The Role of Sleep in Cognition and Emotion

Matthew P. Walker

Sleep and Neuroimaging Laboratory, Department of Psychology & Helen Wills Neuroscience Institute, University of California, Berkeley, California

As critical as waking brain function is to cognition, an extensive literature now indicates that sleep supports equally important, different yet complementary operations. This review will consider recent and emerging findings implicating sleep and specific sleep-stage physiologies in the modulation, regulation, and even preparation of cognitive and emotional brain processes. First, evidence for the role of sleep in memory processing will be discussed, principally focusing on declarative memory. Second, at a neural level several mechanistic models of sleep-dependent plasticity underlying these effects will be reviewed, with a synthesis of these features offered that may explain the ordered structure of sleep, and the orderly evolution of memory stages. Third, accumulating evidence for the role of sleep in associative memory processing will be discussed, suggesting that the long-term goal of sleep may not be the strengthening of individual memory items, but, instead, their abstracted assimilation into a schema of generalized knowledge. Fourth, the newly emerging benefit of sleep in regulating emotional brain reactivity will be considered. Finally, and building on this latter topic, a novel hypothesis and framework of sleep-dependent affective brain processing will be proposed, culminating in testable predictions and translational implications for mood disorders.

Key words: **sleep; learning; memory; encoding; consolidation; association; integration; plasticity; emotion; affect; non-rapid eye movement (NREM) sleep; rapid eye movement (NREM) sleep; offline; slow wave sleep (SWS), slow-wave activity (SWA), sleep spindles**

"If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made."

Allan Rechtschaffen
University of Chicago Sleep Laboratory
Smithsonian, November 1978

Introduction

A perplexing question continues to elude scientific judgment: "Why do we sleep?" In accepting the utility of evolution, as candidly stated by pioneering sleep researcher Allan Rechtschaffen, sleep is likely to support a fundamental need of the organism. Yet, despite the vast amount of time this state takes from our lives, we still lack any consensus function for sleep. In part, this is perhaps because sleep, like its counterpart wakefulness, may serve not one but many functions, for brain and body alike.

Centrally, sleep is a brain phenomenon, and over the past 20 years, an exciting revival has taken place within the neurosciences, one that focuses on the question of why we sleep, and specifically targeting the role of sleep in a number of cognitive and emotional processes. This review aims to provide a synthesis of these recent findings in humans, with the goal of extracting consistent themes across domains of brain function that appear to be regulated by sleep. Providing a mechanistic foundation on which to consider these findings, the first section of this chapter briefly summarizes the brain substrates of sleep: its neurochemistry, neurophysiology, and functional anatomy. The next

Address for correspondence: Matthew P. Walker, Sleep and Neuroimaging Laboratory, Department of Psychology & Helen Wills Neuroscience Institute, University of California, Berkeley, California 94720-1650, USA. Voice: 510-642-5292; fax: 510-642-5293. mpwalker@berkeley.edu

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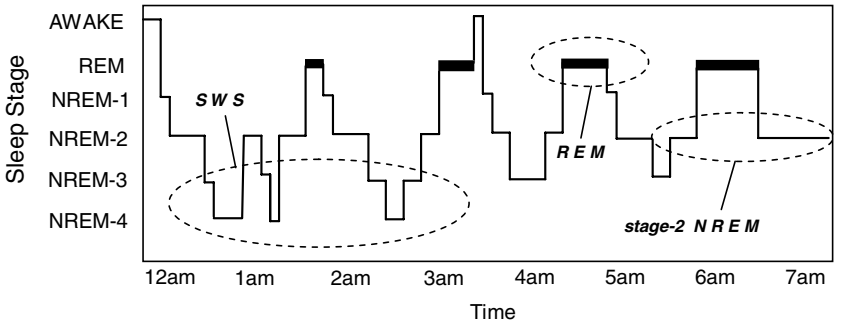

Figure 1. The human sleep cycle. Across the night, NREM and REM sleep cycle every 90 minutes in an ultradian manner, while the ratio of NREM to REM sleep shifts. During the first half of the night, NREM stages 3 and 4 NREM (SWS) dominate, while stage 2 NREM and REM sleep prevail in the latter half of the night. EEG patterns also differ significantly between sleep stages, with electrical oscillations such as slow delta waves developing in SWS, K-complexes and sleep spindles occurring during stage 2 NREM, and theta waves seen during REM.

section explores the role of sleep in memory and brain plasticity and also examines competing models of sleep-dependent learning. The third section addresses the role of sleep beyond memory consolidation, in processes of association, integration, and creativity. The final section discusses the more recent and emerging role for sleep in emotional and affective brain regulation.

Sleep Neurobiology

The sleep of mammalian species has been broadly classified into two distinct types: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, with NREM sleep being further divided in primates and cats into four substages (1–4) corresponding, in that order, to increasing depth of sleep (Rechtschaffen & Kales 1968). In humans, NREM and REM sleep alternate or "cycle" across the night in an ultradian pattern every 90 min (Fig. 1). Although this NREM–REM cycle length remains largely stable across the night, the ratio of NREM to REM within each 90-min cycle changes, so that early in the night stages 3 and 4 of NREM dominate, while stage 2 NREM and REM sleep prevail in the latter half of the night. Interestingly, the functional reasons for this organizing principal (deep NREM early in the night, stage 2 NREM and REM late in the night) remains unknown–another perplexing mystery of sleep.

As NREM sleep progresses, electroencephalographic (EEG) activity begins to slow in frequency. Throughout stage-2 NREM there is the presence of phasic electrical events including K-complexes (large electrical sharp waves in the EEG) and sleep spindles (short synchronized 10–16 Hz) EEG oscillations (Steriade & Amzica 1998). The deepest stages of NREM, stages 3 and 4, are often grouped together under the term "slow wave sleep" (SWS), reflecting the occurrence of low frequency waves (1–4 Hz and <1 Hz), which have themselves been termed "slow-wave activity" (SWA), representing an expression of underlying mass cortical synchrony (Amzica & Steriade 1995). During REM sleep, however, EEG waveforms once again change in their composition, associated with oscillatory activity in the theta band range (4–7 Hz), together with higher frequency synchronous activity in the 30–80 Hz ("gamma") range (Llinas & Ribary 1993; Steriade et al. 1996). Periodic bursts of REM also take place, a defining characteristic of REM sleep, associated with the occurrence of phasic endogenous waveforms expressed in, among other regions, the pons (P), lateral

geniculate nuclei of the thalamus (G), and the occipital cortex (O), and as such, have been termed "PGO waves" (Callaway et al. 1987).

As the brain passes through these sleep stages, it also undergoes dramatic alterations in neurochemistry. In NREM sleep subcortical cholinergic systems in the brain stem and forebrain become markedly less active (Hobson et al. 1975; Lydic & Baghdoyan 1988), while firing rates of serotonergic raphé neurons and noradrenergic locus coeruleus neurons are also reduced relative to waking levels (Aston-Jones & Bloom 1981; Shima et al. 1986). During REM sleep both these aminergic populations are strongly inhibited, while cholinergic systems become as/more active compared to what they are during wake (Kametani & Kawamura 1990; Marrosu et al. 1995), resulting in a brain state largely devoid of aminergic modulation and dominated by acetylcholine.

At a whole-brain systems level, neuroimaging techniques have revealed complex and dramatically different patterns of functional anatomy associated with NREM and REM sleep (for review, see Nofzinger 2005). During NREM SWS, rostral brain-stem regions, thalamic nuclei, basal ganglia, hypothalamus, prefrontal cortex, cingulate corticies, and medial regions of the temporal lobe all appear to undergo reduced activity. However, during REM sleep significant elevations in activity have been reported in the pontine tegmentum, thalamic nuclei, occipital cortex, mediobasal prefrontal lobes, and associated limbic groups, including the amygdala, hippocampus, and anterior cingulate cortex. In contrast, the dorso—lateral prefrontal cortex, posterior cingulate, and parietal cortex appear least active in REM sleep.

Although this summary only begins to describe the range of neural processes that are affected by the brain's daily transit through sleep states, it clearly demonstrates that sleep itself cannot be treated as a homogeneous entity, one which may or may not alter cognitive and emotional processes. Instead, this constellation of sleep stages offers a range of distinct neurobiological mechanisms that can potentially support the modulation, regulation, and preparation of numerous brain functions.

Memory Processing and Brain Plasticity

In considering the role of sleep in memory processing, it is pertinent one appreciate that memories evolve (Walker & Stickgold 2006). Specifically, memories pass through discrete stages in their "life span." The conception of a memory begins with the process of encoding, resulting in a stored representation of an experience within the brain (Paller & Wagner 2002). However, it is now understood that a vast number of postencoding memory processes can take place (Stickgold & Walker 2005a). For memories to persist over the longer time course of minutes to years, an offline, nonconscious operation of event consolidation appears to be necessary, affording memories greater resistance to decay (a process of stabilization), or even improved recollection (a process of enhancement) (Robertson et al. 2004; Walker 2005). Sleep has been implicated in both the encoding and consolidation of memory.

Sleep and Memory Encoding

One of the earliest human studies to report the effects of sleep and sleep deprivation on declarative memory encoding was by Morris et al. (1960), indicating that "temporal memory" (memory involving when events occur) was significantly disrupted by a night of pretraining sleep loss. These findings have been revisited in a more rigorous study by Harrison and Horne (2000), again using the temporal memory paradigm. Significant impairments in retention were evident in a group of subjects deprived of sleep for 36 h, the subjects scoring significantly lower than controls, even in a subgroup that received caffeine to overcome nonspecific effects of lower alertness. Furthermore, the sleep-deprived subjects displayed significantly worse insight into their

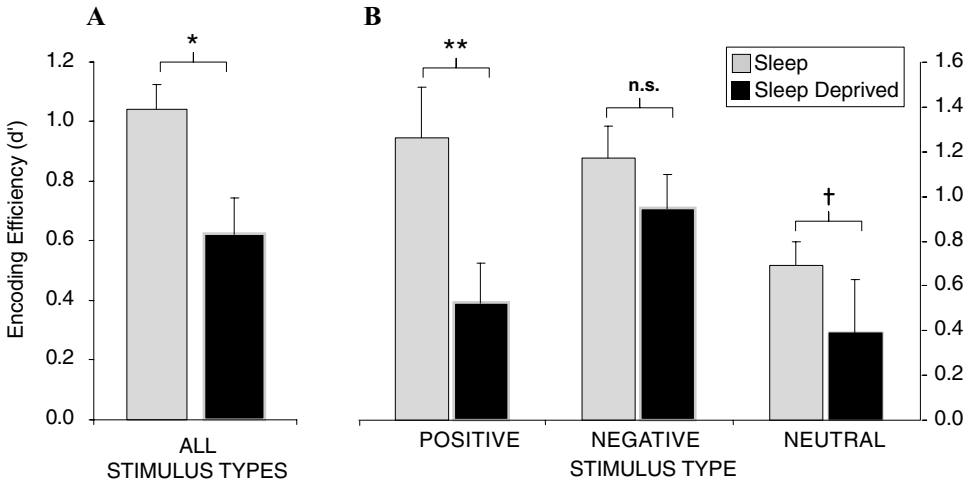

Figure 2. Sleep deprivation and encoding of emotional and nonemotional declarative memory. Effects of 38 h of total sleep deprivation on encoding of human declarative memory (**A**) when combined across all emotional and nonemotional categories; (**B**) When separated by emotional (positive and negative valence) and nonemotional (neutral valance) categories. $^{\dagger}P < 0.08$, $^{*}P < 0.05$, $^{**}P < 0.01$, error bars represent SEM.

memory-encoding performance, resulting in lower predictive ability of performance.

Pioneering work by Drummond and colleagues examined the neural basis of similar memory impairments using functional MRI (fMRI), investigating the effects of 35 h of total sleep deprivation on verbal learning (Drummond et al. 2000). In those who were sleep deprived, regions of the medial temporal lobe were significantly less active during learning, relative to a control group that had slept, while the prefrontal cortex actually expressed greater activation. Most interesting, the parietal lobes, which were not activated in the control group during learning, were significantly active in the deprivation group. Such findings suggest that inadequate sleep prior to learning (at least following one night) produces bidirectional changes in episodic encoding activity, involving the inability of the medial temporal lobe to engage normally during learning, combined with potential compensation attempts by prefrontal regions, which in turn may facilitate recruitment of parietal lobe function (Drummond & Brown 2001).

The impact of sleep deprivation on memory formation may be especially pronounced for emotional material. We have investigated the impact of sleep deprivation on the encoding of emotionally negative, positive, and neutral words (Walker, unpublished results). When combined across all stimulus types, subjects in the sleep-deprived condition exhibited a striking 40% reduction in the ability to form new human memories under conditions of sleep deprivation (Fig. 2A). However, when these data were separated into the three affective categories (negative, positive, or neutral), the magnitude of encoding impairment differed (Fig. 2B). In those that had slept, both positive and negative stimuli were associated with superior retention levels relative to the neutral condition, consistent with the notion that emotion facilitates memory encoding (Phelps 2004). However, there was severe disruption of encoding and hence later retention for neutral and especially positive emotional memory in the sleep-deprived group. In contrast, a relative resistance of negative emotional memory was observed in the deprivation group. These data suggest that, while the effects of sleep deprivation are directionally consistent across memory subcategories, the most profound impact is on the encoding of positive emotional stimuli, and

to a lesser degree, emotionally neutral stimuli. In contrast, the encoding of negative memory appears to be more resistant to the effects of prior sleep loss, at least following one night.

Intriguingly, these data may offer novel insights into affective mood disorders that express co-occurring sleep abnormalities (Benca et al. 1992; Buysse 2004). Indeed, if one compares the profiles of memory encoding in Fig. 2B, it is clear that those who slept encoded and retained a balanced mix of both positive and negative memories. In contrast, those who did not sleep displayed a skewed relative distribution of encoding, resulting in an overriding dominance of negative memories, combined with a retention deficit of positive and neutral memories. This selective alteration in memory encoding may provide an experimental explanation for the higher incidence of depression in populations that suffer sleep disruption (Shaffery et al. 2003; Buysse 2004), which, due to these specific deficits, may impose a negative remembering bias, despite the fact that these subjects experienced equally positive- and negative-reinforcing event histories.

The impact of sleep deprivation on the neural dynamics associated with declarative memory encoding has recently been examined using event-related fMRI (Yoo et al. 2007a). In addition to performance impairments under condition of sleep deprivation, and relative to a control group that slept, a highly significant and selective deficit was identified in bilateral regions of the hippocampus—a structure known to be critical for learning new episodic information (Eichenbaum 2004) (Fig. 3A). While these findings indicated that, at a group level, sleep deprivation markedly impairs hippocampal memory function, when examined within each group separately, the success of encoding, from low to high, was further associated with activity in different regions of the prefrontal lobe. In those that slept prior to learning, the right dorsal/middle lateral prefrontal cortex showed a strong positive relationship with the proficiency of memory encoding. In contrast, a region in the right inferior frontal gyrus (IFG) displayed a significant positive, potentially compensatory, relationship with memory performance in those who were sleep deprived (Figs. 3B & C).

Taken together, this collection of findings indicate the critical need for sleep-before-learning in the preparation of key neural structures for efficient next-day learning. Without adequate sleep, hippocampal function becomes markedly disrupted, resulting in a decreased ability for recording new experiences, the extent of which appears to be further governed by alterations in prefrontal encoding dynamics.

Sleep and Memory Consolidation

Using a variety of behavioral paradigms, evidence for the role of sleep in memory consolidation has now been reported across a diverse range of phylogeny. Perhaps the earliest reference to the beneficial impact of sleep on memory is by the Roman rhetorician Quintilian, who stated:

> *[it] is a curious fact, of which the reason is not obvious, that the interval of a single night will greatly increase the strength of the memory. . . . Whatever the cause, things which could not be recalled on the spot are easily coordinated the next day, and time itself, which is generally accounted one of the causes of forgetfulness, actually serves to strengthen the memory.* (Hammond 2004).

In the early eighteenth and twentieth centuries respectively, David Hartley (Hartley 1801) and Jenkins and Dallenback (Jenkins & Dallenbach 1924) indicated that the strength of a memory may be better preserved by periods of sleep than it is by equivalent periods of time awake. Following the discovery of discrete sleep stages (Aserinsky & Kleitman 1953), research investigating the influence of sleep on memory has become gradually more complex at both a behavioral and mechanistic level. A robust and consistent literature has demonstrated the need for sleep after learning in the subsequent consolidation and enhancement of procedural memories; the evidence for which has recently been reviewed elsewhere (Walker & Stickgold

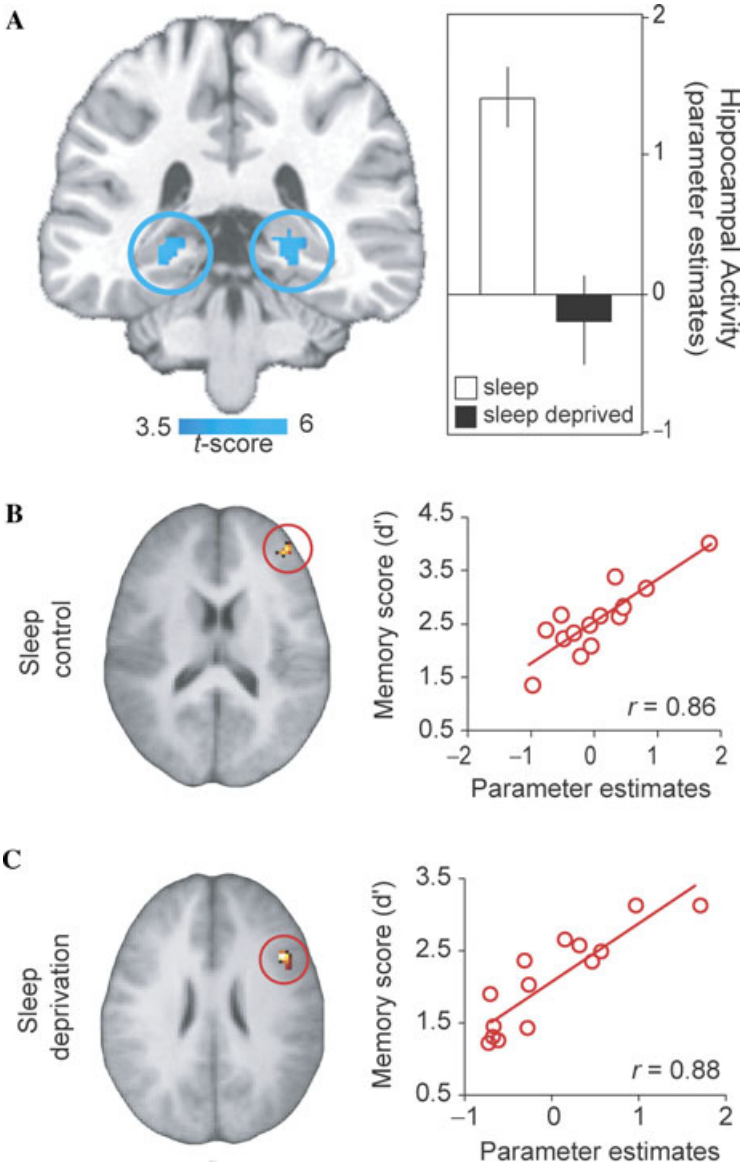

Figure 3. Neural basis of sleep-deprivation-induced encoding deficits. (**A**) Regions of decreased encoding activation in the sleep deprivation group relative to the sleep control group in bilateral posterior hippocampus, together with a histogram of parameter estimates (effect size) of averaged hippocampal activity in each group. Effects are significant at $P < 0.001$; >5 contiguous voxels. (**B**) correlation analysis with memory performance showing regions of significant association between encoding-related activation and memory performance (d') across subjects in the sleep control group (peak – right Middle/dorso-lateral prefrontal cortex), and (**C**) in the sleep deprivation group (peak – right Inferior frontal gyrus). Modified from Yoo et al. 2007a.

2006). Early work focusing on the role for sleep in declarative memory processing was somewhat less consistent, but more recent findings have now begun to reveal a robust beneficial effect of sleep on the consolidation of declarative memory—our focus here (Smith 2001; Ellenbogen et al. 2006b; Walker & Stickgold 2006; Marshall & Born 2007).

Several reports by Born and his colleagues showed offline improvement on a word-pair association task following sleep, an improvement attributed to early night sleep, rich in SWS (Plihal & Born 1997, 1999; Gais & Born 2004). More recently, the same group demonstrated that, in addition to classically defined slow delta waves (0.5–4 Hz), the very slow cortical oscillation (<1 Hz) appears to be important for the consolidation of declarative memories. Following subject learning of a word-pair list, a technique called "direct current stimulation" was used to induce slow oscillation-like field potentials in the prefrontal cortex (in this case, at 0.75 Hz) during early night SWS (Marshall et al. 2006). Direct current stimulation not only increased the amount of slow oscillations during the simulation period (and for some time after), but also enhanced next-day word-pair retention, suggesting a critical role for SWS neurophysiology in the offline consolidation of episodic facts.

Rather than simply testing memory recall, Ellenbogen and colleagues have since revealed the extent of sleep's ability to protect declarative memories using experimentally induced learning disruption (Ellenbogen et al. 2006a). Taking advantage of a classic interference technique called the A-B–A-C paradigm, subjects first learned unrelated word-paired associates, designated as list A-B (e.g., leaf-wheel, etc.). After sleep at night, or wakefulness during the day, half of the subjects in each group learned a new, interfering list containing a new associate paired with the first word, designated as list A-C (e.g., leaf-nail, etc.), before being tested on the original A-B list (e.g., leaf-wheel, etc.). In the groups that did not experience the interfering challenge—that is, those who were simply being trained and then tested on list A-B—sleep provided a modest benefit to memory recollection (Fig. 4A). However, when testing the groups that were exposed to interfering list learning (list A-C) prior to recalling the original list (list A-B), a large and significant protective benefit was seen in those that slept (Fig. 4B). Thus, memories tested after a night of sleep were significantly more resistant to interference, whereas, across a waking day, memories were far more susceptible to this antagonistic learning challenge. Yet it was only by using an interfering challenge, that of the A-C list, that the true benefit of sleep's protection of memory was revealed, a benefit that would not necessarily have been evident in a standard study—test memory paradigm.

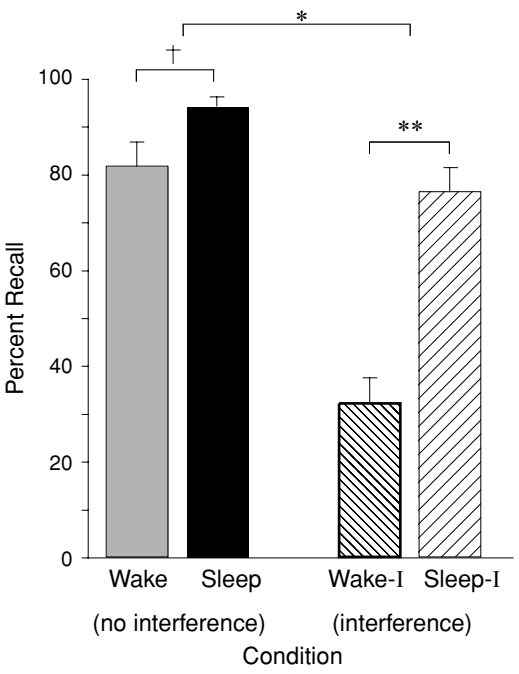

Figure 4. Impact of sleep on the consolidation and stabilization of declarative memory. Percent correct recall for B words from the original A-B pair after a 12-h retention interval of either wake or sleep following no interference or interference learning (list A-C). $^{\dagger}P < 0.10$, $^{*}P < 0.05$, $^{**}P < 0.001$; error bars indicate SEM. Modified from Ellenbogen 2006a.

One mechanism proposed as underlying these effects on hippocampal-dependent learning tasks (see next section, also) is the reactivation of memory representations at night. A considerable number of reports have investigated the firing patterns of large networks of individual neurons across the wake—sleep cycle in animals. The signature firing patterns of these hippocampal and cortical networks, expressed during waking performance of spatial tasks and

novel experiences, appear to be "replayed" during subsequent SWS (and in some studies, also REM) (Wilson & McNaughton 1994; Skaggs & McNaughton 1996; Dave et al. 1998; Dave & Margoliash 2000; Poe et al. 2000; Louie & Wilson 2001; Ribeiro et al. 2004; Jones & Wilson 2005; Ji & Wilson 2007). Homologous evidence has been reported in the human brain using a virtual maze task in combination with positron emission tomography (PET) scanning (Peigneux et al. 2004). Daytime learning was initially associated with hippocampal activity. Then, during posttraining sleep, there was a reemergence of hippocampal activation, specifically during SWS. Most compelling, however, was that the amount of SWS reactivation in the hippocampus was proportional to the amount of next-day task improvement, suggesting that this reactivation is associated with offline memory improvement.

Building on the framework that memories, particularly those involving the hippocampus, are reactivated at night during sleep, Rasch et al. have taken advantage of the classical psychology effect of cue-dependent recall, and translated it into a sleep-dependent consolidation paradigm (Rasch et al. 2007). It is well known that memory can be strongly modulated by smell (Cann & Ross 1989); most of us have associated the smell of a certain perfume or cologne with a particular person, and when we encounter that same perfume again, it often results in the powerful cued recall of memories of that particular person. In this study, however, following learning of a spatial memory task that was paired with the smell of rose, the odor was not re-presented at retrieval, but instead during subsequent SWS that night—a time when consolidation was presumed to be occurring. Relative to a control condition where the odor was not presented again during SWS, the reperfusion of the rose scent at night resulted in significantly improved recall the following day. Moreover, the re-presentation of the odor resulted in greater (re)activation of the hippocampus during SWS. These findings support the role of SWS in the consolidation of individual declarative memories, and may indicate an active reprocessing of hippocampal-bound information during SWS.

Models of Sleep-Dependent Memory Processing

Elucidating the neural mechanisms that control and promote sleep-dependent human memory consolidation remains an active topic of research, and debate (Miller 2007). It is perhaps unlikely that multiple different memory systems, involving diverse cortical and/or subcortical networks, require the same underlying neural mechanisms for their modulation. Even if they do, it is not clear that this process would rely on just one type of sleep-stage physiology (Giuditta et al. 1995). At present, two intriguing models of sleep-dependent plasticity, relevant to declarative memory, have been offered to account for the overnight facilitation of recall, which build on different aspects of neural activity during sleep: (1) hippocampal–neocortical dialogue, (2) synaptic homeostasis hypothesis.

Hippocampal–Neocortical Dialogue

There is considerable agreement that structures within the medial temporal lobe (MTL), most notably the hippocampal complex, are crucial for the formation and retrieval of new declarative memories. These structures are believed to guide the reinstatement of recently formed memories by binding together patterns of cortical activation that were present at the time of initial learning. A classical model of declarative memory consolidation suggests that information initially requires MTL binding, but over time, and by way of slow offline processes, it is eventually integrated into neocortical circuits (Fig. 5). Neocortical structures thus become the eventual storage site for consolidated episodic memories through cross-cortical connections, and, as a consequence, the MTL is not necessary for these memories' retrieval. Therefore, the classical model of memory consolidation holds that neocortical structures become increasing important for

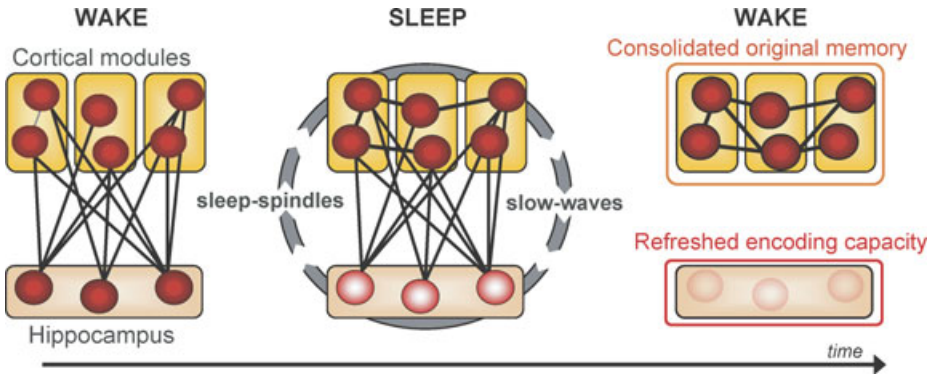

Figure 5. Model of sleep-dependent hippocampal-neocortical memory consolidation. At encoding the hippocampus rapidly integrates information within distributed cortical modules. Successive sleep-dependent reactivation of this hippocampal–cortical network leads to progressive strengthening of cortico-cortical connections, which over time, allow these memories to become independent of the hippocampus and gradually integrated with preexisting cortical memories. Modified from Frankland & Bontempi 2005.

the retention and retrieval of successfully consolidated episodic memories, while the corresponding contribution of the hippocampus progressively decreases (Squire 1992; McClelland et al. 1995; Squire & Zola 1996; Squire 2004). It should be noted, however, that controversy remains about the role of these MTL structures in the retrieval of declarative memories after the passage of time. This has led to the emergence of alternate consolidation models, most notably Nadel and Moscovitch's "multiple trace theory" (Nadel & Moscovitch 1997; Moscovitch & Nadel 1998), which posits that hippocampal involvement is always critical for the retrieval of episodic (but not semantic) memories, and that these memories remain permanently dependent on hippocampal−neocortical connections (for discussion beyond the scope of this review see Frankl & Bontempi 2005).

In addition to its role in binding distributed cortical memory components, Marr and, also, McClelland et al. suggested that the hippocampus plays a critical role in reactivating these networks, specifically during sleep (Marr 1970; McClelland et al. 1995). This process of reactivation, over multiple sleep cycles across a night and/or multiple occurrences of sleep over many nights, would gradually strengthen the initially weak connections between neocortical sites, thereby reinforcing them (Fig. 5). Eventually, this strengthening would allow the original information to be activated in the cortex, independent of the hippocampus. Buzsaki (1996) has since advanced on these ideas, proposing a model of consolidation that involves two stages or states of hippocampal activity, the first involving a mode of "recording" during wake, which shifts to a second stage, involving "playback" mode during NREM SWS, specifically during bursts of neural activity called "sharp-waves."

Interestingly, these models make two predictions about the impact of sleep on declarative memory. The first is that declarative memories from the day prior should be more resistant to interference the next day, due to the increased cortico−cortical connections formed during overnight consolidation (Fig. 5). It is precisely this behavioral effect that was reported in the study by Ellenbogen et al. (2006a) showing greater post-sleep resistance to interference, using the A-B–A-C paradigm. A second and far less considered benefit of this sleep-dependent dialogue is the encoding capacity of the hippocampus (Fig. 5). If the strengthening of cortico−cortical connections takes place during sleep, albeit iteratively, then blocking sleep after hippocampal

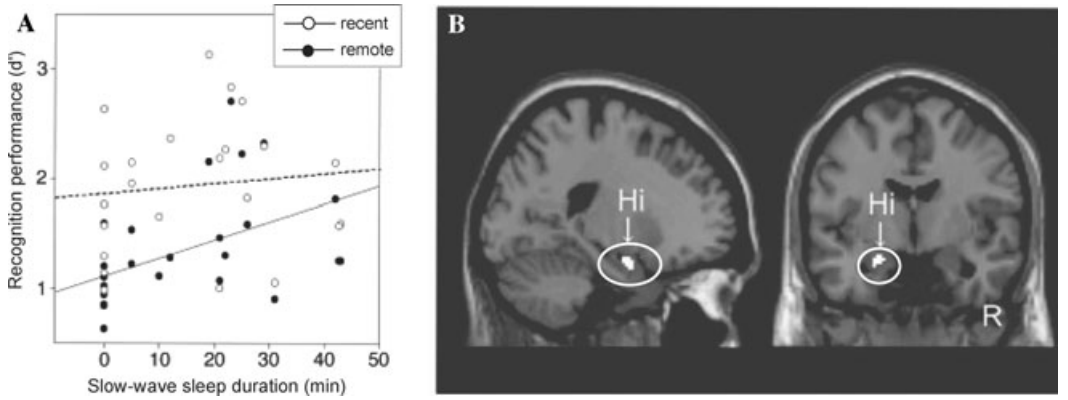

Figure 6. Enhancement of hippocampal declarative memory by daytime naps. (**A**) Correlation of recognition memory for recent and remote items related to individual slow-wave sleep durations. (**B**) Correlation between recognition memory activity and longer slow-wave sleep duration in the left hippocampus (Hi). Modified from Takashima et al. 2006.

learning should negate this offline transfer, preventing the development of independence from (or "refreshing" of) the hippocampus, and by doing so, decrease the capacity for new hippocampal learning the next day. This second premise appears to accurately explain the findings discussed in the section above on memory encoding (Yoo et al. 2007b), which describe a significant impairment of hippocampal encoding activity when sleep has not taken place (through deprivation) being associated with a decreased ability to form new episodic memories.

Two recent reports have provided further evidence in support of this sleep-dependent dialogue and neural transformation of declarative memory. In the first such report, Takashima and colleagues examined the benefit of daytime naps on episodic declarative memory consolidation (Takashima et al. 2006). In addition to a long-term evaluation of memory over 3 months, there was also a short-term evaluation of memory across the first day, which included an intervening nap period (90 min) between training and testing of the original studied ("remote") stimuli. Interestingly, the duration of NREM SWS during the intervening nap correlated positively with later-recognition memory performance (Fig. 6A), yet negatively with retrieval-related activity in the hippocampus (Fig. 6B). Furthermore, with increasing time following learning, there was progressively greater recall activity in medial prefrontal regions, and a continued dissipation of retrieval-related activity within the hippocampus. Advancing on these findings, Maquet and colleagues have since demonstrated that one night of posttraining sleep deprivation, even following recovery sleep, significantly impairs the normal modulation of hippocampal activity associated with episodic memory recollection (Gais et al. 2007). Furthermore, first-night sleep deprivation also prevented an increase in hippocampal connectivity with the medial prefrontal cortex, a development that was only observed in those that slept after learning.

While no one study has yet demonstrated that the neural signature of learning during the day is subsequently reactivated and driven by characteristics of SWS at night, and that the extent of these properties are consequently proportional to the degree of next-day recall and memory reorganization, collectively, they offer an empirical foundation on which to entertain this possibility.

Synaptic Homeostasis Hypothesis

In recent years an orthogonal theory of SWS and learning has emerged, one which postulates a role for sleep in regulating the synaptic connectivity of the brain—principally the

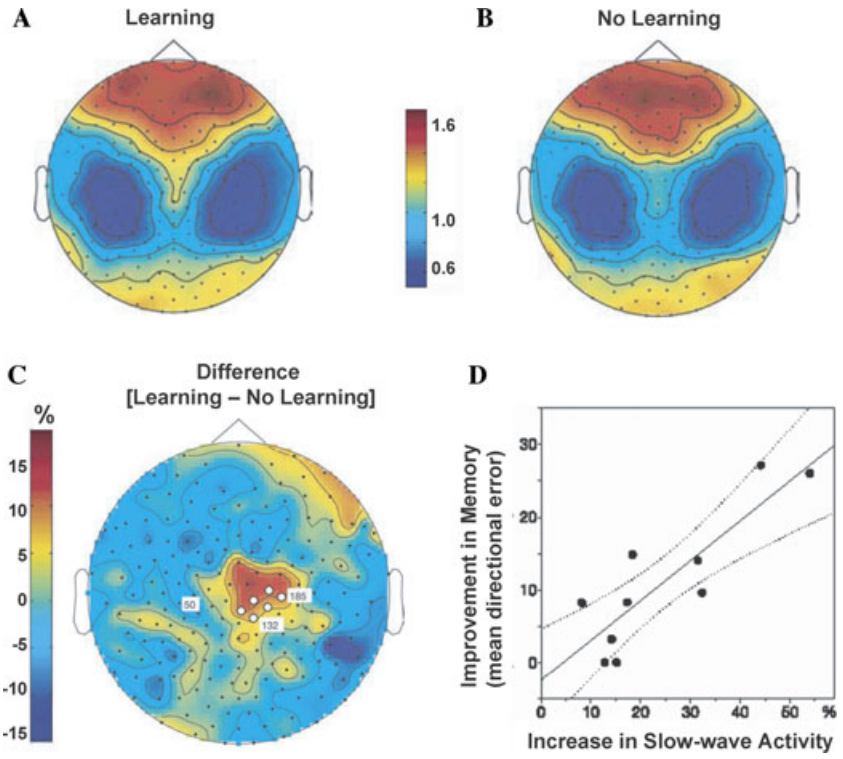

Figure 7. Slow-wave activity and motor-skill memory. Topographical high-density EEG maps of slow-wave activity (SWA) during NREM sleep following either (**A**) motor-skill learning or (**B**) a nonlearning control condition, and (**C**) the subtracted difference between SWA in the learning versus nonlearning condition, demonstrating a local homeostatic increase above the learning-related central-parietal brain region. (**D**) the correlation between the amount of over-night improvement on the task (measured the next day) and the extent of increase in SWA across subjects. Modified from Huber et al. 2004.

neocortex (Tononi & Cirelli 2003, 2006). Their model considers NREM SWS, and specifically the magnitude of slow-wave activity (SWA) of SWS, as a brain-state that promotes the decrease of synaptic connections, not an increase. Accordingly, plastic processes, such as learning and memory occurring during wakefulness, result in a net increase in synaptic strength in diffuse brain circuits. The role of SWS, therefore, and the slow oscillation in particular, is to selectively downscale or "depotentiate" synaptic strength back to baseline levels, preventing synaptic overpotentiation, which would result in saturated brain plasticity. In doing so, this rescaling would leave behind more efficient and refined memory representations the next day, affording improved recall.

A number of human studies by Huber, Tononi, and colleagues have provided evidence supporting their model. For example, it has been shown that learning of a motor-skill adaptation task during the day subsequently triggers locally specific increases in cortical SWA at night, the extent of which is proportional to both the amount of initial daytime learning and the degree of next-day improvement (Fig. 7) (Huber et al. 2004). Furthermore, experimentally impairing the amount of experience-dependent activity during the day (arm immobilization) produced the opposite effect—reduced amounts of SWA activity in associated cortical regions (Huber et al. 2006). These findings substantiate the concept of local sleep-dependent neural pruning by SWS,

the goal of which may be to regulate neural architecture at a highly specific anatomical level, mapping onto corresponding locations of the memory representation.

How can the two concepts of neural reactivation (such as increased fMRI activity during SWS; e.g., Rasch et al. 2007) and neural homeostasis (such as increased slow wave EEG activity; e.g., Huber et al. 2004) be interpreted at a neural synaptic level? It could be argued that both these reported changes reflect either an increased neural reactivation, or an increase in SWA associated with homeostasis and synaptic downscaling. Furthermore, both hypotheses, while distinctly different in a mechanistic sense, could offer complementary benefits at the network level in terms of signal-to-noise ratio (SNR) and may account for overnight memory improvements (Robertson, unpublished). Specifically, homeostatic synaptic downscaling could result in the removal of superfluous neural connections, resulting in improved SNR. However, neural reactivation and strengthening of experience-dependent circuits, done without removing redundant synaptic connects, may equally improve SNR. Therefore, both mechanisms, while different, could produce a similar outcome: enhanced fidelity of the memory representation. Presumably the combination of both would produce perhaps the most optimal and efficient memory trace, yet a careful delineation of these possibilities remains an important goal for future studies.

Interestingly, the homeostasis model would also predict that sleep deprivation, specifically the prevention of SWS, would also negate effective next-day new learning, due to overpotentiation of synaptic connections. Thus, any region that exhibits SWA and is involved in representing memory (e.g., hippocampus), would display a corresponding inability to code further information beyond a normal waking duration (~16 hr in humans). Such a premise may offer an alternative explanation to the marked hippocampal encoding deficits reported under conditions of sleep loss (Yoo et al. 2007b).

A Role for Sleep Spindles?

Independent of both these models, which consider the role of SWS in memory processing, a number of reports have also described an association between learning and the hallmark feature of stage-2 NREM: sleep spindles; short (~1 s) synchronous bursts of activity expressed in the EEG in the 10–16 Hz frequency range (Sejnowski & Destexhe 2000; Steriade 2001; Smith et al. 2004). For example, following learning of a motor-skill memory task, Nishida and Walker (2007) examined posttraining sleep spindles over the motor cortex, evaluating the difference in spindle activity in the learning hemisphere (since subjects perform the task with their left, nondominant, hand), relative to the nonlearning hemisphere (Fig. 8A). Remarkably, when sleep spindle power at electrode sites above the primary motor cortex of the nonlearning hemisphere (left) were subtracted from those in the learning hemisphere (right), representing the within-subject, between-hemisphere difference in spindle activity following learning, a strong predictive relationship to the amount of memory improvement emerged (Figs. 8B & C). Similarly, Fogel et al. (2001) reported increased spindle density after intensive training on a pursuit motor skill task, and Fogel and Smith (2006) reported increased spindle density after combined training on several simple procedural motor tasks.

Such findings indicate that the enhancement of specific memory representations is associated with electrophysiological events expressed at local, anatomically discrete locations of the brain. Contrasting with the proposed impact of SWS, the mechanistic benefit of sleep spindles may be related to their faster stimulating frequency; a range suggested to facilitate long-term potentiation (LTP; a foundational principal of synaptic strengthening in the brain) (Sejnowski & Destexhe 2000; Steriade 2001; Smith et al. 2004), and not synaptic depression. This increase in spindle activity may represent a local, endogenous trigger of intrinsic

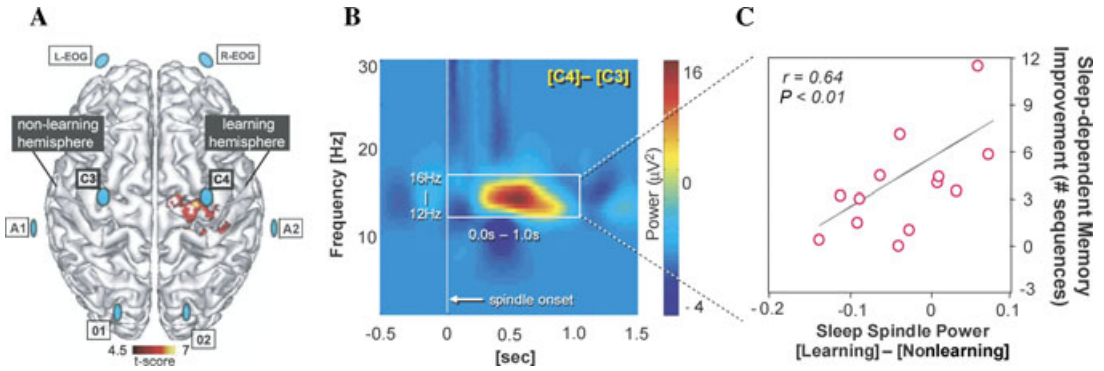

Figure 8. Sleep spindles and motor-skill memory plasticity. (**A**) Sleep-EEG array (blue discs) superimposed on the known overnight plastic reorganization of motor memory, including the right motor cortex (red). (**B**) Difference in sleep spindle activity (power) following task training in the Learning (relative to Non-learning) hemisphere, which (**C**) accurately predicts the amount of postsleep memory improvement across subjects. Modified from Nishida & Walker 2007.

synaptic plasticity, again corresponding topographically to the underlying memory representation (Nishida & Walker 2007).

Increases in posttraining spindle activity are not limited to procedural memory tasks. For example, Gais et al. have shown that there is significantly higher sleep spindle density in subjects that underwent a daytime episodic learning session (encoding of word-pair associates) compared to a control group that did not perform the learning session. Moreover, the spindle density was associated with the proficiency of memory recalled the next day in the learning group (Gais et al. 2002). These findings mirror previous observations by Meier-Koll et al. (1999), who reported a similar increase in spindles following learning of a hippocampally dependent maze task, and by Clemens et al. (2005), who have since identified a correlation between spindle density and overnight verbal memory retention (although not memory for faces). Intriguingly, the study by Huber et al. (2004), which implicates slow oscillatory activity associated with offline memory improvement, also describes similar, albeit near-significant, associations with activity in the sleep spindle frequency range. There may be a combinatory role for spindles in regulating plasticity, together with SWS.

Continued evidence suggests that sleep spindles can be separated into two subtypes: "slow" (11–13 Hz), which have a more anterior distribution, and "fast" (13–15 Hz), which have a more posterior localization (Werth et al. 1997; Zeitlhofer et al. 1997). With this division has also come an interest in understanding functional differences between each of these spindles subtypes. The relevance of this separation from a memory consolidation perspective is highlighted by a recent neuroimaging study demonstrating that fast spindles are associated with, among other regions, significantly greater activation within the hippocampal complex (Schabus et al. 2007). Investigating the role of hippocampal- and extra—hippocampal-dependent memory consolidation in relation to spindle subtypes will be an important challenge for future research.

Reconciling Models

None of these models necessarily is wrong. Instead, aspects of each may afford complementary and synergistically beneficial outcomes for memory. Clues to this possibility lie within the ordered structure of human sleep (Fig. 1), with NREM SWS dominating early in the night and stage-2 NREM and REM prevailing later in the night. When placed in this temporal framework a progression of events emerges that may be optimal for the neuroplastic modulation of memory representations. From a reactivation perspective, the

predominance of hippocampal–neocortical interaction would take place in the early SWS-rich phase of the night, leaving cortico–cortical connections on offer for later processing during stage-2 NREM and REM. Similarly, and even in coincidence, SWS may downscale cortical (and possibly subcortical) plasticity, and it may do so in a learning-dependent manner, again leaving only those representations (or aspects of these representations) which are strongest—including those strengthened by hippocampal–neocortical interplay—for processing during these latter periods of sleep, dominated by faster frequency oscillations.

This concept is analogous to the art of sculpture. During the day, through experience, substantial informational "clay" is acquired on the cortical pedestal; some of it relevant, some not. Once accumulated, the brain's next step is carving out and selecting the strongest and most salient memory representations ("statues")—a mechanism that SWS, occurring first and predominately early in the night, may be ideally suited for. Following such downscaling and/or dynamic selection of memory through translocation, the remaining cortical representations—the rough outline of the sculpted form—may finally be strengthened by faster frequency oscillations, including those of sleep spindles (and potentially PGO-waveburst during REM; (Datta 2000; Datta et al. 2008), more associated with the potentiation of synaptic connections, not their depotentiation. This final step is akin to polishing and improving the detailed features of the memory statue, which, in terms of computational modeling, would offer improved SNR quality within the system. Such a cooperative mechanism, which appreciates the temporal order of the wake–sleep cycle (acquisition, followed by postprocessing), and, within sleep, the ultradian pattern of sleep-stage progression across a night (selection and removal, followed by strengthening), would produce a network of stored information that is not only more efficient, but for those representations remaining, more enhanced. Both these processes would predict improved recall of remodeled individual memories from the prior day and further afford the synaptic capacity for efficient acquisition of new "information clay" the next day.

Association, Integration, and Creativity

As critical as consolidation may be—an operation classically concerned with individual memory items—the association and integration of new experience into preexisting networks of knowledge is equally as important, if not more so. The resulting creation of associative webs of information offers numerous and powerful advantages. Indeed, the final goal of sleep-dependent memory processing may not be the enhancement of individual memories in isolation, but, instead, their integration into a common schema, and by this enhancement, facilitation of the development of universal concepts, a process that forms the basis of generalized knowledge and even creativity.

Association and Integration

Perhaps the earliest demonstration that sleep may be involved in a form of memory generalization was by Fenn et al. (2003). Utilizing an artificial grammar task, subjects were trained and later tested on their ability to transfer phonological categories across different acoustic patterns. The task required forming new mappings from complex acoustical sounds to preexisting linguistic categories, which then generalized to new stimuli. As such, it involved both a declarative process of forming specific memories associated with the learned stimuli, together with a procedural component involving mapping across the set of learned sounds that supports generalization to novel stimuli. During the initial training session there was a significant improvement in recognition performance on the task. However, when retested after a 12-h waking interval, performance had decayed. Yet, if subjects were retested following

a night of sleep, this ability for memory generalization was restored. Supporting this concept, Dumay and Gaskell (2007) also demonstrated that sleep and not equivalent time awake can integrate related but novel phonemes into pre-existing, long-term lexical memory stores overnight.

In a related study by Gomez and colleagues (Gomez et al. 2006), infants were exposed to "phrases" from an artificial language during a learning session—for example, phrases like "pel–wadim–jic"—until the infants became familiar (as indexed by look responses). However, these three syllable units had an embedded rule, which was that the first and last unit formed a relationship of nonadjacency; in this case, pel predicts jic. The infants were then retested several hours later, yet some infants took normally scheduled naps, while others were scheduled at a time when they would not sleep after learning. At later testing, infants again heard the recordings, along with novel phrases in which the predictive relationship between the first and last word was new. Infants who did not sleep recognized the phrases they had learned earlier, yet those who had slept demonstrated a generalization of the predictive relationship to new phrases, suggesting that the intervening process of sleep allowed the reinterpretation of prior experience, and supported the abstraction of commonalities—that is, the ability to detect a general pattern in new information.

Ellenbogen et al. (2007) have since tested this sleep-dependent hypothesis of integration by examining human relational memory—the ability to generalize previously acquired associations to novel situations. Participants initially learned five "premise pairs" (A > B, B > C, C > D, D > E, E > F). Unknown to subjects, the pairs contained an embedded hierarchy (A > B > C > D > E > F). Following an offline delay of 20 min, 12 h across the day, or 12 h containing a night of sleep, knowledge of this hierarchy was tested by examining relational judgments for novel "inference" pairs, either separated by one degree of associative distance (B > D, C > E pairs) or by two degrees of associative distance (B > E pair). Despite all groups achieving near identical premise-pair retention after the offline delay (i.e., the building block pair of the hierarchy), a striking dissociation was evident in the ability to make relational inference judgments. Subjects that were tested soon after learning in the 20 min group showed no evidence of inferential ability, performing at chance levels (Fig. 9A). In contrast, the two 12 h groups displayed highly significant relational memory development. Most remarkable, however, was the observation that if the 12-h period contained a night of sleep, a near 25% advantage in relational memory over the 12 h across the day group was seen for the most distantly connected inferential judgment (the B > E pair; Fig. 9A). Together, these findings demonstrate that human memory integration takes time to develop, requiring slow, offline associative processes. Furthermore, sleep appears to preferentially facilitate this integration by enhancing hierarchical memory binding, biasing the development of the most distant/weak associative links amongst related yet separate memory items (Fig. 9B). It is also interesting to note a further advantage of this sleep-dependent assimilation process. When it stores individual premise-pairs (top row, Fig. 9B) the size/number of items ("bits") of information the brain has to code is ten (A-B, B-C, C-D, D-E, E-F). However, when it the items are formed into a hierarchy, the informational load is compressed, reduced by nearly 50% to just six bits (A-B-C-D-E-F). Therefore, a supplementary benefit of sleep-dependent memory association may be the improved efficiency of memory storage, in addition to a more generalized representation.

Thus, the overnight strengthening and consolidation of individual item memories (reviewed above), may not be the ultimate objective of sleep-dependent memory processing, especially when one considers that declarative (nonemotional) memories decay over the long-term (Wixted & Carpenter 2007). It is then interesting to speculate whether sleep serves to facilitate two complementary objectives for

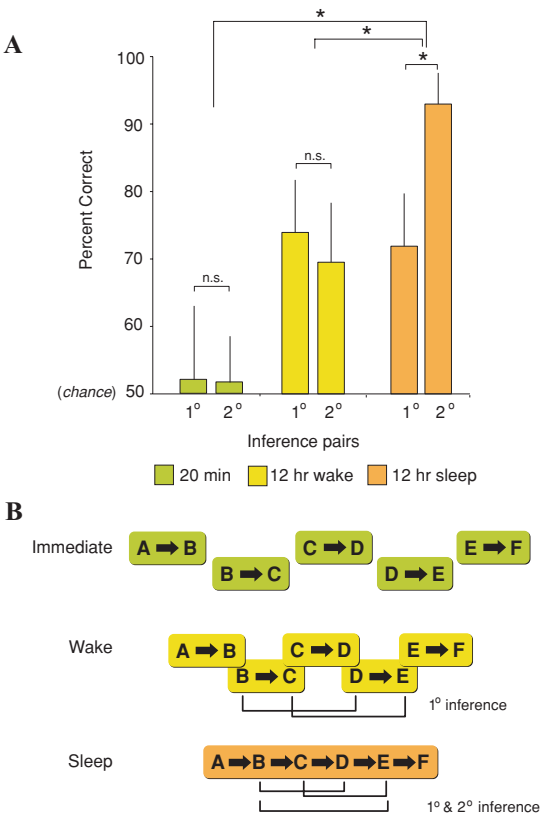

Figure 9. Sleep-dependent integration of human relational memory. (**A**) Delayed inference (associative) memory performance (% correct) in a relational memory task following different offline delays. Immediate testing after just a 20 min offline delay, demonstrated a lack of any inferential ability resulting in chance performance on both 1-degree (first order) and 2-degree and 2-degree (second order) associative judgments. Following a more extended 12-h delay, across the day (Wake group), performance was significantly above chance across both the one and two-degree inference judgments. However, following an equivalent 12-h offline delay, but containing a night of sleep (Sleep group), significantly better performance was expressed on the more distant two-degree inference judgment compared with the one-degree judgment. (**B**) A conceptual model of the effects of sleep on memory integration. Immediately after learning, the representation of each premise is constituted as the choice of one item over another (A > B, etc.), and these premises are isolated from one another despite having overlapping elements. After a 12-h period with no sleep, the premise representations are partially integrated by their overlapping elements, sufficient to support first-order transitive inferences. However, following a 12-h offline period with sleep, the premise representations are fully interleaved, supporting both first- and second-order transitive inferences. $^*P < 0.05$; error bars indicate SEM. Modified from Ellenbogen et al. 2007 and Eichenbaum 2007.

declarative memory, which span different time courses. The first may be an initial process of consolidating individual item (episodic) memories that are novel, which may occur in the relative short term. Over a longer time course, however, and utilizing these recently consolidated item memories prior to their fading, sleep may begin the process of the brain's extraction (of meaning) and abstraction (building associational links with existing information), thereby creating more adaptive semantic networks (McClelland et al. 1995; Squire 2007; Tse et al. 2007). Ultimately, individual item memories would no longer be necessary for the goal that sleep is trying to achieve, and only the conceptual meaning of such experiences would remain. Whether the subsequent loss of item memories is passive or whether sleep plays an active role in this process (Crick & Mitchison 1983) remains to be examined, but this is a testable hypothesis, i.e., *forgetting (individual items) is the price we pay for remembering (general rules)*.

Creativity

One potential advantage of testing associative connections and building cross-linked systems of knowledge is creativity—the ability to take existing pieces of information and combine them in novel ways that lead to greater understanding and offer new, advantageous behavioral repertoires. The link between creativity and sleep, especially dreaming, has long been a topic of intense speculation. Even scientific examples of creativity occurring during sleep are common: from the dreams of both August Kekulé that led to the conception of a simple structure for benzene (Hubert 1985) to those of Dmitry Mendeleyev that initiated the creation of the periodic table of

elements (Strathern 2000) to the late night dreaming of Otto Loewi that inspired the experimental demonstration of neurochemical transmission (Mazzarello 2000).Quantitative data have further demonstrated that solution performance on tests of cognitive flexibility using anagram word puzzles is more than 30% better following awakenings from REM sleep compared with NREM awakenings (Walker et al. 2002). Similarly, a study of semantic priming has demonstrated that, in contrast to the situation in waking, performance following REM sleep awakenings shows a greater priming effect by weakly related words than by strong primes, while strong priming exceeds weak priming in NREM sleep (Stickgold et al. 1999), again indicating the highly associative properties of the REM sleep brain. Even the study of mental activity (dreams) from REM sleep indicates that there is not a concrete episodic replay of daytime experiences, but instead, a much more associative process of semantic integration during sleep (Fosse et al. 2003).

Yet the most striking experimental evidence of sleep-inspired insight is arguably that reported by Wagner and colleagues (Wagner et al. 2004). Using a mathematical "number reduction task" (Thurstone & Thurstone 1941), a process of sleep-dependent creative insight was elegantly demonstrated. Subjects analyzed and worked through a series of 8-digit string problems, using specific addition rules (Fig. 10A). Following initial training, after various periods of wake or sleep, subjects returned for an additional series of trials. When retested after a night of sleep, subjects solved the task, using this "standard" procedure, 16.5% faster. In contrast, subjects who did not sleep prior to retesting averaged less than a 6% improvement. However, hidden in the construction of the task was a much simpler way to solve the problem. On every trial, the last three response digits (e.g., "4–1–9" in Fig. 10A) were the mirror image of the preceding three (i.e., "9–1–4"). As a result, the second response digit always provided the answer to the problem, and using such "insight," subjects could stop after producing the second response digit. Most dramatically, nearly 60% of the subjects who slept for a night between training and retesting discovered this shortcut the following morning (Fig. 10B). In

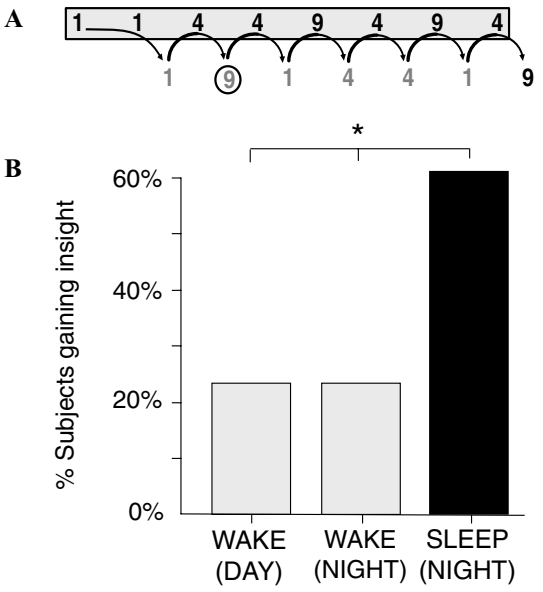

Figure 10. Sleep-dependent production of creative insight. (**A**) Example of the Number Reduction Task. Subjects analyze digits in a 8-digit string of 1s, 4s, and 9s, from left to right, using two rules: (1) If two digits are the same, respond with that digit. Thus, starting from the left, the first two digits are both "1," and hence the response (listed below and to the right of the second digit) is also "1." (2) If two digits are different, respond with the remaining digit. Thus, having produced the response "1," this response and the next digits are analyzed. Since they differ ("1" and "4"), the next response is "the remaining digit, or "9." This response and the next digit, "4" also differ ("9" and "4") and so the next response is the remaining digit, "1." The analysis is continued to the end, and the final response, "9" in this case, is the solution to the problem. This final response is then entered as the answer the problem. However, on every trial, the last three response digits (e.g., "4–1–9" in figure above) are the mirror image of the preceding three (i.e., "9–1–4"). As a result, the second response digit (circled "9") always provides the answer to the problem, resulting in a "shortcut" to solving the problem, if the subject gains this hidden insight. (**B**) Percentage of subjects that gained insight into this hidden rule following an offline delay while awake across the day, awake across the night of following sleep across the night. $^*P < 0.05$. Modified from Wagner et al. 2004.

contrast, no more than 25% of subjects in any of four different control groups that did not sleep had this insight. Sleeping after exposure to the problem therefore more than doubled the likelihood of solving it (although it is interesting to note that this insight was not present immediately following sleep, but took over 100 trials on average to emerge the next day).

In summary, substantial evidence now suggests that sleep serves a metalevel role in memory processing that moves far beyond the consolidation and strengthening of individual memories and, instead, aims to intelligently assimilate and generalize these details offline. In doing so, sleep may offer the ability to test and build common informational schemas of knowledge, providing for increasingly accurate statistic predictions about the world and allowing for the discovery of novel, even creative, next-day solution insights.

Emotional Regulation

Despite substantial research focusing on the interaction between sleep and cognition, especially memory, the impact of sleep and sleep loss on affective and emotional regulation has received more limited research attention. This absence of investigation is perhaps surprising considering that nearly all psychiatric and neurological mood disorders express co-occurring abnormalities of sleep, suggesting an intimate relationship between sleep and emotion. Nevertheless, a number of recent studies evaluating subjective as well as objective measures of mood and affect, combined with insights from clinical domains, offer an emerging understanding for the critical role of sleep in regulating emotional brain function.

Affective Reactivity

Together with impairments of attention and alertness, sleep deprivation is commonly associated with increased subjective reports of irritability and affective volatility (Horne 1985). Using a sleep restriction paradigm (5 h/night), Dinges et al. (1997) reported a progressive increase in emotional disturbance across a one-week period on the basis of questionnaire mood scales. In addition, subjective descriptions in participants' daily journals also indicated increasing complaints of emotional difficulties. Zohar et al. (2005) investigated the effects of sleep disruption on emotional reactivity to daytime work events in medical residents. Sleep loss was shown to amplify negative emotional consequences of disruptive daytime events while blunting the positive benefit associated with rewarding or goal-enhancing activities.

Although these findings help to characterize the behavioral irregularities imposed by sleep loss, evidence for the role of sleep in regulating our emotional brain is surprisingly scarce. To date, only one such study has investigated whether a lack of sleep inappropriately modulates human emotional brain reactivity (Yoo et al. 2007a). Healthy young participants were allowed to sleep normally prior to an fMRI scanning session or were sleep deprived for one night (accumulating approximately 35 h of total sleep loss). During scanning, subjects performed an affective stimulus viewing task involving the presentation of picture slides ranging in a gradient from emotionally neutral to increasingly negative and aversive.

While both groups expressed significant amygdala activation in response to increasingly negative picture stimuli, those in the sleep-deprivation condition exhibited a remarkable +60% greater magnitude of amygdala reactivity, relative to the control group (Figs. 11A & B). In addition to this increased intensity of activation, there was also a threefold increase in the extent of amygdala volume recruited in response to the aversive stimuli in the sleep-deprivation group (Fig. 11B). Perhaps most interestingly, relative to the sleep control group, there was a significant loss of functional connectivity identified between the amygdala and the medial prefrontal cortex (mPFC) in those who were sleep deprived—a

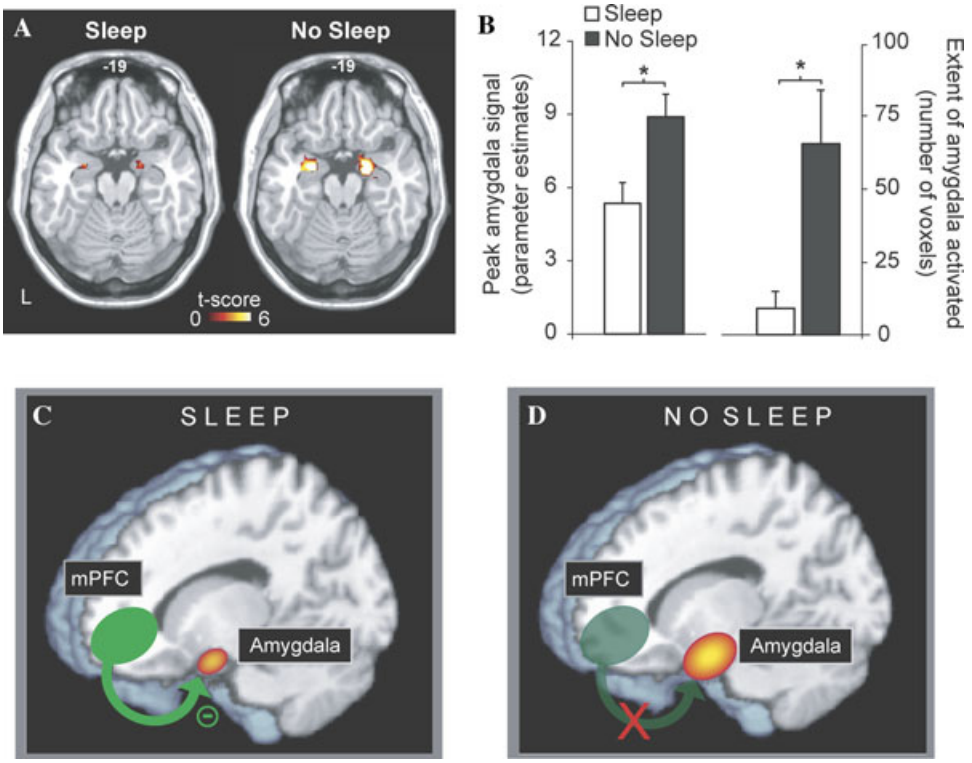

Figure 11. The impact of sleep deprivation on emotional brain reactivity and functional connectivity. (**A**) Amygdala response to increasingly negative emotional stimuli in the sleep deprivation and sleep control groups, and (**B**) corresponding differences in intensity and volumetric extent of amygdala activation between the two groups (average ± SEM. of left and right amygdala). (**C**) Depiction of associated changes in functional connectivity between the medial prefrontal cortex (mPFC) and the amygdala. With sleep, the prefrontal lobe was strongly connected to the amygdala, regulating and exerting and inhibitory top-down control, yet (**D**) Without sleep, however, mPFC connection was decreased, potentially negating top-down control and resulting in an overactive amygdala. $^{*}P < 0.01$; error bars indicate SEM. Modified from Yoo et al. 2007b.

region known to have strong inhibitory projections and hence modulatory impact on the amygdala (Sotres-Bayon et al. 2004). In contrast, significantly greater connectivity in the deprivation group was observed between the amygdala and the autonomic-activating centers of the locus coeruleus.

Thus, without sleep, an amplified hyperlimbic reaction by the human amygdala was observed in response to negative emotional stimuli. Furthermore, this altered magnitude of limbic activity is associated with a loss of functional connectivity with the mPFC in the sleep deprivation condition implying a failure of top-down inhibition by the prefrontal lobe (Figs. 11C & D). It would therefore appear that a night of sleep may "reset" the correct affective brain reactivity to next-day emotional challenges by maintaining functional integrity of this mPFC–amygdala circuit and thus govern appropriate behavioral repertoires (e.g., optimal social judgments and rational decisions). Intriguingly, a similar pattern of anatomical dysfunction has been implicated in a number of psychiatric mood disorders that express co-occurring sleep abnormalities (Davidson 2002; Davidson et al. 2002; New et al. 2007), directly raising the issues of whether such factors (sleep loss and clinical mood disorders) are causally related.

Emotional Information Processing

Sleep's role in declarative memory consolidation, rather than being absolute, may depend on more intricate aspects of the information being learned, such as novelty, meaning to extract, and also the affective salience of the material. Independent of the field of sleep and memory, there is a wealth of evidence demonstrating that memory processing is modulated by emotion (Cahill 2000; McGaugh 2004; Phelps 2004). Experiences which evoke emotions not only encode more strongly, but appear to persist and even improve over time as the delay between learning and testing increases (from hours to days) (Kleinsmith & Kaplan 1963; Walker & Tarte 1963; Levonian 1972; LaBar & Phelps 1998; Sharot & Phelps 2004).

Although these findings indicate a strong influence of emotion on slow, time-dependent consolidation processes, based on the coincident neurophysiology that REM sleep provides and the neurobiological requirements of emotional memory processing (Cahill 2000; McGaugh 2004), work has now begun to test a selective REM-dependent hypothesis of affective human memory consolidation. For example, Hu et al. (2006) compared the consolidation of emotionally arousing and nonarousing picture-stimuli following a 12-h period across a day or following a night of sleep. A specific emotional memory benefit was observed only following sleep and not cross an equivalent time awake. Wagner and colleagues (Wagner et al. 2001) have also shown that sleep selectively favors the retention of previously learned emotional texts relative to neutral texts, and that this affective memory benefit is only present following late-night sleep (a time period rich in stage-2 NREM and REM sleep). Furthermore, this emotional memory enhancement has been shown to persist for several years (Wagner et al. 2006).

Using a nap paradigm, researchers have most recently demonstrated that sleep, and specifically REM neurophysiology, may underlie this consolidation benefit (Nishida et al. in press). Subjects performed two study sessions in which they learned emotionally negative and neutral picture stimuli: one 4 h prior to a recognition memory test, and one 15 min prior to it. In one group, participants slept (90 min nap) after the first study session, while in the other group, participants remained awake. Thus, items from the study sessions tested after 4 h transitioned through different brain-states in each group prior to testing—sleep in the Nap group and no sleep in the No-Nap group—yet experienced identical brain-state conditions when tested after 15 min.

No change in memory for emotional (or neutral stimuli), occurred across the offline delay in the no-nap group. However, a significant and selective offline enhancement of emotional memory was observed in the nap group (Fig. 12A), the extent of which was correlated with the amount of REM sleep (Fig. 12B), and the speed of entry into REM (latency; not shown in figure). Furthermore, spectral analysis of the EEG demonstrated that the magnitude of right-dominant prefrontal theta power during REM (activity in the frequency range of 4.0–7.0 Hz) exhibited a significant and positive relationship with the amount of emotional memory improvement (Figs. 12C & D).

These findings go beyond demonstrating that affective memories are preferentially enhanced across periods of sleep, and indicate that the extent of emotional memory improvement is associated with specific REM sleep characteristics—both quantity and quality. Corroborating these correlations, it has previously been hypothesized that REM sleep represents a brain state particularly amenable to emotional memory consolidation, based on its unique biology (Pare et al. 2002; Hu et al. 2006). Neurochemically, levels of limbic and forebrain ACh are markedly elevated during REM (Vazquez & Baghdoyan 2001), reportedly quadruple those seen during NREM and double those measured in quite waking (Marrosu et al. 1995). Considering the known importance of ACh in the long-term consolidation of emotional learning (McGaugh 2004), this

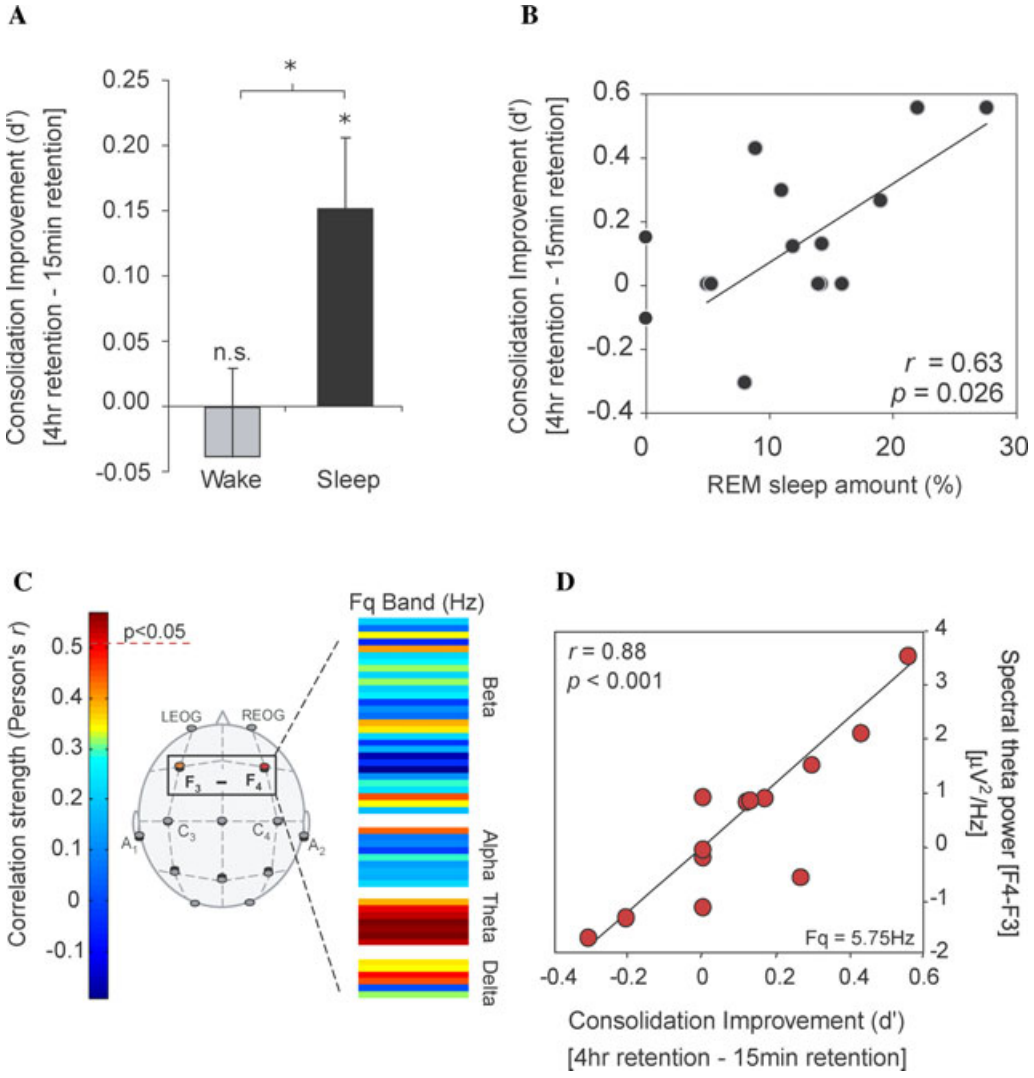

Figure 12. REM sleep enhancement of negative emotional memory consolidation. (**A**) Offline benefit (change in memory recall for 4 h versus 15 min old memories) across the day (wake, grey bar) or following a 90 min nap (sleep, filled bar) (**B**) Correlation between the amount of offline emotional memory improvement in the nap group (i.e. the offline benefit expressed in filled bar of figure A), and the amount of REM sleep obtained within the nap, (**C**) Correlation strength (Pearson's *r*-value) between offline benefit for emotional memory in the sleep group (the benefit expressed in filled bar of figure A) and the relative right versus left prefrontal spectral-band power ([F4 – F3]) within the delta, alpha, theta, and beta spectral bands, expressed in average 0.5 Hz bins increments. Correlation strength is represented by the color range, demonstrating significant correlations within the theta frequency band (hot colors), and (**D**) exhibiting a maximum significance at the 5.75 Hz bin. $^{*}P < 0.05$; error bars indicate SEM. Modified from Nishida et al. unpublished.

pro-cholinergic REM state may result in a selective facilitation of affective memories, similar to that reported using experimental manipulations of ACh (Power 2004). Neurophysiologically, theta oscillations have been proposed as a carrier frequency allowing disparate brain regions that initially encode information to selectively interact offline, in a coupled relationship. By doing so, REM theta may afford the ability to promote the strengthening of specific

memory representations across distributed networks (Buzsaki 2002; Jones & Wilson 2005).

A REM Sleep Hypothesis of Emotional Memory Processing

Beyond the strengthening of emotional memories, there may be an additional consequence of sleep-dependent affective modulation, and one that has significant implications for mood disorders – that is, sleeping to forget. Based on the emerging interaction between sleep and emotion, below I outline a model of affective information processing that may offer brain-based explanatory insights regarding the impact of sleep abnormalities, particularly REM, for the initiation and/or maintenance of mood disturbance.

While there is abundant evidence to suggest that emotional experiences persist in our autobiographies over time, an equally remarkable but far less noted change is a reduction in the affective tone associated with their recall. The reason that affective experiences appear to be encoded and consolidated more preferentially than neutral memories is due to autonomic neurochemical reactions elicited at the time of the experience, creating what we commonly term an "emotional–memory." However, the later recall of these experiences tends not to be associated with anywhere near the same magnitude of autonomic (re)activation as that elicited at the moment of learning/experience – suggesting that, overtime, the affective "blanket" previously enveloped around the memory during encoding has been removed, while the information contained within that experience (the memory) remains.

For example, neuroimaging studies have shown that initial exposure and learning of emotional stimuli is associated with substantially greater activation in the amygdala and hippocampus, relative to neutral stimuli (Kilpatrick & Cahill 2003; Dolcos et al. 2004; Dolcos et al. 2005). In one of these studies (Dolcos et al. 2004), however, when participants were reexposed to these same stimuli during recognition testing many months later, a change in the profile of activation occurred (Dolcos et al. 2005). Although the same magnitude of differential activity between emotional and neutral items was observed in the hippocampus, this was not true in the amygdala. Instead, the difference in amygdala (re)activity compared with neutral items had dissipated over time. This would support the idea that the strength of the memory (hippocampal-associated activity) remains at later recollection, yet the associated emotional reactivity to these items (amygdala activity) is reduced over time.

The hypothesis predicts that this decoupling preferentially takes place overnight, such that we sleep to forget the emotional tone, yet sleep to remember the tagged memory of that episode (Fig. 13). The model further argues that if this process is not achieved, the magnitude of visceral autonomic "charge" remaining within autobiographical memory networks will persist, resulting in the potential condition of chronic anxiety. Based on the consistent relationship identified between REM and emotional processing, combined with its unique neurobiology, the hypothesis proposes that REM sleep provides an optimal biological state for achieving such affective "therapy." Specifically, increased activity within limbic and paralimbic structures (including the hippocampus and amygdala) during REM may first offer the ability for reactivation of previously acquired affective experiences. Second, the neurophysiological signature of REM involving dominant theta oscillations within subcortical as well as cortical nodes may offer large-scale network cooperation at night, allowing the integration and, as a consequence, greater understanding of recently experienced emotional events in the context of preexisting neocortically stored semantic memory. Third, these interactions during REM critically, and perhaps most importantly, take place within a brain that is devoid of aminergic neurochemical concentration (Pace-Schott & Hobson 2002), particularly noradrenergic input from the

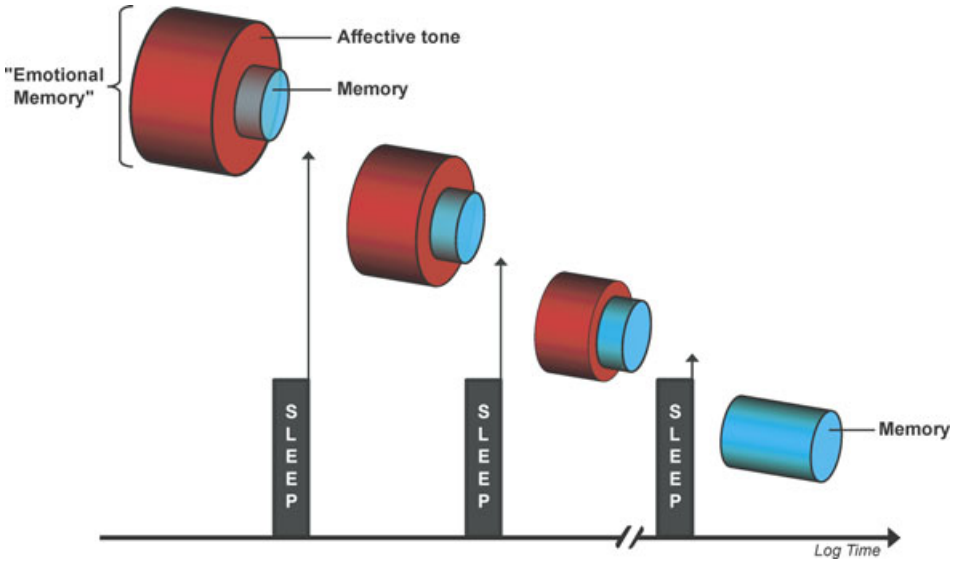

Figure 13. Model of sleep-dependent emotional–memory processing: A sleep to *forget* and sleep to *remember* hypothesis. When formed, a newly encoded "emotional–memory" is created in a milieu of high adrenergic tone, resulting an associated affective "blanket." With multiple iterations of sleep, particularly REM, not only is the informational core (memory) contained within that affective experience strengthened overnight(s), resulting in improved memory for that event, the autonomic tone "enveloped" around the memory becomes gradually ameliorated (emotional forgetting). Over time, the stored information of the original experience ultimately becomes decoupled and freed of its autonomic "charge," leaving just the salient memory of that emotional experience, but without the affective tone previously associated at the time of learning.

locus coeruleus; the influence of which has been linked to states of high stress and anxiety disorders (Sullivan et al. 1999).

In summary, the described neuroanatomical, neurophysiological and neurochemical conditions of REM sleep offer a unique biological theatre in which to achieve, on one hand, a balanced neural potentiation of the informational core of emotional experiences (the memory), yet may also depotentiate and ultimately ameliorate the autonomic arousing charge originally acquired at the time of learning (the emotion), negating a long-term state of anxiety (Fig. 13).

This model compliments previous psychological theories of dreaming by Greenberg (Greenberg et al. 1972a, 1972b) and also Cartwright (Cartwright et al. 1991, 1998, 2006), which suggest that the process of REM-sleep mental activity aids in the resolution of previous emotional conflict, resulting in improved next-day negative mood. Moreover, pioneering work by Cartwright et al. have demonstrated that not only the occurrence of dreaming but the actual content of dreams plays an important role in the recovery from emotional trauma, and can be predictive of clinical remission months later (Cartwright et al. 1991, 1998, 2006). Although the current model offers a neurobiological framework for the overnight modulation and alteration of emotional memories and next-day affective brain reactivity, is does not discount the potential contribution that the mental operation of dreaming itself, beyond the electrophysiological underpinnings of REM, may afford to this process.

The current model also asserts that if the process of divorcing emotion from memory is not achieved across the first night following

an emotional event, a repeat attempt would occur on the second night, since the strength of emotional "tag" associated with the memory would remain high. Should this process fail a second time, the same events would continue to repeat across ensuing nights, potentially with an increasing progressive amount of REM in response. It is just such a cycle of REM-sleep dreaming (nightmares) that represents a diagnostic key feature of post-traumatic stress disorder (PTSD) (Lavie 2001). It may not be coincidental, therefore, that these patients continue to display hyperarousal reactions to associated trauma cues (Harvey et al. 2003; Pole 2007), indicating that the process of separating the affective tone from the emotional experience has not been accomplished. The reason why such a REM mechanism may fail in PTSD remains unknown, although the exceptional magnitude of trauma-induced emotion at the time of learning maybe so great that the system is incapable of initiating/completing one or both these processes, leaving some patients unable to depotentiate, integrate and hence "overcome" the experience.

This model also makes specific experimental predictions as to the fate of these two components – the memory and the emotion. As partially demonstrated, the first prediction would be that, overtime, the veracity of the memory itself would improve, and the extent to which these [negative] emotional experiences are strengthened would be proportional to the amount of postexperience REM sleep obtained, as well as how quickly it is achieved (REM latency).

Secondly, using autonomic physiology measures, these same predictions would hold in the inverse direction for the magnitude of emotional reactivity induced at the time of recall. Together with the neuroimaging studies of emotional memory recall over time, and the psychological studies investigating the role of REM sleep dreaming in mood regulation, a recent fMRI study offers perhaps the strongest preliminary support of this sleep-dependent model of emotional-memory processing (Sterpenich et al. 2007). The investigation demonstrated that subjects who were deprived of sleep the first night after learning arousing emotion picture slides not only showed reduced recalled of the information (the sleep to remember component of the hypothesis), but also showed a lack of reduction in amygdala reactivity when reexposed to these same emotional picture slide at recognition testing – as compared to a control group that did sleep (the sleep to forget component of the hypothesis).

There is, however, a related study that does not conform to these trends. Wagner and colleagues had participants subjectively rate and re-rate emotional picture slides after 3 h of early-night sleep, or 3 h of late-night sleep (Wagner et al. 2002). Valence ratings of unpleasantness actually increased following sleep, compared to new picture slides not seen before. This was true in a group that was also allowed to sleep the entire night. The contrast in this finding to those discussed previously reporting a decrease in emotional reactivity remains unclear. It is of note that when compared not to new items, but to the same items before sleep (baseline ratings), no increase in valance rating was evident. This discrepancy may also be due to the dimension of valence not assessing autonomic emotional reactivity. In fact, subjects also rated these pictures stimuli on the basis of arousal strength, as well as valence. There was no such amplification of arousal reactivity following sleep, demonstrating a numerical decrease overtime, relative to baseline measures. Alternatively, it may be that the assessment of valence is associated with the veracity of the memory, which is strengthened overnight, thereby promoting the recall of perceived pleasantness (or unpleasantness). Arousal (the visceral, autonomic dimension of emotion), in contrast, appears to be reduced over sleep, despite the beneficial strengthening of memory recall.

The model thirdly predicts that a pathological increase in REM (as commonly occurs in depression; (Tsuno et al. 2005; Armitage 2007; Gottesmann & Gottesman 2007)

may disproportionately amplify the strength of negative memories, so much so that, despite concomitant attempts at ameliorating the associated affective tone, would still create a perceived autobiographical history dominated by negative memory excess (which may also facilitate disadvantageous waking rumination). In contrast, the selective decrease of REM, as occurs with many antidepressants, would predict a reduction of such negative memory consolidation and bias, although may curtail the degree of affect decoupling that can occur. Long-term, the balanced extent of accumulated REM should therefore correlate not only with the persistence, in memory, of the emotional experience, it should also be associated with a decreased magnitude of autonomic response associated with recall – all of which are testable objectives for future research.

If such a hypothesis is correct, there would be translation implications for psychiatric and mood disorders. This would require a new appreciation for the palliative role of sleep in treatment regimes, and a consideration of whether altering sleep architecture to regulation the balance of emotion and memory of past experience is a useful and viable possibility.

Conclusions

While not fully complete, we will soon have a new taxonomy of sleep-dependent memory processing, and one that will supersede the polarized all-or-none views of the past (Stickgold & Walker 2005b; Vertes & Siegel 2005). With such findings, we can come to a revised appreciation of how both wake and sleep unite in a symbiotic alliance to coordinate the encoding, consolidation and integration of our memories, the ultimate aim of which maybe to create a generalized catalogue of stored knowledge that does not rely on the verbose retention of all previously learned facts.

Beyond memory and plasticity, a growing number of human neuroscience studies, set on a foundation of clinical insights, point to an exciting role for sleep in regulating affective brain function and emotional experience. Based on the remarkable neurobiology of sleep, and REM in particular, a unique capability for the overnight modulation of affective networks and previously encountered emotional experiences may be possible, redressing and maintaining the appropriate connectivity and hence next-day reactivity throughout limbic and associated autonomic systems.

Ultimately, the timeless maternal wisdom of mothers may have long held the answers to Allan Rechtschaffen's original question "Why do we sleep?" Namely, that "you should sleep on a problem" and when troubled, "get to bed, you'll feel better in the morning."

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Conflicts of Interest

The author declares no conflicts of interest.

References

Amzica, F., & Steriade, M. (1995). Short- and long-range neuronal synchronization of the slow (<1 Hz) cortical oscillation. *J. Neurophysiol.*, *73*, 20–38.

Armitage, R. (2007). Sleep and circadian rhythms in mood disorders. *Acta Psychiatr. Scand. Suppl.*, 104–115.

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility and concurrent phenomena during sleep. *Science*, *118*, 273–274.

Aston-Jones, G., & Bloom, F. E. (1981). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J. Neurosci.*, *1*, 876–886.

Benca, R. M., Obermeyer, W. H., Thisted, R. A., & Gillin, J. C. (1992). Sleep and psychiatric disorders. A meta-analysis. *Arch. Gen. Psychiatry*, *49*, 651–668; discussion 669–670.

Buysse, D. J. (2004). Insomnia, depression and aging. Assessing sleep and mood interactions in older adults. *Geriatrics*, *59*, 47–51; quiz 52.

Buzsaki, G. (1996). The hippocampo-neocortical dialogue. *Cereb. Cortex*, *6*, 81–92.

Buzsaki, G. (2002). Theta oscillations in the hippocampus. *Neuron*, *33*, 325–340.

Cahill, L. (2000). Neurobiological mechanisms of emotionally influenced, long-term memory. *Prog. Brain Res.*, *126*, 29–37.

Callaway, C. W., Lydic, R., Baghdoyan, H. A., & Hobson, J. A. (1987). Pontogeniculooccipital waves: Spontaneous visual system activity during rapid eye movement sleep. *Cell. Mol. Neurobiol.*, *7*, 105–149.

Cann, A., & Ross, D. A. (1989). Olfactory stimuli as context cues in human memory. *Am. J. Psychol.*, *102*, 91–102.

Cartwright, R., Agargun, M. Y., Kirkby, J., & Friedman, J. K. (2006). Relation of dreams to waking concerns. *Psychiatry Res.*, *141*, 261–270.

Cartwright, R., Luten, A., Young, M., Mercer, P., & Bears, M. (1998). Role of REM sleep and dream affect in overnight mood regulation: a study of normal volunteers. *Psychiatry Res.*, *81*, 1–8.

Cartwright, R. D., Kravitz, H. M., Eastman, C. I., & Wood, E. (1991). REM latency and the recovery from depression: getting over divorce. *Am. J. Psychiatry*, *148*, 1530–1535.

Clemens, Z., Fabo, D., & Halasz, P. (2005). Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience*, *132*, 529–535.

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

Datta, S. (2000). Avoidance task training potentiates phasic pontine-wave density in the rat: A mechanism for sleep-dependent plasticity. *J. Neurosci.*, *20*, 8607–8613.

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

Dave, A. S., & Margoliash, D. (2000). Song replay during sleep and computational rules for sensorimotor vocal learning. *Science*, *290*, 812–816.

Dave, A. S., Yu, A. C., & Margoliash, D. (1998). Behavioral state modulation of auditory activity in a vocal motor system. *Science*, *282*, 2250–2254.

Davidson, R. J. (2002). Anxiety and affective style: role of prefrontal cortex and amygdala. *Biol. Psychiatry*, *51*, 68–80.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: perspectives from affective neuroscience. *Annu. Rev. Psychol.*, *53*, 545–574.

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep*, *20*, 267–277.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron*, *42*, 855–863.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2005). Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proc. Natl. Acad. Sci. USA 102*, 2626–2631.

Drummond, S. P., & Brown, G. G. (2001). The effects of total sleep deprivation on cerebral responses to cognitive performance. *Neuropsychopharmacol. 25*, S68–73.

Drummond, S. P., Brown, G. G., Gillin, J. C., Stricker, J. L., Wong, E. C., et al. (2000). Altered brain response to verbal learning following sleep deprivation. *Nature 403*, 655–657.

Dumay, N., & Gaskell, M. G. (2007). Sleep-associated changes in the mental representation of spoken words. *Psychol. Sci. 18*, 35–39.

Eichenbaum, H. (2004). Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron 44*, 109–120.

Eichenbaum, H. (2007). To sleep, perchance to integrate. *Proc. Natl. Acad. Sci. USA*, *104*, 7317–7318.

Ellenbogen, J. M., Hulbert, J. C., Stickgold, R., Dinges, D. F., & Thompson-Schill, S. L. (2006a). Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. *Curr. Biol. 16*, 1290–1294.

Ellenbogen, J. M., Payne, J. D., & Stickgold, R. (2006b). The role of sleep in declarative memory consolidation: passive, permissive, active or none? *Curr. Opin. Neurobiol.*, *16*, 716–722.

Ellenbogen, J., Hu, P., Payne, J.D., Titone, D. & Walker, M.P. (2007). Human relational memory requires time and sleep. *Proc. Natl. Acad. Sci. USA, 104*, 7723–7728.

Fenn, K. M., Nusbaum, H. C., & Margoliash, D. (2003). Consolidation during sleep of perceptual learning of spoken language. *Nature*, *425*, 614–616.

Fogel, S., Jacob, J., & Smith, C. (2001). Increased sleep spindle activity following simple motor procedural learning in humans. Congress Physiological Basis for Sleep Medicine, pp. 123.

Fogel, S. M., & Smith, C. T. (2006). Learning-dependent changes in sleep spindles and Stage 2 sleep. *J. Sleep Res.*, *15*, 250–255.

Fosse, M. J., Fosse, R., Hobson, J. A., & Stickgold, R. J. (2003). Dreaming and episodic memory: a functional dissociation? *J. Cogn. Neurosci.*, *15*, 1–9.

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nat. Rev. Neurosci.*, *6*, 119–130.

Gais, S., Albouy, G., Boly, M., Dang-Vu, T. T., Darsaud, A., et al. (2007). Sleep transforms the cerebral trace of declarative memories. *Proc. Natl. Acad. Sci. USA*, *104*, 18778–18783.

Gais, S., & Born, J. (2004). Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proc. Natl. Acad. Sci. USA*, *101*, 2140–2144.

Gais, S., Molle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *J. Neurosci.*, *22*, 6830–6834.

Giuditta, A., Ambrosini, M. V., Montagnese, P., Mandile, P., Cotugno, M., et al. (1995). The sequential hypothesis of the function of sleep. *Behav. Brain Res.*, *69*, 157–166.

Gomez, R. L., Bootzin, R. R., & Nadel, L. (2006). Naps promote abstraction in language-learning infants. *Psychol. Sci.*, *17*, 670–674.

Gottesmann, C., & Gottesman, I. (2007). The neurobiological characteristics of rapid eye movement (REM) sleep are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia. *Prog. Neurobiol.*, *81*, 237–250.

Greenberg, R., Pearlman, C. A., & Gampel, D. (1972a). War neuroses and the adaptive function of REM sleep. *Br. J. Med. Psychol.*, *45*, 27–33.

Greenberg, R., Pillard, R., & Pearlman, C. (1972b). The effect of dream (stage REM) deprivation on adaptation to stress. *Psychosom. Med.*, *34*, 257–262.

Hammond, N. (2004). *Fragmentary Voices: Memory and Education at Port-Royal*. Gunter Narr Verlag.

Harrison, Y., & Horne, J. A. (2000). Sleep loss and temporal memory. *Q. J. Exp. Psychol.*, *53*, 271–279.

Hartley, D. (1801). *Observations on Man, His frame, his deity, and his expectations (1749/)6691.* Gainesville, FL: Scholars Facsimile Reprint.

Harvey, A. G., Jones, C., & Schmidt, D. A. (2003). Sleep and posttraumatic stress disorder: a review. *Clin. Psychol. Rev.*, *23*, 377–407.

Hobson, J. A., McCarley, R. W., & Wyzinski, P. W. (1975). Sleep cycle oscillation: Reciprocal discharge by two brainstem neuronal groups. *Science*, *189*, 55–58.

Horne, J. A. (1985). Sleep function, with particular reference to sleep deprivation. *Ann. Clin. Res.*, *17*, 199–208.

Hu, P., Stylos-Allen, M., & Walker, M. P. (2006). Sleep facilitates consolidation of emotionally arousing declarative memory. *Psychol. Sci.*, *17*, 891–898.

Huber, R., Ghilardi, M. F., Massimini, M., Ferrarelli, F., Riedner, B. A., et al. (2006). Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat. Neurosci.*, *9*, 1169–1176.

Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature*, *430*, 78–81.

Hubert, A. (1985). *"Kekulé von Stradonitz, Friedrich August."* New York: Macmillan.

Jenkins, J. G., & Dallenbach, K. M. (1924). Obliviscence during sleep and waking. *Am. J. Psychol.*, *35*, 605–12.

Ji, D., & Wilson, M. A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat. Neurosci.*, *10*, 100–107.

Jones, M. W., & Wilson, M. A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.*, *3*, e402.

Kametani, H., & Kawamura, H. (1990). Alterations in acetylcholine release in the rat hippocampus during sleep-wakefulness detected by intracerebral dialysis. *Life Sci.*, *47*, 421–426.

Kilpatrick, L., & Cahill, L. (2003). Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. *Neuroimage*, *20*, 2091–2099.

Kleinsmith, L. J., & Kaplan, S. (1963). Paired-associate learning as a function of arousal and interpolated interval. *J. Exp. Psychol.*, *65*, 190–193.

LaBar, K. S., & Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. *Psychol. Sci.*, *9*, 490–493.

Lavie, P. (2001). Sleep disturbances in the wake of traumatic events. *N. Engl. J. Med.*, *345*, 1825–1832.

Levonian, E. (1972). Retention over time in relation to arousal during learning: an explanation of discrepant results. *Acta Psychol. (Amst.)*, *36*, 290–321.

Llinas, R., & Ribary, U. (1993). Coherent 40-Hz oscillation characterizes dream state in humans. *Proc. Natl. Acad. Sci. USA*, *90*, 2078–2081.

Louie, K., & Wilson, M. A. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron*, *29*, 145–156.

Lydic, R., & Baghdoyan, H. A. (1988). *Handbook Of Behavioral State Control: Cellular and Molecular Mechanisms*. Boca Raton, FL: CRC Press.

Marr, D. (1970). A theory for cerebral neocortex. *Proc. R. Soc. Lond. B Biol. Sci.*, *176*, 161–234.

Marrosu, F., Portas, C., Mascia, M. S., Casu, M. A., Fa, M., et al. (1995). Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. *Brain Res.*, *671*, 329–332.

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.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.*, *102*, 419–457.

Mazzarello, P. (2000). What dreams may come? *Nature*, *408*, 523.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci.*, *27*, 1–28.

Meier-Koll, A., Bussmann, B., Schmidt, C., & Neuschwander, D. (1999). Walking through a maze alters the architecture of sleep. *Percept. Mot. Skills*, *88*, 1141–1159.

Miller, G. (2007). Neuroscience. Hunting for meaning after midnight. *Science*, *315*, 1360–1363.

Morris, G. O., Williams, H. L., & Lubin, A. (1960). Misperception and disorientation during sleep. *Arch. Gen. Psychiatry*, *2*, 247–254.

Moscovitch, M., & Nadel, L. (1998). Consolidation and the hippocampal complex revisited: in defense of the multiple-trace model. *Curr. Opin. Neurobiol.*, *8*, 297–300.

Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.*, *7*, 217–227.

New, A. S., Hazlett, E. A., Buchsbaum, M. S., Goodman, M., Mitelman, S. A., et al. (2007). Amygdala-prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology*, *32*, 1629–1640.

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (In Press). Prefrontal theta during REM sleep enhances emotional memory. *Cereb. Cortex*.

Nishida, M., & Walker, M. P. (2007). Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PloS One*, *2*, e341.

Nofzinger, E. A. (2005). Functional neuroimaging of sleep. *Semin. Neurol.*, *25*, 9–18.

Pace-Schott, E. F., & Hobson, J. A. (2002). The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat. Rev. Neurosci.*, *3*, 591–605.

Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends Cogn. Sci.*, *6*, 93–102.

Pare, D., Collins, D. R., & Pelletier, J. G. (2002). Amygdala oscillations and the consolidation of emotional memories. *Trends Cogn. Sci.*, *6*, 306–314.

Peigneux, P., Laureys, S., Fuchs, S., Collette, F., Perrin, F., et al. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron*, *44*, 535–545.

Phelps, E. A. (2004). Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr. Opin. Neurobiol.*, *14*, 198–202.

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *J. Cogn. Neurosci.*, *9*, 534–547.

Plihal, W., & Born, J. (1999). Memory consolidation in human sleep depends on inhibition of glucocorticoid release. *Neuroreport*, *10*, 2741–2747.

Poe, G. R., Nitz, D. A., McNaughton, B. L., & Barnes, C. A. (2000). Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Res.*, *855*, 176–180.

Pole, N. (2007). The psychophysiology of posttraumatic stress disorder: a meta-analysis. *Psychol. Bull.*, *133*, 725–746.

Power, A. E. (2004). Muscarinic cholinergic contribution to memory consolidation: with attention to involvement of the basolateral amygdala. *Curr. Med. Chem.*, *11*, 987–996.

Rasch, B., Buchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*, *315*, 1426–1429.

Ribeiro, S., Gervasoni, D., Soares, E. S., Zhou, Y., Lin, S. C., et al. (2004). Long-lasting novelty-induced neuronal reverberation during slow-wave sleep in multiple forebrain areas induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. *PLoS Biol.*, *2*, E24.

Rechtschaffen, A., & Kales, A. (1968). *A manual standardized terminology, techniques and scoring system for sleep stages of human subjects*. Bethesda, Maryland, USA: U.S. Department of Health.

Robertson, E. M. (2009). From creation to consolidation: a novel framework for memory processing. *PLoS Biol.*, *7*, e19.

Robertson, E. M., Pascual-Leone, A., & Miall, R. C. (2004). Current concepts in procedural consolidation. *Nat. Rev. Neurosci.*, *5*, 576–82.

Schabus, M., Dang-Vu, T. T., Albouy, G., Balteau, E., Boly, M., et al. (2007). Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. *Proc. Natl. Acad. Sci. USA*, *104*, 13164–13169.

Sejnowski, T. J., & Destexhe, A. (2000). Why do we sleep? *Brain Res.*, *886*, 208–223.

Shaffery, J., Hoffmann, R., & Armitage, R. (2003). The neurobiology of depression: perspectives from animal and human sleep studies. *Neuroscientist*, *9*, 82–98.

Sharot, T., & Phelps, E. A. (2004). How arousal modulates memory: disentangling the effects of attention and retention. *Cogn. Affect Behav. Neurosci.*, *4*, 294–306.

Shima, K., Nakahama, H., & Yamamoto, M. (1986). Firing properties of two types of nucleus raphe dorsalis neurons during the sleep-waking cycle and their responses to sensory stimuli. *Brain Res.*, *399*, 317–326.

Skaggs, W. E., & McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*, *271*, 1870–1873.

Smith, C. (2001). Sleep states and memory processes in humans: procedural versus declarative memory systems. *Sleep Med. Rev.*, *5*, 491–506.

Smith, C. T., Aubrey, J. B., & Peters, K. R. (2004). Different roles for REM and stage 2 sleep in motor learning: A proposed model. *Psychologica Belgica*, *44*, 81–104.

Sotres-Bayon, F., Bush, D. E., & LeDoux, J. E. (2004). Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. *Learn. Mem.*, *11*, 525–535.

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.*, *99*, 195–231.

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiol. Learn Mem.*, *82*, 171–177.

Squire, L. R. (2007). Neuroscience. Rapid consolidation. *Science*, *316*, 57–58.

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. USA*, *93*, 13515–13522.

Steriade, M. (2001). *The Intact and Sliced Brain.* Cambridge, MA: MIT Press.

Steriade, M., & Amzica, F. (1998). Coalescence of sleep rhythms and their chronology in corticothalamic networks. *Sleep Res Online*, *1*, 1–10.

Steriade, M., Amzica, F., & Contreras, D. (1996). Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. *J. Neurosci.*, *16*, 392–417.

Sterpenich, V., Albouy, G., Boly, M., Vandewalle, G., Darsaud, A., et al. (2007). Sleep-related hippocampo-cortical interplay during emotional memory recollection. *PLoS Biol.*, *5*, e282.

Stickgold, R., Scott, L., Rittenhouse, C., & Hobson, J. A. (1999). Sleep-induced changes in associative memory. *J. Cogn. Neurosci.*, *11*, 182–193.

Stickgold, R., & Walker, M. P. (2005a). Memory consolidation and reconsolidation: What is the role of sleep? *Trends Neurosci.*, *28*, 408–415.

Stickgold, R., & Walker, M. P. (2005b). Sleep and memory: the ongoing debate. *Sleep*, *28*, 1225–1227.

Strathern, P. (2000). *Mendeleyev's Dream: The Quest for the Elements*. London: Hamish Hamilton.

Sullivan, G. M., Coplan, J. D., Kent, J. M., & Gorman, J. M. (1999). The noradrenergic system in pathological anxiety: a focus on panic with relevance to generalized anxiety and phobias. *Biol. Psychiatry*, *46*, 1205–1218.

Takashima, A., Petersson, K. M., Rutters, F., Tendolkar, I., Jensen, O., et al. (2006). Declarative memory consolidation in humans: A prospective functional magnetic resonance imaging study. *Proc. Natl. Acad. Sci. USA*, *103*, 756–761.

Thurstone, L. L., & Thurstone, T. G. (1941). Factorial studies of intelligence. *Psychometric Monogr.*, *2*, 94.

Tononi, G., & Cirelli, C. (2003). Sleep and synaptic homeostasis: a hypothesis. *Brain Res. Bull.*, *62*, 143–150.

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Med. Rev.*, *10*, 49–62.

Tse, D., Langston, R. F., Kakeyama, M., Bethus, I., Spooner, P. A., et al. (2007). Schemas and memory consolidation. *Science*, *316*, 76–82.

Tsuno, N., Besset, A., & Ritchie, K. (2005). Sleep and depression. *J. Clin. Psychiatry*, *66*, 1254–1269.

Vazquez, J., & Baghdoyan, H. A. (2001). Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, *280*, R598–601.

Vertes, R. P., & Siegel, J. M. (2005). Time for the sleep community to take a critical look at the purported role of sleep in memory processing. *Sleep*, *28*, 1228–1229; discussion 1230–1233.

Wagner, U., Fischer, S., & Born, J. (2002). Changes in emotional responses to aversive pictures across periods rich in slow-wave sleep versus rapid eye movement sleep. *Psychosom. Med.*, *64*, 627–634.

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., Gais, S., Haider, H., Verleger, R., & Born, J. (2004). Sleep inspires insight. *Nature*, *427*, 352–355.

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, E. L., & Tarte, R. D. (1963). Memory storage as a function of arousal and time with homogeneous and heterogeneous lists. *J. Verbal Learn. Verbal Behav.*, *2*, 113–119.

Walker, M. P. (2005). A refined model of sleep and the time course of memory formation. *Behav. Brain Sci.*, *28*, 51–64.

Walker, M. P., Liston, C., Hobson, J. A., & Stickgold, R. (2002). Cognitive flexibility across the sleep-wake cycle: REM-sleep enhancement of anagram problem solving. *Brain Res. Cogn. Brain Res.*, *14*, 317–324.

Walker, M. P., & Stickgold, R. (2006). Sleep, memory and plasticity. *Annu. Rev. Psychol.*, *10*, 139–166.

Werth, E., Achermann, P., Dijk, D. J., & Borbely, A. A. (1997). Spindle frequency activity in the sleep EEG: individual differences and topographic distribution. *Electroencephalogr. Clin. Neurophysiol.*, *103*, 535–542.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, *265*, 676–679.

Wixted, J. T., & Carpenter, S. K. (2007). The Wickelgren power law and the Ebbinghaus savings function. *Psychol. Sci.*, *18*, 133–134.

Yoo, S. S., Gujar, N., Hu, P., Jolesz, F. A., & Walker, M. P. (2007a). The human emotional brain without sleep – a prefrontal amygdala disconnect. *Curr. Biol.*, *17*, R877–R878.

Yoo, S. S., Hu, P. T., Gujar, N., Jolesz, F. A., & Walker, M. P. (2007b). A deficit in the ability to form new human memories without sleep. *Nat. Neurosci.*, *10*, 385–392.

Zeitlhofer, J., Gruber, G., Anderer, P., Asenbaum, S., Schimicek, P., et al. (1997). Topographic distribution of sleep spindles in young healthy subjects. *J. Sleep Res.*, *6*, 149–155.

Zohar, D., Tzischinsky, O., Epstein, R., & Lavie, P. (2005). The effects of sleep loss on medical residents' emotional reactions to work events: a cognitive-energy model. *Sleep*, *28*, 47–54.