

Sleep in Humans Stabilizes Pattern Separation Performance

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Replay of hippocampal neural representations during sleep is thought to promote systems consolidation of declarative memory. How this reprocessing of memory during sleep affects the hippocampal representation itself, is unclear. Here we tested hippocampal stimulus processing (i.e., pattern separation) before and after periods of sleep and wakefulness in humans (female and male participants). Pattern separation deteriorated across the wake period but remained stable across sleep ($p = 0.013$) with this sleep–wake difference being most pronounced for stimuli with low similarity to targets ($p = 0.006$). Stimuli with the highest similarity showed a reversed pattern with reduced pattern separation performance after sleep ($p = 0.038$). Pattern separation performance was positively correlated with sleep spindle density, slow oscillation density, and theta power phase-locked to slow oscillations. Sleep, presumably by neural memory replay, shapes hippocampal representations and enhances computations of pattern separation to subsequent presentation of similar stimuli.

Key words: consolidation; hippocampus; memory; pattern separation; sleep

Significance Statement

The consolidation of hippocampus-dependent memories is causally related to reactivation during sleep of previously encoded representations. Here, we show that reactivation-based consolidation processes during sleep shape the hippocampal representation itself. We studied the effect of sleep and wakefulness on pattern separation (i.e., orthogonalization of similar representations) and completion performance (i.e., recall of a memory in light of noisy input) that are essential cognitive elements of encoding and retrieval of information by the hippocampus. Our results demonstrate that pattern separation was stabilized after sleep but diminished after wakefulness. We further showed that pattern separation was related to EEG oscillatory parameters of non-REM sleep serving as markers of sleep-dependent memory consolidation and hippocampal reactivation.

Introduction

Whereas the wake state is optimal for the encoding of information, sleep following encoding is considered a brain state favoring the formation of long-term memory (Rasch and Born, 2013). In particular, sleep appears to benefit hippocampus-dependent (i.e., declarative) memory for episodes and facts (Inostroza and Born, 2013). The consolidation of hippocampus-dependent memories during sleep is causally related to the replay of patterns of neural activity that were present during encoding of the information during prior wakefulness (Girardeau et al., 2009; Ego-Stengel and Wilson, 2010). In rats, firing patterns of hippocampal place cell

assemblies evoked during navigating through a maze are replayed during subsequent slow-wave sleep (SWS; Wilson and McNaughton, 1994; O'Neill et al., 2010). Such replay activity can be experimentally induced by presenting cues that were present during prior learning, and again during SWS after learning (Rasch et al., 2007; Bendor and Wilson, 2012), which indeed enhanced the memory encoded before sleep, thus proving the causal role of neural reactivations for the consolidation of hippocampus-dependent memory during sleep. The reactivated memory information is thought to be transmitted to extrahippocampal, mainly neocortical networks serving as long-term store (Diekelmann and Born, 2010). This process is supported by the phase locking of the three prime rhythms of the EEG during SWS accompanying hippocampal replay (i.e., hippocampal ripples that nest into thalamic 12–15 Hz spindle oscillations, which themselves nest into the up-states of the neocortical <1 Hz slow oscillations; Sirota et al., 2003; Clemens et al., 2007; Staresina et al., 2015).

Hippocampal memory reactivations, however, aside from promoting extrahippocampal changes, are expected to also change the features of the hippocampal representation per se, possibly resembling the effects of re-encoding (Karpicke and Roediger, 2008;

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Inostroza and Born, 2013). Pattern separation (PatSep) and pattern completion (PatComp) represent two principal features of hippocampal memory processing (McNaughton and Morris, 1987; O'Reilly and McClelland, 1994). Pattern separation refers to the capability of the hippocampus to form nonoverlapping orthogonal neural representations from similar sequential episodic stimulus inputs (McClelland et al., 1995). Pattern completion refers to the recall of a memory based on the presentation of incomplete, noisy, or degraded stimulus patterns (Norman and O'Reilly, 2003). Based on the hippocampal circuit structure with its recurrent associative networks embedded into the unidirectional trisynaptic pathway, both processes have been linked to computations in different hippocampal subnetworks (O'Reilly and McClelland, 1994; Bartsch et al., 2010; Bartsch et al., 2011). Indeed, it has been shown that the hippocampal dentate gyrus (DG) is essential for pattern separation and that CA3 networks are involved in pattern completion (Guzowski et al., 2004; Leutgeb et al., 2007; Neunuebel and Knierim, 2014). In humans, high-resolution imaging studies confirmed the role of the DG and CA3 in pattern separation and determined that the CA1 area contributed to pattern completion, using mnemonic similarity recognition tasks (Bakker et al., 2008; Yassa et al., 2010, 2011a; Lacy et al., 2011; Berron et al., 2016).

Here, we used the mnemonic similarity task (MST) to study how memory processing during sleep affects representations toward enhancing and/or diminishing pattern separation. We recorded sleep to identify EEG oscillations known to synchronize hippocampal memory replay activity (i.e., spindles) originating from thalamic networks and the neocortical slow oscillations.

Materials and Methods

Participants

Thirteen healthy students (mean age, 23.46 ± 0.5 years; age range, 21–26 years; 10 women) participated in the study. Participants were recruited via advertisement at the university and received monetary compensation (€75) after completion. Participants were free of neurological or psychiatric disorders and did not use any medication. They kept a regular sleep/wake cycle and did not engage in any stressful activities (e.g., exams, night shift) for an interval of at least 6 weeks before the experiments. General sleep quality was assessed via the Pittsburgh Sleep Quality Index (Buysse et al., 1989). None of the subjects had previously participated in an experiment in our laboratory. Participants had to refrain from drinking alcohol and caffeine, from stressful physical activities, and from napping on the experimental days. They were all vigilant and alert according to the subject's report at all time points tests were performed. Every participant gave written informed consent before the study, which was approved by the local ethics committee.

Mnemonic similarity task

The MST is an established recognition memory task that has been shown to tax pattern separation (Kirwan and Stark, 2007; Bakker et al., 2008; Toner et al., 2009; Yassa et al., 2010, 2011b; Ally et al., 2013; Stark et al., 2013; Bennett and Stark, 2016; <http://faculty.sites.uci.edu/starklab/mnemonic-similarity-task-mst/>). The MST comprises an encoding and a recall phase. For the encoding phase, the participant is asked to classify 256 items (i.e., everyday objects) as either an indoor or an outdoor object via button press on a keyboard. Objects are sequentially presented on a computer monitor each for 2 s with a 0.5 s interstimulus interval. The two recall phases of the experiment (immediate and delayed) comprised 192 items (128 old plus 64 new items) each including (1) 64 exact repetitions of the previously seen objects ("targets"), (2) 64 objects that were similar to the previously seen objects ("lures"), and (3) 64 new objects that the participant had not seen before ("foils"). Half of the stimulus set used at encoding (128 items) was used for immediate recall testing, the other half for delayed recall testing. For testing recall, participants indicated (within the 2 s of item presentation) whether a presented object was "old", "sim-

ilar," or "new" by button press. In this context, the answers to lure items were of substantial significance, implying a successful pattern separation when correctly responding "similar" (Toner et al., 2009; Yassa et al., 2010). The order of sets across Wake and Sleep as well as for immediate and delayed recall was randomized, and the stimuli within each set followed a pseudo-randomized order. Responses at recall enabled calculation of two different scores that comprise performance measures of pattern separation and recognition memory:

Pattern separation score. Behavioral pattern separation was determined by the correct discrimination of a lure item from its target counterpart as follows: PatSep score = [p (correct similar response to lures) – p (false similar response to foils)]. The score was thus corrected for a possible response bias toward exhibiting a tendency to use the similar response (Yassa et al., 2010, 2011b; Stark et al., 2013; Bennett and Stark, 2016).

To assess the performance of pattern separation as a function of lure similarity, PatSep scores were calculated for the five degrees of lure similarity to a target object (1–5: most similar to least similar; Yassa et al., 2010; Lacy et al., 2011). The similarity bins were the same as in previous studies (Stark et al., 2013; Bennett and Stark, 2016).

Recognition memory score. Recognition memory was assessed by the number of correct responses to targets. To correct for response bias to preferentially respond with the target button, the number of incorrect target responses to foils was subtracted: recognition memory (RM) score = [p (correct old response to targets) – p (false old response to foils)] (Stark et al., 2013).

Experimental design and procedure

Each participant attended both the Wake and Sleep conditions, following a within-subject crossover design. Participants were randomly assigned to one of the conditions to perform at first. The second condition took place 42.54 ± 5.33 d later. Each condition started with encoding of the MST items (encoding phase) followed by an immediate recall test, followed by a 9 h retention interval covering either nocturnal sleep (Sleep condition) or daytime wakefulness (Wake condition). Thereafter, recall was tested again (delayed recall, Fig. 1). Encoding and immediate recall testing lasted ~30 min, and the delayed recall an additional 15 min.

For the Sleep condition, subjects spent one adaptation night before the test night in the laboratory to habituate to sleeping under laboratory conditions including polysomnographic recordings. On experimental days, encoding and immediate recall took place in the evening from 9:00 to 10:00 P.M. Then, subjects were prepared for polysomnographic recordings, and lights were turned off at 11:00 P.M. Subjects were awakened at 07:00 A.M., and recall testing started at ~7:30 A.M.

After delayed recall testing in the Sleep condition, participants completed a neuropsychological test battery evaluating (1) short-term memory by the Rey Auditory Verbal Learning Test (Rey, 1941), (2) executive function by the Trail Making Test A and B (Reitan, 1979), (3) verbal fluency by the Regensburg Word Fluency Test (Aschenbrenner et al., 2000), (4) working memory by the digit span test (Wechsler, 1997), and (5) general intelligence by the Multiple Choice Vocabulary Intelligence Test (German equivalent of the National Adult Reading Test by Nelson [1982]; Lehl, 2005). Also, handedness was assessed via the Edinburgh Handedness Inventory (Oldfield, 1971).

In the Wake condition, encoding and immediate recall testing took place in the morning between 8:00 and 9:00 A.M., and delayed recall was tested between 6:00 and 7:00 P.M. Participants were told to sleep at least 6 h, but at most 8 h, the night before testing. During the wake interval, participants were not engaged in stressful physical and emotional activities and demanding cognitive tasks like exam preparations.

Polysomnography, EEG power spectra, slow oscillations, and sleep spindles

Polysomnography included recordings of electroencephalogram (EEG) from F3, F4, C3, C4, O1, and O2 (international 10–20 system, referenced to electrodes at the mastoids, ground at AFz), electrooculogram (EOG) from electrodes around the eyes, and electrocardiogram (ECG). Signals were recorded using the SOMNOscreen EEG 10–20 system (Somnomedics) digitized at 128 or 256 Hz and filtered (EEG, 0.2–35 Hz; EOG, 0.2–10 Hz; ECG lowpass, 50 Hz). Sleep stages were scored off-line according to

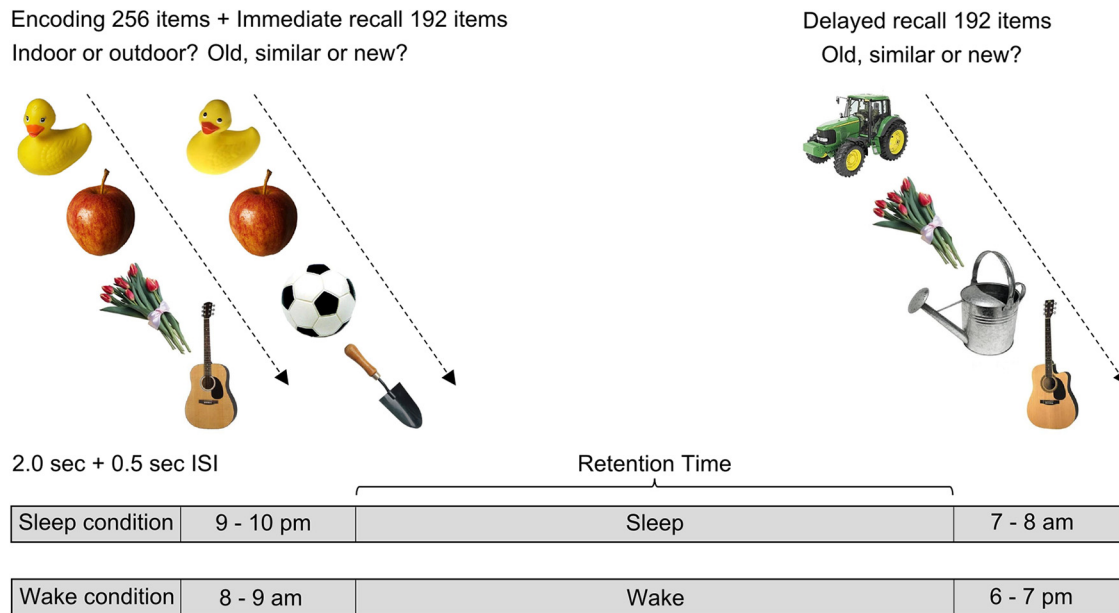


Figure 1. Design and procedures. Each participant performed on a Sleep and a Wake condition separated by at least 3 weeks. Conditions started with encoding of 256 MST items followed by an immediate recognition test (192 items), followed by a 9 h retention interval covering nocturnal sleep (Sleep condition) or daytime wakefulness (Wake condition). Thereafter, delayed recall (192 items not used for immediate recall) was tested. Displayed pictures in the graph are taken from the original image database of the MST. ISI, Interstimulus interval.

American Academy of Sleep Medicine criteria by a trained rater. For each subject, total sleep time, time spent in sleep stage 1 (S1), stage 2 (S2), SWS (i.e., stages 3 and 4), and rapid eye movement (REM) sleep and movement artifacts were detected. Sleep onset was defined with reference to lights off by the first occurrence of stage 1 sleep followed by stage 2 sleep. Analyses were based on the central channels.

More fine-grained EEG analyses were performed to track the association of pattern separation and completion with specific sleep EEG oscillatory parameters during non-REM sleep (S2 and SWS; i.e., specifically with EEG power in different frequency band, slow oscillations, and sleep spindles). Analysis was based on epochs free of visually identified EEG artifacts and performed using the SpiSOP toolbox (<http://www.spisop.org>) based on MATLAB 2015a (MathWorks) and FieldTrip (Oostenveld et al., 2011). Additionally, EEG activity occurring phase-locked to the slow oscillations was explored. Before the analyses, EEG signals were downsampled to 128 Hz. The algorithms are briefly described in the following sections.

Power spectral analyses. Power spectra were calculated on consecutive 5 s intervals of non-REM sleep, which overlapped in time by 4 s. Intervals were tapered by a single Hanning window before applying fast Fourier transformation that resulted in interval power spectra with a frequency resolution of 0.2 Hz. Power spectra were then averaged across all blocks (Welch's method) and normalized by the effective noise bandwidth to obtain power spectral density estimates for all data. Mean power density in the following frequency bands was determined for each EEG channel separately, as follows: slow oscillation (0.5–1 Hz); delta (1–4 Hz); slow-wave activity (0.5–4 Hz); theta (4–8 Hz); slow spindles (9–12 Hz); and fast spindles (12–15 Hz).

Slow oscillation detection. Identification of slow oscillations was performed in non-REM sleep, separately for S2 and SWS. Detection was based on a previously published algorithm (Möller et al., 2002). For each EEG channel, the signal was filtered between 0.5 and 3.5 Hz (–3 dB rolloff) using a digital finite impulse response filter (Butterworth filter, order of 4). Then, all time intervals with consecutive positive-to-negative zero crossings were marked as putative slow oscillation if their durations corresponded to a frequency between 0.5 and 1.11 Hz (Ngo et al., 2013). Putative slow oscillations with lower amplitudes were immediately excluded when both negative and positive half-wave amplitudes were smaller than -15 and $+10$ μV , respectively. A slow oscillation was then identified if its negative half-wave peak potential was >1.25 times the mean of the negative half-wave peak of all putatively detected slow oscil-

lations in the respective EEG channel, and also only if the amplitude of the positive half-wave peak was >1.25 times the mean positive half-wave amplitude of all other putatively detected slow oscillations within this channel. For each individual and channel, the number of slow oscillations, their density (per minutes of non-REM sleep), mean amplitude, and slope (ratio between negative half-wave peak amplitude and the time between the negative peak to the next zero crossing; Riedner et al., 2007) were calculated.

Spindle detection. Spindle identification focused on conventional (fast) spindles in central channels (C3, C4) as they typically occur in centroparietal brain regions (De Gennaro and Ferrara, 2003; Mölle et al., 2011). Spindle frequency peaks were visually identified from non-REM power spectra according to their expected power maximum in the 12–15 Hz band (mean peak, 13.82 ± 0.11 Hz). For each EEG channel, the non-REM epochs signal was filtered with a bandpass of ± 1 Hz (–3 dB cutoff, two filter passings) around the individual spindle frequency peaks. Then, using a sliding window with a size of 0.2 s the root mean square (RMS) was computed, and the resulting signal was smoothed in the same window with a moving average. A spindle was detected when the smoothed RMS signal exceeded an individual amplitude threshold 1.5 times the SD of the filtered signal for 0.5–3 s. The threshold crossings marked the beginning and the end of the spindle event. Spindles were excluded with amplitudes >200 μV . For each subject and channel, absolute spindle counts, spindle density (per 30 s non-REM epochs), mean amplitude, and mean length were calculated. For spindle analyses, data from one outlier (with a spindle density >2 SDs from the mean) were removed (resulting $n = 12$).

EEG activity phase-locked to slow oscillations. Time–frequency power was calculated separately for each detected slow oscillation in frequency steps of 0.2 Hz and a range of 2–24 Hz using continuous Morlet wavelets with a length of 7 cycles that were applied to the EEG every 0.02 s, time locked to the negative slow oscillation peak. Time–frequency data were then averaged for each subject. Averaged time–frequency power values were log transformed (in decibels) and, then, normalized by dividing them by the average power in a ± 2 s window around the negative slow oscillation peak for each respective frequency bin. For statistical comparisons, for each subject the phase-locked power in two frequency bands of interest (Ngo et al., 2013; Schreiner and Rasch, 2015) was averaged across specific time windows (i.e., theta activity; 4–8 Hz) occurring at the slow oscillation down state (-0.5 to $+0.25$ s around the negative slow oscillation peak) and spindle activity (12–16 Hz) occurring at the subsequent

slow oscillation up state (+0.25–1 s with reference to the negative slow oscillation peak).

Statistical analyses

To analyze differences between the Sleep and Wake conditions for MST parameters, difference values (delayed minus immediate recall scores) were calculated. A Shapiro-Wilk test for normality was applied to all parameters before statistical testing. Paired-samples *t* tests were used for the analysis of differences between Sleep and Wake conditions regarding PatSep, and RM scores. Also, one-sample *t* tests against zero were conducted to show a stabilization, decrease, or increase of the difference values of PatSep and RM scores. A two-factorial repeated-measures ANOVA was performed for examining sleep/wake differences regarding the different degrees of lure similarity with Sleep/Wake and lure similarity as within-subject factors. If the sphericity assumption was violated, degrees of freedom were reported according to a Greenhouse–Geisser correction. *Post hoc* paired-samples *t* tests (Fisher's least significant difference method) were performed to identify differences between the Sleep and Wake condition. For a further analysis to depict the relation between the PatSep score and lure similarity, Spearman's ρ values for immediate and delayed recall were separately calculated for every subject. One-sample Wilcoxon signed rank tests against zero were used to demonstrate graded decreases or increases of scores in relation to lure similarity. To examine differences between the correlational coefficients, Wilcoxon signed rank tests were calculated. To analyze the relationship between PatSep scores and sleep EEG parameters, Pearson product-moment correlations were computed for normal distributed and linearly related variables, for other variables Spearman's ρ was used. Considering the exploratory nature of the correlational analysis, correction for multiple comparisons was excluded. All statistical analyses were performed using two-tailed tests. The significance level was set to $p < 0.05$. Data are expressed as the mean \pm SEM.

Results

Each of 13 healthy students was tested during a Sleep and a Wake condition (Fig. 1, experimental design and procedure). On both conditions, the encoding of MST items (color photographs of everyday objects) was followed by an immediate recall and a 9 h retention interval covering either nocturnal sleep or daytime wakefulness. Thereafter, delayed recall of MST items was tested. At recall, subjects were required to judge presented objects as “old target,” “similar lure,” or “new foil” items, enabling the calculation of individual scores of PatSep performance and recognition memory. The assessment of the effects of sleep was based on individual retention scores (i.e., delayed minus immediate recall).

Pattern separation and recognition memory

PatSep scores were distinctly higher after sleep than after wakefulness ($t_{(12)} = -3.08$, $p = 0.010$; Fig. 2). Additionally, the delayed–immediate recall difference revealed that PatSep scores remained stable across sleep (mean score, -3.32 ± 2.98 ; $t_{(12)} = -1.16$, $p = 0.287$, for test against 0), whereas scores strongly decreased across wakefulness (mean score, -20.82 ± 4.24 ; $t_{(12)} = -4.91$, $p = 0.00004$). Regarding recognition memory, the scores were higher after sleep (mean score, -7.54 ± 2.71) than wakefulness (mean score, -23.77 ± 3.12 ; $t_{(12)} = -3.603$, $p = 0.004$; Fig. 2, Table 1).

We examined whether the effects of sleep on the PatSep score depended on the degree of the lure similarity (ranging from 1 to 5, from most similar to least similar to target). The stabilization of PatSep scores after sleep, compared with the decrease across wakefulness, was most pronounced for the least similar (5) lures ($F_{(4,48)} = 8.28$, $p = 0.00004$, Sleep/Wake \times similarity interaction, in a 2×5 repeated-measures ANOVA; Fig. 3a). The effect of sleep decreased with increasing lure similarity and, notably, was

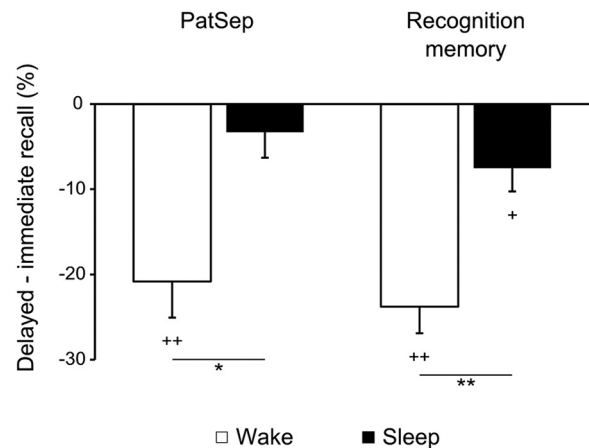


Figure 2. PatSep and recognition memory performance separately for the Sleep (black) and Wake (white) conditions. Mean (\pm SEM) difference values (delayed minus immediate recall performance) are given. PatSep performance deteriorates across the wake interval but remains stable across sleep. * $p < 0.05$; ** $p < 0.01$, for pairwise comparisons between conditions. + $p < 0.05$; ++ $p < 0.01$, for test against zero.

reversed for the most similar lures (lure 1) showing higher PatSep scores after wakefulness than after sleep ($t_{(12)} = 2.33$, $p = 0.038$).

The diminished PatSep score for highly similar lures compared with wakefulness lead to the assumption that participants were here more prone to incorrectly responding “old” to lures instead of “similar.” To prove the hypothesis, we also calculated the 2×5 (Sleep/Wake \times similarity) ANOVA for the probability of incorrectly responding “old” to lures [i.e., also corrected for the response bias, as follows: p (false old response to lures) $- p$ (false old response to foils)]. As expected, the results mirrored the findings regarding the PatSep score. For the least similar lure 5, the old responses were more frequent after wakefulness than after sleep ($t_{(12)} = 4.69$, $p = 0.001$). Conversely, for the most similar lure 1, they were more frequent after sleep than after wakefulness ($t_{(12)} = -2.57$, $p = 0.025$).

To further analyze the dependency of sleep versus wake effects on lure similarity, we calculated correlations between lure similarity and the PatSep score, separately for the Sleep and Wake conditions for every participant. As expected, at immediate recall in both conditions the PatSep score was positively correlated with lure similarity (i.e., PatSep scores were the higher the less similar the lure was; Sleep: $r_s = 0.747 \pm 0.07$, $z = 3.22$, $p = 0.001$, for test against 0; Wake: $r_s = 0.735 \pm 0.07$, $z = 3.19$, $p = 0.001$). The same positive correlation was found after sleep ($r_s = 0.733 \pm 0.06$, $z = 3.18$, $p = 0.001$) but failed to reach significance after wakefulness ($r_s = 0.249 \pm 0.14$, $z = 1.80$, $p = 0.071$). Comparing averaged correlations across participants at immediate and delayed recall revealed that these coefficients significantly differed only in the Wake condition ($z = -2.41$, $p = 0.016$), whereas there was no difference in the Sleep condition ($z = -0.31$, $p = 0.755$; Fig. 3b).

Sleep recordings, slow oscillations, and spindles

Participants in the Sleep condition displayed normal sleep (total sleep time, 446.2 ± 7.1 min; sleep onset latency, 29.0 ± 5.1 min; sleep time in stage 1, 49.8 ± 6.9 min; sleep time in stage 2, 196.2 ± 10.9 min; sleep time in SWS: 105.1 ± 6.3 min; sleep time in REM sleep, 64.3 ± 8.0 min; movement time, 10.3 ± 5.9 min). None of these parameters correlated with the PatSep score (all p values > 0.28).

Correlations between specific EEG oscillatory measures and the PatSep score are summarized in Table 2. Robust relations

Table 1. Overview of responses in the MST in Sleep and Wake conditions

Item type	Target			Lure			Foil		
	Old	Similar	New	Old	Similar	New	Old	Similar	New
Sleep									
Immediate recall	83.54 (3.16)	13.54 (3.02)	3.00 (0.90)	37.92 (4.01)	54.69 (3.85)	7.23 (1.46)	1.31 (0.31)	19.23 (3.44)	79.77 (3.38)
Delayed recall	79.08 (2.40)	15.77 (1.82)	5.23 (1.00)	32.69 (3.14)	50.69 (3.18)	16.62 (2.52)	4.38 (1.29)	18.46 (2.98)	77.15 (3.07)
Wake									
Immediate recall	85.62 (2.86)	12.31 (2.62)	2.15 (0.82)	30.62 (3.99)	62.38 (3.72)	6.85 (1.43)	2.46 (0.31)	19.69 (4.43)	78.23 (4.47)
Delayed recall	62.62 (4.89)	26.85 (4.48)	10.46 (1.97)	32.08 (3.52)	38.69 (3.25)	29.54 (2.69)	3.23 (0.84)	16.77 (2.77)	80.08 (2.93)

Mean (SEM) of response types relative to item types in percentage.

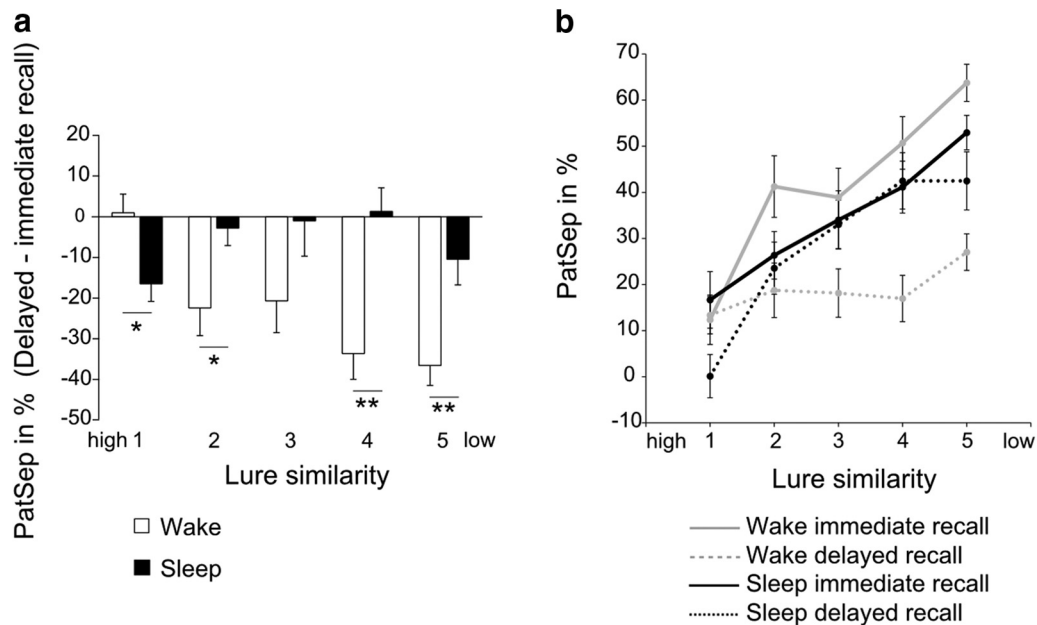


Figure 3. Pattern separation performance as a function of lure similarity. **a**, Mean (\pm SEM) PatSep score across five degrees of lure similarity (1, high similarity; 5, low similarity) separately for the Sleep (black) and Wake (white) conditions. * $p < 0.05$; ** $p < 0.01$ for pairwise comparisons between Sleep and Wake conditions. Difference values (delayed minus immediate recall) are indicated. **b**, Mean (\pm SEM) PatSep scores separately at immediate and delayed recall for the Sleep and Wake conditions depict graded decrease and increase in performance. Note the typical increase in pattern separation performance with decreasing lure similarity seen before sleep and wakefulness intervals (immediate recall) is preserved after sleep but deteriorates after wakefulness (delayed recall).

were revealed for non-REM sleep spindles and slow oscillations. Spindle density as well as slow oscillation density during non-REM sleep were positively correlated with PatSep performance (for central electrode sites: spindles: $r = 0.683$, $p = 0.014$; slow oscillations: $r = 0.613$, $p = 0.026$; Fig. 4*a,b*). Considering evidence that the occurrence of hippocampal memory reactivations is synchronized to neocortical slow oscillation and thalamic spindle activity (Sirota et al., 2003; Staresina et al., 2015), we also explored the relationship of EEG activity occurring phase-locked to the slow oscillation (± 1.5 s around the negative slow oscillation peak) with PatSep performance. The analyses revealed a positive correlation between PatSep performance and phase-locked (4–8 Hz) theta power with a maximum at central channels (at C3: $r = 0.589$, $p = 0.044$; Fig. 4*c*). There was no correlation of PatSep performance with (12–16 Hz) spindle activity occurring phase-locked to the slow oscillation.

Discussion

Our study in humans shows that pattern separation performance stabilized after sleep but deteriorated across a period of wakefulness. The stabilizing effect of sleep on pattern separation was most pronounced for lures with lowest similarity to the target stimulus. For stimuli with the greatest similarity to targets, pattern separation performance after postencoding sleep was signif-

icantly lower than after the wake period. Particularly, we found EEG spindle and slow oscillation density, as well as slow oscillation-locked theta activity during non-REM sleep to be positively correlated with overnight changes in pattern separation performance. The picture arising from these findings is consistent with the notion that neural replay during sleep strengthens hippocampal representations such that similarity-dependent computations of pattern separation are stabilized.

Revealing superior recognition performance after sleep compared with wakefulness, our findings confirm previous studies indicating that sleep supports the formation of distinct representations for discriminative stimuli (Gais et al., 2000; Stickgold et al., 2000; Drosopoulos et al., 2005; Ellenbogen et al., 2009; Fenn et al., 2009; Maurer et al., 2015). The present data go beyond these previous data by indicating that sleep changes recognition behavior strongly depending on the similarity of lures to target stimuli. The clear switch from similar to old responses regarding highly similar lures across sleep may suggest a predominance of pattern completion processes over pattern separation (Toner et al., 2009; Yassa et al., 2010). If this was the case, our results may indicate that reprocessing of representations during sleep simultaneously affects both modes of pattern separation and pattern completion. However, it should also be mentioned here that the validity of the

Table 2. Power density, slow oscillations, and spindles: correlations with pattern separation performance

	Mean (SEM)	Correlations with PatSep retention score	
		<i>r</i>	<i>p</i>
Power density ($\mu V^2/Hz$)			
0.5–1 Hz	329.58 (38.16)	0.352	0.238
0.5–4 Hz	112.27 (11.80)	0.234	0.441
1–4 Hz ^a	86.11 (9.24)	0.143	0.642
4–8 Hz ^a	7.55 (0.77)	−0.236	0.437
9–12 Hz ^a	3.18 (0.66)	−0.352	0.239
12–15 Hz ^a	3.53 (0.43)	−0.104	0.734
Slow oscillations			
Count	1130.23 (90.91)	0.408	0.166
Density (/30 s)	1.93 (0.11)	0.613*	0.026
Amplitude (μV) ^a	169.02 (6.84)	0.197	0.519
Slope ($\mu V/s$)	401.16 (17.72)	0.215	0.480
Spindles			
Count	1659.91 (67.68)	0.039	0.909
Density (/30 s)	2.79 (0.05)	0.683*	0.014
Length (s)	0.85 (0.01)	−0.055	0.866
Amplitude (μV)	31.22 (1.46)	−0.456	0.159

Data are the mean (SEM) for power within distinct EEG frequency bands, slow oscillation, and spindle parameters. Right columns indicate correlations with the PatSep retention score and respective *p* values.

^aCorrelations for frequency bands that were not normally distributed were calculated with Spearman's ρ , all others with Pearson product–moment correlation.

**p* < 0.05.

MST as a measure of hippocampal pattern separation and completion performance has been questioned (Liu et al., 2016). Specifically, the definition of pattern completion performance judging similar lures as old assuming a generalization process regarding target–lure pairs (Yassa and Stark, 2011) does not represent its theoretical construct as the reactivation of memory representations based on noisy or degraded input accurately (Hunsaker and Kesner, 2013). Consequently, since we could only show a shift toward pattern completion indirectly, our interpretation in this regard remains speculative. As the MST has already been validated in several studies for the assessment of pattern separation performance (Yassa et al., 2010, 2011a, Lacy et al., 2011), the paradigm is well suited for comparing our results with previous findings regarding pattern separation, so that we concentrated on those results. Indeed, the pattern separation performance assessed immediately after encoding in both the Sleep and Wake condition was comparable to those of corresponding age groups examined in previous studies (Toner et al., 2009; Yassa et al., 2011b; Stark et al., 2013). While the MST has been used mainly in conjunction with an immediate recall test, we here use this task for assessing how reprocessing affects memory representations across longer retention periods of sleep and wakefulness. Across wakefulness, pattern separation particularly deteriorated, which is reminiscent of changes seen in aged humans (Yassa et al., 2011b; Stark et al., 2013) and in patients with conditions including deficits in episodic memory such as Alzheimer's disease (Ally et al., 2013), mild cognitive impairment (Yassa et al., 2010), and hippocampal damage (Kirwan et al., 2012). Recently, sleep deprivation was identified as another factor interfering with successful pattern separation at memory encoding (i.e., in an immediate recall test) whereby the impairment was restored after a recovery nap (Saletin et al., 2016).

Importantly, in comparison with wakefulness, sleep did not uniformly improve pattern separation performance at all levels of lure similarity, but for lures with the highest similarity to the targets sleep diminished pattern separation. Evidence from studies of neural activity in rats indicates that the dentate gyrus and

CA3 are simultaneously engaged in the processing of pattern separation and completion such that at a certain degree of similarity to a previously learned stimulus, acute stimulus input favors pattern completion operations (Guzowski et al., 2004; Lee et al., 2004; Leutgeb et al., 2004; Vazdarjanova and Guzowski, 2004). Considering this switch from pattern separation to pattern completion with increasing target similarity as a hallmark of hippocampal information processing, the present observation that sleep enhanced pattern separation of dissimilar lures and diminished pattern separation of lures highly similar to the target corroborates the view of a direct impact of sleep on the hippocampal representation of the target stimuli. Neural assembly pattern reactivations during sleep might counter trace decay and, thus, keep the hippocampal representation shaped such that operations of pattern separation are enhanced to stimulus inputs of graded similarity, in comparison with the effects of postencoding wakefulness.

On the other side, the pattern of changes rules out a nonspecific effect of sleep generally enhancing discriminability of stimulus inputs. Other nonspecific confounding effects can likewise be excluded. There are hints that encoding and recall of declarative memory can be affected by circadian factors (Tilley and Warren, 1983). Indeed, in the Sleep and Wake conditions of the present experiments these processes took place at different circadian phases, to avoid stress-inducing effects of sleep deprivation impairing pattern separation (Saletin et al., 2016). However, morning and evening sessions in these conditions differed neither in immediate recall performance on the MST nor in vigilance and tiredness, rendering it unlikely that nonspecific changes in executive function substantially contributed to the differential recall pattern after sleep and wakefulness. Furthermore, participants achieved scores on immediate recall similar to those reported in previous studies (Stark et al., 2013), so that conditions are not only comparable to each other but also to findings beyond our experiment.

Also our exploratory analysis of relations to sleep EEG oscillatory parameters highlighted consistent positive correlations of spindle and slow-oscillation density as well as of theta activity occurring phase-locked to slow oscillations with pattern separation performance after sleep, which further corroborates the view of sleep, specifically non-REM sleep, being the primary factor mediating the effects on hippocampal memory. The correlation with sleep spindle density, a measure being independent of the duration of non-REM sleep, underscores the idea that spindles are genuinely involved in processes of memory consolidation. Indeed, a large body of findings suggests that spindle activity originating from thalamic networks enhances consolidation in different memory domains, including hippocampus-dependent spatial memories (Meier-Koll et al., 1999; Gais et al., 2002; Schabus et al., 2004; Eschenko et al., 2006; Saletin et al., 2011). Spindles phase lock hippocampal ripples and co-occurring neural memory reactivations to the excitable trough of the spindle oscillation (Clemens et al., 2007; Bergmann et al., 2012; Staresina et al., 2015). Concurrently, the slow oscillations drive hippocampal ripples and neural reactivations such that they preferentially occur during the depolarizing slow-oscillation up phase (Sirota et al., 2003; Ji and Wilson, 2007; Staresina et al., 2015).

Against this backdrop, improved pattern separation performance associated with enhanced spindle and slow oscillation density might reflect that memory reactivation and ripples occurring in hippocampal networks during the excitable phase of the spindle and slow oscillation cycle, respectively, are more effective in keeping the respective memory representation. Enhanced EEG theta activity occurring in synchrony with the up-to-down transition of

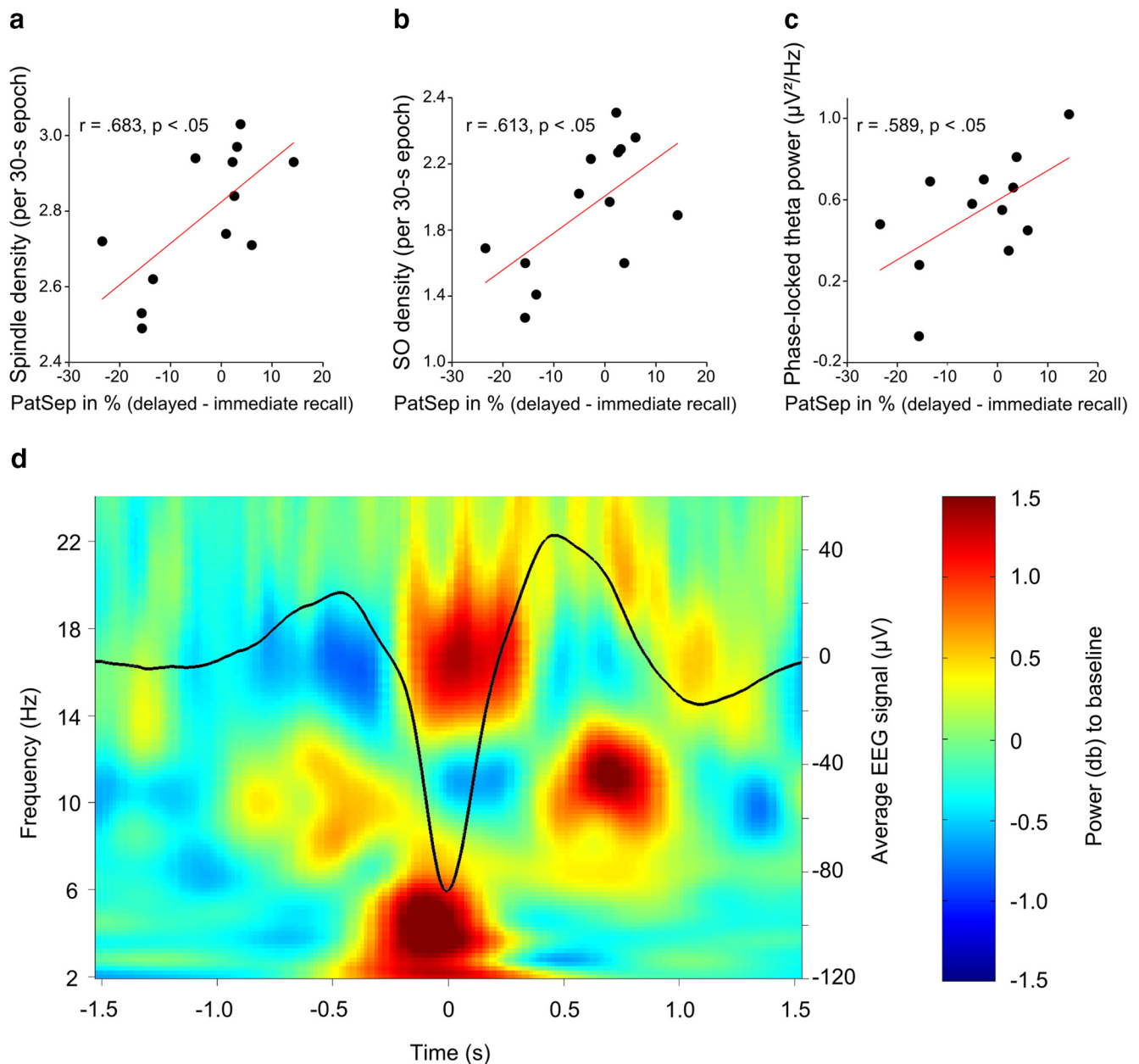


Figure 4. EEG spindle density, slow-oscillation density and slow oscillation-associated theta activity during non-REM sleep are related to pattern separation performance. **a, b**, Correlation between PatSep performance and spindle density (**a**; $n = 12$) and slow oscillation density (**b**; $n = 13$) during non-REM sleep (SWS and S2, recordings from C3/C4). **c**, Correlation between PatSep performance and phase-locked theta (4–8 Hz) power (at C3) during slow oscillation (i.e., in a -0.5 to 0.25 s window around the negative slow oscillation peak; $n = 12$). Slow oscillations were identified in non-REM sleep (SWS and S2). **d**, Averaged time–frequency plot of EEG wavelet power during slow oscillations (at C3) in a ± 1.5 s time window around the negative slow oscillation peak (0 s) for a 2–24 Hz frequency band ($n = 12$).

the slow oscillation might likewise be connected to a more effective hippocampal processing of memory information. In the wake state, theta oscillations are robust indicators of ongoing encoding and retrieval in hippocampal networks (Klimesch et al., 2006; Nyhus and Curran, 2010). Similarly, during sleep, increases in frontal EEG theta activity were observed in humans when hippocampal memory representations were experimentally reactivated by presenting reminder cues during non-REM sleep (Schreiner and Rasch, 2015; Schreiner et al., 2015). The cuing-evoked increase in theta activity might well reflect re-encoding of information during hippocampal reactivation, although the origin of scalp-recorded EEG theta activity in humans is obscure (Klimesch, 1996; Klimesch et al., 1996). In natural conditions, the

neocortical slow oscillation synchronizes neural reactivations of memory information in hippocampal networks to the slow oscillation upstate (Ji and Wilson, 2007; Diekelmann and Born, 2010). Against this backdrop, our observation of a positive correlation between pattern separation performance after sleep and theta activity occurring in synchrony with the slow oscillation during sleep fits well with the notion that hippocampal memory reactivations go along with a re-encoding and shaping of the hippocampal representations, thereby enhancing pattern separation and completion during the processing of stimuli with graded similarity. Altogether, our findings provide first-time evidence in humans supporting the notion that reactivation-based consolidation processes during sleep affect the hippocampal representation itself

such that hippocampal computations of pattern separation are enhanced.

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