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Temporal dynamics of negative emotional memory reprocessing during sleep

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Memory reprocessing during sleep is a well-established phenomenon in numerous studies. However, it is unclear whether the intensity of memory reprocessing is consistently maintained throughout the night or exhibits dynamic changes. This study investigates the temporal dynamics of negative emotional memory reprocessing during sleep, with a specific focus on slow oscillation (SO)-spindle coupling and its role in memory reprocessing. In the first experiment ($N = 40$, mean age = 22.5 years), we detected the negative emotional memory reprocessing strength in each sleep cycle, we found that the 2nd sleep cycle after negative emotional memory learning constitute the most sensitive window for memory reprocessing, furthermore, SO-spindle coupling signals in this window plays a role in stabilizing negative emotional memory. To verify the role of SO-spindle coupling in negative emotional memory reprocessing, we utilized transcranial alternating current stimulation (tACS) to disrupt SO-spindle coupling during the 2nd sleep cycle ($N = 21$, mean age = 19.3 years). Notably, the outcomes of the tACS intervention demonstrated a significant reduction in the recognition of negative emotional memories. These findings offer new insights into the mechanisms that regulate emotional memory consolidation during sleep and may have implications for addressing psychiatric disorders associated with pathological emotional memory.

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INTRODUCTION

Emotional memory is considered more stable than neutral memory and plays a pathogenic role in the development of psychiatric disorders [1, 2]. During subsequent sleep periods, memory trace created during encoding is reactivated, which selectively enhances emotional memories [3, 4]. Rodent studies have shown that reactivation is stronger for experiences resulting in aversive memories than for memories of "safe" experiences [5, 6]. These findings underscore the importance of exploring when emotional memory reactivation occurs during sleep [7–9].

Previous studies have focused mostly on exploring memory reactivation during sleep, proceeding from the hypothesis that reactivation is a continuous process that occurs throughout sleep at night. In animal studies, reactivation is often assessed by measuring cofiring in hippocampal cells showing a correlation between learning and sleep, a method used to gauge the intensity of memory reactivation. However, the intensity of memory reactivation reported in these studies was not constant but varied dynamically [5, 6]. Therefore, to gain deeper insight into the mechanisms of memory reactivation, identifying the periods during sleep in which these mechanisms are most strongly affected becomes crucial. Importantly, considering the intermittent nature of memory reactivation, it may not consistently manifest during all recording processes, especially in studies in which activity during sleep was recorded for a short time.

Additionally, it's crucial to identify the unique sleep signals that distinguish emotional memory reactivation from other memory types. The most prominent electrophysiological signals in the hippocampus and neocortical networks during nonrapid eye movement (NREM) and rapid eye movement (REM) sleep include slow oscillations (SOs), sleep spindles, sharp-wave ripples, and theta-wave activity [3, 10–12]. These sleep rhythms have been identified in memory functions during sleep. Recent studies have revealed the important effects of SO-spindle coupling on memory reactivation and consolidation [13–15]. Despite extensive research, there is still much to uncover regarding how these specific sleep signals affect the consolidation of emotional memories. By delving deeper into this topic, we can better understand how the brain reprocesses and stores emotional memories during sleep.

Recent advancements in artificial intelligence significantly enhanced our capacity to decipher and comprehend the intricate processes associated with memory consolidation during sleep. Notably, Horikawa et al. showed that it is possible to uncover the subjective content of dreams during sleep [16], and Yuta et al.

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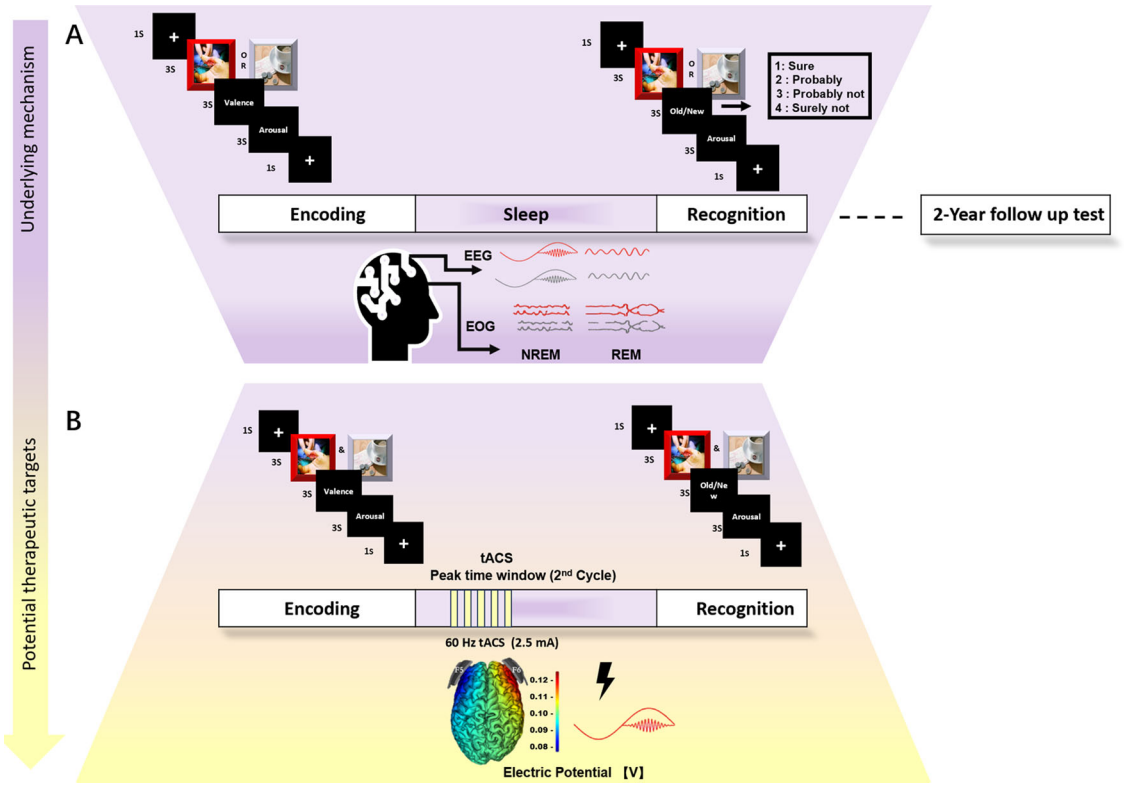

Fig. 1 Study design. A Study design for experiment 1. This experiment used a balanced crossover design. Participants memorized emotional and neutral materials on two nights, 1 week apart. During post-learning sleep, sleep-specific signals under EEG & EOG channels were included for further analysis. Recognition performance was tested on day 1 after sleep and 2 years later. **B** Study design for Experiment 2. Cross-hemispheric tACS targeting inhibited negative emotional memory preprocessing during sleep. This experiment used a balanced crossover design. Participants memorized both negative and neutral materials together before sleeping. Then, the participants were subjected to cross-hemispheric tACS or sham tACS on two nights, which were separated by 1 week. Cross-hemispheric tACS was initiated after the subject entered stable slow-wave sleep (SWS) or stage 2 of NREM sleep for at least 4 min. Each stimulation session lasted 5 min. Recognition performance was tested 1 day after sleep.

reported that the process of dreaming may be coordinated with eye movements during REM sleep [17, 18].

This study aimed to explore the window in which negative emotional memories are reprocessed during sleep, and to determine the role of sleep-specific signals in this process. In the first experiment, the participants were presented with either negative or neutral images prior to a full night's sleep in a controlled laboratory setting. During post-learning sleep, electroencephalography (EEG) and electrooculography (EOG) were employed to record brain activity and eye movement signals, respectively. Subsequently, pattern classification methods were employed to detect information on previously learned materials in the EEG and EOG activities recorded during sleep. Based on the above analysis, a high-frequency transcranial alternating current stimulation (tACS) intervention was used to selectively inhibit the reprocessing of negative emotional memories by targeting specific time windows and neural signals.

MATERIALS AND METHODS

Participants

Eligible participants were aged 17–25 years old students from universities in both experiment 1 and 2. The experimental time was adjusted to the participants' habitual sleep time (bedtime: 23:30–7:30). Participants were requested to abstain from all caffeine- and alcohol-containing beverages and from intense physical activity for 3 days before the experiment. The study was approved by the Ethics Committee of the Peking University Institute of Mental Health, and written informed consents were obtained from all participants. Our experimental data was collected from 2018 to 2021 at the Peking University Health Science Center.

The sample size was determined using G*Power software to ensure adequate power for detecting a pre-specified effect size with a significance level (α) of 0.05 and a power (1-β) of 0.80. For Experiment 1, where all participants learned both neutral and negative memory materials, the required sample size was approximately 34 participants. For Experiment 2, where all participants received both tACS and sham stimulation, with a significance level (α) of 0.1, the required sample size was approximately 24 participants.

The initial exclusion criteria were as follows: (1) individuals who were colorblind and color deficient; (2) individuals who had a psychiatric history of severe trauma and sleep disorders; (3) individuals who have had a cochlear implant, cardiac pacemaker, or any brain devices and/or implants; (4) individuals who had hyperalgesia, skin damage, or inflammation in the stimulated area; and (5) individuals who had worked the night shift during the last year. This initial screening ensured that only participants who met the specific criteria relevant to the study's objectives were included.

Experimental design

In both experiment 1 and experiment 2, we employed a within-subject design. To ensure that the variations in sleep EEG responses to different learning conditions were not attributable to inter-individual differences, each participant served as their own control. Specifically, all participants underwent all learning conditions, and their sleep data were subsequently compared across these conditions.

Experiment 1: Participants were required to sleep in the experimental environment for three nights. The first night was an adaptation night to get familiar with the experimental environment and equipment. In the next two experimental nights, participants encoded negative emotional or neutral images before sleep. The order of negative or neutral memory materials was randomized across the two nights which apart at least 1 week. Recognition performance was tested during the next day and 2 years later as well (Fig. 1A).

Experiment 2: To further verify the neurophysiological biomarker in experiment 1, the sleep signal, which related with negative emotional memories, was disrupted by tACS stimulation to retest its function for memory consolidation. Participants in experiment 2 also slept three nights in laboratory. It should be noted that incorporated both negative and neutral images in each night. The first night was an adaptation night. On next two experimental nights, participants memorized both negative and neutral images during encoding. In recognition test as experiment 1. Participants had to indicate whether they had seen the image before (Fig. 1B). Following the learning sessions, participants slept and received either active or sham stimulation during the 2nd sleep cycle. The order of the two interventions (tACS or sham) was randomized across all participants. The participants were blinded to which night they would receive sham stimulation.

Procedure

The memory task included 280 emotional pictures from the International Affective Picture System and Chinese Affective Picture System [19], which was performed using E-prime 2.0 software (Psychology Software Tools, Inc.; http://www.pstnet.com). The pictures of preliminary pilot study were filtered to create a standardized norm. In this pilot study, participants were asked to rate the degree of valence and emotional arousal of each picture on several 9-point Likert scales. The negative images were rated higher in emotional arousal ($T_{(39)} = 6.638$; $p < 0.001$) and lower in valence than the neutral images ($T(39) = -8.456$; $p < 0.001$; see Fig. S1 in the Supplementary Material). The learning phase started with the presentation of an initial fixation crosshair (1000 ms), followed by the presentation of the target picture (3000 ms) and then the presentation of a blank screen (500 ms). After this, a "prompt" encouraging participants to score the valence (3000 ms) and arousal (3000 ms) of the images appeared on the screen. The recognition test included the 140 trials (80 original pictures and 60 new foils). Participants had to indicate whether they had seen the image before (1-sure, 2-probably, 3-probably not, or 4-surely not), and rate the arousal level of the images. For overall recognition memory performance, responses of 1 and 2 were considered 'old' responses, and responses of 3 and 4 were considered 'new' responses. For accurate recognition memory performance, only a response of 1 was considered an 'old' response, and a response of 4 was considered a 'new' response.

In both experiment 1 and 2, the participants were asked not to memorize the new materials after 6:00 pm before arriving at the laboratory. To prevent participants' emotions from interfering with their performance in the emotional memory task, they were asked to complete the Positive and Negative Affect Scale before memory encoding occurred (see Table S4 in the Supplementary Material).

PSG recording and sleep quality control

The polysomnographic (PSG) was performed at the sleep laboratory of the Peking University Health Science Center. The participants arrived at 9:30 pm, and at 10:00 pm, they started to study the computer-based memory task materials. Then prepared for PSG recording that would continue throughout the night. The PSG recordings began at 11:30 pm and ended at 7:30 am the following morning. Specifically, we maintained a consistent temperature range of 22–24 °C, used soundproofing materials to minimize noise, and controlled light exposure by using blackout curtains and ensuring complete darkness during sleep sessions.

EEG and EOG recording were conducted using a PSG system (Grael Sleep Recording System; Compumedics, Melbourne, Australia). The recording included data from EEG leads (F3, F4, C3, C4, O1, and O2; connecting the mastoid), bilateral electrooculogram leads, anterior tibialis and submentalis electromyogram leads, and an electrocardiogram. The data acquisition rate was 250 Hz, with high- and low-pass filters set to 0.3 Hz and 35 Hz, respectively, and a notch filter of 50 Hz. All electrode impedances were less than 5 kΩ. The 30 s epochs were visually scored independently by two technicians according to the AASM 2.6 sleep scoring criteria [20]. To preprocess the data, a high-pass filter of 0.3 Hz and a low-pass filter of 35 Hz were applied. Artifacts caused by facial chewing and body muscle activity were identified and removed. Gross body movement artifacts were marked according to AASM standards. After preprocessing, sleep structure analysis was conducted by Registered Polysomnographic Technologist according to AASM standards. Participants who had issues with post-learning sleep were excluded based on the following criteria: difficulty falling asleep (sleep onset after 1:00 am), frequent sleep disturbances (≥5 times per night), prolonged periods of arousal (>30 minutes), or early awakening (before 6:00 am). Data cleaning was performed using Profusion Sleep Software.

EEG analyses

The EEG data were processed with custom MATLAB scripts using the EEGLAB toolbox (http://www.sccn.ucsd.edu/eeglab/) and Fieldtrip libraries (http://fieldtrip.fcdonders.nl/). To assess whether memory reprocessing occurs over time, we divided the entire night of sleep into five NREM-REM cycles, which included a whole sequence of sleep stages [20].

Theta wave detection

We detected theta signal in both NREM and REM states. Algorithms based on those in Ladenbauer and Molle et al. [19, 21] to evaluate theta waves (4–8 Hz). A fast Fourier transform was used to calculate the spectral power per electrode. On each of these 15 s segments of EEG data, a Hanning window was applied before calculating the power spectra (frequency resolution of 0.06 Hz). Subsequently, the mean power was calculated for each EEG channel for the above theta frequencies.

SO detection

Detection of the SO events for each subject, condition, and electrode was based on a standard detection algorithm developed in a previous study [19, 21]. First, a lowpass filter with 0.16 and 1.25 Hz was applied to the EEG data. Second, the periods of the SO candidates were determined as the time between two successive positive-to-negative zero crossings in the filtered signals. For the next step, events that met the SO duration criteria (0.8–2 s duration time, corresponding to 0.5–1.25 Hz) were selected. Third, the event amplitudes were determined for the remaining SO candidates (through-to-peak amplitudes between two positive and negative zero crossings). Events that also met the SO amplitude criteria (>75% percentile of SO candidate amplitudes, i.e., 25% of events with the largest amplitudes) were considered SO events. Finally, artifact-free epochs (from −2.5 to +2.5 s) time-locked to the SO downstate in the filtered signal were extracted from the unfiltered raw signal for all events.

Spindle detection

The spindle signals were identified in both NREM and REM states. During the NREM state, we detected the stage 2 of NREM (N2) sleep and slow-wave sleep (SWS). During the REM sleep, we detected whole stages, these spindles shared similar spiking patterns with NREM spindles [22]. In the EEG channels, spindles were detected by the frequencies between 12–16 Hz, and the analytical amplitude was extracted after applying the Hilbert transform. After bandpass filtering, a root mean square signal was calculated with a temporal resolution of 0.05 s using a time window of 0.1 s. We noted the signal that met the amplitude criterion (threshold at 75%) and time criterion (0.5–3 s). Events without artifacts were defined as 5-s long sleep-spindle epochs [23].

SO-spindle coupling event detection

SO-spindle event co-occurrence analysis was performed by testing a list of test events (time-points) to fall within specified target events (time-points with offsets and pre- and post-time windows). Tests and Targets were listed in separate tables with corresponding time-points and matching columns. Results were reported per Test, with each matched Target given in a line with complete table content. Matches were filtered for identical and duplicate matches to ensure accuracy.

Based on the individualized and normalized spindle peak-locked epochs, we first low-pass filtered the time-locked data by 2 Hz and subsequently extracted the phase angle of the SO-component corresponding to the spindle amplitude peak using a Hilbert transform. The main parameter, 'SO-spindle coupling count,' was derived by identifying overlapping SO and spindle events within the specified window. The 'power of the SO-spindle coupling signals' was calculated by measuring the amplitude of the combined signals within the specified window.

After data cleaning, the remaining 40 participants' EEG data retained all electrode channels (F3, F4, C3, C4, O1, and O2, connected to the mastoid) for experiment 1; While in experiment 2, there remained 21 participants' EEG data that retained all electrode channels. Post-cleaning, all participants exhibited consistent sleep structure under both experimental conditions (learning negative emotional memory and learning neutral memory), with

no significant differences (see Table S2 in the Supplementary Material). Additionally, there were no significant differences in sleep structure across all sleep cycles (see Table S5 in the Supplementary Material).

tACS intervention protocol

We used two 25 cm^2 stimulation annular electrodes positioned bilaterally at frontal locations F5 and F6 based on the 10−20 EEG system [24]. Electrode impedance was controlled below 5 kΩ before sleep. tACS electrode placement was guided by current-flow modeling (see Fig. 1B) using HD-Explore and HD-Targets (Soterix Medical).

Principles of cross-hemispheric tACS stimulation in modulating SO-spindle coupling signals

In experiment 2, we applied sinusoidal transcranial alternating current stimulation (tACS), known for its capacity to modulate neuronal oscillations by both entrainment and desynchronization effects [25, 26]. Neuronal oscillations, often emanating from two symmetrical neural generators located in each hemisphere, can be influenced by such stimulation. Cross-hemispheric sinusoidal tACS, according to modeling studies, has the potential to interfere with neural activities that rely on the synchronization of phases between hemispheres [26]. Given that SO are pivotal in driving the coupling between slow oscillations and spindle activities, predominantly originating from the prefrontal cortex, we specifically directed our cross-hemispheric stimulation at this region [19, 27, 28]. Our hypothesis was that by applying sinusoidal tACS across the hemispheres at the frontal region, we could disrupt the generation of slow oscillations and, consequently, the interaction between slow oscillations and spindle signals.

Stimulation procedure

Each subject participated in two experimental nights, during which they underwent five sessions of sinusoidal or sham cross-hemispheric tACS during sleep. tACS of 2–3 mA was performed during the 2nd sleep cycle at a frequency of 60 Hz. To reduce the likelihood of the subject waking up, a 15 s-graduated fade-up and 15 s-graduated fade-down were used to initiate and terminate the stimulation, respectively. tACS was initiated after the subject maintained stable SWS or N2 sleep for at least 4 min. tACS was administered in a manner in which each stimulation was applied for 5 min, and then, there was a stimulation-free interval of (at least) 1 min before the next stimulation. During the stimulation process, we monitored the changes in sleep EEG signals and stopped the stimulation as soon as the subject transitioned from SWS or stage N2 to stage N1, REM sleep, or even wakefulness. No participants-reported pain during sleep. The stimulation duration and intensity parameters were within safe limits and did not exceed the tested protocols.

Statistical analysis

The statistical analysis was performed using SPSS software (version 20.0; SPSS, Chicago, IL, USA) and R 3.6.1 software. As for the sleep related neurophysiology indexes, the difference in sleep architecture between the two learning conditions (negative and neutral materials) was determined using paired t tests. The differences in cycle density and duration between the two learning conditions (negative and neutral materials) were evaluated using two-way repeated-measures ANOVA (time point × memory type).

SO-spindle coupling count distributions in the three learning conditions was derived from repeated-measures ANOVA (number of cycles × memory type). In assessing the assumption of sphericity for our repeated measures ANOVA, Mauchly's Test was conducted, the results indicated that the assumption of sphericity was not violated, as evidenced by a non-significant Mauchly's Test ($p > 0.05$).

The SO-spindle coupling between the successful and unsuccessful recall groups in the 2-year delayed negative image recall test was derived from a linear mixed-effect model control with baseline coupling counts (number of cycles × memory type). This model considers the impact of missing data, ensuring a more accurate analysis. The statistical significance threshold for all behavioral and EEG analyses was set at $p < 0.05$.

Correlations between memory performance and sleep-specific signals were determined using the Pearson correlation test with a Bonferroni-adjusted level of 0.008 (0.05/6). These comparisons include the five individual sleep cycles as well as the combined analysis of all cycles throughout the entire night.

Ensemble classification algorithm (semipositive definite programming-based support vector machine model)

In experiment 1, we implemented an ensemble classification algorithm (a semipositive definite programming-based support vector machine model) by analyzing EEG and EOG data acquired during sleep to determine what types of materials subjects had learned prior to sleep; these data were collected following subjects' exposure to different types of memory materials (negative emotional and neutral). This approach was based on our hypothesis that different memory materials would elicit unique brain activity patterns during sleep, indicative of memory reprocessing [29]. In this study, we adopted a within-subject design. Specifically, the data were derived from 40 subjects, with each subject contributing two distinct sleep recordings: one following the learning of neutral memory materials and another following the learning of negative emotional memory materials. This approach allowed us to closely examine the neural differences in post-learning sleep patterns associated with different memory types.

Data analysis based on sleep cycles

Our analysis was structured around sleep cycles, each defined from the onset of NREM sleep to the end of subsequent REM sleep [30].

For the features in each sleep cycle, we performed a detailed sleep feature extraction process on the data from six EEG electrodes and two EOG electrodes. In each sleep cycle, 95 features were analyzed during NREM sleep, and 132 features were analyzed during REM sleep. For EEG, the features included the energy, density, duration, and peak-to-trough characteristics of SOs, spindles, SO-spindle coupling, theta waves, and slow-wave activity (SWA), among others. The EOG data analysis focused on the quantification of eye movement signals during different sleep structures, including the number, duration, and speed aspect of eye movements.

Training and testing data

The classifier was trained using a leave-one-out test approach. In this method, for each iteration of training and testing, the classifier was trained on almost all the available data, with one data point left out. The single data point excluded from the training set was subsequently used to test the classifier. This process was repeated so that each data point in the dataset was used exactly once as test data.

Significance testing

We determined the significance of the classification results by comparing the accuracy of the actual dataset against that of multiple permutation datasets, with $p < 0.001$ indicating statistical significance.

Individual feature classification

For each feature in the model corresponding to the second sleep cycle, we performed an individual classification task to determine its accuracy in distinguishing between negative emotional and neutral memory materials. The methodology involves calculating feature weights by considering the additive contribution of various dimensions of each waveform, such as frequency characteristics, density, count, amplitude, and duration for features like slow waves and sleep spindles.

RESULTS

Demographic information

Experiment 1: Fifty-six healthy students were enrolled (eight females, mean age = 22.05 ± 1.41 years). Sixteen participants were excluded because they had difficulty falling asleep at night, and forty participants were ultimately included in the analysis (see Table S1 in the Supplementary Material for demographic characteristics; see Table S2 in the Supplementary Material for sleep architectures).

Experiment 2: Twenty-four participants were enrolled (ten females, mean age = 19.27 ± 1.09 years). Three participants were excluded because they had difficulty falling asleep at night, and twenty-one participants were ultimately included in the analysis (see Table S6 in the Supplementary Material for demographic characteristics; see Table S7 in the Supplementary Material for sleep architectures).

Post-sleep enhancement of negative emotional memory retention

Forty individuals participated in experiment 1. For the memory recognition d'scores, the linear mixed-effects model for repeated measures (MMRM) revealed a significant main effect of time point ($F_{1,\ 40} = 62.97$, $p < 0.001$) and main effect of memory point ($F_{1,\ 40} = 11.14$, $p < 0.001$), without a significant interaction between time and memory points. Paired comparisons showed that negative emotional memories were recognized better than neutral memories both 1 day and 2 years later ($d = 3.80$, 95% CI [0.19 to 0.75], $p < 0.01$; see Fig. 2). Additionally, both the negative and neutral memory recognition scores significantly decreased from day 1 to 2 years later ($d = 9.26$, 95% CI [−1.42 to −0.85], $p < 0.001$).

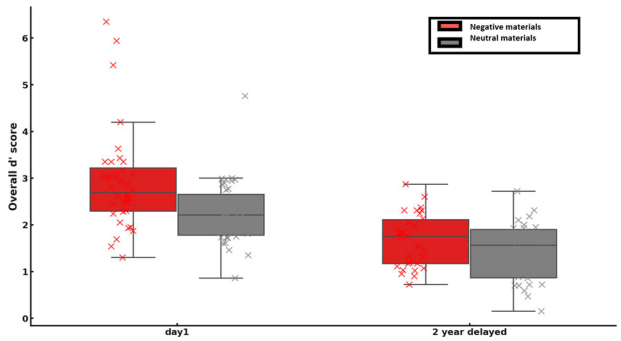

Fig. 2 Improved retention of negative emotional memories after sleep. Behavioral results for negative (red) and neutral (gray) image recognition scores. Left: negative emotional memory d'scores; right: neutral memory d'scores. Bar graphs show the mean (± standard error of mean) memory d'scores. The overall d'scores indicate a significant main effect for memory across time and a significant main effect for time across all memory type conditions (***$p < 0.001$), as derived from a linear mixed-effects model for repeated measures (MMRM).

Distinguishing negative emotional memory reprocessing during sleep

We divided the data for an entire night's sleep into approximately five sleep cycles based on temporal progression. To ensure uniformity in the duration of sleep cycles across participants, our study assessed the variations in cycle duration and the cyclic sample size, ensuring that every participant had similar sleep cycle segmentation in both post-learning sleep of negative emotional memories and post-learning sleep of neutral memories (see Table S5 in the Supplementary Material).

To detect the negative emotional memory reprocessing strength in each sleep cycle, an ensemble classifier model was used (for a detailed description, see *Methods-Ensemble classification algorithm*). The model was adept at discerning whether subjects had learned negative emotional or neutral memory materials prior to sleep based on sleep feature signals from various sleep cycles features (EEG features and EOG features; see methods). The effective differentiation of memory types by a classifier in certain sleep cycles indicates the occurrence of memory reprocessing within those cycles. The model most accurately distinguished negative emotional memory reprocessing during the 2nd sleep cycle, and classification accuracies after the leave-one-out test were close to 80% during the 2nd sleep cycle in both NREM and REM sleep periods (see Fig. 3A). Thus, the 2nd sleep cycle after emotional memory learning may constitute the most sensitive window for memory reprocessing.

The significance of the classifier was confirmed in a permutation test by comparing predictive performance between randomly labeled data and real data [31]. Our results showed that the classifier accuracy of the real data was significantly greater than that of the remaining 1000 randomly labeled iterations ($p < 0.001$; see Fig. 3).

Sleep features in the reprocessing of negative emotional memories

Then, we evaluated the contribution of sleep microstructure features in the classifier during the 2nd sleep cycle. Figure 4A shows

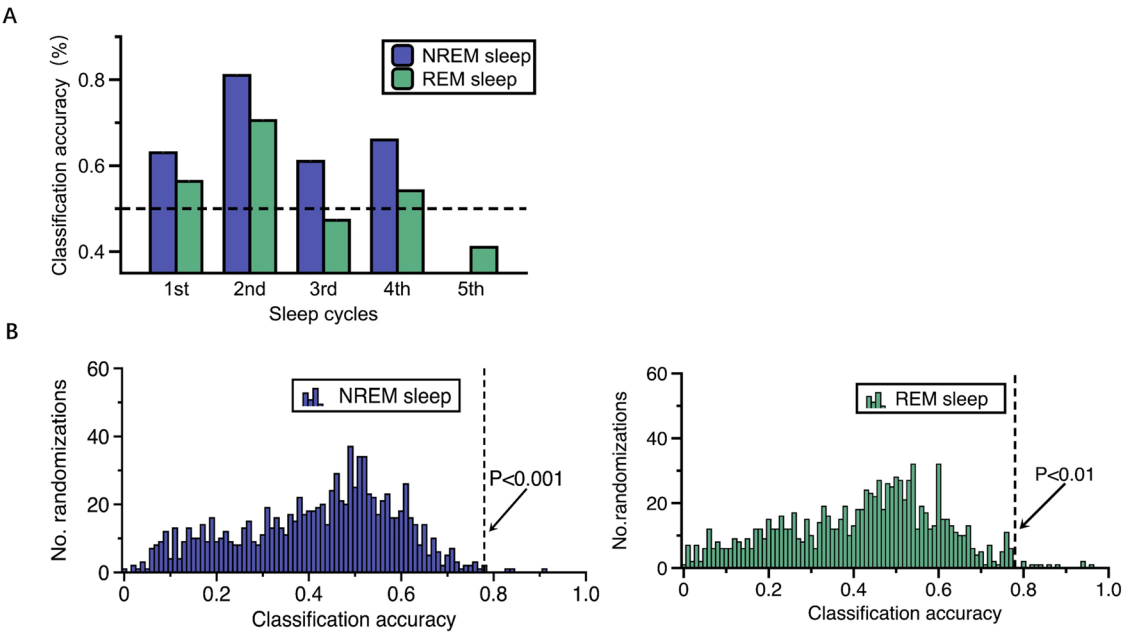

Fig. 3 Distinguishing reactivation patterns between negative emotional memories and neutral memories in each sleep cycles. A Two different encoding conditions (negative images and neutral images) can be determined by an ensemble classification algorithm during different sleep cycles. To test the stability of this classifier accuracy, participant data was evaluated with a leave-one-out test, where patterns detected in one set of subjects during training can be generalized to data from a new subject. **B** To test the significance of this classifier, we used permutation test classification rates that are higher than can be expected from data sets with random labeling of the data, that is, not containing any information.

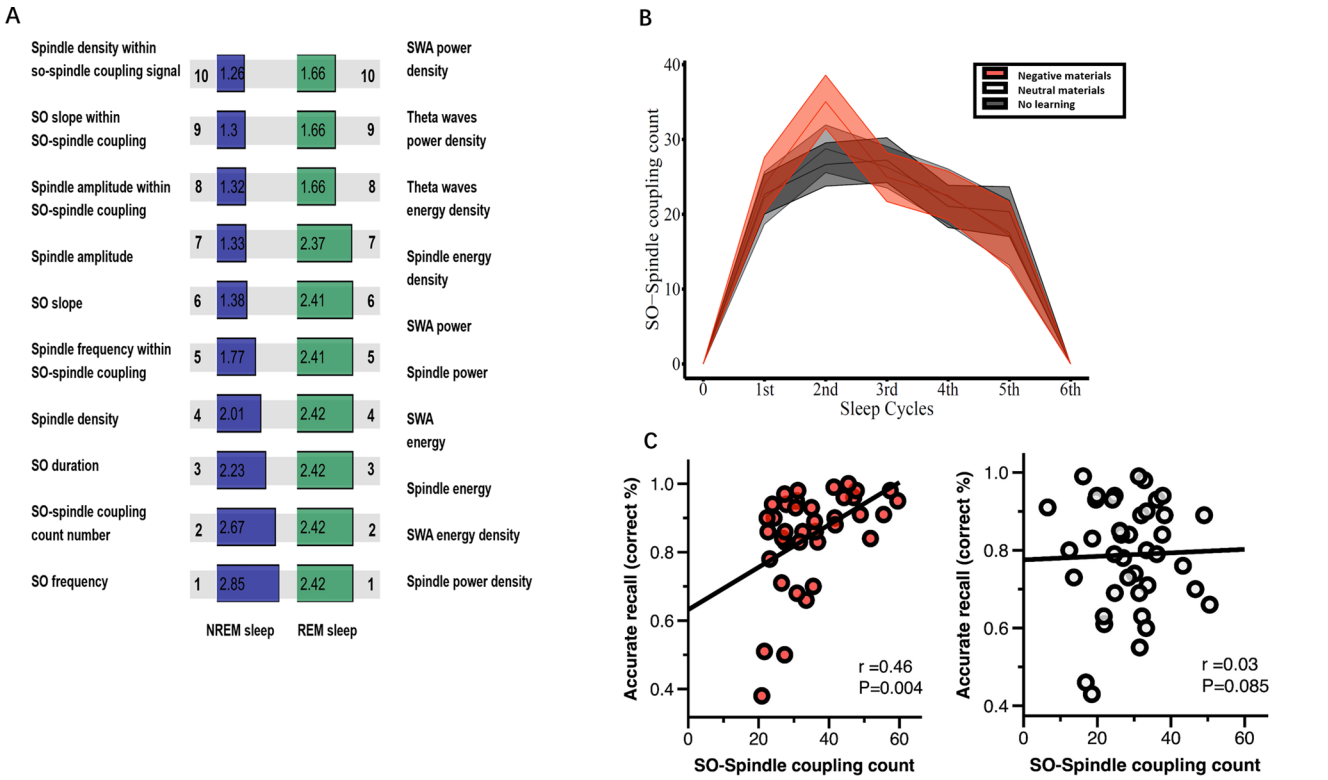

Fig. 4 Feature contributions to emotional memory reactivation. A Top 10 features of negative emotional memory reactivation in NREM and REM sleep. To obtain the contribution weights of the top 10 features, the ensemble classifier model was trained and tested once for each feature to determine the classification accuracy, thus obtaining the predictive weight of each feature. Subsequently, the predictive accuracy of the top 10 features was aggregated across all subjects (NREM features, blue; REM features, green). **B** Post-learning SO-spindle coupling count among three conditions; red: negative memory condition; gray: neutral memory condition. black dotted line: no data were memorized during the nighttime adaptation period. ***$p < 0.001$ as determined via repeated-measures ANOVA (number of cycles × memory type). A Mauchly's test was conducted, the results indicated that the assumption of sphericity was not violated, as evidenced by a non-significant Mauchly's Test ($p > 0.05$). **C** Correlation between memory performance and SO-spindle coupling count during the 2nd sleep cycle; red: negative memory condition; gray: neutral memory condition. **$p < 0.01$, with a Bonferroni-adjusted α-level of 0.008 (0.05/6).

the top 10 features of the NREM and REM sleep-based classifiers of the different feature classes considered in this study. The predictive features preferentially appeared as higher scores for SO-spindle coupling (feature weight: 8.32), SO (feature weight: 6.46), and spindle (feature weight: 3.34) for the NREM sleep-based classifier. The top three predictive features for the REM sleep-based classifier were spindle (feature weight: 9.62), slow wave (feature weight: 8.91), and theta wave activities (feature weight: 3.32).

Next, we examined the relationship between memory consolidation and the strength of memory-reprocessing signals in the 2nd sleep cycle. First, we compared the sleep features during negative emotional materials, neutral materials and no-learning condition. Our results showed that the number of SO-spindle couplings during the 2nd sleep cycle after learning negative materials was selectively higher than that in the other learning conditions (two-way repeated-measures ANOVA, $F_{8,\ 17} = 2.88$, $p < 0.05$; see Fig. 4B). Post hoc analysis revealed that the number of SO-spindle couplings was greater in the negative condition than in the neutral condition during the 2nd sleep cycle ($d = 0.75$, LS mean difference 7.851, 95% CI 4.49–11.28, $p < 0.001$), as was the number of SO-spindle couplings in the negative condition and no-learning condition during the 2nd sleep cycle ($d = 0.62$, LS mean difference 6.004, 95% CI [2.76–9.24], $p < 0.01$). It is crucial to account for individual variability. Therefore, we present the distribution of SO-spindle coupling signals for each individual under different learning conditions (see Fig. S2 in the Supplementary Material). This detailed examination further corroborates our findings, showing a consistent pattern across participants. The individual-level data reinforces the conclusion that negative emotional learning selectively enhances SO-spindle coupling during sleep.

We subsequently performed partial correlation analysis to further explore whether SO-spindle coupling was related to the recall of negative emotional and neutral memories after a whole night of sleep. We observed a robust and positive correlation between SO-spindle coupling and negative memory performance during the 2nd sleep cycle ($n = 38$, $r = 0.46$, $p_{Bonferroni\text{-}adjusted} < 0.008$; see Fig. 4C). Such positive correlations were not observed in other cycles or in the total summed SO-spindle coupling data. Interestingly, the correlation between neutral memory performance and SO-spindle coupling after learning was not significant in any cycle or for the total summed SO-spindle coupling count (see Fig. 4C and Fig. S3 in the Supplementary Material). These results highlighted the preferential processing of negative emotional memories during sleep and underscore the crucial role of SO-spindle coupling in the negative emotional memory reprocessing process during the 2nd sleep cycle. In addition to the SO-spindle coupling signal, we analyzed the relationship between other sleep-specific oscillations and memory recognition performance. We found that there was no correlation between memory performance and other sleep-specific oscillations in the 2nd sleep cycle (see Fig. S4 in the Supplementary Material).

SO-spindle coupling during memory reprocessing predicts delayed advantages of negative emotional memory

Next, we examined how sleep is linked to emotional memory stabilization over time. We divided the 2-year delayed negative

memory sample based on memory performance. A positive memory d′ score (with an overall memory d-score >1.5) was considered successful; otherwise, recognition was considered unsuccessful. A linear MMRM revealed an optimal model fit for the number of SO-spindle couplings in each sleep cycle × memory interaction ($F_{4,\ 98} = 3.01$, $p < 0.05$). A post hoc test revealed that the number of SO-spindle couplings was significantly greater in the successful recognition group than in the unsuccessful recognition group during the 2nd sleep cycle ($d = 1.14$, LS mean difference 10.407, 95% CI [2.90–17.90], $p < 0.01$). Additionally, the SO-spindle coupling count in other sleep cycles was equally distributed compared to that in the unsuccessful recall group ($p > 0.05$; see Fig. 5).

Furthermore, a regression model including the count of reprocessing-related SO-spindle coupling in different sleep cycles was created to predict 2-year delayed emotional memory performance. The results showed that the number of SO-spindle couplings in the 2nd sleep cycle could predict only emotional memory performance 2 years later ($\beta = -0.259$, $p < 0.05$; Exp (B) = 0.772), and the SO-spindle coupling count during other cycles did not predict emotional memory performance ($p > 0.05$; see Table S3 in the Supplementary Material). These results indicated that SO spindle coupling plays a role in stabilizing emotional memory during memory reprocessing.

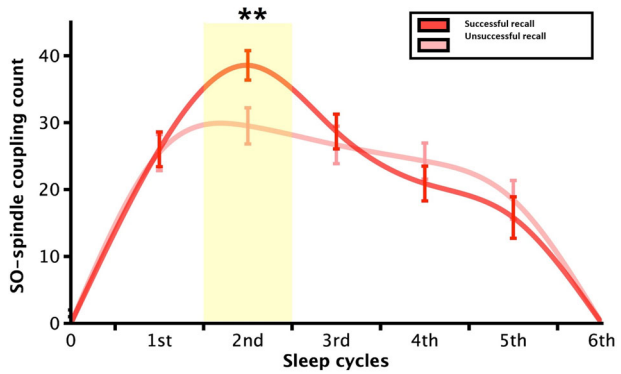

Fig. 5 Post-learning SO-spindle coupling predicted delayed advantages of emotional memory. Post learning SO-spindle coupling count between successful recall and un-successful recall group in the 2-year delayed negative image recall test, red: successful recall; pink: un-successful recall. **$p < 0.01$, derived from linear mixed effect model control with baseline coupling count (number of cycles × memory type).

tACS intervention disrupted SO-spindle coupling signals

To further verify the effect of SO-spindle coupling signal in the second sleep cycle on negative emotional memory reprocessing, we conducted an intervention test. In this study, we used a noninvasive intervention (cross-hemispheric tACS) to disrupt SO-spindle coupling signals and compared the effects of sinusoidal tACS and sham tACS on the memory reprocessing of neutral and negative emotions. Twenty-one participants memorized both negative and neutral materials before sleeping, and active/sham tACS interventions were administered separately during the 2nd sleep cycle-NREM phase; experiments in each condition were performed one week apart.

Compared with those of the sham tACS intervention, the power of sleep SO-spindle coupling signals was significantly lower on nights with sinusoidal tACS intervention (see Fig. 6A) at both inter-stimulation intervals ($F_{1,\ 4} = 7.92$, $p < 0.05$) and across all subjects after all average stimulation intervals ($T_{20} = -3.06$, $p < 0.05$).

Moreover, the count of SO-spindle coupling signals was significantly lower on nights with sinusoidal tACS intervention (Fig. 6B) at both inter-stimulation intervals ($F_{1,\ 4} = 5.92$, $p < 0.05$) and across all subjects after averaging all stimulation intervals ($T_{20} = -2.33$, $p < 0.05$).

tACS intervention selectively inhibited negative emotional memory reprocessing

It remains unclear whether negative or neutral materials are preferentially processed during sleep when individuals memorize both types of material simultaneously. Therefore, we tested whether the SO-spindle coupling signal in the 2nd sleep cycle was selectively correlated with negative emotional memory after the subjects had memorized two types of materials. In line with

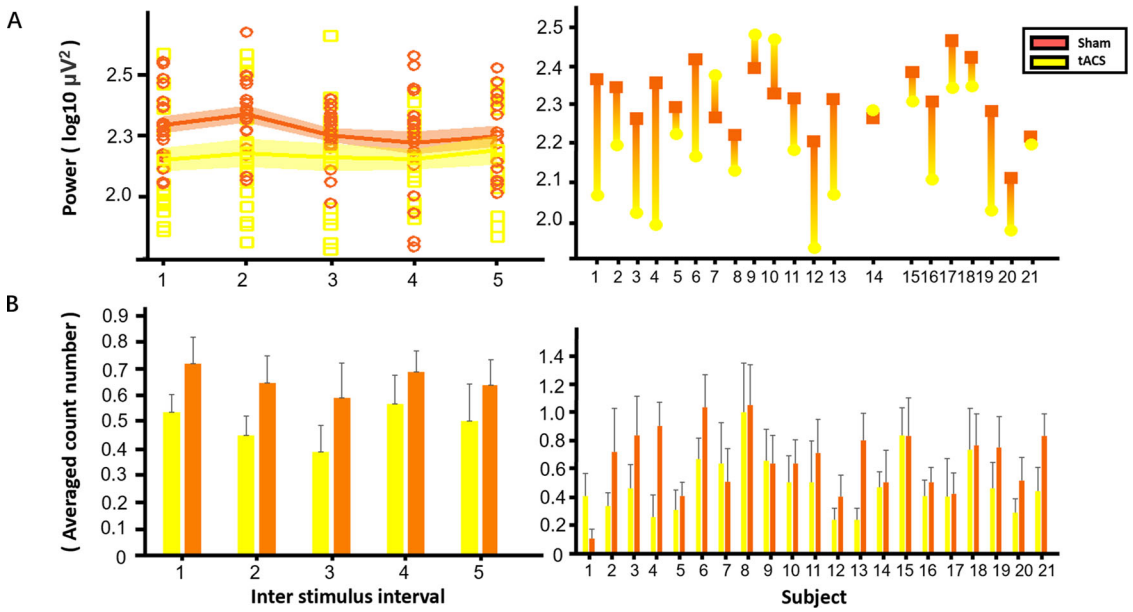

Fig. 6 tACS intervention inhibits SO-spindle coupling. A The power of the SO-spindle coupling signals ($F_{1,\ 4} = 7.92$, $p < 0.05$) was lower than that of the sham intervention in the inter-stimulation intervals after tACS intervention. **B** The count of SO-spindle coupling signals ($F_{1,\ 4} = 5.92$, $p < 0.05$) in the inter stimulation intervals after sinusoidal tACS intervention was lower than that after sham tACS intervention. Each stimulation session lasted for 5 min, with intervals of at least 1 min between sessions.

this purpose, our results showed that the SO-spindle coupling count was associated with negative emotional memories ($r = 0.52$, $p = 0.008$, uncorrected). While, the correlation between neutral memory performance and SO-spindle coupling was not significant ($p > 0.05$). Which suggests that negative emotional memories may preferentially processed over neutral memories during sleep without intervention (see Fig. S5 in the Supplementary Material). While the results suggest that negative emotional memories may be preferentially processed over neutral memories during sleep without intervention, the differences observed are marginal and heavily reliant on the statistical threshold ($p < 0.05$). The scatter plots in Fig. S5 show similar distributions, indicating that the interpretation should be approached with caution.

Finally, we compared the behavioral memory performance following the two interventions. A two-way repeated-measures analysis of variance (ANOVA) revealed a significant intervention type × memory type interaction ($F_{1, 20} = 5.931$; $p < 0.05$). Post-hoc test showed that, in the sham tACS condition, sleep played a preferential role in enhancing negative emotional memory reprocessing ($d = 1$, 95% CI [0.10–0.23], $p < 0.001$). This selective enhancement effect was disrupted by the tACS intervention in the 2nd sleep cycle, in which the recognition scores of negative emotional materials were lower than those of the sham intervention ($d = 0.49$, 95% CI [−0.16 to −0.01], $p < 0.05$); see Fig. 7).

DISCUSSION

Memory reprocessing is a time-sensitive process that provides a pivotal window for vigilant monitoring and precise calibration, particularly in the context of patients with pathological emotional memories, such as those afflicted by anxiety disorders and posttraumatic stress disorder. Our study successfully identified a specific window of negative emotional memory reprocessing occurs during sleep. Furthermore, we demonstrated that SO-spindle coupling during the 2nd sleep cycle following memorization of emotional memory materials is a reliable indicator of memory reprocessing, and predicting long-term memory performance. Finally, high-frequency tACS intervention selectively inhibited negative emotional memory reprocessing by targeting SO-spindle coupling during the 2nd sleep cycle.

Our findings indicated that negative emotional memory reprocessing occurs primarily during the 2nd sleep cycle. Our results provide compelling evidence of the existence of a centralized processing period for memory consolidation during sleep. Specifically, we observed a high density of SO-spindle coupling during the 2nd sleep cycle, which strongly indicated the probability of memory reprocessing. In line with this finding, a previous study showed that sleep deprivation during a specific 3-h window after learning disrupts hippocampal synaptic plasticity and memory [32]. Furthermore, a similar pattern was reported in an animal study in which cell assembly reactivation peaked 3-5 h following training [6]. Although we must acknowledge that nonsignificant classification accuracy may be present during other sleep cycles, memory reprocessing may still occur for a few memories during these cycles. However, emotional memory reactivation during the 2nd sleep cycle was the most predictive factor of memory performance. As our results showed in the see Fig. S4 in the Supplementary Material, such reprocessing-related signals (i.e., SO-spindle coupling) are closely related to emotional memory performance only during a specific period (i.e., the 2nd sleep cycle) rather than during other cycles or being related to total night-averaged sleep signals. Furthermore, SO-spindle coupling during the 2nd sleep cycle predicts recognition of emotional memory 2 years later.

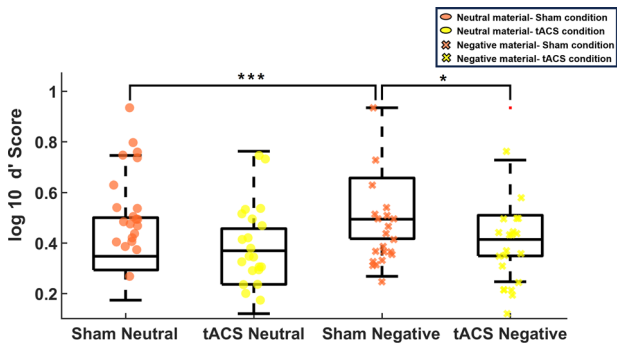

Fig. 7 tACS intervention disrupts negative emotional memory. The results of the multiple comparison analysis showed that the recognition scores of negative emotional memories after sinusoidal tACS intervention were lower than those after sham intervention ($d = 0.49$, 95% CI [−0.16 to −0.01], $p < 0.05$); The recognition of neutral memories was similar in both the tACS and sham conditions ($p > 0.01$). **$p < 0.01$ as determined by repeated-measures ANOVA, the Shapiro–Wilk tests for all conditions indicate that the data follow a normal distribution ($p > 0.05$).

Sleep following learning may serve as a therapeutic window for the precise inhibition of emotional memory consolidation [33]. A previous study revealed that cross-hemispheric tACS disrupts SO signals [26]. Our results highlight the role of post-learning SO-spindle coupling in stabilizing negative emotional memories. In the present study, we confirmed the effect of cross-hemispheric high-frequency tACS by interfering with SOs to disrupt SO-spindle coupling signals. More importantly, we found that high-frequency tACS applied during NREM sleep inhibited negative emotional memory reprocessing. According to previous evidence, SO-spindle coupling is critical for gating information flow between relevant brain areas and driving memory processing [34]. In NREM sleep, neocortical SOs coordinates the system consolidation of memories by driving thalamocortical sleep spindles and hippocampal ripple events [35, 36]. Importantly, hippocampus–amygdala correlation patterns occur most commonly during hippocampal sharp wave ripples (SWRs; 80–140 Hz), a type of local field potential recorded from the hippocampus [5]. Furthermore, reprocessing-related SWRs also promote communication between the hippocampus, thalamus, and neocortex [3, 37, 38]. One tentative interpretation of our findings is that cortical SO-spindle coupling reactivates memory traces in the hippocampus while regulating synaptic plasticity in the neocortex and amygdala [39, 40].

We found that both NREM and REM of 2nd sleep cycle are involved in memory reprocessing. Although we found interesting signals REM sleep, however, its functions could not be explained. First, our feature-ranking test results emphasized the contribution of spindle signals to memory reprocessing during REM sleep. However, we did not find a positive correlation between REM-specific spindles and emotional memory performance. Spindles are often found in REM sleep, especially in early onset REM sleep [41]; these spindles share similar spiking patterns with NREM spindles but essentially originate from phasic REM sleep [22]. The onset of REM sleep requires highly stabilized NREM sleep, which is often accompanied by high spindle activity [42]; hence, spindles in REM sleep can promote NREM-REM state transition [43]. However, the function of REM spindle states in memory consolidation is poorly understood. Second, EOG signals play a crucial role in REM sleep, and some studies have focused on EOG signals that are highly synchronized with brain activity during sleep [44, 45]. However, we did not find any evidence for the EOG signals that promote memory performance. Pertinently, the classifier models or correlational analysis were not the only method for proving the relevance of EOG signals in memory performance. Therefore, the mechanism by which REM sleep affects emotional memory processing remains unclear [46, 47]. According to a recent study, REM sleep is associated with somato-dendritic decoupling, which may prevent the reinforcement of fear responses [48]. It is possible that memory consolidation depends on cyclic competition between the two sleep states.

In conclusion, negative emotional memories undergo stronger reactivation during sleep. This process occurs within a specific time window and involves specific neurophysiological markers, where SO-spindle coupling in the 2nd sleep cycle plays an important role in the preferential stabilization of negative emotional memory. These findings highlight the potential of noninvasive neuromodulation techniques to regulate emotional memory, and raise the possibility of potential therapeutic applications in negative emotion-related psychiatric disorders.

DATA AVAILABILITY

The dataset analyzed in the present study as well as scripting and plotting code are available from the corresponding authors via email on reasonable request.

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AUTHOR CONTRIBUTIONS

ST: conceptualization, investigation, software, formal analysis, writing—original draft, visualization. XZ: data curation, writing—review & editing. PL: data curation. FW: supervision. LS: formal analysis, supervision. YG: writing—review & editing. KY: data curation, writing—review & editing. YB: conceptualization, supervision. TF: resources. SL: conceptualization, supervision. JS: resources, supervision. LL: conceptualization, supervision, funding acquisition. JD: conceptualization, methodology, resources, supervision, funding acquisition.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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