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The Role of Sleep in Directed Forgetting and Remembering of Human Memories

Jared M. Saletin[1], Andrea N. Goldstein[1,2] and Matthew P. Walker[1,2]

[1]Sleep and Neuroimaging Laboratory, Department of Psychology and [2]Helen Wills Neuroscience Institute, University of California, Berkeley, CA 94720-1650, USA

Address correspondence to Matthew P. Walker, Department of Psychology, Tolman Hall 3331, University of California, Berkeley, CA 94720-1650, USA. Email: mpwalker@berkeley.edu.

Ample evidence supports a role for sleep in the offline consolidation of memory. However, circumstances exist where forgetting can be as critical as remembering, both in daily life and clinically. Using a directed forgetting paradigm, here, we investigate the impact of explicit cue instruction during learning, prior to sleep, on subsequent remembering and forgetting of memory, after sleep. We demonstrate that sleep, relative to time awake, can selectively ignore the facilitation of items previously cued to be forgotten, yet preferentially enhance recall for items cued to be remembered; indicative of specificity based on prior waking instruction. Moreover, the success of this differential remember/forget effect is strongly correlated with fast sleep spindles over the left superior parietal cortex. Furthermore, electroencephalography source analysis of these spindles revealed a repeating loop of current density between selective memory-related regions of the superior parietal, medial temporal, and right prefrontal cortices. These findings move beyond the classical notion of sleep universally strengthening information. Instead, they suggest a model in which sleep may be more ecologically attuned to instructions present during learning while awake, supporting both remembering and targeted forgetting of human memories.

Keywords: consolidation, forgetting, memory, sleep, spindles

Introduction

A substantive literature now implicates non-rapid eye movement (NREM) sleep, and its associated oscillations, in the consolidation and hence later recall of declarative memory (Molle et al. 2002; Schabus et al. 2004; Clemens et al. 2005; Schmidt et al. 2006; Gais et al. 2007; Diekelmann and Born 2010). However, the capacity to forget can, in certain contexts, be as important as the need for remembering, both in day-to-day life (e.g., forgetting last week's parking spot in preference for today's) and clinically (e.g., posttraumatic stress disorder and addiction). Item forgetting has been shown to decrease neural resources required for targeted remembering (Kuhl et al. 2007) and is considered to reflect a potential weakening or suppression of memory representations (Levy and Anderson 2002). As a consequence, forgetting has been proposed to afford improved efficiency of subsequent recall under specific conditions (Block 1971; Anderson et al. 2004; Levy and Anderson 2008).

Contrary to the role of sleep in subsequent remembering, earlier frameworks included speculation of a role for sleep in promoting forgetting (Ekstrand 1972). Since the concept of memory weakening (Crick and Mitchison 1983), the notion of sleep differentially modulating remembering and forgetting has remained increasingly relevant considering the hypothesized adaptive potential benefit of forgetting (Anderson et al. 2004; Kuhl et al. 2007). Investigations examining emotional memory consolidation suggest that sleep may selectively treat some aspects of episodic experiences with preference over others. For example, a collection of reports have demonstrated that offline periods of sleep not only result in superior retention of emotional memories compared with neutral memories (Wagner et al. 2001; Hu et al. 2006; Nishida et al. 2009) but benefit specific emotional aspects of these episodic experiences (Payne et al. 2008; Payne and Kensinger 2010), indicative of discriminatory processing. Despite these long-standing theoretical conceptions (Crick and Mitchison 1983), a role for sleep in managing the offline balance between directed memory retention and loss remains largely unknown.

Using a validated directed-forgetting task (Bjork 1998; MacLeod 1999; Lee et al. 2007; Wylie et al. 2008; Hsieh et al. 2009; Nowicka et al. 2011), here, we investigate the impact of explicit cue instruction during encoding, prior to sleep, on differential offline remembering and forgetting of memory, after sleep. In contrast to recent work evaluating the impact of sleep on the resistance to forgetting (Ellenbogen et al. 2006; Baran et al. 2010; Racsmany et al. 2010), we specifically tested the hypothesis that, relative to equivalent time awake, sleep selectively facilitates recall of words previously cued for remembering, yet negates such facilitation of items instructed to be forgotten. Moreover, motivated by the homology in functional anatomy associated with sleep spindles (Schabus et al. 2007) and those networks known to support selective remembering and forgetting in specific frontoparietal regions (Wylie et al. 2008; Nowicka et al. 2011), we additionally sought to determine whether NREM spindle oscillations promoted this differential directed forgetting memory effect.

Materials and Methods

Participants and Design

Forty-six healthy participants, age 18–30 years, were randomly assigned to either the Nap (n = 23, 10 males, age 20.04 ± 2.08 [mean ± standard deviation {SD}]) or the No-Nap (n = 23, 10 males, age 20.89 ± 3.07 [mean ± SD]) group. Participants abstained from caffeine and alcohol for the 48 h before and during the entire course of the study and kept a normal sleep-wake rhythm (7–9 h of sleep per night, with morning wake time between 06:30 and 08:30) for the 2 nights prior to study participation, as verified by sleep logs. Total sleep the night before testing did not differ between the Nap and No-Nap groups (7.89 h ± 0.15, 7.65 h ± 0.20 [mean ± standard error of the mean {SEM}], respectively, P = 0.34), and mean rise times also did not differ significantly between groups (08:33 ± 6 min, 08:29 ± 5 min [mean ± SEM], respectively, P = 0.48). The study was approved by the local human studies committee, with all participants providing written informed consent. Participants were assigned to either a Nap group (Fig. 1*a*) and were given 100-min sleep opportunity from 14:30 to 16:10 or a No-Nap group and were asked to remain in the laboratory throughout the study, monitored by research personnel.

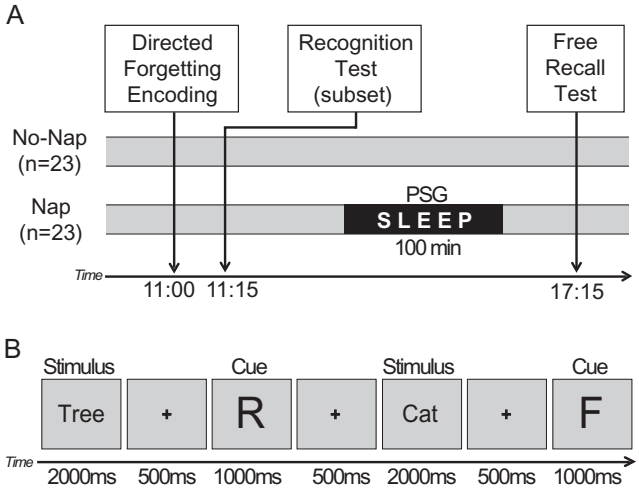

Figure 1. Study design. (*a*) Time course of experiment for both the No-Nap and Nap groups, respectively, describing training, immediate test, and delayed test sessions. The nap involved a 100-min sleep opportunity from 14:30 to 16:10 recorded using 19-channel EEG polysomnography. (*b*) Schematic for the directed forgetting task, demonstrating 2 representative trials. Words were presented in the center of the screen for 2000 ms, followed by a fixation cross for 500 ms and then a large letter cue indicating that participants should remember the prior word (R) or forget the prior word (F). While these R and F cues are shown in black font in the schematic, they were green and red, respectively, in the actual task.

Directed Forgetting Task

At 11:00, all participants, regardless of group assignment, were trained on a directed forgetting task (Fig. 1*a*). Conforming to previous paradigms (MacLeod 1999; Lee et al. 2007; Wylie et al. 2008; Nowicka et al. 2011), participants studied 100 words presented one at a time on a computer screen (gray background, black Courier New font, 50 point, center screen) for 2000 ms, followed by a 500 ms blank gray screen, after which a cue appeared instructing them to either remember (large green "R") or forget (large red "F") the previously presented word (both gray background, Courier New font, 150 point, center screen, 1000 ms; and for trial structure, see Fig. 1*b*). Based on literature suggesting that postcue intervals may impact rehearsal strategies, a short, restricted postcue duration (time between offset of cue and onset of next trial) of 500 ms was used so as to circumvent rehearsal influences (MacLeod 1999; Lee et al. 2007).

To ensure equivalent and robust encoding of both word types in both experimental groups (Nap and No-Nap), an immediate recognition test was performed following training at 11:15 (Fig. 1*a*) for half of the stimuli (25 words cued to be forgotten, 25 words cued to be remembered). Recognition testing, rather than free recall, was used for this immediate test purpose to control item exposure across all participants during this probe, prior to the wake or sleep experimental manipulation. This immediate recognition test contained 100 trials, 50 of which contained words seen during encoding (25 of each cue type), with an additional 50 novel words used as foils. Foils had the same psycholinguistic properties as the original words (see Supplementary Information). During each recognition trial, a word was presented on the screen for 1000 ms (gray background, black Courier New font, 50 point, center screen). After this presentation, the screen was cleared and participants were instructed to make a corresponding "old/new" keypad judgment. The next trial did not begin until a response was given. As with encoding, all words were presented in a pseudorandomized order, preventing more than 4 words of any one class from appearing successively. Recognition memory accuracy was calculated as the subtracted difference between the proportion of correctly identified "old" words (hit rate) and the proportion of incorrectly identified "new" words (false alarm rate) (Snodgrass and Corwin 1988; Hornberger et al. 2006; Uncapher and Rugg 2008; Vilberg and Rugg 2008).

Following the offline sleep/wake manipulation (details below), both groups performed a 5-min computerized delayed free recall test at 17:15 (Fig. 1*a*). Participants were instructed to freely recall as many words as they could from the initial learning (encoding) session, regardless of the cue previously associated with that word. Participants typed their entries one at a time on screen, and after pressing the ENTER key, the answer was cleared and the next recalled word could be entered.

Free recall responses were classified as "R-words" (recalled words previously cued to be remembered), "F-words" (recalled words previously cued to be forgotten), "Foils" (recalled words previously presented as foils during the immediate recognition test), and "Intrusion" (recalled words never previously presented). Responses were also standardized as percentages of total recall (R-words + F-words + Error). This complementary way of evaluating recall success by standardizing to total recall amount is especially important considering that tests of free recall commonly lead to low word counts, including those of directed forgetting experiments (MacLeod 1975, 1999; Bjork 1998; Lee et al. 2007). An R–F difference measure, capturing the efficiency of the directed forgetting effect, was calculated by subtracting the proportion of F-words words recalled from the proportion of R-words words recalled. This R–F difference measure afforded a standardized score across participants, normalized to the number of recall attempts, similar to the principle of signal-detection theory in traditional memory paradigms (Snodgrass and Corwin 1988).

Sleep Recordings

Those participants in the Nap group were given a 100-min sleep opportunity in the sleep laboratory from 14:30 to 16:10 (Fig. 1*a*), while those in the No-Nap group remained awake in the laboratory monitored by research personnel. During the sleep opportunity, polysomnography sleep monitoring was recorded using a Grass Technologies Comet XL system (Astro-Med, Inc.). Electroencephalography (EEG) was recorded at 19 standard locations conforming to the International 10–20 System (Jasper 1958), specifically (FP1, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T5, P3, PZ, P4, T6, O1, O2). Electrooculography was recorded at the right and left outer canthi (right superior; left inferior). Electromyography was recorded via 3 electrodes (one mental, 2 submental). Finally, electrocardiography was recorded at 2 sites: below both the left and right clavicles. Reference electrodes were placed at both the left and right mastoid (A1, A2). Data were sampled first at 800 Hz by the amplifier and then digitized at 400 Hz. All data were stored unfiltered (recovered frequency range of 0.1–100 Hz), except for a 60-Hz notch filter. For recording only, each channel was referenced to a forehead scalp reference. Sleep staging was performed in accordance with standardized techniques (Rechtschaffen and Kales 1968).

Sleep Spindle Analysis

Sleep spindles represent short synchronous bursts of activity between 12 and 15 Hz (Eschenko et al. 2006; Ferrarelli et al. 2007), having been related to offline declarative memory processing (Schabus et al. 2004; Clemens et al. 2005; Diekelmann and Born 2010). Furthermore, fast sleep spindles, rather than slow, are selectively associated with activity in the hippocampus, lateral and medial PFC, as well as posterior parietal regions (Schabus et al. 2007).

Sleep spindles were detected through an established algorithm (Ferrarelli et al. 2007; Nishida and Walker 2007). In short (but see Ferrarelli et al. [2007] for details), the amplitude of the rectified signal from NREM sleep was used as a unique time series, identifying amplitude fluctuations exceeding threshold values, with the lower and upper values set at 2 and 8 times the average amplitude. The peak amplitude for each spindle was defined as the local maximum above the threshold, with the beginning and end of the spindle defined as points immediately preceding or following this peak, when the amplitude of the time series dropped below the cutoff threshold. All EEG analyses were performed in MATLAB 7.5 (The Mathworks), including the add-in toolbox EEGLAB (http://sccn.ucsd.edu/eeglab/).

Prior to analysis, each EEG channel was rereferenced to the average of the left and right mastoid, allowing for commonality of reference. NREM epochs were extracted based on visual scoring. All NREM epochs for each participant were concatenated into a single NREM time series. Artifacts in the time series were removed by visual rejection. Following

artifact rejection, EEG was band-pass filtered using a finite impulse response function, set between 12 and 15 Hz (frequency range defined by that used previously with the current algorithm [Ferrarelli et al. 2007] and commonly used for spindle detection [Eschenko et al. 2006]). The algorithm-determined spindles were restricted only to those events falling within this frequency range. The spindles were then classified as either fast (13.5–15 Hz) or slow (12–13.5 Hz). These frequency splits were derived from a median split of the frequency range of 12–15 Hz (Ferrarelli et al. 2007), similar to previous reports (Knoblauch et al. 2003; Milner et al. 2006). Spindle density was calculated for each channel by dividing the number of spindles (fast or slow) by the total amount of NREM time (adjusted for artifact-rejected signal), representing the number of spindles occurring per min in a given channel.

sLORETA Source Analysis

Scalp EEG represents the synchronous activity of many different neuronal sources. There is no one unique solution for the inverse problem (identification of these sources given a distribution of scalp EEG), and therefore, more than one solution and methodology exists (Pascual-Marqui et al. 1999). One such solution, standardized low-resolution tomography (Pascual-Marqui 2002), in which computations are made using a head model based on the MNI152 template (Mazziotta et al. 2001). Solution space is limited to cortical gray matter, making sLORETA more precise than other methods of source localization that are not anatomically constrained and is made up of 6239 voxels at 5-mm resolution (Pascual-Marqui 2002). While the anatomical precision of sLORETA and of all source analysis varies depending on EEG the number of electrodes in the EEG montage (Laarne et al. 2000; Ryynanen et al. 2006), numerous studies have validated the sLORETA approach using montage arrays of similar resolution (Pascual-Marqui et al. 1999; Isotani et al. 2001; Veiga et al. 2003; Bela et al. 2007; Clemens et al. 2008, 2009; Tislerova et al. 2008; Ponomarev et al. 2010) or lower (Ventouras et al. 2007).

Validation of the LORETA source has been described in a number of combined EEG/functional magnetic resonance imaging (fMRI) reports, demonstrated strongly convergent cortical LORETA localizations with those identified by event-related fMRI cognitive task paradigms (Vitacco et al. 2002; Mulert et al. 2004), together with the localization of state-dependent changes in basic vigilance levels (Olbrich et al. 2008). Additional validation has been received from depth recordings of epileptic patients, where sLORETA accurately tracks the source localization of anatomically confirmed epileptic seizure foci (Zumsteg et al. 2006).

Prior to source current-density calculation, all electrode channels were registered and transformed into 3D Montreal Neurological Institute space, yielding a spatial transformation matrix used to invert the EEG signal according to the sLORETA solution. Continuous unfiltered NREM EEG was marked for the onset of each fast spindle in a specified channel (see Results). A 4-s epoch was selected around the spindle event: 1000 ms prior to spindle onset and the 3000 ms postonset. Baseline correction was performed on each epoch (implemented with the EEGLAB function pop_rmbase), utilizing the 1000 ms prior to spindle onset, thereby correcting the remaining 3000 ms for baseline activity nonspecific to the sleep spindle event. The 1000 ms baseline period was not included in further analyses. EEG epochs were averaged first within- and then between-participants, yielding a single 4000 ms grand-averaged epoch. Finally, to remove activity not related to sleep spindles, this grand-averaged EEG was filtered to the spindle frequency range (12–15 Hz). Separate sLORETA current density was calculated for each time point in the 3000 ms time series independently. Current-density maps were then rendered on uninflated cortical surfaces (Holmes et al. 1998).

Statistical Analysis

Statistical analyses were conducted in JMP 8.0 (SAS). All P values reported are two-tailed. Immediate recognition performance was submitted to paired and independent Student t-tests as appropriate for within- and between-subject comparisons, respectively. Delayed free recall data were analyzed first using a 2 × 3 mixed-level analysis of variance with within-subject factor word type (3 levels: R-words, F-words, Error) and between-subject factor group (2 levels: No-Nap, Nap). The efficiency of directed forgetting, indexed by the R–F difference measure, was compared between groups using an independent Student t-test. The relationship between fast sleep spindles and directed forgetting memory performance was investigated via Pearson's bivariate correlation. Significance values were corrected for multiple comparisons (see Supplementary Information).

Results

Immediate Recognition

At immediate testing, when compared between groups, memory accuracy ([hit rate - false alarm rate]) was identical for both R-words (t_{44} = 1.37, P = 0.18) and F-words (t_{44} = 0.97, P = 0.34). Within each group, performance was significantly greater for R-words than for F-words (Nap: t_{22} = 9.43, P < 0.0001, No-Nap: t_{22} = 8.25, P < 0.0001). Furthermore, the difference in memory accuracy between R-words and F-words (R-F) was not significantly different between the 2 groups (t_{44} = 0.48, P = 0.63). These findings indicate that, prior to any sleep or wake offline manipulation, 1) the level of encoding for each word class was identical between the groups, 2) the task successfully led to the presence of a significant directed forgetting effect in both groups, and 3) the magnitude of this directed forgetting manipulation was equivalent between groups.

Delayed Free Recall

Free recall performance was collapsed across words that were either included or not in the immediate recognition test, as the exposure of a subset of items at this immediate test did not unduly influence the response (for detailed analysis and discussion of data separated on the basis of immediate recognition test exposure, see Supplementary Information, and Supplementary Table S2).

Following the sleep or wake offline periods, both groups recalled significantly more R-words than F-words ($F_{2,43}$ = 58.06, P < 0.0001; Fig. 2*a*). Additionally, there was a significant main effect of group ($F_{1,44}$ = 6.44, P = 0.015), with the Nap group recalling more words in total than the No-Nap group. Critically, this benefit of sleep was not due to equal improvement of both word types. Specifically, there was a significant group by cue-type recall interaction ($F_{2,43}$ = 6.17, P = 0.004), such that those in the Nap group, relative to the No-Nap group, showed a preferential recall of R-words, yet this benefit occurred in the absence of any such enhanced recall of F-words. Thus, sleep did not ubiquitously facilitate all items. Instead, sleep provided a superior recall advantage for words previously cued for remembering but did so without concomitant enhancement of items previously cued for forgetting, indicative of specificity based on prior waking instruction. One alternative explanation is that sleep-enhanced memory of the cue associations rather than modulating the word items themselves allowing facilitation of knowledge in the nap group of which items to recall. This appears unlikely, however, since the Nap group, relative to the No-Nap group, showed no converse decrease in recall for items cued to-be-forgotten.

The effectiveness of directed forgetting on free recall was further characterized as a proportional difference score. Specifically, the number of F-words recalled was subtracted from the number of R-words recalled (expressed as proportion of total recall), yielding the R–F efficiency score. This difference

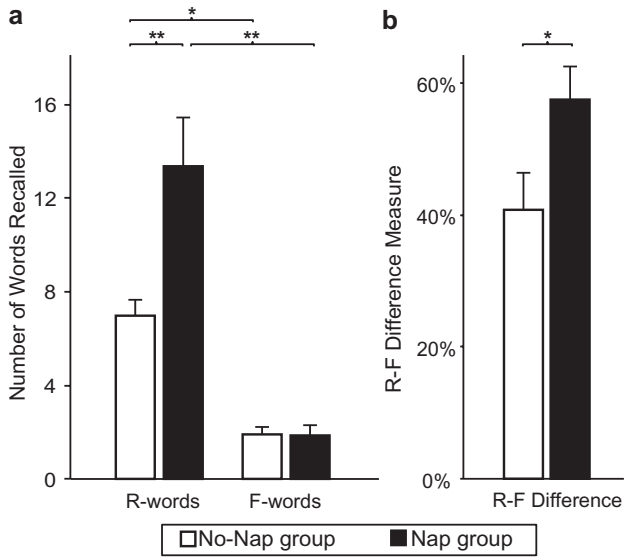

Figure 2. Behavioral data. Memory performance: (*a*) Number of words recalled based on prior cue instruction (Remember, R-words; Forget, F-words) in the Nap and No-Nap groups and (*b*) the efficiency measure of directed forgetting, calculated as the subtraction of these scores (R–F; expressed as a proportion of total recall; Supplementary Information). Between group comparisons (line across bars) reflect significance at: * <0.05 and ** <0.01. Error bars represent SEM.

measure further demonstrated significantly greater recall of R- relative to F-words in the Nap relative to No-Nap group (t_{44} = 2.18, P = 0.03; Fig. 2*b*). Supplemental analyses further demonstrated that this effect between groups was not dependent upon the reexposure of a subset of the words at immediate recognition (Supplementary materials). Therefore, based on instruction given during initial learning, and compared with equivalent time awake, sleep was capable of more efficiently managing the balance between differential later recall of items cued for remembering relative to those cued for forgetting. A series of supplemental analyses confirmed that these results were not due to the influence of floor effects in F-word recall (see Supplementary Information).

Sleep Physiology Association

We next sought to determine whether aspects of sleep physiology within the Nap group were associated with the observed selective enhancement to words cued to be remembered and not to words cued to be forgotten. We focused a priori on fast sleep spindles based on their associated functional anatomy (Schabus et al. 2007; Walker 2009) converging with that anatomy supporting directed forgetting (Wylie et al. 2008; Nowicka et al. 2011). As with recent work demonstrating local physiological beyond global sleep-stage associations with memory (Huber et al. 2004; Marshall et al. 2006) (see Supplementary Information), we found strong and significant relationships between fast sleep spindles and the directed-forgetting efficiency score (R-F difference) in multiple posterior electrode sites (Fig. 3*b*). Correction for multiple comparisons revealed that P3, situated over the left superior parietal lobe and commonly associated with episodic memory processing (Uncapher and Wagner 2009), retained significance (Fig. 3*c*, r = 0.66, P = 0.0006). Slow sleep spindles showed no such significant associations (see Supplementary Information).

In addition to the predictive spindle relationship with the R–F difference score, fast sleep spindles predicted recall of R-words and F-words independently and in opposing directions. Specifically, fast spindles 1) significantly and positively correlated with the proportion of R-words recalled at a number of posterior parietal sites, yet 2) negatively correlated with the proportion of F-words recalled at a number of frontal sites, although none of these correlations survive stringent correction for multiple comparisons (see Supplementary Information). Therefore, while fast sleep spindles did differentially predict the recall of R- and F-words independently, these relationships were markedly less significant than that identified for the R-F efficiency score, with only the latter surviving correction for multiple comparisons. Such findings support a framework whereby sleep spindles modulate the proportional balance between remembering and forgetting (encapsulated by the R-F efficiency score), more so than influencing either of these word types independently.

sLORETA Source Analysis

Considering the hypothesized role of parietal-frontal networks, combined with medial temporal lobe structures, in episodic memory processing (Uncapher and Wagner 2009; Shimamura 2010), sLORETA source analysis was used to characterize the neural sources of the identified P3 fast sleep spindles. Since sleep spindles have no one peak, current source density was calculated across the spindle time series (Fig. 3 and Supplementary movie S1). This time course analysis revealed a repeating loop of activity throughout a network in the superior parietal cortex, lateral prefrontal cortex as well as anterior and posterior cingulate cortex (Fig. 3 and Supplementary movie S1). This recursive pattern of regional source activity is of note considering the congruent overlaps with networks previously implicated in supporting selective remembering and forgetting of memories (Wylie et al. 2008; Hauswald et al. 2010; Nowicka et al. 2011).

Discussion

A corpus of evidence implicates NREM sleep physiology in the consolidation of episodic declarative memory, leading to superior memory retention relative to equivalent time periods awake (Marshall and Born 2007; Walker 2009; Diekelmann and Born 2010). In previous study designs, participants are either explicitly informed of a later retrieval test at the time of initial encoding, thereby emphasizing a need for remembering (Gais et al. 2002; Backhaus et al. 2008; Ellenbogen et al. 2009) or are not made aware of the later postsleep test (Gais et al. 2006; Wagner et al. 2006; Ellenbogen et al. 2007; Yoo et al. 2007; Schabus et al. 2008; Tucker and Fishbein 2008). It has therefore remained unclear whether selective cue instruction for remembering or forgetting at the time of initial learning, prior to consolidation, has a significant impact on the degree of subsequent successful recall, following offline time delays. Furthermore, and related to theoretical proposals (Freud 1913; Crick and Mitchison, 1983), an additionally untested hypothesis is whether the offline consolidation trajectory of instructed remembering and forgetting is modulated by the different brain states of wake or sleep (or specific sleep-stage physiology). Considering the proposed adaptive function of forgetting, affording reduced competition among relevant representations (Block 1971; MacLeod 1999; Anderson and Green 2001; Levy and Anderson 2002; Anderson 2003), a role for sleep in the

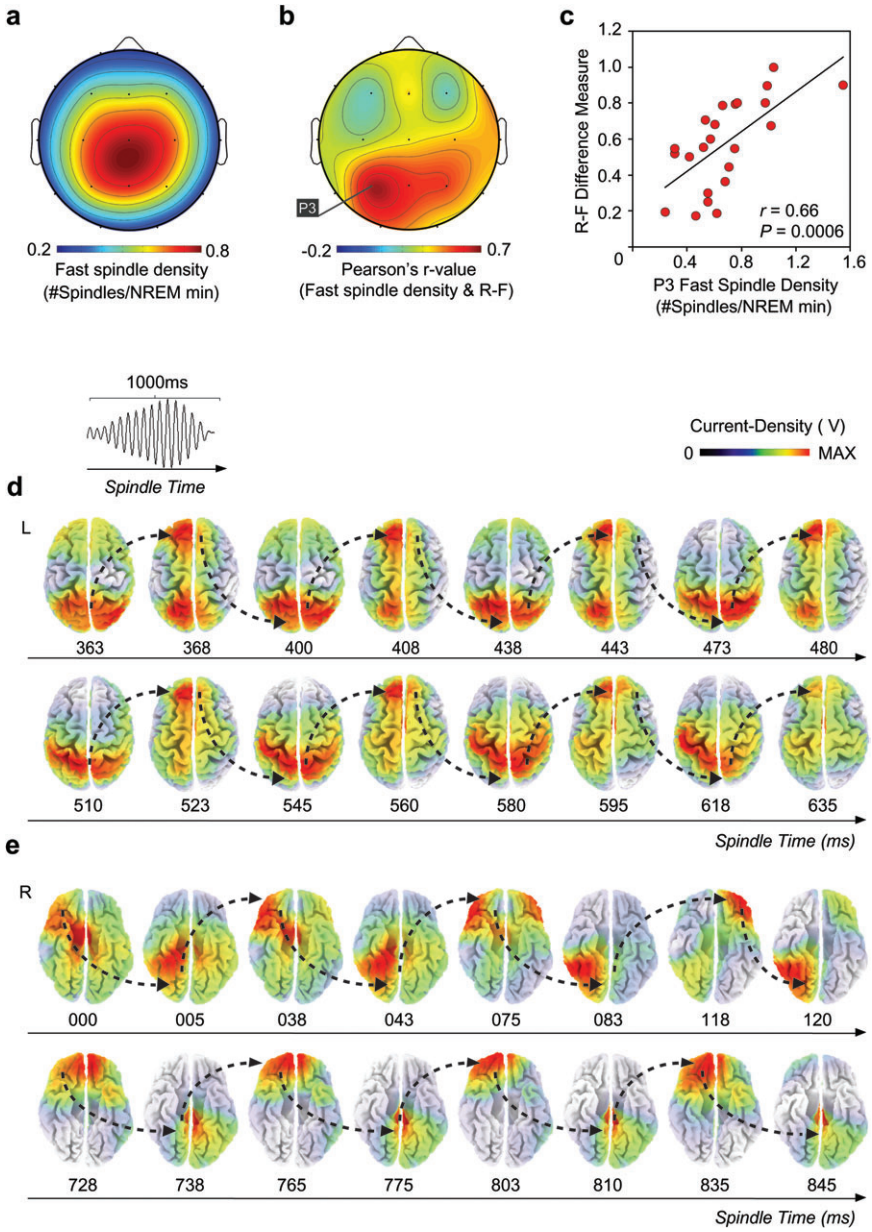

Figure 3. Physiological data. Relationship between memory performance and sleep spindles: (a) topographic plot for fast sleep spindle density in the nap-group (color bar indicates density [number of spindles/minute of NREM]), (b) correlation topographical plot demonstrating strength of relationship between fast sleep spindle density and R–F score. Note spindle activity at the P3 (left parietal) electrode site showing the strongest relationship (color bar indicates r value), (c) scatter-plot and linear regression of the relationship between fast sleep-spindle density at P3 and the R–F score across participants in the nap-group. sLORETA source analysis. (d-e) sLORETA source of fast sleep spindles identified by onset in P3 (P3 spindle shown in upper left), demonstrating a propagation loop of current–density between frontal, medial-temporal, and parietal networks across the spindle time series. Columns represent time points. Current source density plotted on (d) superior and (e) inferior cortical surfaces. Time in milliseconds is given below each column, relative to the onset of the sleep spindle. Color bar represents the sLORETA dynamic current density across the time series. Dash arrows indicate the dominant movement of current density in the reoccurring loop. A separate movie file of this same spindle source time series is provided in Supplementary movie S1, which offers a more dynamic illustrates of this current source oscillation.

balanced dynamics of remembering and forgetting increases in potential relevance.

Focusing on these questions, the current findings contribute to a more nuanced understanding of sleep-dependent memory processing, complementing but also moving beyond the established notion of sleep universally strengthening information (Marshall and Born 2007; Walker 2009; Diekelmann and Born 2010). Our results suggest that sleep's role in memory processing can be, at least within the context of a directed forgetting paradigm, differentially modulated by instructions present at the time of initial learning. While both the Nap and No-Nap groups expressed equivalent proportions of cued remembering and forgetting at immediate testing, which also indicated robust encoding of both these item types, the subsequent offline periods of wake or sleep resulted in significantly different recall rates for each item class. Specifically, sleep, relative to wake, preferentially facilitated one class of cued items—those instructed to-be-remembered—without

facilitating another class of cued items—those instructed to-be-forgotten. As a result, sleep served to more efficiently maximize the directed-forgetting effect; a process conceptually similar to an improved signal (R-words) to noise (F-words) retention ratio. It is of note that these findings differ to previous reports demonstrating a unidirectional benefit of sleep in the prevention of forgetting over time, which did not involve or examine the impact of instructional manipulation of encoding prior to sleep (Ellenbogen et al. 2006; Baran et al. 2010; Racsmany et al. 2010) nor assessed intentional forgetting rather than attempted memory suppression (Fischer et al. 2010). In contrast, the current study demonstrates a differential sensitivity of the sleep-dependent consolidation process toward intentional and adaptive forgetting and remembering (Anderson 2003), based on explicit prior waking instruction.

In addition to between-group differences in directed forgetting, moving beyond sleep-stage associations (Fischer et al. 2010), strong predictive relationships were identified between the efficiency of the remember–forget effect and fast sleep spindles in the Nap group, especially at electrode P3 located over left superior parietal cortex. Consistent with the hypothesis of sleep governing the bidirectional modulation of each item class, we additionally found that fast spindles separately and positively correlated with the proportion of words cued for remembering at posterior parietal regions, yet negatively correlated with words cued for forgetting at several frontal locations. Although it is important to note that these correlations for each word class alone did not survive stringent correction for multiple comparisons, the inverse nature of these relationships suggests that the correlation identified with the R-F difference measure was not simply driven by an exclusive association with R-words (or F-words) alone.

These associations build on an increasing collection of reports implicating sleep spindles in memory processing, describing learning-dependent increases in spindles following initial memory encoding (Gais et al. 2002; Eschenko et al. 2006; Fogel and Smith 2006; Morin et al. 2008; Fogel et al. 2009), as well as correlations (often topographic) with the success of postsleep memory retention (Clemens et al. 2005, 2006; Fogel and Smith 2006; Nishida and Walker 2007; Tamaki et al. 2008). Our findings further suggest that spindles can additionally support the differential later recall of items cued for remembering, yet do so without a concomitant facilitation of items cued for forgetting, indicative of selectivity, rather than indiscriminant facilitation.

Conceivably, such a process of specificity would require an offline mechanism capable of supporting item selection, based on prior cues and the subsequent preferential consolidation of these selected representations. Properties of sleep spindles appear well positioned to support such processing for a number of potential reasons. First, neuroimaging studies have identified inferior prefrontal, superior parietal, and medial temporal lobe structures in promoting successful instructed remembering over forgetting (Anderson et al. 2004; Kuhl et al. 2007; Wylie et al. 2008; Hauswald et al. 2010; Nowicka et al. 2011); regions that overlap with those associated with fMRI correlates of fast sleep spindles (Schabus et al. 2007; Wylie et al. 2008). Second, previous EEG studies further indicate strong spindle-dependent coherence between homologous frontal and parietal networks (Achermann and Borbély 1998; Anderer et al. 2001; Ventouras et al. 2007; Gumenyuk et al. 2009). Third, surface spindles are temporally linked with sharp-wave ripples occurring in the hippocampus and surrounding rhinal cortex (Clemens et al. 2007; Marshall and Born 2007; Diekelmann and Born 2010), the activity of which is proposed to play a role in dynamics of hippocampal–neocortical memory processing (Molle et al. 2002; Schabus et al. 2004; Clemens et al. 2005; Schmidt et al. 2006; Gais et al. 2007; Diekelmann and Born 2010). Fourth, source analyses of fast spindles in the current study revealed a similar convergent network of recurrent activity in superior parietal, temporal, and inferior frontal cortex. Based on this evidence, such spindle activity may provide a putative anatomical framework for selective item offline memory processing. In such a model (Shimamura, in press), parietal cortex would allow for the binding of top-down intentional information (e.g., selective cues) sourced from prefrontal cortex, with bottom-up item memory information from medial temporal areas, including hippocampus resulting in selective and discriminatory item consolidation.

In summary, here, we demonstrate that sleep, relative to time awake, can selectively enhance recall for words previously cued for remembering, without such facilitation of items instructed to be for gotten. Moreover, the efficiency of sleep in differentially responding to cued remembering and forgetting correlated with fast sleep spindles over left parietal cortex. Furthermore, source analysis associated with these spindles identified a network loop of current density between parietal, medial-temporal, and prefrontal memory networks that may support selective offline memory processing. More generally, the concept of sleep differentially modulating memory based on prior cue instructions may have implications clinically, where the capacity for selective retention of certain information, while forgoing maintenance of unwanted experiences, represents a desirable target.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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References

Achermann P, Borbély AA. 1998. Coherence analysis of the human sleep electroencephalogram. Neuroscience. 85:1195–1208.

Anderer P, Klösch G, Gruber G, Trenker E, Pascual-Marqui RD, Zeitlhofer J, Barbanoj MJ, Rappelsberger P, Saletu B. 2001. Low-resolution brain electromagnetic tomography revealed simultaneously active frontal and parietal sleep spindle sources in the human cortex. Neuroscience. 103:581–592.

Anderson MC. 2003. Rethinking interference theory: executive control and the mechanisms of forgetting. J Mem Lang. 49:415–445.

Anderson MC, Green C. 2001. Suppressing unwanted memories by executive control. Nature. 410:366–369.
Anderson MC, Ochsner KN, Kuhl B, Cooper J, Robertson E, Gabrieli SW, Glover GH, Gabrieli JD. 2004. Neural systems underlying the suppression of unwanted memories. Science. 303:232–235.
Backhaus J, Hoeckesfeld R, Born J, Hohagen F, Junghanns K. 2008. Immediate as well as delayed post learning sleep but not wakefulness enhances declarative memory consolidation in children. Neurobiol Learn Mem. 89:76–80.
Baran B, Wilson J, Spencer RM. 2010. REM-dependent repair of competitive memory suppression. Exp Brain Res. 203:471–477.
Bela C, Monika B, Marton T, Istvan K. 2007. Valproate selectively reduces EEG activity in anterior parts of the cortex in patients with idiopathic generalized epilepsy. A low resolution electromagnetic tomography (LORETA) study. Epilepsy Res. 75:186–191.
Bjork RA. 1998. Intentional forgetting in perspective: comments, conjectures, and some directed remembering. In: Golding JM, MacLeod CM, editors. Intentional forgetting: interdisciplinary approaches. Hillsdale (NJ): Erlbaum. p. 453–481.
Block R. 1971. Effects of instructions to forget short-term memory. J Exp Psychol. 89:9.
Clemens B, Bank J, Piros P, Bessenyei M, Veto S, Toth M, Kondakor I. 2008. Three-dimensional localization of abnormal EEG activity in migraine: a low resolution electromagnetic tomography (LORETA) study of migraine patients in the pain-free interval. Brain Topogr. 21:36–42.
Clemens B, Piros P, Bessenyei M, Varga E, Puskas S, Fekete I. 2009. The electrophysiological "delayed effect" of focal interictal epileptiform discharges. A low resolution electromagnetic tomography (LORETA) study. Epilepsy Res. 85:270–278.
Clemens Z, Fabo D, Halasz P. 2005. Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience. 132:529–535.
Clemens Z, Fabó D, Halász P. 2006. Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. Neurosci Lett. 403:52–56.
Clemens Z, Molle M, Eross L, Barsi P, Halasz P, Born J. 2007. Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. Brain. 130:2868–2878.
Crick F, Mitchison G. 1983. The function of dream sleep. Nature. 304:111–114.
Diekelmann S, Born J. 2010. The memory function of sleep. Nat Rev Neurosci. 11:114–126.
Ekstrand BR. 1972. To sleep, perchance to dream (about why we forget). In: Duncan CP, Sechrest L, Melton AW, editors. Human memory: Festschrift for Benton J. Underwood. New York (NY): Appleton-Century-Crofts. p. 59–82.
Ellenbogen J, Hu P, Payne J, Titone D, Walker M. 2007. Human relational memory requires time and sleep. Proc Natl Acad Sci U S A. 104:7723–7728.
Ellenbogen J, Hulbert J, Jiang Y, Stickgold R. 2009. The sleeping brain's influence on verbal memory: boosting resistance to interference. PLoS One. 4:e4117.
Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL. 2006. Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. Curr Biol. 16:1290–1294.
Eschenko O, Molle M, Born J, Sara S. 2006. Elevated sleep spindle density after learning or after retrieval in rats. J Neurosci. 26:12914–12920.
Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, Watson A, Bria P, Tononi G. 2007. Reduced sleep spindle activity in schizophrenia patients. Am J Psychiatry. 164:483–492.
Fischer S, Diekelmann S, Born J. 2010. Sleep's role in the processing of unwanted memories. J Sleep Res. doi: 10.1111/j.1365-2869.2010.00881.x.
Fogel S, Smith C. 2006. Learning-dependent changes in sleep spindles and stage 2 sleep. J Sleep Res. 15:250–255.
Fogel SM, Smith CT, Beninger RJ. 2009. Evidence for 2-stage models of sleep and memory: learning-dependent changes in spindles and theta in rats. Brain Res Bull. 79:445–451.
Freud S. 1913. The interpretation of dreams. London: G. Allen & Company, ltd.
Gais S, Albouy G, Boly M, Dang-Vu TT, Darsaud A, Desseilles M, Rauchs G, Schabus M, Sterpenich V, Vandewalle G, et al. 2007. Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci U S A. 104:18778–18783.
Gais S, Lucas B, Born J. 2006. Sleep after learning aids memory recall. Learn Mem. 13:259–262.
Gais S, Molle M, Helms K, Born J. 2002. Learning-dependent increases in sleep spindle density. J Neurosci. 22:6830–6834.
Gumenyuk V, Roth T, Moran JE, Jefferson C, Bowyer SM, Tepley N, Drake CL. 2009. Cortical locations of maximal spindle activity: magnetoencephalography (MEG) study. J Sleep Res. 18:245–253.
Hauswald A, Schulz H, Iordanov T, Kissler J. 2010. ERP dynamics underlying successful directed forgetting of neutral but not negative pictures. Soc Cogn Affect Neurosci. doi: 10.1093/scan/nsq061.
Holmes CJ, Hoge R, Collins L, Woods R, Toga AW, Evans AC. 1998. Enhancement of MR images using registration for signal averaging. J Comput Assist Tomogr. 22:324–333.
Hornberger M, Rugg MD, Henson RN. 2006. ERP correlates of retrieval orientation: direct versus indirect memory tasks. Brain Res. 1071:124–136.
Hsieh LT, Hung DL, Tzeng OJ, Lee JR, Cheng SK. 2009. An event-related potential investigation of the processing of remember/forget cues and item encoding in item-method directed forgetting. Brain Res. 1250:190–201.
Hu P, Stylos-Allan M, Walker MP. 2006. Sleep facilitates consolidation of emotional declarative memory. Psychol Sci. 17:891–898.
Huber R, Ghilardi MF, Massimini M, Tononi G. 2004. Local sleep and learning. Nature. 430:78–81.
Isotani T, Lehmann D, Pascual-Marqui RD, Kochi K, Wackermann J, Saito N, Yagyu T, Kinoshita T, Sasada K. 2001. EEG source localization and global dimensional complexity in high- and low-hypnotizable subjects: a pilot study. Neuropsychobiology. 44:192–198.
Jasper HH. 1958. The ten-twenty electrode system of the International Federation. Electroencephalogr Clin Neurophysiol Suppl. 10:367–380.
Knoblauch V, Martens WL, Wirz-Justice A, Cajochen C. 2003. Human sleep spindle characteristics after sleep deprivation. Clin Neurophysiol. 114:2258–2267.
Kuhl BA, Dudukovic NM, Kahn I, Wagner AD. 2007. Decreased demands on cognitive control reveal the neural processing benefits of forgetting. Nat Neurosci. 10:908–914.
Laarne PH, Tenhunen-Eskelinen ML, Hyttinen JK, Eskola HJ. 2000. Effect of EEG electrode density on dipole localization accuracy using two realistically shaped skull resistivity models. Brain Topogr. 12:249–254.
Lee YS, Lee HM, Tsai SH. 2007. Effects of post-cue interval on intentional forgetting. Br J Psychol. 98:257–272.
Levy BJ, Anderson MC. 2002. Inhibitory processes and the control of memory retrieval. Trends Cogn Sci. 6:299–305.
Levy BJ, Anderson MC. 2008. Individual differences in the suppression of unwanted memories: the executive deficit hypothesis. Acta Psychol (Amst). 127:623–635.
MacLeod CM. 1975. Long-term recognition and recall following directed forgetting. J Exp Psychol Hum Learn Mem. 104:271–279.
MacLeod CM. 1999. The item and list methods of directed forgetting: test differences and the role of demand characteristics. Psychon Bull Rev. 6:123–129.
Marshall L, Born J. 2007. The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci. 11:442–450.
Marshall L, Helgadottir H, Molle M, Born J. 2006. Boosting slow oscillations during sleep potentiates memory. Nature. 444:610–613.
Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, et al. 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos Trans R Soc Lond B Biol Sci. 356:1293–1322.
Milner CE, Fogel SM, Cote KA. 2006. Habitual napping moderates motor performance improvements following a short daytime nap. Biol Psychol. 73:141–156.

Molle M, Marshall L, Gais S, Born J. 2002. Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. J Neurosci. 22:10941–10947.
Morin A, Doyon J, Dostie V, Barakat M, Hadj Tahar A, Korman M, Benali H, Karni A, Ungerleider LG, Carrier J. 2008. Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. Sleep. 31:1149–1156.
Mulert C, Jager L, Schmitt R, Bussfeld P, Pogarell O, Moller HJ, Juckel G, Hegerl U. 2004. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage. 22:83–94.
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.
Nishida M, Walker M. 2007. Daytime naps, motor memory consolidation and regionally specific sleep spindles. PLoS One. 2:e341.
Nowicka A, Marchewka A, Jednoróg K, Tacikowski P, Brechmann A. 2011. Forgetting of emotional information is hard: an fMRI study of directed forgetting. Cereb Cortex. 21:539–549.
Olbrich S, Mulert C, Karch S, Trenner M, Leicht G. 2009. EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement. Neuroimage. 45:319–332.
Pascual-Marqui RD. 2002. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol. 24(Suppl D):5–12.
Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MC, Hell D, Koukkou M. 1999. Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Res. 90:169–179.
Payne JD, Kensinger EA. 2010. Sleep leads to changes in the emotional memory trace: evidence from fMRI. J Cogn Neurosci. doi:10.1162/jocn.2010.21526.
Payne JD, Stickgold R, Swanberg K, Kensinger EA. 2008. Sleep preferentially enhances memory for emotional components of scenes. Psychol Sci. 19:781–788.
Ponomarev VA, Gurskaia OE, Kropotov Iu D, Artiushkova LV, Muller A. 2010. The comparison of clustering methods of EEG independent components in healthy subjects and patients with post concussion syndrome after traumatic brain injury. Fiziol Cheloveka. 36:5–14.
Racsmany M, Conway MA, Demeter G. 2010. Consolidation of episodic memories during sleep: long-term effects of retrieval practice. Psychol Sci. 21:80–85.
Rechtschaffen A, Kales A. 1968. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles (CA): US Government Printing Office, US Public Health Service.
Ryynanen OR, Hyttinen JA, Malmivuo JA. 2006. Effect of measurement noise and electrode density on the spatial resolution of cortical potential distribution with different resistivity values for the skull. IEEE Trans Biomed Eng. 53:1851–1858.
Schabus M, Dang-Vu TT, Albouy G, Balteau E, Boly M, Carrier J, Darsaud A, Degueldre C, Desseilles M, Gais S, et al. 2007. Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A. 104:13164–13169.
Schabus M, Gruber G, Parapatics S, Sauter C, Klosch G, Anderer P, Klimesch W, Saletu B, Zeitlhofer J. 2004. Sleep spindles and their significance for declarative memory consolidation. Sleep. 27:1479–1485.
Schabus M, Hoedlmoser K, Pecherstorfer T, Anderer P, Gruber G, Parapatics S, Sauter C, Kloesch G, Klimesch W, Saletu B, et al. 2008. Interindividual sleep spindle differences and their relation to learning-related enhancements. Brain Res. 1191:127–135.
Schmidt C, Peigneux P, Muto V, Schenkel M, Knoblauch V, Munch M, de Quervain DJ, Wirz-Justice A, Cajochen C. 2006. Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. J Neurosci. 26:8976–8982.
Shimamura AP. Episodic Retrieval and the Cortical Binding of Relational Activity. Cognitive, Affective, and Behavioral Neuroscience. In press.
Snodgrass JG, Corwin J. 1988. Pragmatics of measuring recognition memory: applications to dementia and amnesia. J Exp Psychol Gen. 117:34–50.
Tamaki M, Matsuoka T, Nittono H, Hori T. 2008. Fast sleep spindle (13–15 hz) activity correlates with sleep-dependent improvement in visuomotor performance. Sleep. 31:204–211.
Tislerova B, Brunovsky M, Horacek J, Novak T, Kopecek M, Mohr P, Krajca V. 2008. LORETA functional imaging in antipsychotic-naive and olanzapine-, clozapine- and risperidone-treated patients with schizophrenia. Neuropsychobiology. 58:1–10.
Tucker M, Fishbein W. 2008. Enhancement of declarative memory performance following a daytime nap is contingent on strength of initial task acquisition. Sleep. 31:197–203.
Uncapher MR, Rugg MD. 2008. Fractionation of the component processes underlying successful episodic encoding: a combined fMRI and divided-attention study. J Cogn Neurosci. 20:240–254.
Uncapher MR, Wagner AD. 2009. Posterior parietal cortex and episodic encoding: insights from fMRI subsequent memory effects and dual-attention theory. Neurobiol Learn Mem. 91:139–154.
Veiga H, Deslandes A, Cagy M, Fiszman A, Piedade RA, Ribeiro P. 2003. Neurocortical electrical activity tomography in chronic schizophrenics. Arq Neuropsiquiatr. 61:712–717.
Ventouras EM, Alevizos I, Ktonas PY, Tsekou H, Paparrigopoulos T, Kalatzis I, Soldatos CR, Nikiforidis G. 2007. Independent components of sleep spindles. Conf Proc IEEE Eng Med Biol Soc. 2007:4002–4005.
Vilberg KL, Rugg MD. 2008. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. Neuropsychologia. 46:1787–1799.
Vitacco D, Brandeis D, Pascual-Marqui R, Martin E. 2002. Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. Hum Brain Mapp. 17:4–12.
Wagner U, Gais S, Born J. 2001. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem. 8:112–119.
Wagner U, Hallschmid M, Rasch B, Born J. 2006. Brief sleep after learning keeps emotional memories alive for years. Biol Psychiatry. 60:788–790.
Walker MP. 2009. The role of sleep in cognition and emotion. Ann N Y Acad Sci. 1156:168–197.
Wylie GR, Foxe JJ, Taylor TL. 2008. Forgetting as an active process: an FMRI investigation of item-method-directed forgetting. Cereb Cortex. 18:670–682.
Yoo S, Hu P, Gujar N, Jolesz F, Walker M. 2007. A deficit in the ability to form new human memories without sleep. Nat Neurosci. 10:385–392.
Zumsteg D, Lozano AM, Wennberg RA. 2006. Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. Clin Neurophysiol. 117:1602–1609.