Heart Rate Variability During REM Sleep is Associated with Reduced Negative Memory Bias

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Abstract

Emotional memories change over time, but the mechanisms supporting this change are not well understood. Memory consolidation during sleep has been shown to selectively prioritize negative experiences while forgetting neutral memories. Whereas studies examining the role of vagal heart rate variability (HRV) during waking in memory consolidation have shown that vagal HRV is associated with enhanced memory of positive experiences at the expense of negative ones. However, no studies have explored how HRV during sleep contributes to emotional memory processing. Accordingly, we aimed to investigate the neural and vagal contributions during sleep to the processing of neutral and negative memories. To do so, we examined the impact of pharmacological vagal suppression, using zolpidem, on overnight emotional memory consolidation in a double-blind, placebo-controlled, within-subject, cross-over design. Thirty-two participants encoded neutral and negative pictures in the morning, then were tested on picture recognition before and after a night of sleep. Zolpidem or a placebo drug were administered in the evening before overnight sleep, monitored with electroencephalography and electrocardiography. Results showed that higher vagal HRV in Non-Rapid Eye Movement Sleep slow wave sleep (NREM SWS) and Rapid Eye Movement Sleep (REM) was associated with greater overnight improvement for neutral pictures in the placebo condition. Additionally, higher vagal HRV during REM was associated with an emotional memory tradeoff (i.e., greater memory for neutral at the expense of negative images), indicating a potential role for REM vagal HRV in forming a positive memory bias overnight. As previously reported, zolpidem reduced vagal HRV during SWS and increased NREM sigma power, and this vagal suppression eliminated the positive memory bias. Lastly, we used a stepwise linear mixed effects regression framework to investigate how NREM sigma power and vagal HRV during REM independently explained the variance in the emotional memory tradeoff effect and found that including vagal HRV significantly improved the model's fit. Overall, these results suggest that neural and vagal signals synergistically interact in the processing of emotional memories, with REM vagal HRV playing a specific role in contributing to the positive memory bias.

Introduction

The arc of healthy emotional memory processing changes over time, beginning with heightened emotional reactivity and intense reliving of the episodic experience, followed by a gradual reduction in affective response and a strengthening of the memory for episodic details (van der Helm & Walker, 2011; Walker, 2010). Although the psychological components of this process are somewhat understood, the underlying mechanisms driving this process are not. Several lines of evidence suggest an important role of sleep, with studies showing that, compared with wake, sleep may prioritize the consolidation of negative memories at the expense of neutral memories, the so-called emotional memory tradeoff effect (Nishida et al., 2009; van der Helm & Walker, 2011; Wagner et al., 2006; Wiesner et al., 2015). On the other hand, studies examining the role of autonomic activity during waking, specifically the vagal/parasympathetic component of heart rate variability (HRV), have shown that vagal HRV is associated with increasing memory of positive experiences at the expense of negative ones (Cho et al., 2023). However, no studies have investigated how HRV during sleep contributes to emotional memory processing. The current study investigates the neural and autonomic contributions during sleep to the processing of neutral and negative memories.

Although studies demonstrate the importance of sleep in emotional memory processing, there are mixed results as to the relative importance of the different sleep stages (Cox et al., 2018; Denis et al., 2022; Groch et al., 2013; Lipinska et al., 2019; Payne et al., 2008; Schäfer et al., 2020). Nap studies examining the differential effects of NREM and REM sleep have indicated that NREM sleep is selectively related to the consolidation of negative, episodic information, with no added benefit from REM sleep (Cellini et al., 2016; Payne et al., 2015). These findings align with overnight studies that pharmacologically increased NREM spindle activity (12-15 Hz) using zolpidem and reported that increased spindle activity was associated with greater memory for negative than neutral stimuli, compared with placebo (Kaestner et al., 2013; Simon et al., 2022). However, REM sleep has also been emphasized (Ackermann & Rasch, 2014; Goldstein & Walker, 2014), with studies showing that REM-rich sleep, rather than SWS-rich sleep, enhances emotional text compared to neutral text (Wagner et al., 2001). Additionally, studies suggest positive correlations between negative emotional memory and minutes of REM overnight (Wiesner et al., 2015) and during a daytime nap (Nishida et al., 2009). Carr and Nielsen investigated the effect of REM sleep on positive, negative, and neutral cued words, or words signaled to be remembered prior to sleep, and found that a nap with REM, compared to wake or a nap with only NREM, enhanced the memory for positive, compared to negative, cued words (Carr & Nielsen, 2015). Similarly, another study demonstrated that a nap with REM, compared to wake, showed reduced ratings of fearful expressions and increased ratings of happy faces (Gujar et al., 2011), indicating that REM sleep modulated emotional reactivity towards positive stimuli. In contrast, REM deprivation led to decreased arousal ratings to negative stimuli, suggesting that REM may exacerbate negative emotional arousal (Lara-Carrasco et al., 2009). These mixed results have been reflected in meta-analyses, indicating that the effect of sleep and its stages may be context or content specific (Lipinska et al., 2019; Schäfer et al., 2020). Therefore, although NREM and REM sleep have been associated with emotional memories, more research is needed to further explore this relationship and other potential mechanisms through which sleep processes emotional memories, e.g., vagal HRV.

Resting daytime HRV has been associated with emotion regulation (Malik & Camm, 1993; Sakaki et al., 2016). HRV, or variation in time between successive heartbeats, reflects the ability of the parasympathetic system to self-regulate in response to environmental change; for example, higher HRV signifies more effective transition from a high sympathetic arousal state (e.g., during stressful situations) to a relaxed state (Malik & Camm, 1993). A recent study by Cho et al. (2023) used HRV biofeedback to examine how causally increasing resting HRV affected the neural mechanisms of emotional memory processing (Cho et al., 2023). They reported that increasing HRV was associated with greater memory overall, as well as a memory bias favoring positive over negative images, and this effect was mediated by changes in left amygdala-medial prefrontal cortex (mPFC) functional connectivity (Cho et al., 2023). Other studies using HRV biofeedback have shown increased HRV led to increased connectivity between the PFC and cortical regions that support cognition (Schumann et al., 2021), which may be the underlying mechanisms for studies suggesting a positive correlation between higher HRV and greater executive functioning. For example, these studies have found that an association between higher HRV and improved working memory (Hansen et al., 2003; Suriya-Prakash et al., 2015), enhanced decision making (Forte et al., 2021), efficient attentional control (Park et al., 2012), and better executive functioning (Thayer et al., 2009; Williams et al., 2019). Overall, these findings emphasize the role of HRV in emotion regulation and the enhancement of positive memories, which may be supported by broader executive functioning.

A growing body of research indicates that HRV during sleep may also support memory processes. Sleep strongly modulates ANS activity, with an overall reduction in heart rate and an increase in the parasympathetic component of HRV (high-frequency HRV: HF HRV; 0.15-0.4 Hz) during NREM sleep (Chen et al., 2020b, 2020a; Trinder et al., 2012; Whitehurst et al., 2018). REM sleep, in comparison, is a mixed autonomic state with both high sympathetic and parasympathetic activity (Chen et al., 2020; Chen et al., 2021). Critically, autonomic activity during NREM and REM has been differentially related to improvement in sleep-dependent processing (Chen et al., 2020; Chen et al., 2021; Whitehurst et al., 2016). Whitehurst et al. (2016) examined the effect of implicit priming on enhancing post-nap performance on a creativity task and measured the sleep and HRV variables associated with performance improvement. They reported that HF HRV during REM sleep and REM minutes accounted for a large amount of variance in improved performance over sleep (Whitehurst et al., 2016). Notably, REM minutes and HF HRV were not correlated with each other, suggesting that these features of sleep may be contributing non-overlapping mechanisms. Prior literature suggests a role for vagal HRV in offline cognitive enhancement, yet no studies have investigated the role of overnight vagal HRV in emotional memory processing.

The current study examined the impact of vagal activity, as measured by HF HRV, during sleep on emotional memory processing. The study was conducted as a reanalysis of an existing dataset in which participants were tested on an emotional memory task before and after a night of sleep with placebo or a pharmacological intervention, zolpidem, which was used to reduce HF HRV during SWS. We hypothesized that higher vagal activity during sleep would improve memory for neutral images in the placebo condition and that reducing vagal activity in the zolpidem condition would increase the emotional memory bias, resulting in greater memory for emotional compared with neutral images. We also hypothesized that incorporating vagal activity during sleep into the existing model of NREM sigma power, as described by Simon et al., (2022), would

significantly enhance the model's accuracy in predicting the overnight consolidation of emotional memory.

Methods

Participants

Thirty-three healthy participants between the ages of 18 and 30 (M_{age} = 20.5 years [SD = 2.91], 16 females) provided informed consent, which was approved by the Western Institutional Review Board and the University of California, Riverside Human Research Review Board. All participants were healthy with no personal history of neurological, psychological, or other chronic illness and were naïve to or had limited contact with (< 2 lifetime use and no use in last year) zolpidem. Our exclusion criterion included irregular sleep/wake cycles, past history or present diagnosis of a sleep disorder, personal or familial history of diagnosed psychopathology, substance abuse/dependence, loss of consciousness greater than 2 minutes, a history of epilepsy, current use of psychotropic medications, non-correctable visual impairments, or any cardiac or respiratory illness that might affect cerebral metabolism. Participants were assessed for inclusion in-person using a modified Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (First et al., 1997), self-report questionnaires examining current and past health and wellness, and underwent a medical evaluation with the study physician, including a toxicology screening for schedule I and II drug substances. Participants were compensated monetarily for their participation.

Experimental Design (see Fig. 1 for Schematic)

The current work utilized data previously published in two studies that addressed: 1) the effect of sigma activity on emotional memory consolidation (Simon et al., 2022), and 2) the effect of HRV on episodic and working memory . We used a double-blind, placebo-controlled, within-subject, cross-over design, with visit order randomized and counterbalanced, to examine the role of HRV during sleep on sleep-dependent emotional memory processing. In study 1, we showed that zolpidem, compared with placebo, increased sigma power and increased emotional memory tradeoff. In study 2, we showed that zolpidem, compared with placebo, suppressed HRV during SWS and increased a tradeoff between episodic and working memory. The current paper was designed examine the effect of suppressing vagal activity during sleep, using zolpidem, on overnight emotional memory consolidation.

Procedures

All participants reported to the lab between 8:00 AM and 9:00 AM and completed the encoding phase of the Emotion Picture Task (EPT). Afterwards, participants remained in the lab until 2:00 PM to undergo hourly monitoring of their vitals (blood pressure, heart rate, and subjective measurements). Participants were asked to refrain from exercise, sleep, caffeine, or other drug substances between sessions. Participants returned to the lab at 9:00 PM to complete EPT Test 1. Participants were then given 10-mg dose of placebo or zolpidem and polysomnography was administered. Vitals were monitored again until lights out at approximately 11:00 PM. All

participants were woken up by 9:00 AM and provided breakfast and a break. EPT Test 2 was administered at approximately 10:30 AM. Participants completed this protocol twice, once for each drug condition (see Fig. 1 for schematic).

Drug Protocol

Directly before lights out, participants ingested either 10-mg of placebo or zolpidem, a positive allosteric modulator of GABAA receptors with a short half-life (1.5–4.5 h) and rapid onset which was prepared by the MDMX Corona Research Pharmacy. Zolpidem is a GABAA agonist that has been shown to decrease average heart rate (Sinha & Yadav, 2020) and overall HRV (Machado et al., 2011, Chen et al., 2021), while increasing relative fast sigma power and sleep spindle density (Mednick et al., 2013; Simon et al., 2022; Zhang et al., 2020). The zolpidem and the placebo capsules were visually indistinguishable.

Polysomnography

This study used a 32-channel electroencephalography (EEG) cap (EASYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10–20 System (Jasper, 1958). There were 22 neural channels, 2 electrocardiogram (ECG), 2 electromyogram (EMG), 2 electrooculogram (EOG), a ground, a reference channel, and 2 mastoid recordings. EEG was recorded at a 1000-Hz sampling rate and preprocessed in BrainVision Analyzer 2.0 (BrainProducts, Munich Germany). During preprocessing, all neural electrodes were re-reference to the contralateral mastoid and artifacts and arousals were removed via visual inspection. Low pass (0.3 Hz) and high-pass filters (35 Hz) were applied to all neural and EOG channels. The raw data was scored using eight neural electrodes (F3, F4, C3, C4, P3, P4, O1, O2), EMG, and EOG according to Rechtschaffen and Kales in 30-s epochs (Rechtschaffen & Kales, 1968). Then, wake after sleep onset (WASO) and minutes in each sleep stage (NREM Stage 1, NREM Stage 2, NREM Stage 3, and REM) were calculated.

Simon et al. (2022) examined the impact of sleep frequency bands on overnight emotional memory consolidation. Following their protocol, we analyzed relative fast sigma power (12-15 Hz) from the central channels (C3 and C4) in NREM N2 and SWS, given that sigma power is most prominent over the central channels (Simon et al., 2022). Based on their results, we focused on C4 in these set of analyses.

Emotion Picture Task (EPT)

Stimuli

The EPT consisted of three phases: an encoding phase and two retrieval phases, see Figure 1. The pre-sleep retrieval phase was in the evening, approximately 12-hours after encoding (Test 1), and the post-sleep retrieval phase was the next morning after a night of sleep in the lab and 24-hours after encoding (Test 2). Participants were shown and asked to remember negative and neutral pictures from the International Affective Picture System, or IAPS (Lang et al., 1997). The standard IAPS ratings ranged from 1, more unpleasant and less arousing, to 9, more pleasant and

highly arousing. These standard IAPS ratings were used to control for arousal and valence to maximize the difference between neutral, low arousing (valence: $M = 5.13$; $SD = 1.44$; arousal: $M = 3.87$; $SD = 2.19$) and negative, highly arousing (valence: $M = 2.88$; $SD = 1.57$; arousal: $M = 5.52$; $SD = 2.09$) pictures. The negative and neutral pictures were counterbalanced across condition without repetition. This task was administered on a Windows computer using Matlab with Psychtoolbox. Our task code (encoding and recognition test) is freely available online at https://github.com/MednickLab/GenericMemoryTask.

Figure 1: Experimental Design Schematic

Encoding and Testing Procedure

We controlled for primacy and recency effects by displaying 4 neutral pictures before and 4 after the stimulus set. During the encoding phase, participants were shown 20 negative and 20 neutral pictures for 500 ms. A fixation marker was always presented for 1000 ms before each picture. Each retrieval test involved half of the initially presented pictures along with 20 new pictures – 10 negative and 10 neutral. For each picture, participants had unlimited time to determine whether it was old (shown at encoding) or new. See Figure 2 for EPT task example.

Figure 2: Emotional Picture Task Paradigm

Performance Measures

Memory performance using discriminability index (d') was calculated using the z transform of hit rate (% of pictures correctly identified as present) minus the false alarm rate (% of pictures incorrectly identified as present) at both Test 1 and Test 2 (see Supplementary Materials). Higher d' scores signify better performance. We calculated overnight memory performance by the difference between Test 1 and Test 2 d' (Test 2 d' – Test 1 d') separately for neutral and negative pictures. More positive overnight memory performance indicates better performance for the morning test compared to the evening test. We also created an emotional memory tradeoff score derived by subtracting the neutral overnight memory performance from the negative overnight memory performance (negative d' difference– neutral d' difference). For this score, positive scores would suggest a negative memory bias (negative better than neutral), whereas negative scores would suggest positive memory bias (neutral better than negative).

Heart Rate Variability (HRV)

ECG data was collected using a modified Lead II Einthoven configuration. We analyzed HRV of the R-waves series during the night using Kubios HRV Analysis Software 2.2 (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland), according to the Task Force guidelines (Electrophysiology Task Force of the European Society of Cardiology and the North American Society of Pacing and, 1996). The Kubios software automatically detected R-peaks of the QRS signal on the ECG. The identified R-peaks were visually examined, and incorrect R-peaks were manually edited by trained technicians. Artifacts were removed by the Kubios software using the provided automatic medium filter. Missing beats were corrected via cubic spline interpolation and then inter-beat intervals were calculated. Additionally, a third-

order polynomial filter was applied to the time series to remove trend components. The RR intervals (ms; time interval between consecutive R-peaks) were analyzed with a MATLAB-based algorithm (Chen et al., 2021; Whitehurst et al., 2018) using an autoregressive model, with the model order set at 16 (Boardman et al., 2002).

HRV Measures

We calculated and selected HF HRV (0.15–0.40 Hz; ms^2) as the overall measure of HRV because it is considered an index of vagal tone, and previous research has shown that zolpidem selectively suppresses vagal (HF HRV) tone, but has no impact on low-frequency (LF; 0.04 to 0.15 Hz; ms^2) HRV (Chen et al., 2021; Machado et al., 2011). HF had skewed distributions, and therefore, it was transformed by taking the natural logarithm. HRV was calculated based on consecutive artifact-free 5-minute windows to remain consistent with previous nocturnal sleep studies (Ako et al., 2003; Brandenberger et al., 2003; de Zambotti et al., 2014). The entire 5-minute window needed to be free from stage transitions, arousal, or movements. We calculated and analyzed HRV for NREM SWS and REM sleep.

Data Reduction and Cleaning

The initial dataset included 33 records for each drug condition. Two participants withdrew from the study before completing both drug conditions due to scheduling conflicts – one did not complete the zolpidem visit and the other did not complete the placebo visit. Whenever possible, we retained the data for the visit these two participants did complete. Therefore, 31 participants successfully completed the entire study, including both drug conditions.

EPT

Negative or neutral performance data was removed when there were fewer than five out of ten hits. Therefore, negative performance data was removed for two participants in the placebo condition and three participants in the zolpidem condition. Neutral performance data was removed for four participants in the placebo condition and four participants in the zolpidem condition. After cleaning, the placebo condition contained 30 participants' negative performance data and 28 participants' neutral performance data. After cleaning, the zolpidem condition contained 29 participants' negative performance data and 28 participants' neutral performance data. For between drug condition analyses, only the 31 participants that completed both visits were used: 23 participants after cleaning.

HRV

HRV data was lost due to experimental error for both visits for two participants and for the placebo visit of another two participants. The autoregressive model used to calculate HRV metrics required consecutive undisturbed windows of sleep without stage transitions, arousals, or movement, which resulted in some participants lacking sufficient HRV data for a sleep stage. For SWS sleep, the dataset included HRV data for 28 participants in the zolpidem condition and 27 in the placebo group before cleaning. For REM sleep, the dataset included HRV data for 29 participants in the zolpidem condition and 27 in the placebo group before cleaning. We cleaned

the data for each drug condition independently. We removed HRV data that were 2.5 standard deviations above or below the mean for that sleep stage before we took the natural logarithm. This resulted in the exclusion of one participant's SWS HRV in the placebo condition, one participants' SWS HRV in the zolpidem condition, and one participants' REM HRV in the zolpidem condition. After data cleaning, the final dataset included SWS HRV data for 27 participants in the zolpidem condition and 26 in the placebo group and REM HRV data for 28 participants in the zolpidem condition and 27 in the placebo group.

Statistical Analyses

All analyses were performed in R version 4.3.2 using packages lme4, ggplot2, dplyr, tidyr, lme4, and rstatix.

Associations between Vagal Activity and Emotional and Neutral Memory

We first computed Pearson's *r* to assess the relation between HRV within each sleep stage and overnight memory performance, both for negative and neutral images. We also calculated the 95% confidence interval for the correlation and the t-statistic, both of which test the null hypothesis that there is no significant correlation between the two variables. These relations were assessed separately for each drug condition (zolpidem and placebo). In addition, we statistically compared the correlations between HRV within each sleep stage and negative versus neutral memory performance using the Fisher r-to-z transformation. We computed the emotional difference score (EmoDiff) by subtracting the fisher-transformed z-scores for negative and neutral stimuli (negative z-score – neutral z-score). The magnitude of the EmoDiff score indicates the size of the difference in standard deviation units. A positive EmoDiff score indicates that the correlation between HRV and memory performance for negative images is stronger than the correlation between HRV and memory performance for neutral images. A negative EmoDiff score indicates that the correlation between HRV and memory performance for neutral images is stronger than the correlation between HRV and memory performance for negative images. We corrected for multiple comparisons using the Holm-Bonferroni method, corrected correlations were statistically significant if $p_{adj}<0.05$.

Vagal Activity and the Emotional Memory Tradeoff Effect

We computed Pearson's *r*, a 95% confidence interval, and a test t-statistic to assess the relation between HRV within each sleep stage and emotional memory tradeoff score. These relations were assessed separately for each drug condition (zolpidem and placebo). We corrected for multiple comparisons using the Holm-Bonferroni method, corrected correlations were statistically significant if $p_{adj}<0.05$.

Comparing the Impact of Sigma Power and Vagal Activity on the Emotional Memory Tradeoff Effect

Building off the findings of Simon et al., we used a regression framework to determine whether including HRV and sigma power in the model explains a significant amount of variance in the emotional memory tradeoff effect. We ran stepwise linear mixed effects models, first with a base

model that included the emotional memory tradeoff as the dependent variable, condition and mean centered weight as covariates, and a random fixed effect for each subject. We included mean centered weight as a covariate in each of these analyses to account for the different rates of drug absorption due to the weight of our participants (Simon et al., 2022). The sigma model included SWS sigma power and an interaction term between condition and sigma power. The HRV model expanded upon the sigma model by including REM HRV and another interaction term between condition and REM HRV. The interaction terms allowed us to determine whether the effect of condition on the emotional memory tradeoff effect varies depending on REM HRV or sigma power. For model selection, we calculated each model's adjusted marginal R^2. Since all models include a common random effect term for each subject, we used the adjusted marginal R^2, rather than the conditional R^2, because it represents the portion of variance explained by the fixed effects only and is more in line with the intuitive definition of R^2 (Sotirchos et al., 2019). We then ran likelihood ratio tests between the sigma model and the full model that included both sigma power and HRV.

Results

We first confirmed the HRV results as published in Chen et al. with zolpidem significantly reducing HRV during SWS (Chen et al., 2021). Second, in the placebo condition, we confirmed the behavioral results of greater overnight consolidation of neutral memories than negative memories (Simon et al., 2022). Third, in the zolpidem condition, we replicated the result that there was greater overnight retention of negative memories compared to neutral memories (Simon et al., 2022). For the replications of prior literature, see the supplementary materials.

Table 1. Summary of Sigma and HRV Parameters Across Sleep Stages

Associations between Vagal Activity and Emotional and Neutral Memory

Here, we examined overnight performance change for negative and neutral pictures in relation to HRV during SWS and REM sleep in both the placebo and zolpidem conditions, using Pearson's *r* correlations.

Placebo: Overnight performance change (Test 2 – Test 1) for neutral pictures was positively correlated with SWS HRV ($r=0.520$, $p_{adj}=.011$) and REM HRV ($r=0.550$, $p_{adj}=.010$). Individuals with higher vagal HRV during SWS and REM showed better memory performance for neutral pictures in the morning, given their pre-sleep baseline performance, compared to individuals with lower vagal autonomic tone. We found no significant results for HRV and the overnight performance change for negative pictures (all $p_{adj}=1$), suggesting a selective enhancement of neutral memories over negative with increased HRV during SWS and REM.

Zolpidem: As predicted, the reduction in HRV in the zolpidem condition eliminated the bias towards neutral memories that was found in the placebo condition. As such, we found no significant correlations between the overnight performance change for neutral images and HRV in any sleep stage (all $p_{adj}=1$). There were also no significant correlations between the overnight performance change for negative images and HRV in any sleep stage (all $p_{adj}=1$). This suggests

that significant reductions in HRV impairs the overnight processes that lead to a bias towards neutral memories.

Figure 1. Correlations Between Vagal Activity and the Overnight Performance Change in Emotional and Neutral Memory.

Table 2. Correlations Between Vagal Activity and the Emotional and Neutral Memory

To further investigate this potential positive memory bias with higher vagal autonomic function, we tested whether the correlations for memory performance and HRV measures were significantly different between negative and neutral memories. We computed the EmoDiff score, or the Holm–Bonferroni corrected Fisher r-to-z transformations, to compare the differences between these correlations.

Placebo: We found significant differences between the correlations between HRV and negative overnight performance versus neutral overnight performance change, for both SWS (EmoDiff = -2.240, p_{adj}=.025) and REM (EmoDiff = -2.538, p_{adj}=.022). These results suggest that higher HRV across sleep stages predicted a selective enhancement in overnight memory for neutral compared with negative memories, indicative of a reduced negative memory bias, or an increased positive memory bias.

Zolpidem: Again, zolpidem, which significantly lowered vagal autonomic tone, eliminated the positive memory bias for neutral over negative memories. For the zolpidem condition, there were no significant differences in the relation between HRV and the overnight performance change for neutral or negative images (all p_{adj}=.926).

Table 3. Differences between Fisher-Transformed Z-scores for Vagal Activity and Emotional and Neutral Memory.

Vagal Activity and the Emotional Memory Tradeoff Effect

Given that we demonstrated a unique contribution of HRV during sleep to negative and neutral memory processing, we, next, examined the emotional memory tradeoff score (negative overnight performance change – neutral overnight performance change) to investigate a possible trade-off between higher HRV and greater neutral memory at the expense of negative memory. As explained in the Methods, more positive scores indicate a negative memory bias (negative better than neutral), whereas negative scores indicate a positive memory bias (neutral better than negative).

Placebo: There was a significant negative correlation between the emotional memory tradeoff score and REM HRV (r=-0.460, p_{adj}=.034), that is, individuals with higher HRV during REM exhibited greater memory for neutral images at the expense of negative images (positive overnight memory bias). No significant correlation for SWS HRV (r=-0.360, p_{adj}=.069) was found.

Zolpidem: Adding zolpidem eliminated significant associations between the emotional memory tradeoff score and HRV measures during SWS ($r=-0.260$, $p_{adj}=.380$) and REM ($r=-0.170$, $p_{adj}=.380$). These findings suggest that reducing HRV neutralizes the positive memory bias, leading to a non-significant negative correlation where negative images are remembered more.

Table 4. Correlations Between Vagal Activity and the Emotional Memory Tradeoff Effect

Figure 2. Correlations Between Vagal Activity and the Emotional Memory Tradeoff Effect**.**

Comparing the Impact of Sleep Spindles and Vagal Activity on the Emotional Memory Tradeoff Effect

Given the concurrent enhancing effects on spindles by zolpidem, we examined the degree to which both spindles and HRV contribute to the emotional memory trade-off effect using a regression framework. The base model tested the effect of drug condition, the sigma model tested the effect of SWS sigma power and its interaction with condition, and the full model added REM HRV and its interaction with condition. Using likelihood ratio tests, we determined whether the addition of REM HRV significantly improved the model's explanatory power. This analysis helped quantify the additional variance in the emotional memory tradeoff effect accounted for by HRV, offering deeper insights into its physiological influences.

Base Model: We ran stepwise linear mixed effects models with a base model including the emotional memory tradeoff as the dependent variable, drug condition and centered weight as covariates, and a random fixed effect for each subject. The base model determined the effect of drug condition and centered weight on the emotional memory tradeoff effect. For the base model, drug condition had a statistically significant effect on emotional memory tradeoff ($\beta = 0.853$, $t = 2.731$, $p = .010$). This result indicates that the zolpidem conditions, compared to placebo, had a higher emotional memory tradeoff score, and therefore, greater memory for negative pictures at the expense of neutral pictures. There was not a significant effect of centered weight ($\beta < 0$, $t = -0.053$, $p = .958$). The base model had an adjusted marginal R^2 of 0.077.

Sigma Model: Next, we included SWS sigma power and an interaction between condition and sigma power into the base model. There was a significant interaction between condition and sigma power during SWS ($\beta = -2.618$, $t = -2.110$, $p = .042$). Thus, as previously shown, the impact of sigma power on the emotional memory tradeoff score significantly differed between the zolpidem and placebo conditions, with stronger correlation in zolpidem than placebo (negative β coefficient). Additionally, there was a significant fixed effect for drug condition ($\beta = 2.164$, $t = 3.148$, $p = .004$), indicating that, compared to placebo, zolpidem had greater emotional memory tradeoff towards negative pictures. There was not a significant fixed effect for sigma power ($\beta = 2.159$, $t = 1.697$, $p = .096$). The fast sigma model had an adjusted marginal R^2 of 0.127.

Full Model: Here, we tested the emotional memory tradeoff score as the dependent variable and drug condition, centered weight, SWS sigma power and REM HRV as covariates, and a random effect of subject ID. This model also included two interactions terms: an interaction between condition and SWS sigma power and an interaction between condition and REM HRV. After

controlling for the separate effects of condition and centered weight, there was a significant fixed effect for REM HRV ($\beta = -0.563$, $t = -2.753$, $p = .008$) and for sigma power ($\beta = 3.322$, $t = 3.192$, $p = .003$). The significant interaction between condition and sleep sigma power during SWS remained ($\beta = -12.837$, $t = -2.387$, $p = .021$). Yet, there was not a significant interaction between condition and REM HRV ($\beta = 0.253$, $t = 0.797$, $p = .429$) or a significant fixed effect for drug condition ($\beta = 0.693$, $t = 0.330$, $p = .743$). These results suggest that while REM HRV and SWS sigma power independently contribute to the emotional memory tradeoff, the interaction between REM HRV and condition does not significantly influence memory consolidation. This indicates that REM HRV has a distinct role in emotional memory consolidation and its effect was not significantly modulated by the drug condition. This model had an adjusted marginal R^2 of 0.365.

The sigma model built upon the base model to also include SWS sigma power and explained approximately 12.7% of the variance based on the fixed effects. By adding REM HRV, the full model explained approximately 36.5% of the variance. We ran a likelihood ratio test to compare the sigma and full models and showed that including HRV in the model significantly improves its fit ($\chi^2 = 9.4603$, $p = .008$), providing evidence that HRV contributes to the explanation of variance in the emotional memory tradeoff effect. Therefore, REM HRV is a crucial predictor for overnight emotional memory consolidation and should be included in models aiming to understand this process.

Table 5. Model Comparison Results.

Discussion

We investigated how vagal activity during sleep impacts overnight memory consolidation of emotional and neutral pictures. In order to achieve this goal, we tested participants on an emotional picture task before and after a night of sleep where we measured both EEG (to evaluate brain oscillations) and ECG (to measure vagal HRV). We examined the role of HRV in this process, using a within subjects, double blind, crossover design, where we compared placebo to a pharmacological intervention, zolpidem, which has been shown to selectively suppress HRV during SWS (Chen et al., 2021). First, building on prior findings (Simon et al., 2022), our results show a drug condition effect on the emotional memory tradeoff, where the placebo condition enhanced neutral memories over negative memories, while the zolpidem condition enhanced negative memories compared to neutral. Second, in the placebo condition, we found that the overnight performance change for neutral pictures was positively associated with vagal HRV during SWS and REM, but there was no association with negative memories. Pharmacologically suppressing overnight vagal activity with zolpidem eliminated associations between neutral memory performance and vagal HRV during sleep. Third, we examined associations between HRV during SWS and REM and the emotional memory tradeoff score in each drug condition. In the placebo condition, we found that higher REM HRV, but not SWS HRV, was significantly correlated with greater memory for neutral images at the expense of negative images, whereas in the zolpidem condition the association disappeared. Finally, using a stepwise linear regression model, we found that REM HRV significantly contributed to explaining the underlying patterns

in the emotional memory tradeoff effect. Together, these results suggest that vagal HRV during REM sleep provides substantial explanatory power into the mechanisms of emotional memory consolidation.

We first replicated prior findings using this dataset (Simon et al., 2022) to show a drug condition effect on the emotional memory tradeoff (see supplementary materials or Simon et al., 2022). The placebo condition enhanced neutral memories over negative memories, which is inconsistent with direction of the tradeoff that is typically hypothesized. However, when we pharmacologically increased NREM spindle activity (12-15 Hz) using zolpidem, the traditional tradeoff emerged, and greater spindle activity was associated with greater memory for negative than neutral images. This effect was also found by Kaestner et al. and contrasts results indicating that emotional memories are strengthened more than non-emotional memories during sleep (Nishida et al., 2009; Wagner et al., 2001, 2006; Wiesner et al., 2015). The mixed results surrounding the emotional memory tradeoff effect have been reviewed in meta-analyses that conclude the effect of sleep and its stages may be context or content specific (Lipinska et al., 2019; Schäfer et al., 2020). These studies often fail to consider the role of HRV in this process, and our results bring forward an underlying mechanism that may help alleviate discrepancies in results. Although it may be unexpected that HRV during sleep would modulate the emotional memory tradeoff, our results are congruous with research investigating the association between daytime HRV and emotional memory and regulation (Cho et al., 2023; Thayer & Lane, 2000).

Second, we aimed to extend the behavioral findings to explore the role of HRV in emotional memory consolidation. We found, in the placebo condition, that the overnight performance change for neutral pictures was positively associated with vagal HRV during SWS and REM, yet there was no association with negative memories. Our results align with prior literature showing that increasing daytime HRV through biofeedback induces a significant and similar bias for positive and neutral images, compared to negative (Cho et al., 2023). They also found that decreasing daytime HRV did not lead to the same biases, and there were no significant differences in neutral, negative, or positive images (Cho et al., 2023). Our results extend these findings by showing that decreasing HRV during sleep, using zolpidem, similarly eliminates the associations between HRV and memory performance. Taken together, these results indicate that HRV may play comparable roles during wake and sleep in emotional memory processing, specifically to enhance the consolidation of non-emotional and positive memories, while shifting the focus away from negative memories.

Third, we examined if, in addition to consolidating neutral images, HRV during SWS and REM was associated with the emotional memory tradeoff. Indeed, we found that, in the placebo group, the tradeoff, or positivity memory bias for neutral stimuli at the expense of negative stimuli, was positivity associated with HRV during REM, but not SWS. The lack of association for HRV during SWS suggests that HRV during REM sleep specifically is contributing to the shift in bias away from negative stimuli. These findings support the hypothesis that REM sleep processes emotions and emotional memories (Goldstein & Walker, 2014; van der Helm & Walker, 2011; Walker, 2010). REM sleep may enable the mPFC to exert greater regulatory control over the amygdala through its facilitation of mPFC-amygdala connectivity, and thereby, modulate the emotional significance of memories (Walker, 2010). The amygdala during REM, compared to wake, also plays a more dominant role in regulating the ANS, with its activity being more

closely linked to HRV (Desseilles et al., 2006). Our findings expand the mechanisms (e.g., functional brain connectivity) contributing to emotion regulation during REM to include HRV. Daytime HRV has often been used to represent emotion regulation ability because it reflects the feedback mechanisms between the central nervous system (CNS) and the ANS (Friedman & Thayer, 1998; Thayer & Lane, 2000). Therefore, higher HRV indicates a more effective transition from a heightened state, such as during stressful situations, to a more relaxed state (Malik & Camm, 1993). This feedback and communication between the CNS and ANS allows for the interruption of negative thoughts or behavior, promoting a shift towards emotion regulation. Thus, the increased connectivity within the CNS and between the CNS and ANS during REM may be the underlying mechanisms supporting our results that individuals with higher HRV during REM develop a bias away from negative memories after sleep, possibly indicating better emotion regulation. Cho et al., along with investigating a bias for emotional and neutral images after HRV biofeedback, also explored whether there was a tradeoff in bias (e.g., positive minus negative bias), and showed that participants that increased their daytime HRV, compared to those that decreased their daytime HRV, induced a positive emotional memory bias tradeoff, which was mediated by changes in left amygdala-mPFC resting-state functional connectivity (Cho et al., 2023). This suggests that increasing HRV enhances amygdala-PFC connectivity and emotion regulation, which is supported by other studies (Nashiro et al., 2023; Sakaki et al., 2016), and that more effective emotion regulation may be related to "focusing on the positive." Our results suggest that a positivity bias may emerge overnight through heightened vagal HRV and more effective emotion regulation during REM sleep. This effect cannot solely be attributed to "focusing on the positive" during learning, since pre-sleep memory performance for negative and neutral images did not significantly differ (as previously reported by Simon et al., 2022 using this dataset). Therefore, it appears that HRV during REM sleep contributes to the emergence of a positivity bias and these processes are altered and diminished when vagal HRV is suppressed, as shown with zolpidem.

Our final aim was to investigate whether including both REM HRV and NREM sleep features would give us the best model of the emotional memory tradeoff effect. Building on prior research demonstrating that increasing spindles switches the tradeoff from more neutral to more negative overnight memory consolidation (Kaestner et al., 2013; Simon et al., 2022), we sought to evaluate the inclusion of REM HRV in this process. We used a stepwise linear regression framework and found a significant role of REM HRV in explaining the underlying patterns in overnight emotional memory consolidation. This improvement was evident even while using the adjusted R^2, which penalizes models for added complexity of additional regressors (Sotirchos et al., 2019). These results underscore the need for more holistic and comprehensive models that include both brain and body features across the sleep stages. The sequential model of sleep-dependent memory processing postulates that both NREM and REM are essential and play distinct, yet complementary roles in memory consolidation (Cairney et al., 2015; Giuditta et al., 1995; Walker & Stickgold, 2010). Overall, our findings support and extend this sequential model to include the contribution of vagal HRV during both NREM and REM. Future investigations into overnight memory consolidation should examine the role of HRV to ensure a more thorough understanding of the mechanisms underlying this process.

We propose that, while REM sleep is primarily responsible for emotional memory processing, vagal HRV during sleep is specifically critical for the rescuing of non-emotional, neutral

memories. Emotional memories are typically considered to be strong, more resistant to forgetting, and preferentially processed during sleep, compared to non-emotional, weaker memories (Payne & Kensinger, 2010; Wagner et al., 2001, 2006). We propose that vagal HRV during SWS and REM plays a crucial role in consolidating non-emotional, weak memories and HRV during REM helps to facilitate their integration into the memory network, and thereby rescue them from forgetting. Our supplementary findings suggest that participants who weakly encoded neutral pictures before sleep had greater subsequent HRV during SWS and REM (see supplementary materials). This increase in nighttime HRV then strengthened and integrated these weak neutral memories into the memory network overnight for better recall in the morning compared to the evening. These results align with a hypothesis proposed by Walker & Stickgold (2010), which suggests that SWS strengthens recently acquired memories and REM sleep supports the integration of the memories strengthened during prior SWS into broader networks of related knowledge. Numerous studies have supported this theory, showing that REM sleep is critical for creating associations with weakly learned concepts (Cai et al., 2009; Stickgold et al., 1999; Walker et al., 2002). Along with our results, other studies have demonstrated a specific role of HRV during REM in enhancing the accessibility of weak memories and facilitating their incorporation into the existing network (Whitehurst et al., 2016; Yuksel et al., 2024). Yuksel et al. found that, in participants with PTSD, increased REM vagal HRV predicted better retention of extinction memories, while disrupted REM sleep and reduced REM vagal HRV were linked to the failure to unlearn strong fear memories and replace them with weaker, prioritized extinction memories (Yuksel et al., 2024). These findings, taken together with the current study, indicate that overnight vagal HRV may facilitate peak normalization across multiple sleep cycles, effectively equalizing the strength of initially weak memories with those of stronger ones, while REM vagal activity, specifically, also integrates them into the existing network, making weak memories more accessible for later use. Our results also indicate that when vagal HRV during SWS is suppressed by zolpidem, the initial rescuing effect of weak, non-salient memories by HRV no longer occurs, as we did not find a significant relation between HRV and pre-sleep neutral images in the zolpidem condition. The disruption to initial consolidation of weak memories through HRV during SWS may then prevent the future integration of weak memories during REM, as evidenced by the lack of overnight consolidation of neutral memories in our study. The comparable levels of REM HRV in the zolpidem condition are insufficient to rescue these memories, further supporting the idea that HRV during both SWS and REM are essential for this effect. Since HRV appears to play a larger role in consolidating non-emotional, weak memories, it is unsurprising that in the zolpidem condition, we did not find a significant relationship between HRV and the processing of negative images, either before sleep or overnight.

This study has several limitations that should be considered when interpreting the results. First, we did not collect subjective valence or arousal ratings for the images, so we cannot assess changes in emotions after sleep. This is particularly important because the majority of literature relates daytime HRV to emotional health, rather than emotional memory, like explored here. Second, in our supplementary materials, we failed to replicate the wake findings from Cho et al. (2023) indicating higher resting state HRV leads to a positivity bias. These discrepancies may stem from a lack of positive images or varying experimental methods, such as the time of HRV recording (we recorded right before bed) and the ingestion of a drug right before our resting state, which could act as a confounding factor to influence HRV measurements, even if the pill

was placebo. Therefore, future work should aim to disentangle the overnight processing of emotions and emotional memories with positive, negative, and neutral images. Third, we did not conduct an immediate memory test – the first test was administered after a delay of approximately 12 waking hours. There may have been changes in memory from initial learning to the first test that are not captured in this study. Fourth, this study did not have an habituation night, which may have led to a "first night effect," with disturbed sleep (Agnew Jr. et al., 1966). Although to mitigate this effect, we counterbalanced picture sets, drug order, and randomized the presentation of image valences. However, we cannot fully discount its potential influence. Finally, although we did not directly measure respiration, we analyzed the high-frequency HRV peak (to account for respiratory rate, which can impact HRV. HF peak showed no significant differences between the two drug conditions and varied within a narrow range (0.22 to 0.26 Hz), suggesting that respiratory activity is unlikely to have significantly influenced zolpidem's effects on HRV and memory. Nonetheless, this possibility cannot be entirely ruled out.

Future research should replicate these findings in daytime sleep to investigate whether these findings hold true for any sleep period, or solely for nighttime sleep. In addition, subsequent studies should also test the hypotheses proposed here that overnight vagal HRV facilitates peak normalization across multiple sleep cycles and REM vagal activity integrates weak memories into the existing network. These studies should also explore how the connectivity between the CNS and ANS during sleep plays a role in this process. Additionally, future work should explore the role of dreaming during REM sleep and HRV while dreaming in emotional memory reactivation and processing. Prior research has shown that dreaming predicted lower emotional tone of negative memories after sleep (Zhang et al., 2024) and that dreaming involves a spike in sympathetic activity followed by increased in vagal activity, which may reflect emotion regulation while dreaming (Nardelli et al., 2021). During REM, emotional memories may be reactivated during dreams initially with a sympathetic response, which is then modulated by descending projections from the CNS instructing the ANS to activate the parasympathetic vagal brake. Taken together, these findings suggest that the reactivation of emotional experiences during dreaming may activate emotion regulation pathways in the brain and the body. However, more research is needed to support this idea.

Conclusion

Our study provides important evidence supporting a role of vagal HRV during REM in emotional memory processing. We show that higher REM HRV, but not SWS HRV, significantly contributes to the overnight emergence of a positive memory bias, with greater memory for neutral images at the expense of negative images after a night of normal sleep. These results underscore the importance of considering physiological features into models of sleep-dependent memory consolidation. Additionally, given that higher daytime HRV has been linked to less depression, anxiety, and stress, our findings highlight the importance of nighttime HRV in effective emotion regulation and its potential role in mitigating adverse mental health symptoms.

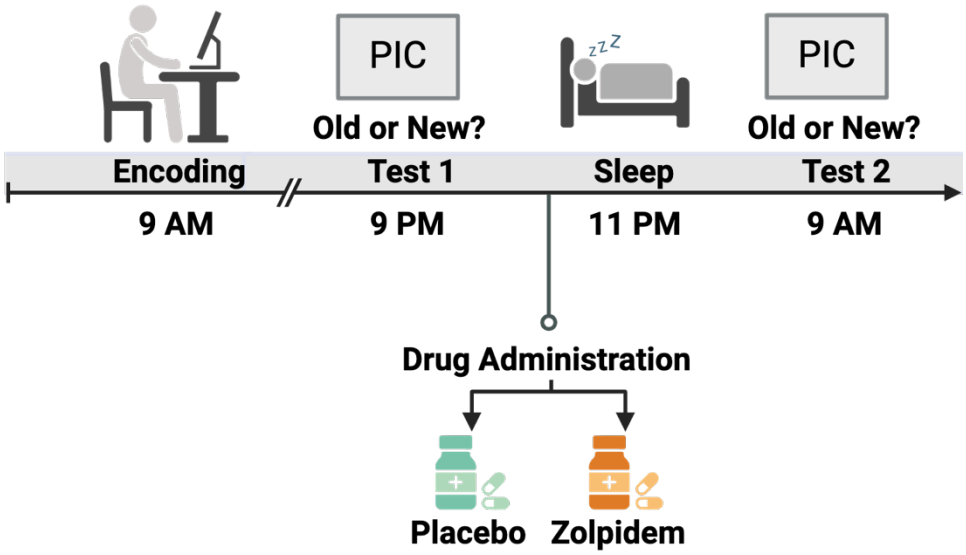

Figure 1: Experimental Design Schematic. This figure was created using BioRender.com

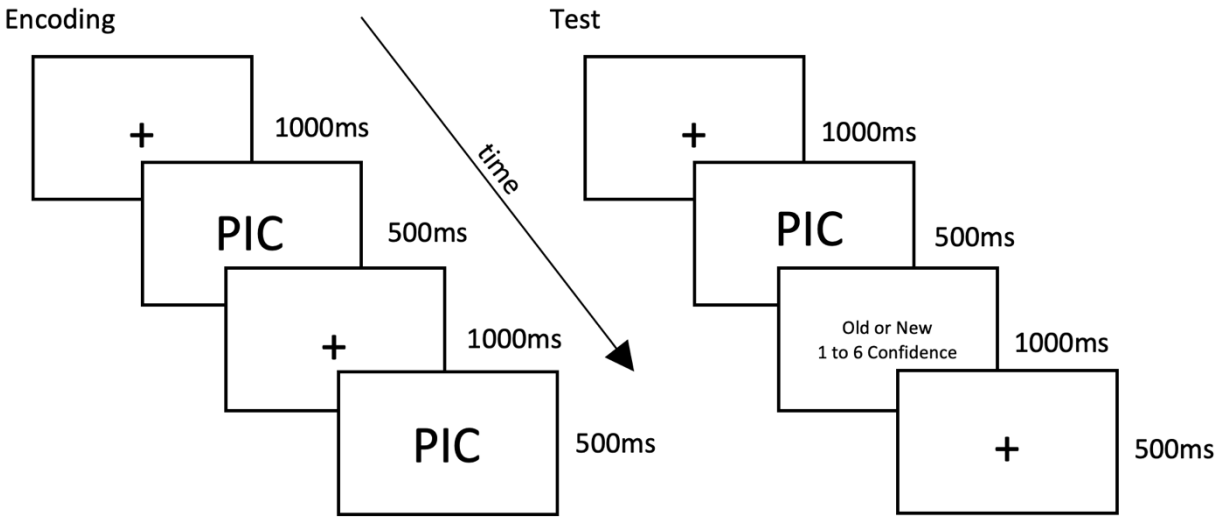

Figure 2: Emotional Picture Task Paradigm

	N2					SWS					REM				
	PBO		ZOL			PBO		ZOL			PBO		ZOL		
Measure	**Mean**	**SD**	**Mean**	**SD**	**Difference (p)**	**Mean**	**SD**	**Mean**	**SD**	**Difference (p)**	**Mean**	**SD**	**Mean**	**SD**	**Difference (p)**
C4 Spindle Power	1.423	0.551	1.722	0.749	**0.006**	0.468	0.214	0.631	0.398	**0.002**	-	-	-	-	-
C3 Spindle Power	1.417	0.534	1.766	0.801	**0.002**	0.525	0.257	0.653	0.437	**0.042**	-	-	-	-	-
HF (ln)	6.568	0.945	6.487	0.935	0.545	6.058	1.105	6.060	1.094	**0.034**	6.445	1.011	6.446	1.001	0.133

Table 1. Summary of Sigma and HRV Parameters Across Sleep Stages

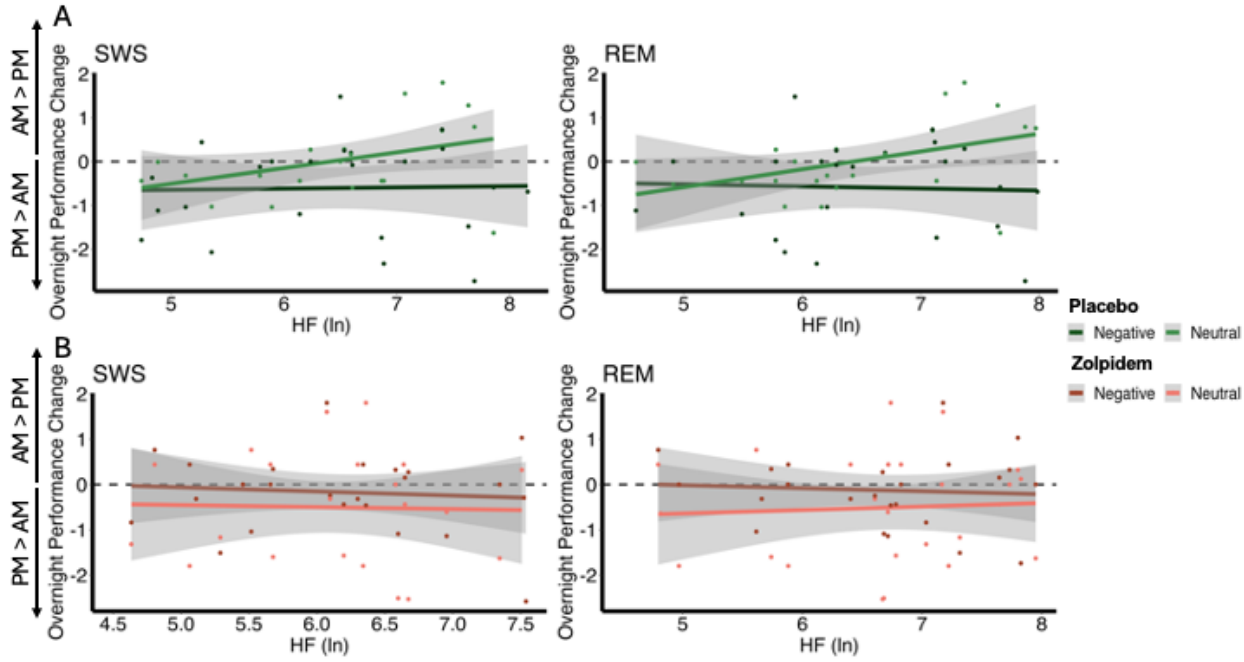

Figure 1. Correlations Between Vagal Activity and the Overnight Performance Change in Emotional and Neutral Memory. (A) In the placebo condition, overnight performance change for neutral images positively correlated with HRV during SWS (r=0.520, p_{adj}=.011), and with HRV during REM (r=0.550, p_{adj}=.010). However, no significant association was found between negative images and HRV during SWS (r=-0.057, p_{adj}=1), or with HRV during REM (r=-0.099, p_{adj}=1). (B) In the zolpidem condition, there were no significant correlations between overnight performance change for neutral or negative images and HRV during SWS (all p_{adj}=1) or with HRV during REM (all p_{adj}=1).

			SWS					REM				
EPT	**HRV**	**Condition**	**Test Statistic**	**r**	**p_adj**	**p**	**Confidence**	**Test Statistic**	**r**	**p_adj**	**p**	**Confidence**
Neutral Overnight Performance Change	HF (ln)	PBO	2.778	0.520	**0.011**	**0.011**	[0.135, 0.766]	3.089	0.550	**0.010**	**0.005**	[0.188, 0.780]
Neutral Overnight Performance Change	HF (ln)	ZOL	0.525	0.110	1.000	0.604	[-0.306, 0.492]	0.292	0.060	1.000	0.773	[-0.336, 0.436]
Negative Overnight Performance Change	HF (ln)	PBO	-0.273	-0.057	1.000	0.788	[-0.442, 0.346]	-0.478	-0.099	1.000	0.638	[-0.476, 0.308]
Negative Overnight Performance Change	HF (ln)	ZOL	-0.427	-0.089	1.000	0.674	[-0.468, 0.317]	-0.348	-0.072	1.000	0.731	[-0.455, 0.332]

Table 2. Correlations Between Vagal Activity and the Emotional and Neutral Memory

			SWS			REM		
EPT	**HRV**	**Condition**	**p_adj**	**p**	**EmoDiff**	**p_adj**	**p**	**EmoDiff**
Overnight Memory Consolidation	HF (ln)	Pbo	**0.025**	**0.025**	-2.240	**0.022**	**0.011**	-2.538
Overnight Memory Consolidation	HF (ln)	Zol	0.926	0.463	-0.734	0.926	0.627	-0.486

Table 3. Differences between Fisher-Transformed Z-scores for Vagal Activity and Emotional and Neutral Memory.

			SWS					REM				
EPT	**HRV**	**Condition**	**Test Statistic**	**r**	**p_adj**	**p**	**Confidence**	**Test Statistic**	**r**	**p_adj**	**p**	**Confidence**
Emotional Memory Tradeoff	HF (ln)	PBO	-1.903	-0.360	0.069	0.069	[-0.658, 0.029]	-2.558	-0.460	**0.034**	**0.017**	[-0.713, -0.092]
Emotional Memory Tradeoff	HF (ln)	ZOL	-1.347	-0.260	0.380	0.190	[-0.583, 0.133]	-0.905	-0.170	0.380	0.374	[-0.515, 0.212]

Table 4. Correlations Between Vagal Activity and the Emotional Memory Tradeoff Effect

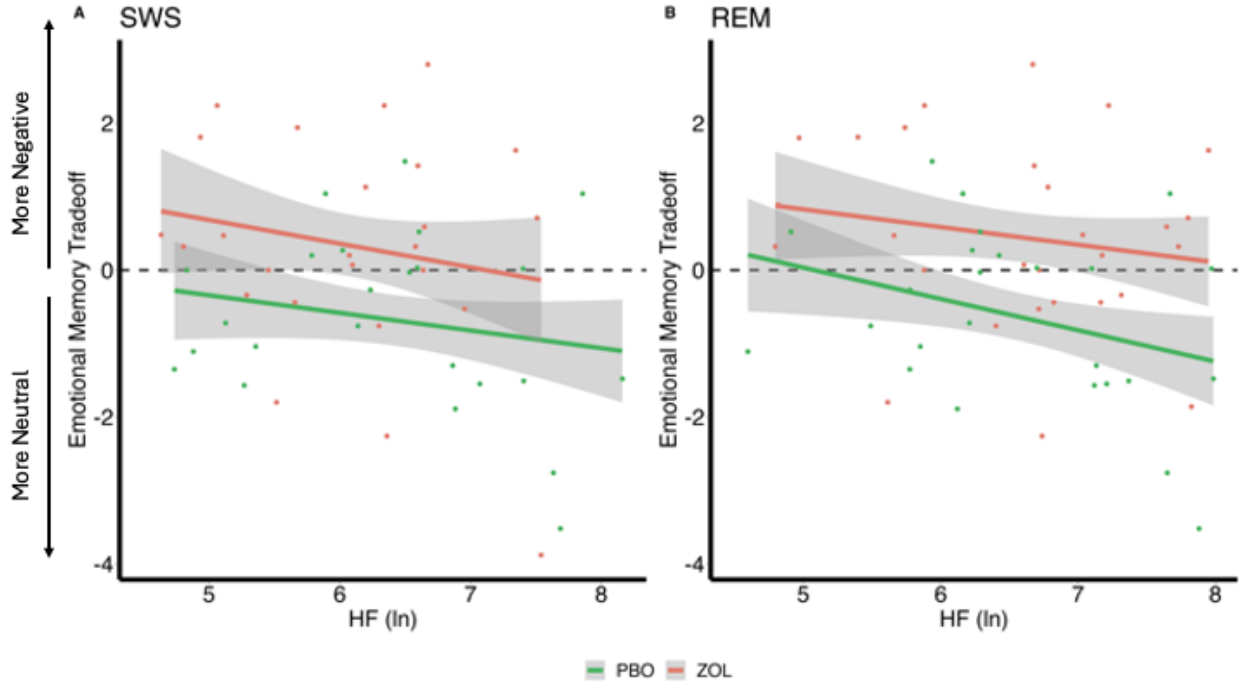

Figure 2. Correlations Between Vagal Activity and the Emotional Memory Tradeoff Effect**.** (A) There were no significant correlations between the emotional memory tradeoff effect and HRV

during SWS for either the placebo (r=-0.36, p_{adj}=.069) or zolpidem condition (r=-0.26, p_{adj}=.38). (B) In the placebo condition, the emotional memory tradeoff effect negatively correlated with HRV during REM (r=-0.46, p_{adj}=.034), but this association was eliminated by the zolpidem (r=-0.17, p_{adj}=.38).

Model	Term	Estimate	Std. Error	Test Statistic	p	Marginal R2
Base Model	(Intercept)	-0.660	0.268	-2.451	**0.017**	0.076
	ConditionZOL	0.852	0.312	2.730	**0.010**	
	`Centered Weight`	-0.001	0.007	-0.053	0.958	
Sigma Model	(Intercept)	-1.613	0.656	-2.457	**0.017**	0.126
	ConditionZOL	2.164	0.687	3.147	**0.003**	
	`SWS C4 Sigma Power`	2.159	1.272	1.696	0.095	
	`Centered Weight`	0.001	0.007	0.141	0.888	
	ConditionZOL:`SWS C4 Sigma Power`	-2.618	1.240	-2.111	**0.042**	
Full Model: HRV & Sigma Power	(Intercept)	1.587	1.392	1.140	0.260	0.365
	ConditionZOL	0.692	2.098	0.330	0.742	
	`SWS C4 Sigma Power`	3.322	1.040	3.191	**0.002**	
	`REM HF (ln)`	-0.564	0.204	-2.754	**0.008**	
	`Centered Weight`	0.005	0.005	1.068	0.290	
	ConditionZOL:`SWS C4 Sigma Power`	-2.837	1.188	-2.387	**0.021**	
	ConditionZOL:`REM HF (ln)`	0.253	0.317	0.797	0.429	

Table 5. Model Comparison Results. Bold text indicates significance at $p \leq .05$. We used adjusted marginal R^2, reflecting variance explained by fixed effects, as the means of model comparison. Overall, the full model including both REM HRV and SWS sigma was the best fit for the data and significantly improved the fit (χ^2 =9.4603, p = .008).

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