *Psychopharmacology (Berl)* **236**(1)**,** 355-367. https://doi.org/10.1007/s00213-018-4994-5.

Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T and Pitman RK (2000) De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *J Abnorm Psychol* **109**(2)**,** 290-298.

Pace-Schott EF, Germain A and Milad MR (2015a) Effects of sleep on memory for conditioned fear and fear extinction. *Psychol Bull* **141**(4)**,** 835-857. https://doi.org/10.1037/bul0000014.

Pace-Schott EF, Germain A and Milad MR (2015b) Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. *Biol Mood Anxiety Disord* **5,** 3. https://doi.org/10.1186/s13587-015-0018-9.

Pace-Schott EF, Milad MR, Orr SP, Rauch SL, Stickgold R and Pitman RK (2009) Sleep promotes generalization of extinction of conditioned fear. *Sleep* **32**(1)**,** 19-26.

Pace-Schott EF, Seo J and Bottary R (2023) The influence of sleep on fear extinction in trauma-related disorders. *Neurobiol Stress* **22,** 100500. https://doi.org/10.1016/j.ynstr.2022.100500.

Pace-Schott EF, Tracy LE, Rubin Z, Mollica AG, Ellenbogen JM, Bianchi MT, Milad MR, Pitman RK and Orr SP (2014) Interactions of time of day and sleep with between-session habituation and extinction memory in young adult males. *Exp Brain Res* **232**(5)**,** 1443-1458. https://doi.org/10.1007/s00221-014-3829-9.

Palagini L, Baglioni C, Ciapparelli A, Gemignani A and Riemann D (2013) REM sleep dysregulation in depression: state of the art. *Sleep Med Rev* **17**(5)**,** 377-390. https://doi.org/10.1016/j.smrv.2012.11.001.

Pappens M, Schroijen M, Sutterlin S, Smets E, Van den Bergh O, Thayer JF and Van Diest I (2014) Resting heart rate variability predicts safety learning and fear extinction in an interoceptive fear conditioning paradigm. *PLoS One* **9**(9)**,** e105054. https://doi.org/10.1371/journal.pone.0105054.

Paul F, Alpers GW, Reinhard I and Schredl M (2019) Nightmares do result in psychophysiological arousal: A multimeasure ambulatory assessment study. *Psychophysiology* **56**(7)**,** e13366. https://doi.org/10.1111/psyp.13366.

Pena DF, Childs JE, Willett S, Vital A, McIntyre CK and Kroener S (2014) 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* **8,** 327. https://doi.org/10.3389/fnbeh.2014.00327.

Pena DF, Engineer ND and McIntyre CK (2013) Rapid remission of conditioned fear expression with extinction training paired with vagus nerve stimulation. *Biol Psychiatry* **73**(11)**,** 1071-1077. https://doi.org/10.1016/j.biopsych.2012.10.021.

Pyne JM, Constans JI, Wiederhold MD, Gibson DP, Kimbrell T, Kramer TL, Pitcock JA, Han X, Williams DK, Chartrand D, Gevirtz RN, Spira J, Wiederhold BK, McCraty R and McCune TR (2016) Heart rate variability: Pre-deployment predictor of post-deployment PTSD symptoms. *Biol Psychol* **121**(Pt A)**,** 91-98. https://doi.org/10.1016/j.biopsycho.2016.10.008.

Richards A, Kanady JC and Neylan TC (2020) Sleep disturbance in PTSD and other anxiety-related disorders: an updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms. *Neuropsychopharmacology* **45**(1)**,** 55-73. https://doi.org/10.1038/s41386-019-0486-5.

Rissling MB, Dennis PA, Watkins LL, Calhoun PS, Dennis MF, Beckham JC, Hayano J and Ulmer CS (2016) Circadian Contrasts in Heart Rate Variability Associated With Posttraumatic Stress Disorder Symptoms in a Young Adult Cohort. *J Trauma Stress* **29**(5)**,** 415-421. https://doi.org/10.1002/jts.22125.

Rowe K, Moreno R, Lau TR, Wallooppillai U, Nearing BD, Kocsis B, Quattrochi J, Hobson JA and Verrier RL (1999) Heart rate surges during REM sleep are associated with theta rhythm and PGO activity in cats. *Am J Physiol* **277**(3)**,** R843-849. https://doi.org/10.1152/ajpregu.1999.277.3.R843.

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH and Keller MB (2003) 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* **54**(5)**,** 573-583. https://doi.org/10.1016/s0006-3223(02)01866-8.

Saguin E, Gomez-Merino D, Sauvet F, Leger D and Chennaoui M (2021) Sleep and PTSD in the Military Forces: A Reciprocal Relationship and a Psychiatric Approach. *Brain Sci* **11**(10). https://doi.org/10.3390/brainsci11101310.

Schenker MT, Ince S, Ney LJ, Hsu CK, Zuj DV, Jordan AS, Nicholas CL and Felmingham KL (2022) Sex differences in the effect of subjective sleep on fear conditioning, extinction learning, and extinction recall in individuals with a range of PTSD symptom severity. *Behav Res Ther* **159,** 104222. https://doi.org/10.1016/j.brat.2022.104222.

Schneider M and Schwerdtfeger A (2020) Autonomic dysfunction in posttraumatic stress disorder indexed by heart rate variability: a meta-analysis. *Psychol Med* **50**(12)**,** 1937-1948. https://doi.org/10.1017/S003329172000207X.

Seligowski AV, Webber TK, Marvar PJ, Ressler KJ and Philip NS (2022) Involvement of the brain-heart axis in the link between PTSD and cardiovascular disease. *Depress Anxiety* **39**(10-11)**,** 663-674. https://doi.org/10.1002/da.23271.

Seo J, Oliver KI, Daffre C, Moore KN, Gazecki S, Lasko NB, Milad MR and Pace-Schott EF (2022) Associations of sleep measures with neural activations accompanying fear conditioning and extinction learning and memory in trauma-exposed individuals. *Sleep* **45**(3). https://doi.org/10.1093/sleep/zsab261.

Shaffer F and Ginsberg JP (2017) An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health* **5,** 258. https://doi.org/10.3389/fpubh.2017.00258.

Shvil E, Sullivan GM, Schafer S, Markowitz JC, Campeas M, Wager TD, Milad MR and Neria Y (2014) Sex differences in extinction recall in posttraumatic stress disorder: a

pilot fMRI study. *Neurobiol Learn Mem* **113,** 101-108. https://doi.org/10.1016/j.nlm.2014.02.003.

Siepmann M, Weidner K, Petrowski K and Siepmann T (2022) Heart Rate Variability: A Measure of Cardiovascular Health and Possible Therapeutic Target in Dysautonomic Mental and Neurological Disorders. *Appl Psychophysiol Biofeedback* **47**(4)**,** 273-287. https://doi.org/10.1007/s10484-022-09572-0.

Singh D, Norman KA and Schapiro AC (2022) A model of autonomous interactions between hippocampus and neocortex driving sleep-dependent memory consolidation. *Proc Natl Acad Sci U S A* **119**(44)**,** e2123432119. https://doi.org/10.1073/pnas.2123432119.

Souza RR, Oleksiak CR, Tabet MN, Rennaker RL, Hays SA, Kilgard MP and McIntyre CK (2021) Vagus nerve stimulation promotes extinction generalization across sensory modalities. *Neurobiol Learn Mem* **181,** 107425. https://doi.org/10.1016/j.nlm.2021.107425.

Souza RR, Powers MB, Rennaker RL, McIntyre CK, Hays SA and Kilgard MP (2022) Timing of vagus nerve stimulation during fear extinction determines efficacy in a rat model of PTSD. *Sci Rep* **12**(1)**,** 16526. https://doi.org/10.1038/s41598-022-20301-9.

Souza RR, Robertson NM, Mathew E, Tabet MN, Bucksot JE, Pruitt DT, Rennaker RL, Hays SA, McIntyre CK and Kilgard MP (2020) Efficient parameters of vagus nerve stimulation to enhance extinction learning in an extinction-resistant rat model of PTSD. *Prog Neuropsychopharmacol Biol Psychiatry* **99,** 109848. https://doi.org/10.1016/j.pnpbp.2019.109848.

Souza RR, Robertson NM, McIntyre CK, Rennaker RL, Hays SA and Kilgard MP (2021) Vagus nerve stimulation enhances fear extinction as an inverted-U function of stimulation intensity. *Exp Neurol* **341,** 113718. https://doi.org/10.1016/j.expneurol.2021.113718.

Souza RR, Robertson NM, Pruitt DT, Gonzales PA, Hays SA, Rennaker RL, Kilgard MP and McIntyre CK (2019) Vagus nerve stimulation reverses the extinction impairments in a model of PTSD with prolonged and repeated trauma. *Stress* **22**(4)**,** 509-520. https://doi.org/10.1080/10253890.2019.1602604.

Spoormaker VI, Schroter MS, Andrade KC, Dresler M, Kiem SA, Goya-Maldonado R, Wetter TC, Holsboer F, Samann PG and Czisch M (2012) Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. *Hum Brain Mapp* **33**(10)**,** 2362-2376. https://doi.org/10.1002/hbm.21369.

Spoormaker VI, Sturm A, Andrade KC, Schroter MS, Goya-Maldonado R, Holsboer F, Wetter TC, Samann PG and Czisch M (2010) The neural correlates and temporal sequence of the relationship between shock exposure, disturbed sleep and impaired consolidation of fear extinction. *J Psychiatr Res* **44**(16)**,** 1121-1128. https://doi.org/10.1016/j.jpsychires.2010.04.017.

Stocker RPJ, Khan H, Henry L and Germain A (2017) 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* **32**(3)**,** 349-368. https://doi.org/10.1093/arclin/acx003.

Straus LD, Norman SB, Risbrough VB, Acheson DT and Drummond SPA (2018) REM sleep and safety signal learning in posttraumatic stress disorder: A preliminary study in military veterans. *Neurobiol Stress* **9,** 22-28. https://doi.org/10.1016/j.ynstr.2018.07.001.

Suarez-Jimenez B, Albajes-Eizagirre A, Lazarov A, Zhu X, Harrison BJ, Radua J, Neria Y and Fullana MA (2020) Neural signatures of conditioning, extinction learning, and extinction recall in posttraumatic stress disorder: a meta-analysis of functional magnetic resonance imaging studies. *Psychol Med* **50**(9)**,** 1442-1451. https://doi.org/10.1017/S0033291719001387.

Szeska C, Richter J, Wendt J, Weymar M and Hamm AO (2020) Promoting long-term inhibition of human fear responses by non-invasive transcutaneous vagus nerve stimulation during extinction training. *Sci Rep* **10**(1)**,** 1529. https://doi.org/10.1038/s41598-020-58412-w.

Thayer JF, Ahs F, Fredrikson M, Sollers JJ, 3rd and Wager TD (2012) 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* **36**(2)**,** 747-756. https://doi.org/10.1016/j.neubiorev.2011.11.009.

Thayer JF and Lane RD (2000) A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord* **61**(3)**,** 201-216. https://doi.org/10.1016/s0165-0327(00)00338-4.

Thayer JF and Lane RD (2009) Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. *Neurosci Biobehav Rev* **33**(2)**,** 81-88. https://doi.org/10.1016/j.neubiorev.2008.08.004.

Ulmer CS, Hall MH, Dennis PA, Beckham JC and Germain A (2018) 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* **41**(12). https://doi.org/10.1093/sleep/zsy174.

Velasco ER, Florido A, Milad MR and Andero R (2019) Sex differences in fear extinction. *Neurosci Biobehav Rev* **103,** 81-108. https://doi.org/10.1016/j.neubiorev.2019.05.020.

Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, Keane TM and Marx BP (2018) The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychol Assess* **30**(3)**,** 383-395. https://doi.org/10.1037/pas0000486.

Wehrle R, Kaufmann C, Wetter TC, Holsboer F, Auer DP, Pollmacher T and Czisch M (2007) Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods. *Eur J Neurosci* **25**(3)**,** 863-871. https://doi.org/10.1111/j.1460-9568.2007.05314.x.

Wendt J, Konig J, Hufenbach MC, Koenig J, Thayer JF and Hamm AO (2019) Vagally mediated heart rate variability and safety learning: Effects of instructions and number of extinction trials. *Psychophysiology* **56**(10)**,** e13404. https://doi.org/10.1111/psyp.13404.

Wendt J, Neubert J, Koenig J, Thayer JF and Hamm AO (2015) Resting heart rate variability is associated with inhibition of conditioned fear. *Psychophysiology* **52**(9)**,** 1161-1166. https://doi.org/10.1111/psyp.12456.

Whitehurst LN, Cellini N, McDevitt EA, Duggan KA and Mednick SC (2016) Autonomic activity during sleep predicts memory consolidation in humans. *Proc Natl Acad Sci U S A* **113**(26)**,** 7272-7277. https://doi.org/10.1073/pnas.1518202113.

Whitehurst LN, Subramoniam A, Krystal A and Prather AA (2022) Links between the brain and body during sleep: implications for memory processing. *Trends Neurosci* **45**(3)**,** 212-223. https://doi.org/10.1016/j.tins.2021.12.007.

Wicking M, Steiger F, Nees F, Diener SJ, Grimm O, Ruttorf M, Schad LR, Winkelmann T, Wirtz G and Flor H (2016) Deficient fear extinction memory in posttraumatic stress disorder. *Neurobiol Learn Mem* **136,** 116-126. https://doi.org/10.1016/j.nlm.2016.09.016.

Yetton BD, Niknazar M, Duggan KA, McDevitt EA, Whitehurst LN, Sattari N and Mednick SC (2016) Automatic detection of rapid eye movements (REMs): A machine learning approach. *J Neurosci Methods* **259,** 72-82. https://doi.org/10.1016/j.jneumeth.2015.11.015.

Zhang Y, Ren R, Sanford LD, Yang L, Zhou J, Zhang J, Wing YK, Shi J, Lu L and Tang X (2019) Sleep in posttraumatic stress disorder: A systematic review and meta-analysis of polysomnographic findings. *Sleep Med Rev* **48,** 101210. https://doi.org/10.1016/j.smrv.2019.08.004.

Zuj DV, Palmer MA, Lommen MJ and Felmingham KL (2016) The centrality of fear extinction in linking risk factors to PTSD: A narrative review. *Neurosci Biobehav Rev* **69,** 15-35. https://doi.org/10.1016/j.neubiorev.2016.07.014.