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Novel Electrophysiological Signatures of Learning and Forgetting in Human Rapid Eye Movement Sleep

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Despite the known behavioral benefits of rapid eye movement (REM) sleep, discrete neural oscillatory events in human scalp electroencephalography (EEG) linked with behavior have not been discovered. This knowledge gap hinders mechanistic understanding of the function of sleep, as well as the development of biophysical models and REM-based causal interventions. We designed a detection algorithm to identify bursts of activity in high-density, scalp EEG within theta (4–8 Hz) and alpha (8–13 Hz) bands during REM sleep. Across 38 nights of sleep, we characterized the burst events (i.e., count, duration, density, peak frequency, amplitude) in healthy, young male and female human participants (38; 21F) and investigated burst activity in relation to sleep-dependent memory tasks: hippocampal-dependent episodic verbal memory and nonhippocampal visual perceptual learning. We found greater burst count during the more REM-intensive second half of the night ($p < 0.05$), longer burst duration during the first half of the night ($p < 0.05$), but no differences across the night in density or power ($p > 0.05$). Moreover, increased alpha burst power was associated with increased overnight forgetting for episodic memory ($p < 0.05$). Furthermore, we show that increased REM theta burst activity in retinotopically specific regions was associated with better visual perceptual performance. Our work provides a critical bridge between discrete REM sleep events in human scalp EEG that support cognitive processes and the identification of similar activity patterns in animal models that allow for further mechanistic characterization.

Key words: **electrophysiology; forgetting; learning; memory; REM sleep; sleep**

Significance Statement

Current understanding of sleep and its role in cognitive processes is incomplete due to a lack of discrete electrophysiological events in human rapid eye movement (REM) sleep detectable via scalp EEG. Our work remedies this gap in knowledge by designing an open-source, computational approach to identify electrophysiological alpha and theta burst events in REM sleep. Additionally, we provide evidence that these burst events are functionally important for learning and memory. Defining burst events in human REM will contribute to the development of a comprehensive mechanistic model of how sleep as a whole, and REM specifically, facilitate cognitive processes and provide a deeper understanding of the fundamental electrophysiological properties of REM sleep that are distinct from non-REM sleep.

Introduction

Rapid eye movement (REM) sleep, first identified in the 1950s (Aserinsky and Kleitman, 1953), is conserved across most species (Peever and Fuller, 2017) and is significant for developmental and cognitive processes (Mirmiran, 1986; Graven and Browne, 2008; Cai et al., 2009; Blumberg et al., 2013; Goldstein and Walker, 2014; Boyce et al., 2017; Park and Weber, 2020). Yet, beyond minutes in REM and general spectral power in specific bands, no discrete events in the human scalp electroencephalogram (EEG) have been linked to cognition. This gap in knowledge has hindered understanding of the function of REM, as well as sleep more generally, since REM comprises up to 20% of total sleep (Carskadon and Dement, 2011). The potential impact of this missing link is illustrated by robust findings in non-REM (NREM) sleep where several physiologically relevant events have been identified in both humans and animals, which cover a range of brain regions, spectral frequencies, and time scales: e.g., cortical slow oscillations (SOs, 0.5–1 Hz),

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corticothalamic spindles (12–15 Hz), and hippocampal sharp wave ripples (SWRs, 80–120 Hz; Steriade et al., 1993; Gais et al., 2002; De Gennaro and Ferrara, 2003; Mednick et al., 2013; Ngo et al., 2013; Staresina et al., 2015; Latchoumane et al., 2017; Klinzing et al., 2019). Studies have demonstrated causal associations between memory improvement and NREM events individually, as well as the coordination of these rhythms, where faster rhythms (spindles and ripples) are nested in slower rhythms (SOs; Mednick et al., 2013; Ngo et al., 2013; Staresina et al., 2015; Latchoumane et al., 2017; Klinzing et al., 2019). These findings have been highly generative for mechanistic models of systems consolidation (Tononi and Cirelli, 2003; Diekelmann and Born, 2010; Lewis and Durrant, 2011; Mednick et al., 2011). No such biophysical models exist for REM sleep, or sleep as a whole, due to a lack of electrophysiological events tied to function.

REM sleep is characterized as a distinct state from NREM, consisting of wake-like EEG along with REMs, vivid dreaming, and muscle atonia (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957; Jouvet and Michel, 1959). Early work by Carlyle Smith and colleagues demonstrated an association between REM and memory in humans and animal models (Smith, 1995). Following these behavioral findings, animal models linked specific REM events to behavior, such as Ponto-Geniculo-Occipital (PGO) waves (Jouvet and Michel, 1959; Brooks and Bizzi, 1963; Kaufman and Morrison, 1981; Datta, 1997; Datta et al., 1998, 2008; Datta and O'Malley, 2013). However, there is no evidence of PGO waves in human scalp EEG, and similar waves in humans have only been detected with more invasive intracranial EEG (Lim et al., 2007; Fernández-Mendoza et al., 2009; Andrillon et al., 2015), reducing their translatability to systems level modeling in relation to human cognitive processes. Other REM events, such as muscle twitches and REMs, have been implicated in motor learning and sensorimotor development (Blumberg et al., 2013; Sokoloff et al., 2015; Brooks and Peever, 2016), and auditory targeted memory reactivation cues time locked to REMs showed greater memory improvement than cues not locked to REMs (Smith and Weeden, 1990). Additionally, learning increased the density of REMs, and the direction and amplitude of REMs may be related to the internal representation of header direction in animal navigation (De Koninck et al., 1989; Smith and Lapp, 1991; Senzai and Scanziani, 2022). Yet there is still limited understanding of underlying neural correlates of REMs and how they are functionally tied to sleep-dependent memory processes (e.g., whether they drive or merely reflect cognitive processing; Peigneux et al., 2003; van den Berg et al., 2023).

Studies on scalp EEG signals during human REM sleep have examined spectral power in relation to cognitive processes. Increased theta power is associated with sleep-dependent improvement in emotional memory processing (Nishida et al., 2009), although this relationship has not been found across a majority of studies (Davidson and Pace-Schott, 2021). Potentially these mixed findings are due to the fact that total theta power was examined, rather than a more specific measure of power within a burst event. Additionally, theta power during REM sleep has been associated with visual perceptual learning (VPL), where VPL is marked by long-term improved performance in a visual task and is thought to be a marker of brain plasticity (Sasaki et al., 2010). Specifically, increased theta power in posterior regions is associated with increased resilience to VPL interference (Tamaki et al., 2020), with time in REM sleep also associated with VPL (Karni et al., 1994; Stickgold et al., 2000; Mednick et al., 2003, 2013). To date, REM sleep alpha bursts and theta bursts in human scalp EEG have been previously identified, but their functional relation to learning and memory remains unknown (Cantero and Atienza, 2000; Cantero et al., 2002; Harrington et al., 2021). While one study did successfully manipulate theta bursts during REM sleep via auditory stimulation, theta manipulation was not significantly predictive of memory improvement (Harrington et al., 2021). Thus, while prior studies suggest a critical role of REM sleep in human VPL processing (nonhippocampal) and recent findings from animal studies have demonstrated mechanistic shaping of hippocampal memories at the synaptic and systems level during REM sleep (Li et al., 2017; Izawa et al., 2019; Zhou et al., 2020), no human studies have tied distinct REM sleep events in human scalp EEG to cognitive processes.

Identifying such events provides a metric superior to total power metrics for several reasons. First, identifying a physiological burst gives temporal and spatial markers of a neural event that can be then used for further processing, such as the analysis of spatiotemporal patterns of burst activity across the EEG manifold and identification of similar activity patterns in animal models that allow for further mechanistic characterization. Additionally, burst events can help in the development of neural network models that attempt to understand how different brain regions communicate and lead to specific functional outcomes. Furthermore, burst activity allows for the development of interventions that target specific events and potentially lead to breakthrough treatments for disorders of memory or REM-related neurological (e.g., Parkinson's Disease) and mental (e.g., Depression) disorders (Berger and Riemann, 1993; Boeve, 2013; Jozwiak et al., 2017).

The present study's goals were (1) to characterize burst events in human EEG during overnight REM sleep and (2) to examine their relation to hippocampal and nonhippocampal memory performance and sleep-dependent change in performance. We designed an algorithm to detect burst events in human scalp EEG during REM sleep. We examine burst events in the theta (4–8 Hz) and alpha (8–12 Hz) bands based on a priori hypotheses. Given prior work showing REM sleep total theta power in posterior brain regions is involved in VPL, we hypothesized that REM sleep theta bursts in those regions would be related to the VPL task performance. We also examined the relation between REM sleep theta and alpha bursts and episodic (hippocampal) word pair consolidation, given animal literature demonstrating a role for REM sleep in hippocampal forgetting mechanisms (Izawa et al., 2019; Zhou et al., 2020).

Materials and Methods

Participants

Participant data for this study consisted of the placebo group of a larger pharmacological study (original study: Byrne et al., 2020). The present study's participants comprised 38 healthy, young adults (ages 18–35 years; 21F) who completed prescreening assessments to determine their sleep and general health status. Participants had no current or history of visual impairments, major psychological or medical conditions, or sleep disorders and additionally were not taking any medications that would affect cognitive function, vision, or sleep. All participants included in the study self-reported consistent sleep habits, with a typical sleep time between 11 P.M. and 1 A.M. and wake time between 6 and 8 A.M. All participants completed an orientation session at the beginning of the study where they reviewed study processes. During this session, participants provided informed consent and upon completion, were enrolled in the study. Participants were instructed to continue with their regular sleep schedule for the week leading up to their experimental visit in

lab and were monitored by a daily sleep diary. For the 24 h period before and through the experimental visit, participants were instructed not to consume any caffeine or alcohol, and to get at least 7 h of sleep the night prior to the study. This study and procedures were approved by the Institutional Review Board at University of Riverside.

Procedure and assessment measures

Participants engaged in learning and memory tasks before and after overnight sleep in the lab with 64-channel EEG recorded during sleep. All participants reported to the lab at 9 A.M. on Day 1 to complete the presleep tasks (Test 1), including the VPL Texture Discrimination Task (TDT) and episodic memory Word Pair Association (WPA) task described below. Participants left the lab and then returned later the same evening to sleep in lab monitored by polysomnography (EEG details below). In the morning participants engaged in Test 2 where they completed the same tasks postsleep (Fig. 1*a*).

TDT

For the TDT (Fig. 1*b*), visual stimuli were generated using the Psychtoolbox in Matlab (MathWorks). At each trial, participants saw a screen with a central fixation cross for 600 ms and were instructed that this indicated the beginning of each trial. Following the fixation cross, participants saw a blank screen for 300 ms, a texture target screen that contained a central and peripheral target for 17 ms, a blank screen of varying duration between 50–400 ms, and then a mask screen for 100 ms. The central target could be either the letter "L" or "T" in random orientations and the peripheral target contained three slanted bars in either horizontal or vertical array. Subjects were trained in one of two potential peripheral target positions (i.e., Upper Left or Upper Right) that were randomized across participants. The background for this peripheral texture stimulus consisted of either horizontal or vertical elements that contrasted with the slanted lines such that there was a difference between peripheral target and background.

Following the mask screen participants were presented with a response screen for 2 s, where they used the keyboard keys 1 and 2 to indicate both the central and peripheral targets. For instance, if a participant saw a target stimulus with the letter "L" in the middle and a peripheral target in the vertical position, they would indicate this by typing the letter "1" twice on the keyboard. Typing the first "1" indicated the "L" (where a 2 would indicate "T") and typing the second "1" indicated the vertical orientation of the peripheral target (typing a "2" would indicate horizontal orientation). After the response screen, participants were presented a feedback screen for 250 ms which consisted of a fixation cross that turned green if the participant's response was correct and turned red if incorrect. The interstimulus interval (ISI) is the time between the Target and Mask screen excluding the stimulus presentation itself. Participants completed 10 blocks each with 15 trials. Across blocks, the ISI became progressively shorter: 400, 300, 250, 200, 167, 150, 134, 117, 100, and 50 ms.

Word pair association task

Participants also completed the episodic memory WPA task (Fig. 1*c*) in the morning of their overnight in lab (Encoding and Test 1) and the morning directly after sleeping in lab (Test 2). At Encoding, participants were shown 200 word pairs on the screen and instructed that they would be tested on the association between these words. At each test, participants were shown 150 pairs, of which one-third of the word pairs were paired together exactly as they had been during encoding (intact), another third were words participants saw during encoding (rearranged), but were paired together incorrectly, and the remaining third were new words paired together (new). Participants responded to each word pair indicating whether they thought the test word pairs were intact, rearranged, or new. The words shown at Test 1 and Test 2 were different such that 100 of the 200 word pairs shown at encoding were shown at Test 1, and then the other 100 of the 200 encoded pairs were used for Test 2. The additional 50 novel word pairs also differed between test

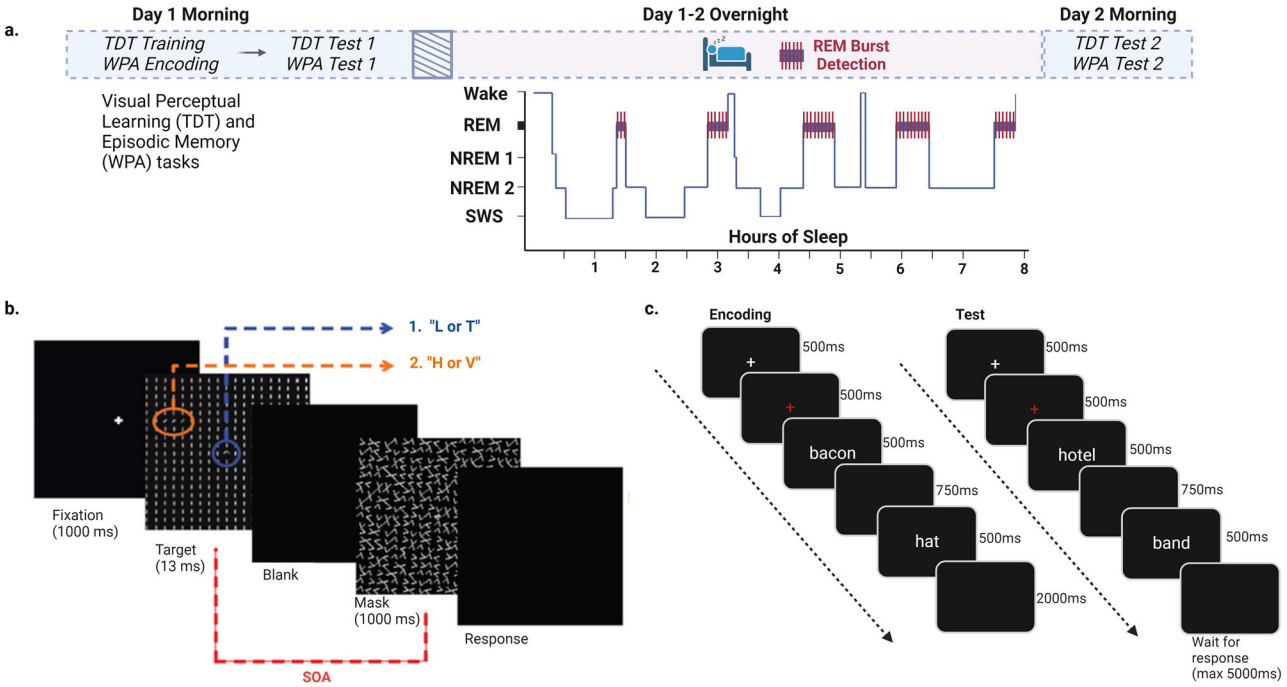


Figure 1. ***a***, Timeline of experimental protocol. ***b***, Texture Discrimination Task: First, participants are presented with a fixation screen with a plus in the center to remind them to focus on the middle of the screen. Next the target screen briefly flashes, containing an array of bars with a fixation letter in the center of the screen (either an L as shown in this example, or a T) and a peripheral target composed of three slanted bars in either a vertical, as shown in the image, or horizontal array (labeled in the image key as H or V, for horizontal or vertical). Following this, participants see a blank screen, then a mask screen, and finally a response screen. At the response screen, participants used the keyboard to report both the central (T or L) and peripheral (horizontal or vertical) targets. The ISI, i.e., the time between the Target and Mask screen (excluding the stimulus presentation itself), is varied (400–50 ms). ***c***, WPA task: At encoding, participants are presented with 200 word pairs presented one after the other and instructed to remember the pair. During testing, subjects determine whether word pairs are correctly or incorrectly paired or completely new words.

sessions. Word pairs were not repeated at Test 1 and Test 2 to avoid reintroducing a rehearsal of word pairs at Test 1 that would inflate recall and represent a false baseline, consistent with methods of Zhang and colleagues (Zhang et al., 2022). As each set of words presented at Test 1 and Test 2 were randomized, a participant's performance on each half of the word pairs is representative of their encoding of the overall word pair list.

Polysomnography

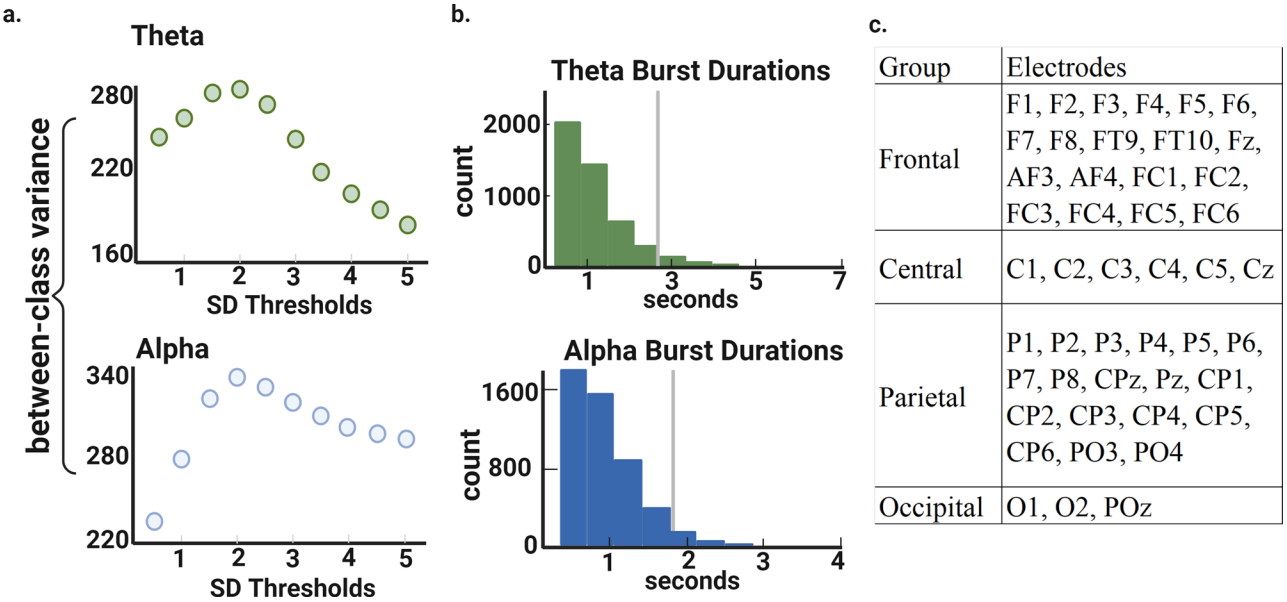
Participants were fitted with a 64-channel EASYCAP with electrodes placed according to the 10–20 system. Out of these 64 channels, 56 were neural electrodes, with the remaining consisting of two electrocardiogram (ECG), two electromyogram (EMG), two mastoid, one ground, and one common reference channel located at FCz. EEG was recorded at 1,000 Hz sampling rate. EEG data were preprocessed using BrainVision Analyzer 2.0 (Brain Products) and were downsampled to 256 Hz and IIR filtered with 0.5 to 35 Hz. EEG data were then contralaterally referenced to the mastoid channels, and each channel was mean centered. To classify sleep stages, the whole-night sleep data were visually scored in 30 s epochs per Rechtschaffen and Kale's manual (Kales and Rechtschaffen, 1968). Per this scoring method, the overnight sleep recordings are identified into seven stages: Wake, Stage 1, Stage 2, Stage 3, Stage 4, REM, and movement time. Wake is classified as high background alpha activity with continued alpha activity in occipital regions with closed eyes, as well as presence of eye movements and blinks when eyes are open. Stage 1 is defined as low-amplitude mixed frequency activity with vertex waves, as well as if sleep spindles and REMs are absent for >3 min after a period of other sleep. Stage 2 is marked by K-complexes and sleep spindles, while Stages 3 and 4 are marked by delta band activity. REM sleep is characterized by low-amplitude mixed frequency similar to Stage 1, except that vertex waves are not present, and REM is additionally identified by low muscle tone and eye movements along with absence of spindles and k-complexes. As alpha band activity may be prominent during Wake, Stage 1, or REM, we distinguished REM when the epoch contained low muscle tone as well as the absence of vertex waves. During scoring, noisy epochs or segments of arousals were scored as such and the entire epoch was removed from further analysis.

Burst detection

Bursts were identified during REM sleep epochs using the following detection methods. All neural channels were bandpass filtered to isolate the theta (4–8 Hz) and alpha (8–13 Hz) bands using a Hamming windowed sinc FIR filter. The Hilbert transform was then used to extract the phase and amplitude of each filtered signal. Mean and standard deviation of the amplitude signal were calculated across time using a 30 s sliding window. Bursts were detected using an amplitude threshold, with bursts defined as EEG amplitude above 2 standard deviations from the mean within a given window. The threshold of 2 standard deviations (SD) was selected using Otsu's method for parameter selection (Otsu, 1979; Djonlagic et al., 2020). Theta and alpha thresholds were determined independently. For each, between-class variance was calculated according to Otsu's methods for the following potential thresholds: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 SDs. For both theta and alpha, between-class variance peaked at 2 SDs (Fig. 2) indicating this is a suitable threshold which maximizes between-class variance between burst and nonburst activity. Burst detection also included a threshold of 2 for the minimum number of cycles needed to define a burst, where a full cycle was defined based on the number of times the phase intersected 0, with two consecutive intersections indicating one full cycle. To ensure the bursts identified by the sliding window did not overlap, we merged overlapping bursts such that if Burst A and Burst B overlapped, we defined a new Burst C in their place which consisted of the start point of Burst A and end point of Burst B. Additionally, only theta bursts whose duration ranged from 0.5 to 3 s and alpha bursts whose duration ranged from 0.5 to 2 s were included in analysis. The lower cutoff of 0.5 s was selected based on the minimum amount of time needed to observe two cycles of the slowest oscillation the algorithm is designed to detect. The upper cutoff was then identified by examining the distribution of burst durations. For theta bursts, over 95% of identified bursts fell within 3 s, while for alpha, over 95% of bursts fell within 2 s (Fig. 2). Going forward, the terminology of "REM bursts" refers to burst events during REM sleep identified by the algorithm.

Data analysis

Burst characteristics. REM theta and alpha bursts were identified as detailed in the Burst Detection section. As the second half of the night is more REM sleep intensive (Carskadon and Dement, 2011), REM bursts were categorized by halves of the night. The night was separated into halves based on total sleep duration (for sleep architecture, see Fig. 3*a*), and the following burst characteristics were calculated per half: duration, count, density, peak frequency, and power. Duration of bursts across each half of the night was calculated as the sum of all burst time across the respective half of the night. Count for bursts was measured as the number of individual bursts identified. Density for bursts was measured as the number of bursts per minute. Peak frequency was



c.

Group	Electrodes
Frontal	F1, F2, F3, F4, F5, F6, F7, F8, FT9, FT10, Fz, AF3, AF4, FC1, FC2, FC3, FC4, FC5, FC6
Central	C1, C2, C3, C4, C5, Cz
Parietal	P1, P2, P3, P4, P5, P6, P7, P8, CPz, Pz, CP1, CP2, CP3, CP4, CP5, CP6, PO3, PO4
Occipital	O1, O2, POz

Figure 2. ***a***, Between-class variance (*y*-axis) for theta and alpha across standard deviation thresholds (*x*-axis), each showing a peak at 2 standard deviations. ***b***, Histograms showing the distribution of theta and alpha burst durations in seconds (*x*-axis). The vertical line at each indicates the 95% threshold. ***c***, Electrodes groupings (per Malerba et al., 2019).

calculated within each individual burst event. Power was calculated as the sum of amplitude squared for all points identified in a burst divided by the number of points making up the burst. *t* tests were conducted for each metric between first and second half of the night to examine whether these burst characteristics changed across the night.

TDT analysis. TDT performance was measured as percent of correct trials as a function of ISI, using a Weibull function to calculate the threshold ISI interval which yielded 80% performance accuracy. These scores were calculated for presleep and postsleep performance. Note that a higher score indicates lower performance, as this indicates the ISI threshold for 80% performance. As such, a score of 200 would indicate that an ISI of 200 ms is needed to achieve 80% performance, while a score of 100 would indicate that only an ISI of 100 ms is needed to achieve 80% performance, indicating the participant performs better at faster intervals. Two participants did not reach a performance level of 80% accuracy at any trial and thus were excluded from further TDT analyses, leaving a total of $n = 36$.

The 80% ISI metric was calculated separately for Test 1 (presleep) and Test 2 (postsleep), and a *t* test was used to examine whether participants performance significantly better or worse postsleep compared with presleep. Additionally, we were interested in how performance changed over sleep. To assess performance change over sleep, we calculated the difference score between test sessions by subtracting Test 1 (presleep) from Test 2 (postsleep). As lower scores indicate better performance, a negative difference score indicates that the participant had a lower threshold postsleep compared with presleep. Conversely, if the difference score was positive, this means that the participant had a higher threshold postsleep compared with presleep, indicating that their performance declined over sleep.

Since visual information is processed in the contralateral hemisphere, the trained hemisphere is considered the hemisphere contralateral to the visual field where the peripheral target was presented, while the untrained is ipsilateral to the peripheral target. As such, for peripheral targets that were presented in the Upper Left visual field, the trained brain hemisphere would correspond to the EEG electrodes on the right side of the brain and vice versa for targets presented in the Upper Right. We followed a standard analysis method to examine brain activity during sleep in relation to TDT performance by subtracting the activity in the untrained hemisphere from activity in the trained hemisphere (Tamaki et al., 2020; Tamaki and Sasaki, 2022). Prior research indicates that during sleep, power in the trained region reflects nontask-related baseline activity and learning-related activity, while power in the untrained region reflects solely baseline activity, thus a trained–untrained metric is preferable to examining raw power in the trained region alone (Tamaki and Sasaki, 2022). As prior research indicated that total theta power in certain posterior regions was related to VPL (Tamaki et al., 2020), we specifically examined electrodes O1, O2, PO3, PO4, P3, and P4, and the trained–untrained metric was created from these pairs. For example, if a participant were trained in the Upper Right quadrant, then the trained hemisphere would correspond with left side electrodes (i.e., O1, PO3, and P3), the untrained hemisphere would correspond with right side electrodes (i.e., O2, PO4, and P4), and the trained–untrained metric would consist of the difference between left and right electrodes (i.e., O1-O2, PO3-PO4, and P3-P4, respectively).

WPA analysis. WPA performance was measured by an accuracy score calculated as the ratio of correctly identified word pairs (intact, rearranged, and novel) compared with the total number of word pairs presented at test. This metric was calculated separately at Test 1 (presleep) and Test 2 (postsleep). Similar to TDT, we also examined the difference in performance over sleep for WPA. This was calculated in a similar manner, with Test 1 subtracted from Test 2 to yield a difference score. As a higher accuracy score indicates better performance, a positive difference score on this task indicates that the participant improved over sleep, while a negative difference score indicates that their performance declined over sleep. Since we did not have a priori expectations for regions of interest, burst activity was examined across the electrode manifold in relation to this task. Finally, one participant did not complete this task leaving $n = 37$ for this task.

Correlational analyses between task performance and burst activity. As described above, three performance metrics were calculated per task: Test 1 (presleep), Test 2 (postsleep), and the difference score (Test 2–Test 1). To examine task performance in relation to burst activity, we ran correlations between each performance metric and burst activity. For burst activity, we utilized median burst power to assess the central tendency of burst activity. Correlations were run for metrics in the REM-dominant second half of the night. The following describes specific steps per task.

For TDT correlations, burst activity was measured as trained–untrained median burst power for the electrodes of interests, with three pairings of posterior electrodes of interest (O1-O2, PO3-PO4, and P3-P4). Correlations were run separately between each electrode pair and task performance at Test 1, Test 2, and the difference score (i.e., power at O1-O2, P03-P04, and P3-P4 and each task performance metric). For WPA analysis, we did not have a priori expectations about which regions may relate to task performance, thus we averaged electrodes in frontal, central, parietal, and occipital regions (based on Malerba et al., 2019; Fig. 2). Correlations were then run between regional burst power and WPA performance metrics.

To assess if burst power may explain more variance in task performance than total band power, we additionally examined REM sleep total band power in relation to task performance. The same analyses were run as described in the preceding section, but with total band power instead of burst activity. Total band power included all activity within the alpha or theta band, respectively, including high-amplitude activity defined as bursts, as well as remaining low-amplitude activity that did not meet the criteria for burst detection. For the WPA analysis, an additional comparison with nonburst power was included in response to the burst and total power results (detailed in Results, Episodic memory and REM burst power). Nonbursts comprised all activities during REM outside of burst time points including low-amplitude band activity. As no significant results were found between total theta power and TDT performance (detailed in Results, VPL and REM burst power), nonburst power was not examined separately in the main analysis and thus is not accounted for in the multiple corrections described below for TDT. However, for thoroughness, a supplemental correlational analysis was conducted which determined theta nonburst activity did not significantly predict TDT performance ($ps > 0.05$).

To account for multiple comparisons, the *p* values for both TDT and WPA correlations were adjusted by false discovery rate (Storey, 2002) to account for number of regions (TDT, three electrode pairs; WPA, four regional electrode groupings), number of bands (TDT, theta; WPA, theta and alpha), number of power metrics (TDT, burst and total; WPA, burst, total, and nonburst), and the three performance metrics (Test 1, Test 2, and the difference score).

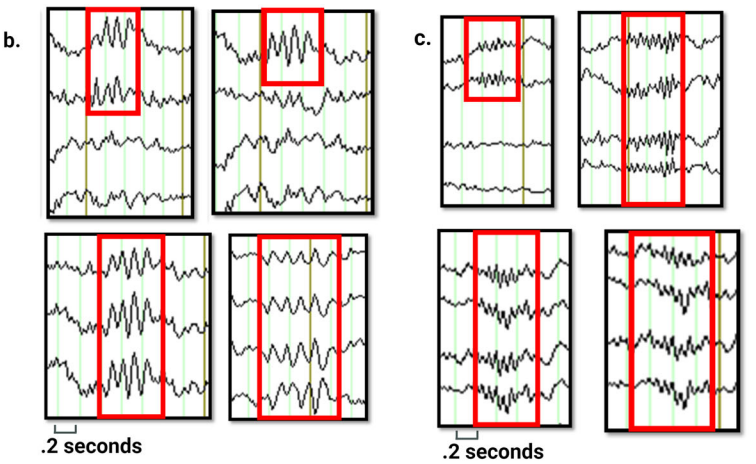
Results

REM burst characteristics

First, we visually examined REM bursts, which denote burst activity identified by our automated detection method during REM sleep (see Materials and Methods, Burst detection). Figure 3*b* shows examples of REM theta burst events identified by the detection algorithm and Figure 3*c* shows examples of REM alpha burst events identified by the detection algorithm. NREM and REM sleep are unevenly distributed across a night of sleep, with the majority of NREM sleep occurring in the first half of the night and the majority of REM sleep occurring in the second half of the night (Carskadon and Dement, 2011). Therefore, we examined REM burst characteristics of count, duration, density, and power across the first and second half of the night separately. Figure 2, *d* and *e*, shows descriptive statistics for these burst metrics. For burst count, both theta and alpha bursts had greater burst count in the second half of the night

a.

Sleep Stage	Mean	SD
TIB (hours)	7.96	.49
TST (hours)	7.27	.56
Stage 1 (mins)	19.41	13.46
Stage 2 (mins)	208.46	33.19
SWS (mins)	110.63	33.54
REM (mins)	97.85	21.88



d.

1st Half Night	Theta Mean	Theta SD	Alpha Mean	Alpha SD
Count (per person per ch)	258.84	115.52	207.40	91.16
Duration (seconds)	1.23	.14	1.06	.16
Density (bursts per min per ch)	8.60	.64	6.88	.80
Peak frequency (per person per ch)	5.43	.05	10.05	.03
Power (μV^2) (per person per ch)	60.67	35.59	53.09	43.23

e.

2nd Half Night	Theta Mean	Theta SD	Alpha Mean	Alpha SD
Count (per person per ch)	583.86	137.59	474.01	127.49
Duration (seconds)	1.12	.10	.90	.08
Density (bursts per min per ch)	8.62	.46	6.97	.81
Peak frequency (per person per ch)	5.05	.03	9.94	.05
Power (μV^2) (per person per ch)	67.62	48.11	46.03	31.25

Figure 3. ***a***, Sleep architecture. ***b***, Examples of REM theta bursts identified by our burst detection algorithm. ***c***, Examples of REM alpha bursts identified by our burst detection algorithm. ***d***, ***e***, Burst characteristics in the first (***d***) and second (***e***) halves of the night.

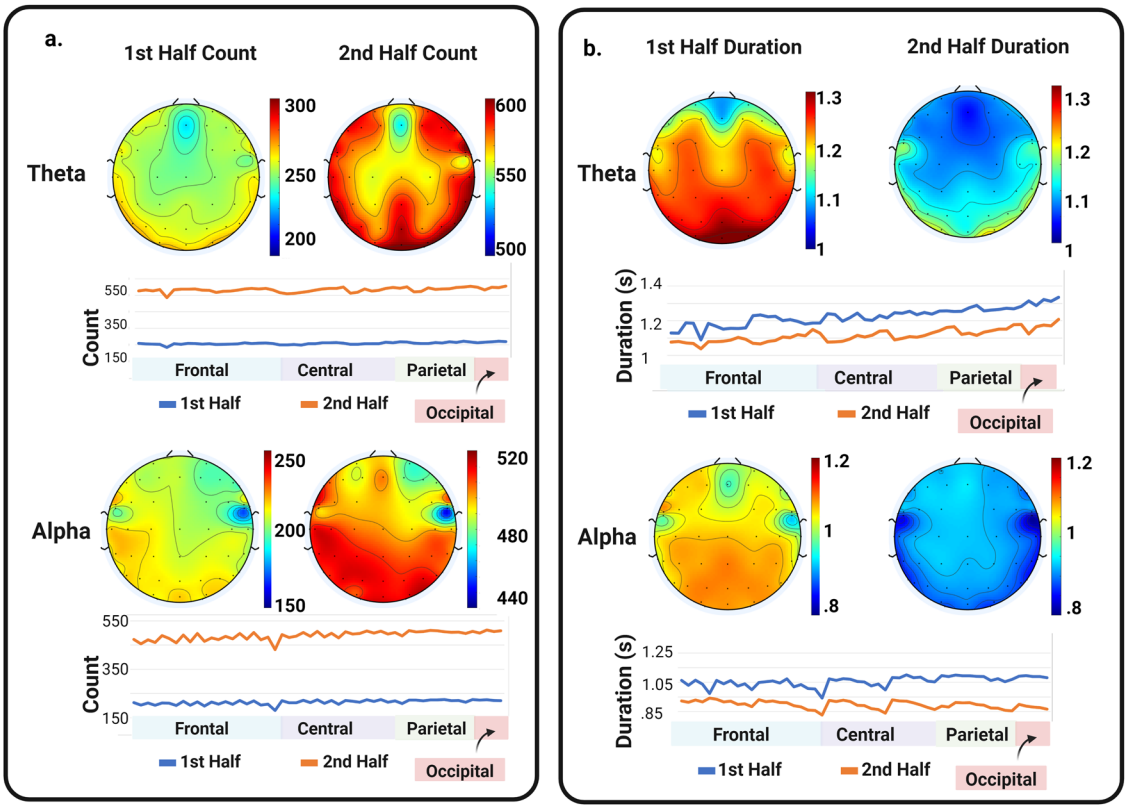


Figure 4. ***a***, For burst count, both theta and alpha bursts had greater burst count in the second half of the night compared with the first (theta: $t_{(37)} = 11.99$, $p < 0.0001$, Cohen's $d = 2.56$; alpha: $t_{(37)} = 11.83$, $p < 0.0001$, Cohen's $d = 2.39$). ***b***, For burst duration (seconds), both theta and alpha bursts had longer burst duration in the first half of the night (theta: $t_{(37)} = 5.7$, $p < 0.0001$, Cohen's $d = 0.90$; alpha: $t_{(37)} = 6.81$, $p < 0.0001$, Cohen's $d = 1.26$).

compared with the first (theta: $t_{(37)} = 11.99$, $p < 0.0001$, Cohen's $d = 2.56$; alpha: $t_{(37)} = 11.89$, $p < 0.0001$, Cohen's $d = 2.41$; Fig. 4*a*). For burst duration, both theta and alpha bursts had longer burst duration in the first half of the night (theta: $t_{(37)} = 5.7$, $p < 0.0001$, Cohen's $d = 0.90$; alpha: $t_{(37)} = 6.82$, $p < 0.0001$, Cohen's $d = 1.26$; Fig. 4*b*). For peak frequency, both theta and alpha bursts had greater peak frequency in the first half of the night (theta: $t_{(37)} = 19.33$, $p < 0.0001$, Cohen's $d = 9.20$; alpha: $t_{(37)} = 7.40$, $p < 0.0001$, Cohen's $d = 2.67$). There were no significant differences in density across night halves in either theta or alpha bursts (theta: $t_{(37)} = 0.40$, $p > 0.05$, Cohen's $d = 0.04$; alpha: $t_{(37)} = 1.36$, $p > 0.05$, Cohen's $d = 0.11$). There were also no significant differences in power across halves of the night in either theta or alpha bursts (theta: $t_{(37)} = 0.7$, $p > 0.05$, Cohen's $d = 0.16$; alpha: $t_{(37)} = 2.02$, $p > 0.05$, Cohen's $d = 0.19$).

Burst associations with learning and memory

Next, we examined task performance before and after sleep on a VPL task and an episodic memory (see Fig. 1 for protocol and tasks and the methods section for specifications of each task). All p values reported in the Results are adjusted for multiple corrections as described in the Materials and Methods. For VPL, we found that participants had better visual perceptual performance (lower 80% ISI) at Test 2 ($t_{(35)} = -3.54$, $p < 0.01$, Cohen's $d = -0.57$; Fig. 5*a*). For the episodic memory task, we found that participants displayed forgetting over sleep, with greater performance presleep compared with postsleep ($t_{(36)} = 7.00$; $p < 0.0001$; Cohen's $d = 0.89$; Fig. 5*b*). These results replicate previous findings examining VPL via the TDT task and episodic memory via the WPA task presleep and postsleep (Stickgold et al., 2000; Mednick et al., 2003; Zhang et al., 2022).

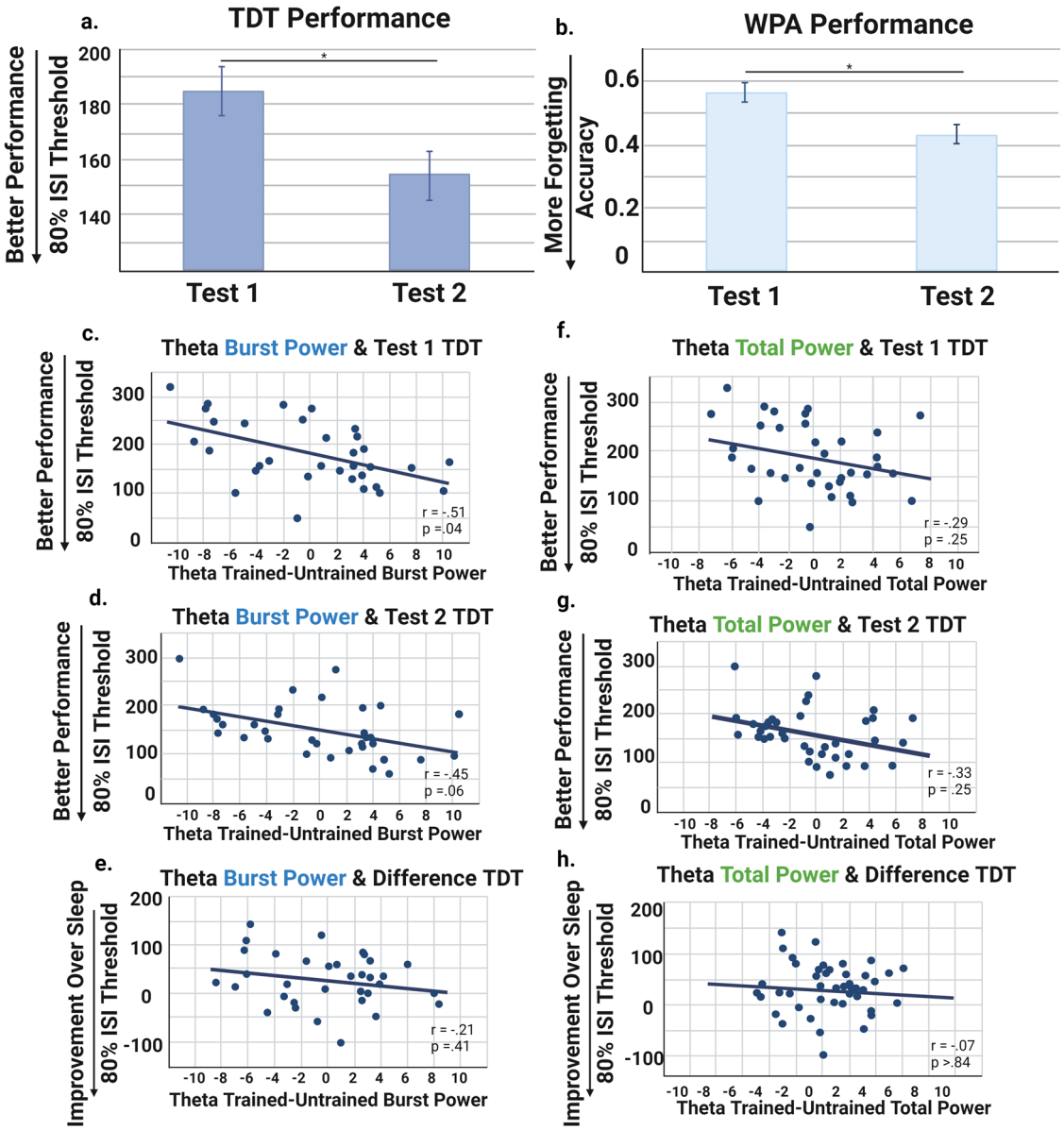


Figure 5. ***a***, TDT performance: Participants showed better visual perceptual performance (lower 80% ISI) postsleep compared with presleep. ***b***, WPA performance: Participants displayed forgetting over sleep, with greater performance presleep compared with postsleep. ***c***, ***d***, Theta burst power significantly correlated with TDT task performance at Test 1 (***c***) and trending toward significance at Test 2 (***d***), with higher power associated with better task performance (lower ISI). ***e***, There was no significant relation with the difference in performance over sleep. ***f–h***, Theta total power was not significantly related to task performance at Test 1, Test 2, or the difference score.

VPL and REM burst power

We next examined our hypothesis that power in the REM sleep theta bursts would be associated with VPL (TDT) performance. As explained in the analysis section, we utilized a trained–untrained metric of burst power in posterior regions (Tamaki and Sasaki, 2022) and examined burst power in relation to VPL task performance presleep, postsleep, and the difference score over sleep. We found a significant correlation between theta burst power in the second half of the night and task performance in electrodes P3-P4 presleep and trending toward significance postsleep, but not for the difference in performance over sleep (Test 1: $r = -0.51$, $p = 0.04$; Test 2: $r = -0.45$, $p = 0.06$; difference score: $r = -0.21$, $p > 0.05$; Fig. 5*c–e*). Total theta power in this electrode pairing was not significantly related to VPL task performance (Fig. 5*f–h*), suggesting that our finding is specific to theta burst activity. We additionally conducted a *z* test comparison for correlations from dependent samples (Lenhard and Lenhard, 2014), which determined that the magnitude of the correlation between burst power and task performance was significantly different than that of total power at both Test 1 and Test 2 (Test 1: $z = -4.15$, $p < 0.01$; Test 2: $z = -2.24$, $p < 0.05$). This indicates that burst power is a significantly stronger predictor of VPL than total power. Neither burst nor total power in the other electrode pairings were significantly related to VPL ($ps > 0.05$). Together, this suggests that highly local, retinotopically specific REM theta burst power during REM-rich sleep may be a marker of greater perceptual performance but may not be involved in sleep-dependent perceptual learning.

Episodic memory and REM burst power

Next, we conducted analyses to examine the extent to which power in the theta and alpha bursts could predict episodic task (WPA) performance and examined total power in both bands to examine if burst power was a better predictor of performance than total power. As we did not have a priori hypotheses for regional specificity of REM sleep burst activity and episodic memory, we examined burst activity across all regional groupings described in the Materials and Methods.

Alpha burst power in the second half of the night was significantly correlated with episodic memory performance at Test 1 (presleep) for parietal and occipital regions (parietal: $r = 0.55$, $p = 0.01$; occipital: $r = 0.53$, $p = 0.01$; Fig. 6), while correlations with alpha total power only reached significance in the occipital region ($r = 0.54$; $p = 0.01$; Fig. 6). For Test 2 (postsleep) performance, neither burst power nor total power in any region was significantly related to task performance ($ps > 0.05$; Fig. 6). Burst power was significantly negatively correlated with the difference score in central, parietal, and occipital regions (central: $r = -0.47$, $p = 0.04$; parietal: $r = -0.57$, $p = 0.01$; occipital: $r = -0.56$, $p = 0.01$; Fig. 6), while total power metrics only reached significance in the occipital and central regions (occipital: $r = -0.55$, $p = 0.01$; central: $p = 0.05$, $r = -0.46$; Fig. 6). Finally, no alpha metrics for Test 2 ($ps > 0.05$; Fig. 6) nor theta metrics in relation to any task performance ($ps > 0.05$) were significantly related to episodic memory performance.

As some regions reached significance for both alpha burst power as well as total power, we additionally analyzed alpha nonburst power (see Materials and Methods for definition of nonburst activity) in relation to task performance to examine if significance in the alpha total power band was due to burst or nonburst activity. All *p* values reported above in this section were already adjusted for this inclusion of nonburst activity in analyses as detailed in the Methods. In examining alpha nonburst

a.

Alpha & WPA Performance P-Values

REGION	Burst			Non-Burst			Total		
	Test 1	Test 2	Difference	Test 1	Test 2	Difference	Test 1	Test 2	Difference
Front	0.44	0.84	0.24	0.33	0.84	0.84	0.44	0.84	0.24
Central	0.07	0.44	0.04	0.74	0.90	0.62	0.07	0.44	0.05
Parietal	0.01	0.20	0.01	0.62	0.84	0.44	0.20	0.44	0.20
Occipital	0.01	0.24	0.01	0.44	0.69	0.42	0.01	0.20	0.01

b.

Alpha & WPA Performance R-Values

REGION	Burst			Non-Burst			Total		
	Test 1	Test 2	Difference	Test 1	Test 2	Difference	Test 1	Test 2	Difference
Front	0.24	0.07	-0.33	0.09	0.08	-0.08	0.24	0.07	-0.32
Central	0.43	0.25	-0.47	0.13	0.04	-0.18	0.42	0.25	-0.46
Parietal	0.55	0.36	-0.57	0.19	0.07	-0.24	0.34	0.23	-0.35
Occipital	0.53	0.32	-0.56	0.25	0.15	-0.27	0.54	0.35	-0.55

c.

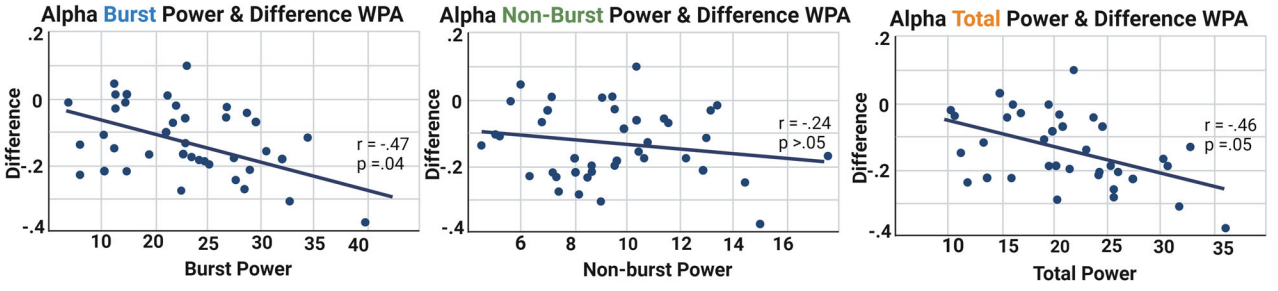


Figure 6. ***a***, *p* values for each region defined in the methods for the correlations between power metrics (alpha burst power, alpha nonburst power, and alpha total power) and WPA task performance at Test 1, Test 2, and the difference score. Figures are separated by burst, total, and nonburst alpha power metrics. ***b***, *R* values for each region defined in the methods for the correlations between power metrics (alpha burst power, alpha nonburst power, and alpha total power) and WPA task performance at Test 1, Test 2, and the difference score. ***c***, Representative scatterplots from the central region for the correlations between alpha burst, nonburst, and total power and task performance difference over sleep.

activity, we found no significant correlation with task performance Test 1, Test 2, or for the difference score ($ps > 0.05$; Fig. 6), indicating that the significance in the total power band is driven by burst activity. Finally, we examined whether alpha burst activity potentially reflected microarousals by measuring if alpha bursts coincided with a general increase in power across all frequencies. Power across all bands was calculated during burst time points and nonburst time points and averaged per subject. A t test between all power bands during bursts compared with power outside of bursts showed no significant difference ($t_{(37)} = 0.43$; $p > 0.05$; Cohen's $d = 0.08$), suggesting that alpha bursts do not reflect microarousals.

Given that greater alpha burst power was associated with better baseline memory performance as well as greater forgetting over sleep, this provides the first evidence that REM alpha burst power identified in human scalp EEG is involved in episodic memory and forgetting processes over sleep. Moreover, while both alpha burst and total power were associated with task performance at Test 1 and the Difference score, total power failed to reach significance in certain regions where burst power did (Fig. 6*a*,*b*), suggesting that alpha burst power during REM sleep is a more robust metric to examine in relation to episodic memory.

Discussion

The present study elucidates novel electrophysiological signatures of learning and memory in human REM sleep. We first validated and used our burst detection method to identify bursts along the theta and alpha frequency bands during REM sleep. Then, we characterize burst activity between NREM-dominant sleep in the first half of the night and REM-rich sleep in the second half. Additionally, we provide evidence that implicates REM bursts in cognitive processes by showing that (1) retinotopically specific theta burst activity is associated with perceptual processing, but not with perceptual learning, (2) alpha bursts are involved in baseline memory and sleep-dependent forgetting of episodic memories, and (3) these behavioral associations were not consistently present in total power of alpha and theta, suggesting specificity of these findings to scalp EEG burst activity. Our results provide a technique to examine specific EEG burst events during REM sleep and implicate these REM bursts in cognition across hippocampal and nonhippocampal memory domains.

While techniques to elucidate EEG events during sleep have been well established, these techniques have remained largely confined to NREM sleep (Steriade et al., 1993; Rasch and Born, 2013). Though identifying electrophysiological burst events in human REM is not common, the concept of burst detection during sleep has been well documented particularly for spindle events in NREM (Schimicek et al., 1994; Huupponen et al., 2007; Nonclercq et al., 2013; Adamantidis et al., 2019). With these approaches in mind, we built a computational method for REM sleep based in signal processing to identify EEG burst events. We next examined burst characteristics of count, density, duration, and power across the first and second half of the night. As the second half of the night is more REM intensive, it is unsurprising that both theta and alpha bursts have greater count during second half of the night. However, burst density in either theta or alpha band did not differ between first and second halves of the night, suggesting that their rates of occurrence remain somewhat consistent across the night. Interestingly, we also found that theta and alpha bursts had a significantly longer duration on average during the first half of the night. Additionally, we found greater peak frequency for both alpha and theta bursts in the first half of the night. However, no differences in power in either alpha or theta bursts were found between the NREM-dominant first half and REM-rich second half. More work is needed to understand characteristic differences of burst activity across the night, and whether shorter versus longer burst events have different functional significance in relation to cognition. Future work is also needed to examine spatiotemporal features of REM bursts across the electrode manifold as well as individual differences in REM burst expression. This will allow for comparison and identification of similar activity in animal models which contributes to greater mechanistic understanding of REM sleep.

After characterizing REM burst events, we examined our hypothesis that theta burst activity during REM sleep would relate to VPL. We found evidence that REM theta burst activity in posterior regions is a marker of generally greater perceptual performance, yet not an indicator of sleep-dependent VPL gains. While previous work indicates that time spent in REM predicts sleep-dependent VPL performance gains (Mednick et al., 2003, 2013), we did not find evidence that REM burst activity is related to these gains. Similarly, Tamaki and colleagues showed that increased total theta power during REM was significantly related to better resilience to interference for VPL due to more stable perceptual performance, but not to VPL improvement (Tamaki et al., 2020). This study had participants complete a VPL task before and after a nap monitored by EEG alongside magnetic resonance spectroscopy to measure excitatory/inhibitory (E/I) balance, with higher E/I ratios indicating greater plasticity. They found that decreased E/I balance during REM was correlated with greater total theta power in posterior brain regions, which was associated with more stable perceptual performance that was less vulnerable to future interference. This suggests that total theta power during REM is related to reduced plasticity which is thought to stabilize learning and reduce retrograde interference. Our results are consistent with this finding, as greater theta burst power was associated with better perceptual performance, which would likely make the perceptual representation more stable. Future research should examine REM theta burst activity in the context of resilience to interference.

We additionally examined how REM burst activity related to hippocampal-dependent episodic memory. We found evidence that REM alpha bursts are implicated in forgetting processes for episodic memory, with increased alpha burst power during REM associated with more forgetting over sleep. Previous work in animal models has identified mechanisms of forgetting for hippocampal-dependent memory in REM, finding that enhancing activity of REM-active neurons projecting to the hippocampus-induced greater forgetting (Izawa et al., 2019). Studies have also demonstrated that REM sleep may be critical for experience-dependent dendritic spine pruning with functional implications to memory (Zhou et al., 2020). This study demonstrated that REM deprivation specifically was associated with decreased spine elimination after both monocular deprivation and cued fear conditioning paradigms. Synaptic pruning is a key feature of experience-dependent synaptic plasticity, eliminating unneeded synapses; thus it is hypothesized that REM-dependent pruning may play a role in reducing plasticity to weaken memories tagged as not critical and to secure more space for salient memory storage (Gaarder, 1966; Crick and Mitchison, 1995; Li et al., 2017). Recent research examining aperiodic activity during REM sleep, a potential proxy for E/I balance, suggests that REM sleep is linked to experience-dependent plasticity and provides support for the idea that

REM sleep downregulates aperiodic activity, which may play a role in sleep-dependent episodic memory consolidation (Lendner et al., 2023). Our finding of an association between alpha bursts and episodic forgetting is intriguing and identifies a potential target for future research to elucidate whether alpha bursts events play a role in synaptic downscaling during REM sleep and how this may work in conjunction with processes of neural recalibration during NREM and REM sleep. Potentially there are complementary, sequential processes during NREM and REM which support both the strengthening of information tagged as salient followed by downscaling of weaker information later forgotten. More work is needed to fully understand the role and mechanisms of REM burst events in relation to NREM burst events (e.g., sharp wave ripples, sleep spindles, slow oscillations) and episodic memory.

Our results are consistent with the hypothesis that downscaling processes during REM impact sleep-dependent forgetting for hippocampal-dependent memory (Crick and Mitchison, 1983). We suggest that REM alpha bursts are potentially a mechanism in human REM involved in the forgetting process. Wake alpha has been shown to be involved in intentional forgetting, with successful active forgetting correlated with an increase in alpha power that is associated with a downregulation of to-be-forgotten memory traces (Klimesch et al., 1994; Jensen and Mazaheri, 2010; Park et al., 2014; Scholz et al., 2021). REM alpha burst power may therefore be tied to synaptic downregulation processes during REM, such as synaptic pruning, which facilitates forgetting. Prior animal research reported that spontaneous reactivation of hippocampal neurons during REM sleep occurs in a theta-specific pattern concordant with the induction of both LTP and with its reversal, depotentiation, during the REM sleep state (Poe et al., 2000). However, we did not find significance for theta metrics in relation to episodic memory; this may be due to a lack of concordance between theta bursts derived from scalp EEG and hippocampal theta. As the present study provides correlational, but not causal, evidence for REM alpha bursts and forgetting, further experimental interventions are needed to determine mechanisms and processes that are critical for episodic memory and forgetting.

Limitations

This experiment measured cognitive performance in two domains, VPL, and episodic memory. Theta is also implicated in other domains, such as emotional memory, during REM-dependent processing (Nishida et al., 2009; Hutchison and Rathore, 2015). Future studies should examine if REM burst activity is involved in other memory domains such as emotional memory. Additionally, our episodic memory task separated encoded material into two lists, half tested at immediate retrieval and half at delayed retrieval to avoid practice effects. This procedure prioritizes attaining an accurate baseline but does not allow for assessment of forgetting of item-specific information. Future studies should consider how REM alpha bursts may affect item-specific episodic memories. Also, we did not include an interference paradigm with our VPL task so we were not able to assess burst events in relation to resilience to interference. Previous work provides evidence that total theta power during REM sleep is associated with resilience to interference and lower E/I balance (Tamaki et al., 2020). Further work should examine theta REM burst activity compared with nonburst activity in relation to resilience to interference and E/I to further examine functional differences between burst and nonburst activity.

Summary

In conclusion, we define a computational approach to identify and characterize electrophysiological events in REM sleep, which current research lacks. Additionally, we provide evidence that these burst events are functionally important for learning and memory. We provide evidence that retinotopically specific theta burst power during REM sleep is a marker of perceptual processing but not perceptual learning. Participants with greater posterior theta burst power during REM sleep showed superior perceptual performance both before and after sleep. As the overnight change in performance was not significant, we suggest that more theta burst power during REM is a marker of perceptual processing. Additionally, we provide support for the hypothesis that alpha bursts during REM are mechanistically involved in episodic memory and sleep-dependent forgetting of hippocampal-dependent memories. Defining burst events in REM contributes to the development of a comprehensive mechanistic model of how REM and NREM sleep work in conjunction to facilitate memory formation, as well as provide deeper understanding of the fundamental electrophysiological properties of REM sleep that are distinct from NREM sleep.

References

Adamantidis AR, Gutierrez Herrera C, Gent TC (2019) Oscillating circuitries in the sleeping brain. Nat Rev Neurosci 20:746–762.

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

Aserinsky E, Kleitman N (1953) Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. Science 15:454–455.

Berger M, Riemann D (1993) REM sleep in depression—an overview. J Sleep Res 2:211–223.

Blumberg MS, Coleman CM, Gerth AI, McMurray B (2013) Spatiotemporal structure of REM sleep twitching reveals developmental origins of motor synergies. Curr Biol 23.

Boeve BF (2013) Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease. Lancet Neurol 12:469–482.

Boyce R, Williams S, Adamantidis A (2017) REM sleep and memory. Curr Opin Neurobiol 44:167–177.

Brooks DC, Bizzi E (1963) Brain stem electrical activity during deep sleep. Arch Ital Biol 101:648–665.

Brooks PL, Peever J (2016) A temporally controlled inhibitory drive coordinates twitch movements during REM sleep. Curr Biol 26:1177–1182.

Byrne KN, McDevitt EA, Sheremata SL, Peters MW, Mednick SC, Silver MA (2020) Transient cholinergic enhancement does not significantly affect either the magnitude or selectivity of perceptual learning of visual texture discrimination. J Vis 20:5.

Cai DJ, Mednick SA, Harrison EM, Kanady JC, Mednick SC (2009) REM, not incubation, improves creativity by priming associative networks. Proc Natl Acad Sci U S A 106:10130–10134.

Cantero JL, Atienza M (2000) Alpha burst activity during human REM sleep: descriptive study and functional hypotheses. Clin Neurophysiol 111:909–915.

Cantero JL, Atienza M, Salas RM (2002) Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: different electroencephalographic phenomena within the alpha band. Neurophysiol Clin 32:54–71.

Carskadon MA, Dement WC (2011) Chapter 2 – normal human sleep: an overview.

Crick F, Mitchison G (1983) The function of dream sleep. Nature 304:111–114.

Crick F, Mitchison G (1995) REM sleep and neural nets. Behav Brain Res 69:147–155.

Datta S (1997) Cellular basis of pontine ponto-geniculo-occipital wave generation and modulation. Cell Mol Neurobiol 17:341–365.

Datta S, Li G, Auerbach S (2008) Activation of phasic pontine-wave generator in the rat: a mechanism for expression of plasticity-related genes and proteins in the dorsal hippocampus and amygdala. Eur J Neurosci 27:1876–1892.

Datta S, O'Malley MW (2013) Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. J Neurosci 33:4561–4569.

Datta S, Siwek DF, Patterson EH, Cipolloni PB (1998) Localization of pontine PGO wave generation sites and their anatomical projections in the rat. Synapse 30:409–423.
Davidson P, Pace-Schott E (2021) Go to bed and you might feel better in the morning—the effect of sleep on affective tone and intrusiveness of emotional memories. Curr Sleep Med Rep 7:31–46.
De Gennaro L, Ferrara M (2003) Sleep spindles: an overview. Sleep Med Rev 7:423–440.
De Koninck J, Lorrain D, Christ G, Proulx G, Coulombe D (1989) Intensive language learning and increases in rapid eye movement sleep: evidence of a performance factor. Int J Psychophysiol 8:43–47.
Dement W, Kleitman N (1957) The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. J Exp Psychol 53:339–346.
Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114–126.
Djonlagic I, et al. (2020) Macro and micro sleep architecture and cognitive performance in older adults. Nat Hum Behav 5:123–145.
Fernández-Mendoza J, Lozano B, Seijo F, Santamarta-Liébana E, Ramos-Platón MJ, Vela-Bueno A, Fernández-González F (2009) Evidence of subthalamic PGO-like waves during REM sleep in humans: a deep brain polysomnographic study. Sleep 32:1117–1126.
Gaarder K (1966) A conceptual model of sleep. Arch Gen Psychiatry 14:253–260.
Gais S, Mölle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22:6830–6834.
Goldstein AN, Walker MP (2014) The role of sleep in emotional brain function. Annu Rev Clin Psychol 10:679–708.
Graven SN, Browne JV (2008) Sleep and brain development: the critical role of sleep in fetal and early neonatal brain development. Newborn Infant Nurs Rev 8:173–179.
Harrington MO, Ashton JE, Ngo H-VV, Cairney SA (2021) Phase-locked auditory stimulation of theta oscillations during rapid eye movement sleep. Sleep 44:zsaa227.
Hutchison IC, Rathore S (2015) The role of REM sleep theta activity in emotional memory. Front Psychol 6:154468.
Huupponen E, Gómez-Herrero G, Saastamoinen A, Värri A, Hasan J, Himanen S-L (2007) Development and comparison of four sleep spindle detection methods. Artif Intell Med 40:157–170.
Izawa S, et al. (2019) REM sleep–active MCH neurons are involved in forgetting hippocampus-dependent memories. Science 365:1308–1313.
Jensen O, Mazaheri A (2010) Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front Hum Neurosci 4:186.
Jouvet M, Michel F (1959) Electromyographic correlations of sleep in the chronic decorticate & mesencephalic cat. C R Seances Soc Biol Fil 153:422–425.
Jozwiak N, Postuma RB, Montplaisir J, Latreille V, Panisset M, Chouinard S, Bourgouin P-A, Gagnon J-F (2017) REM sleep behavior disorder and cognitive impairment in Parkinson's disease. Sleep 40:zsx101.
Kales A, Rechtschaffen A (1968) *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Washington, DC: United States Government Printing Office.
Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D (1994) Dependence on REM sleep of overnight improvement of a perceptual skill. Science 265:679–682.
Kaufman LS, Morrison AR (1981) Spontaneous and elicited PGO spikes in rats. Brain Res 214:61–72.
Klimesch W, Schimke H, Schwaiger J (1994) Episodic and semantic memory: an analysis in the EEG theta and alpha band. Electroencephalogr Clin Neurophysiol 91:428–441.
Klinzing JG, Niethard N, Born J (2019) Mechanisms of systems memory consolidation during sleep. Nat Neurosci 22:1598–1610.
Latchoumane C-FV, Ngo H-VV, Born J, Shin H-S (2017) Thalamic spindles promote memory formation during sleep through triple phase-locking of cortical, thalamic, and hippocampal rhythms. Neuron 95:424–435.e6.
Lendner JD, et al. (2023) Human REM sleep recalibrates neural activity in support of memory formation. Sci Adv 9:eadj1895.
Lenhard W, Lenhard A (2014) Hypothesis tests for comparing correlations.
Lewis PA, Durrant SJ (2011) Overlapping memory replay during sleep builds cognitive schemata. Trends Cogn Sci 15:343–351.
Li W, Ma L, Yang G, Gan W-B (2017) REM sleep selectively prunes and maintains new synapses in development and learning. Nat Neurosci 20:427–437.
Lim AS, Lozano AM, Moro E, Hamani C, Hutchison WD, Dostrovsky JO, Lang AE, Wennberg RA, Murray BJ (2007) Characterization of REM-sleep associated ponto-geniculo-occipital waves in the human pons. Sleep 30:823–827.
Malerba P, Whitehurst LN, Simons SB, Mednick SC (2019) Spatio-temporal structure of sleep slow oscillations on the electrode manifold and its relation to spindles. Sleep 42:zsy197.
Mednick S, Nakayama K, Stickgold R (2003) Sleep-dependent learning: a nap is as good as a night. Nat Neurosci 6:697–698.
Mednick SC, Cai DJ, Shuman T, Anagnostaras S, Wixted JT (2011) An opportunistic theory of cellular and systems consolidation. Trends Neurosci 34:504–514.
Mednick SC, McDevitt EA, Walsh JK, Wamsley E, Paulus M, Kanady JC, Drummond SPA (2013) The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. J Neurosci 33:4494–4504.
Mirmiran M (1986) The importance of fetal/neonatal REM sleep. Eur J Obstet Gynecol Reprod Biol 21:283–291.
Ngo H-VV, Martinetz T, Born J, Mölle M (2013) Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 78:545–553.
Nishida M, Pearsall J, Buckner RL, Walker MP (2009) REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 19:1158–1166.
Nonclercq A, Urbain C, Verheulpen D, Decaestecker C, Van Bogaert P, Peigneux P (2013) Sleep spindle detection through amplitude–frequency normal modelling. J Neurosci Methods 214:192–203.
Otsu N (1979) A threshold selection method from gray-level histograms. IEEE Trans Syst Man Cybern 9:62–66.
Park H, Lee DS, Kang E, Kang H, Hahm J, Kim JS, Chung CK, Jensen O (2014) Blocking of irrelevant memories by posterior alpha activity boosts memory encoding. Hum Brain Mapp 35:3972–3987.
Park S-H, Weber F (2020) Neural and homeostatic regulation of REM sleep. Front Psychol 11:1662.
Peever J, Fuller PM (2017) The biology of REM sleep. Curr Biol 27:R1237–R1248.
Peigneux P, et al. (2003) Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. Neuroimage 20:125–134.
Poe GR, Nitz DA, McNaughton BL, Barnes CA (2000) Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. Brain Res 855:176–180.
Rasch B, Born J (2013) About sleep's role in memory. Physiol Rev 93:681–766.
Sasaki Y, Nanez JE, Watanabe T (2010) Advances in visual perceptual learning and plasticity. Nat Rev Neurosci 11:53–60.
Schimicek P, Zeitlhofer J, Anderer P, Saletu B (1994) Automatic sleep-spindle detection procedure: aspects of reliability and validity. Clin Electroencephalogr 25:26–29.
Scholz S, Dutke S, Busch NA (2021) Oscillatory correlates of intentional forgetting: the role of theta and alpha power in item-method directed forgetting. eNeuro 8:5.
Senzai Y, Scanziani M (2022) A cognitive process occurring during sleep is revealed by rapid eye movements. Science 377:999–1004.
Smith C (1995) Sleep states and memory processes. Behav Brain Res 69:137–145.
Smith C, Weeden K (1990) Post training REMs coincident auditory stimulation enhances memory in humans. Psychiatr J Univ Ott 15:85–90.
Smith C, Lapp L (1991) Increases in number of REMs and REM density in humans following an intensive learning period. Sleep 14:325–330.
Sokoloff G, Uitermarkt BD, Blumberg MS (2015) REM sleep twitches rouse nascent cerebellar circuits: implications for sensorimotor development. Dev Neurobiol 75:1140–1153.
Staresina BP, Bergmann TO, Bonnefond M, van der Meij R, Jensen O, Deuker L, Elger CE, Axmacher N, Fell J (2015) Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat Neurosci 18:1679–1686.
Steriade M, McCormick DA, Sejnowski TJ (1993) Thalamocortical oscillations in the sleeping and aroused brain. Science 262:679–685.
Stickgold R, James L, Hobson JA (2000) Visual discrimination learning requires sleep after training. Nat Neurosci 3:1237–1238.

Storey JD (2002) A direct approach to false discovery rates. J R Stat Soc B Stat Methodol 64:479–498.
Tamaki M, Sasaki Y (2022) Sleep-dependent facilitation of visual perceptual learning is consistent with a learning-dependent model. J Neurosci 42: 1777–1790.
Tamaki M, Wang Z, Barnes-Diana T, Guo D, Berard AV, Walsh E, Watanabe T, Sasaki Y (2020) Complementary contributions of non-REM and REM sleep to visual learning. Nat Neurosci 23:1150–1156.
Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150.
van den Berg NH, Gibbings A, Baena D, Pozzobon A, Al-Kuwatli J, Ray LB, Fogel SM (2023) Eye movements during phasic vs. tonic REM sleep are biomarkers of dissociable EEG processes for the consolidation of novel problem-solving skills. Sleep 46:zsad151.
Zhang J, Whitehurst LN, Mednick SC (2022) The role of sleep for episodic memory consolidation: stabilizing or rescuing? Neurobiol Learn Mem 191:107621.
Zhou Y, Lai CSW, Bai Y, Li W, Zhao R, Yang G, Frank MG, Gan W-B (2020) REM sleep promotes experience-dependent dendritic spine elimination in the mouse cortex. Nat Commun 11:4819.