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REVIEW

Sleep-Dependent Memory Processing

Matthew P. Walker, PhD

While the functions of sleep remain largely unknown, one exciting hypothesis is that sleep contributes importantly to processes of memory and brain plasticity. Over the last decade, a large body of work has provided substantive evidence supporting this role of sleep in what is becoming known as sleep-dependent memory processing. This review offers a summary of these data, focusing specifically on the role of sleep in (1) memory encoding, (2) memory consolidation (along with the brain basis of this process), and (3) neural plasticity. The clinical ramifications of such findings are also explored. (HARV REV PSYCHIATRY 2008;16:287–298.)

Keywords: consolidation, declarative, encoding, learning, memory, neuroimaging, NREM, plasticity, procedural, REM, sleep

There is a now a renaissance of sleep research in the biological sciences, centered on the question of why we sleep at a brain and body level, with increasing emphasis placed on the role of sleep in memory and plasticity. Although this resurgence is relatively recent in the annals of sleep research, the topic itself has a surprisingly long history. In the early nineteenth century, the British psychologist David Hartley proposed that dreaming might alter the strength of associative memory links within the brain. Yet it was not until 1924 that Jenkins and Dallenbach performed the first systematic studies of sleep and memory, testing Ebbinghaus's theory of memory decay, demonstrating that memory retention was better following a night of sleep than after an equivalent amount of time awake. They concluded, however, that the memory benefit following sleep was passive and resulted from a lack of sensory interference during sleep. They did not consider the possibility that the physiological state of sleep itself could actively orchestrate these memory modifications. It is only in the past half-century, following the discovery of rapid eye movement (REM) and non-REM (NREM) sleep, that research began testing the hypothesis that sleep, or even specific stages of sleep, actively participated in the process of memory development. This overview explores what has come to be known as sleep-dependent memory processing and its associated brain basis, sleep-dependent plasticity, and will focus on evidence in humans, with implications for clinical translation.

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DELINEATIONS AND DEFINITIONS

Sleep States

It is important to note that the brain does not remain in one, single physiological state across the 24-hour day. It cycles, instead, through periods of differing neural and metabolic activity that are associated with distinct biological states, most obviously divided into those of wake and sleep. Sleep itself has been broadly divided into REM and NREM sleep, which alternate across the night in humans in a 90-minute cycle (Figure 1A). In primates and felines, NREM sleep has been further divided into substages 1 through 4, corresponding to increasingly deeper states of sleep (Figure 1A). The deepest NREM stages, stages 3 and 4, are collectively

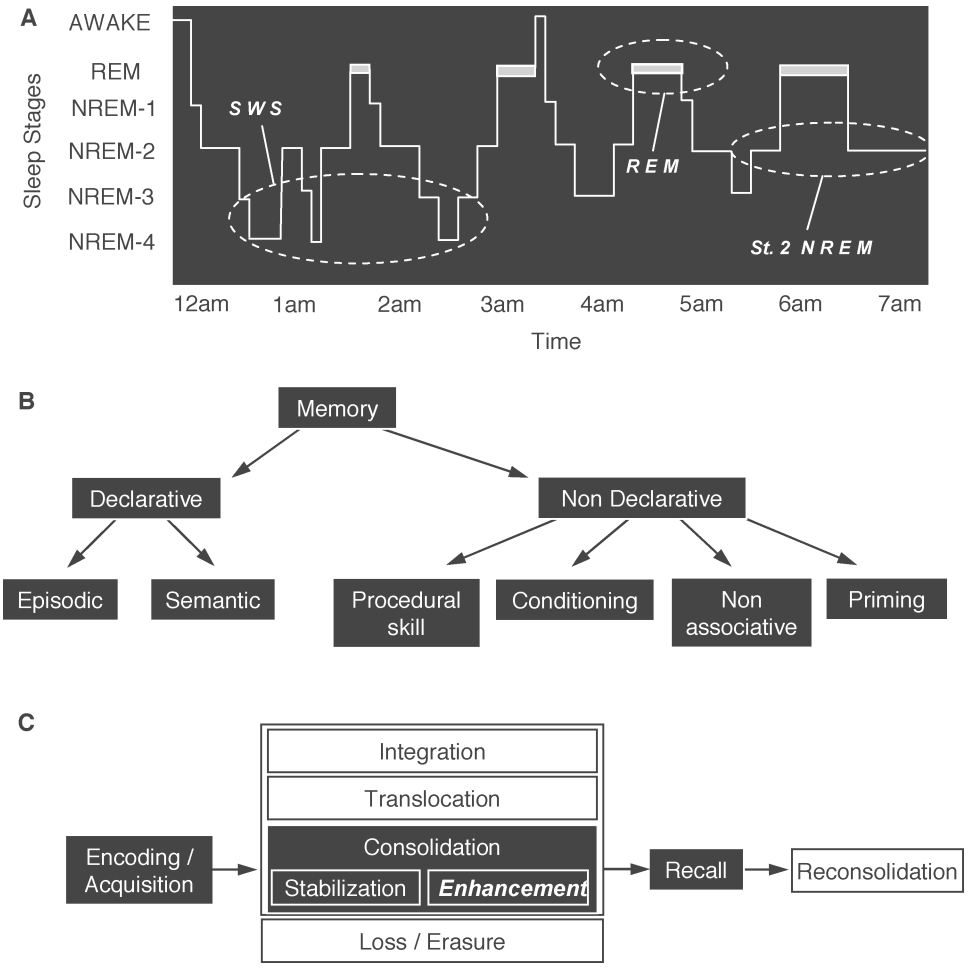

FIGURE 1. The sleep cycle, memory systems, and memory stages. (*A*) The human sleep cycle. Across the night, rapid eye movement (REM) and non-REM (NREM) sleep cycle every 90 minutes in an ultradian manner, while the ratio of NREM to REM sleep shifts. During the first half of the night, NREM stages 3 and 4 slow-wave sleep (SWS) dominate, whereas stage 2 NREM and REM sleep prevail in the latter half of the night. Electroencephalogram patterns also differ significantly between sleep stages, with electrical oscillations such as K-complexes and sleep spindles occurring during stage 2 NREM, slow (0.5–4 Hz) delta waves developing in SWS, and theta waves seen during REM. (*B*) Memory systems. Human memory is most commonly divided into declarative forms, including episodic and semantic memory, and nondeclarative forms, including an array of different types including procedural skill memory. (*C*) Developing stages of memory. Following initial encoding of a memory, several ensuing stages are proposed, beginning with consolidation and including integration of the memory representation and translocation of the representation or erasure of the memory. Also, following later recall, the memory representation is believed to become unstable once again, requiring periods of reconsolidation.

referred to as "slow wave sleep" (SWS), based on a prevalence of low-frequency cortical oscillations in the electroencephalogram (EEG).[1] Dramatic changes in brain electrophysiology, neurochemistry, and functional anatomy accompany these sleep stages, making them biologically distinct from the waking brain, and dissociable from one another.[2] Thus, sleep cannot be treated as a homogeneous state, which either does or does not affect memory. Instead, each sleep stage possesses a set of physiological and neurochemical mechanisms that may contribute uniquely to memory processing and plasticity.

Memory Categories

In the same way that sleep cannot be considered homogeneous, the spectrum of memory categories believed to exist in the human brain, as well as the processes that create and sustain memory, appears equally diverse. Although often used as a unitary term, memory is not a single entity. Human memory has been subject to several different classification schemes, the most popular based on the distinction between declarative and nondeclarative memory[3] (Figure 1B). Declarative memory can be considered as the

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consciously accessible memories of fact-based information (i.e., knowing what). Several subcategories of the declarative system exist, including episodic memory (autobiographical memory for events of one's past) and semantic memory (memory for general knowledge, not tied to specific events). Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, especially the hippocampus, a structure that is thought to form a temporally ordered retrieval code for neocortically stored information, and to bind together disparate perceptual elements of a single event. In contrast, nondeclarative memory is expressed through action and behavior, and includes procedural memory (i.e., knowing how), such as the learning of actions, habits, and skills, as well as implicit learning, and appears to depend on diverse neural anatomies.

Although these categories offer convenient and distinct separations, they rarely operate in isolation in real life. For example, language learning requires a combination of memory sources, ranging from nondeclarative memory for procedural motor programs for articulating speech, to memory of grammatical rules and structure, and to aspects of declarative memory for the source of word selection. This diversity must be kept in mind as we consider the role of sleep in learning and memory.

Memory Stages

Just as memory cannot be considered monolithic, there similarly does not appear to be one sole event that creates or sustains it. Instead, memory appears to develop in several unique stages over time (Figure 1C). For example, memories can be initially formed or encoded by engaging with an object or performing an action, leading to the formation of a representation of the object or action within the brain. After encoding, the memory representation can undergo several subsequent stages of development, the most commonly recognized of which is consolidation. The term memory consolidation classically refers to a process whereby a memory, through the simple passage of time, becomes increasingly resistant to interference from competing or disrupting factors in the absence of further practice.[4] That is to say, the memory becomes more stable.

Recent findings have begun to extend the definition of consolidation. For example, consolidation can be thought of as serving not only to stabilize memories, but also to enhance them—two processes that may be mechanistically distinct.[5] Whereas the stabilization phase of consolidation appears to occur largely across time, independent of brain state, the enhancement stage appears to occur primarily, if not exclusively, during sleep, either restoring previously lost memories or producing additional learning, both without the need for further practice. From this perspective, the enhancement phase of memory consolidation causes either the active restoration of a memory that had shown behavioral deterioration, or the enhancement of a memory over its simple maintenance. Thus, consolidation can be expanded to include more than one phase of post-encoding memory processing, with each phase occurring in specific brain states such as wake or sleep, or even in specific stages of sleep. Finally, following its initial consolidation, a memory can be retained for days to years, during which time it can be recalled.

Although this overview focuses primarily on the effects of sleep on encoding and consolidation, it is important to note that additional post-encoding stages of memory processing should also be appreciated. These stages include the integration of recently acquired information with past experiences and knowledge (a process of memory association), the anatomical reorganization of memory representations (memory translocation), reactivation and reconsolidation of memory through recall, and even the active erasure of memory representations—all of which appear to occur outside of awareness and without additional training or exposure to the original stimuli. It is interesting to note that sleep has already been implicated in many of these steps.[6]

SLEEP AND MEMORY ENCODING

While the majority of studies have investigated the influence of sleep *after* learning on posttraining consolidation (see sections below), some research has examined the role of sleep *before* learning, in preparing the brain for the initial memory encoding.

One of the earliest studies to report the effects of sleep deprivation on declarative memory encoding found that "temporal memory"—a test probing for when events occur by requiring subjects to discriminate the recency of previously shown items—was significantly disrupted by a night of pretraining deprivation.[7] These findings have been recently revisited by Harrison and Horne[8] in more rigorous studies, again using the temporal-memory paradigm. Significant impairments of temporal memory were evident in a group deprived of sleep for 36 hours, who scored significantly lower than did controls who slept normally. Indeed, significant impairment was evident even in a sleep-deprived subgroup that received caffeine to overcome nonspecific effects of lower arousal. Furthermore, the sleep-deprived subjects displayed significantly worse insight into their memory-encoding performance.

Using similar periods of sleep deprivation, neuroimaging reports have begun to investigate the neural basis of these effects. For example, Drummond and colleagues[9] have demonstrated that 35 hours of total sleep deprivation resulted in significantly worse acquisition of verbal learning.

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Surprisingly, however, subjects showed more prefrontal cortex activation during learning when sleep deprived than when not sleep deprived. In contrast, regions of the medial temporal lobe were significantly less activated during learning when sleep deprived. Perhaps most interesting, the parietal lobes, which were not activated during encoding following normal sleep, were significantly activated after sleep deprivation. These findings confirm that sleep deprivation induces a significant behavioral impairment in verbal learning, and suggest that such deficits are mediated by a dynamic set of bidirectional changes—overcompensation by prefrontal regions combined with a failure of the medial temporal lobe to engage normally, leading to compensatory activation in the parietal lobes.

We recently investigated the impact of sleep deprivation on declarative memory encoding of both emotional and nonemotional material.[10] Subjects were either sleep deprived for 36 hours or allowed to sleep normally prior to a learning session composed of sets of emotionally negative, positive, and neutral words. Overall, subjects in the sleep-deprived condition exhibited a 40% reduction in memory retention relative to subjects who had slept normally prior to encoding (Figure 2A)—results that represent a striking impairment of declarative memory formation under conditions of sleep deprivation. When these data were separated into the three emotional categories (positive, negative, or neutral), the encoding deficit remained, although the magnitude of effect differed across the emotion categories (Figure 2B). In the sleep control group, both positive and negative stimuli were associated with superior retention levels relative to the neutral condition, consonant with the notion that emotion facilitates memory encoding.[11] In the sleep-deprived group, however, there was severe disruption of encoding and hence later memory retention for neutral and especially positive emotional memory; the retention deficit was a statistically significant 59% relative to those who slept normally. Most interesting, however, was the resistance of negative emotional memory to sleep deprivation, showing a markedly smaller (19%) and nonsignificant impairment.

From a clinical standpoint, these data may offer novel insights into affective mood disorders that express co-occurring sleep abnormalities.[12] Indeed, if one compares the two profiles of memory encoding (Figure 2B), it is clear that the sleep control group completes the encoding session with a balanced mix of both positive and negative memories. In contrast, those in the deprivation group had a skewed distribution, finishing the encoding session with an overriding dominance of negative memories and far fewer positive or neutral memories. This alteration in memory-encoding composition may provide a novel memory explanation for the higher incidence of depression in populations expressing impairments in sleep.[12,13]

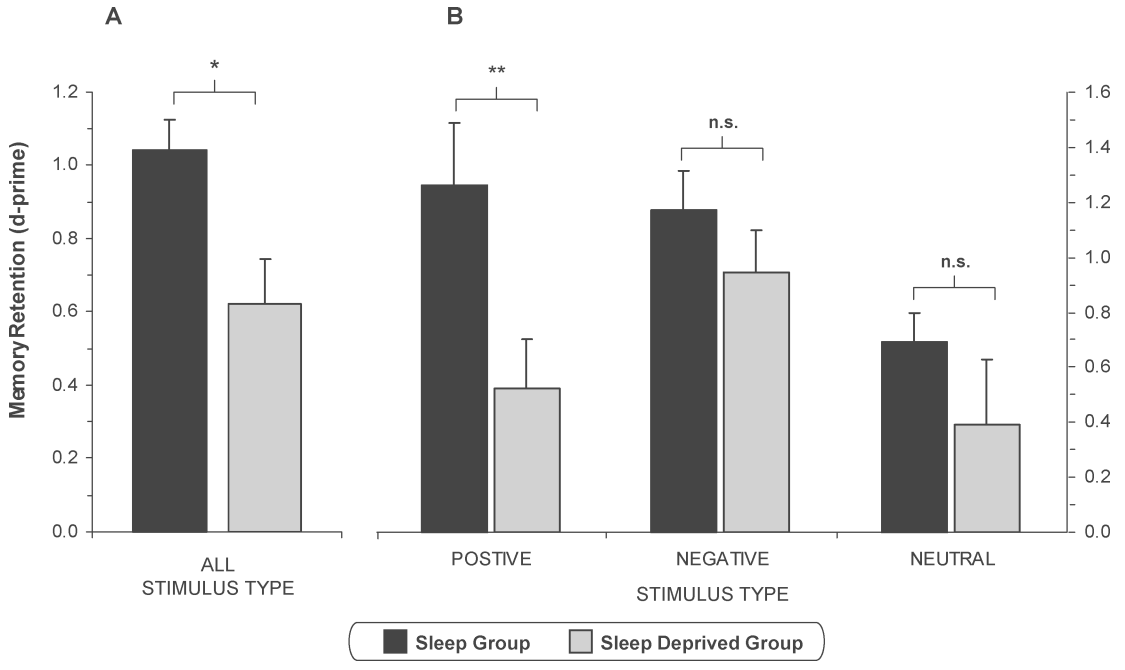

FIGURE 2. Sleep deprivation and encoding of emotional and nonemotional declarative memory. Effects of 36 hours of total sleep deprivation on encoding of human declarative memory (*A*) when combined across all emotional and nonemotional categories. (*B*) Effects when separated into emotional (positive and negative valence) and nonemotional (neutral valance) categories. $^{*}p < 0.05$; $^{**}p < 0.01$; error bars indicate standard error of the mean.

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In a recent follow-up study, we have started using functional MRI (fMRI) to explore the neural basis of impaired memory encoding following sleep loss.[14] In a protocol similar to that described above, young healthy subjects either were deprived of sleep for 36 hours prior to a learning session (sleep-deprivation group) or slept normally (sleep control group). At the learning session, performed during fMRI scanning, subjects were presented with a series of picture slides to learn (all neutral). When learning-related brain activation patterns were contrasted between the two groups, no significant differences were identified in prefrontal, parietal, or occipital regions. A highly selective, highly significant decreased level of activation was evident, however, in bilateral posterior hippocampal regions in the sleep-deprivation condition, compared to the sleep control condition (Figure 3).

These data illustrate that the condition of sleep loss can exert precise, selective impairments within the medial temporal lobe (MTL) and, in particular, the hippocampus during attempted new learning—deficits that are associated with a reduced capacity for memory formation. Of clinical relevance, these impairments in hippocampal encoding activity, along with the associated reduction in efficiency of new learning, show a remarkable correspondence with similar MTL impairments in activation reported in elderly cohorts (e.g., see Gutchess et al.).[15] These parallels suggest that the signature memory deficits observed in older adults may reflect an association not with age itself, but with impaired sleep, which—unlike other contributing cognitive factors in aging, such as reduced blood flow or white matter atrophy—is a potentially reversible circumstance.

SLEEP AND MEMORY CONSOLIDATION

In addition to the importance of sleep *before* learning, a plethora of work also demonstrates the critical requirement of sleep *after* learning, for later memory consolidation. Using a variety of behavioral paradigms, evidence of sleep-dependent memory consolidation has now been found in numerous species, including human and nonhuman primates, cats, rats, mice, and zebra finch.

Declarative Memory

Much of the early work investigating sleep and memory in humans focused on declarative learning tasks and offered mixed conclusions, some in favor of sleep-dependent memory processing and others against it. For example, De Koninck and colleagues[16] demonstrated significant increases in post-training REM sleep following intensive foreign language learning, with the degree of successful learning correlating with the extent of REM sleep increase. Such findings would suggest that REM sleep plays an active role in memory consolidation and that posttraining increases in such sleep reflect a homeostatic response to the increased demands for such consolidation. Other studies have reported no alteration, however, of posttraining sleep architecture following learning of a verbal memory task.[17–23] Recently, however, several studies by Born and his colleagues[24,25] have shown improvement on a word-pair associates task after early night sleep, rich in SWS, as well as modification of this posttraining sleep. These findings are striking in their consistency relative to earlier studies, which showed more

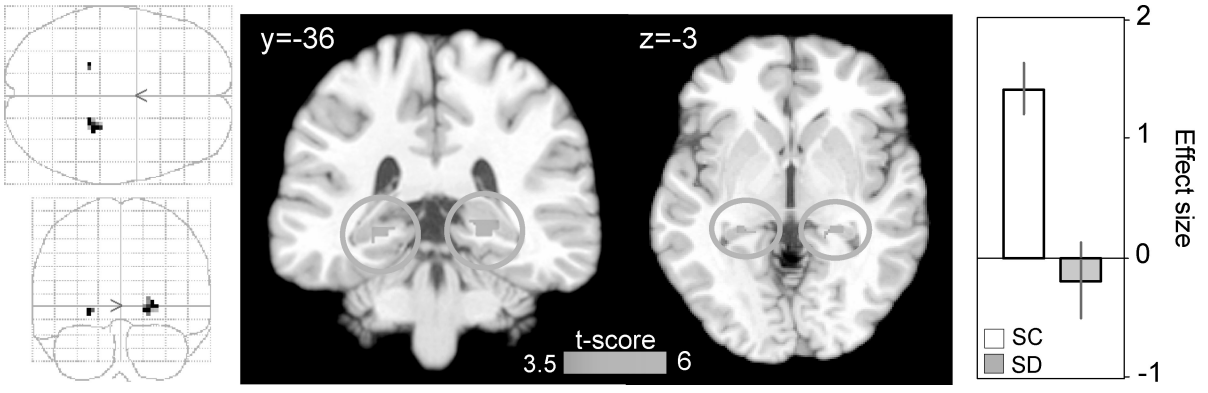

FIGURE 3. Regions of significantly reduced fMRI activation in the sleep-deprivation (SD) group relative to the sleep control (SC) group in bilateral posterior hippocampal regions ([peak Montreal Neurological Institute (MNI) space coordinates (x, y, z)]: left: -27, -33, 0, Z score = 3.53; right: 24, -36, -3, Z score = 3.52). From left to right of each figure are glass brain maximum-intensity plots, followed by corresponding color displays of significant difference (circled) on coronal and axial slices (respectively), together with histograms of parameter estimates (effect size) in the SC and SD groups ($n = 14$ in each) for averaged activity across the peak voxels in left and right posterior hippocampus. Histogram y-axis is in arbitrary units relative to baseline. Error bars represent standard error. Images are displayed in neurological convention, with left side corresponding to left hemisphere. Effects are significant at $p < 0.001$; > 5 contiguous voxels.

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variable effects. The discrepancy may partially reflect, however, the nature of the word pairs used. Whereas previous studies used unrelated word pairs, such as dog–leaf, Born and colleagues used related word pairs, such as dog–bone. The nature of the learning task thus shifts from forming and retaining completely novel associations (dog–leaf) to the strengthening or tagging of well-formed associations (dog–bone) for subsequent recall. Thus, sleep's role in declarative memory consolidation, rather than being absolute, might depend on more specific aspects of the consolidation task, such as the degree of semantic association.

Instead of simply testing memory recall or accuracy after sleep, Ellenbogen and colleagues[26] have recently used experimentally induced learning disruption to reveal the extent of sleep's ability to protect declarative memories. 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). 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), before being tested on the original A-B list. In the groups that did not experience the interfering challenge—simply being trained and then tested on list A-B—sleep provided a modest benefit to memory recollection (Figure 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 were able to sleep (Figure 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, 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.

A further example of such experimental subtlety pertains to the emotional nature of the material being learned. For example, it has been shown that late-night sleep, rich in REM sleep, selectively favors retention of emotional declarative texts relative to neutral texts.[27] Moreover, this benefit has been shown to persist, and to continue to be expressed, at least four years later, attesting to the longevity and ecological benefit of such sleep-dependent enhancements.[28] We have also investigated the time course of emotional and neutral episodic declarative memory consolidation across the day and overnight.[29] When the wake and sleep time periods were combined, significantly better emotional memory recognition was observed relative to neutral memory—again consistent with the notion that emotion enhances memory (Figure 5A). When the data were separated according to the wake and sleep periods, however, a remarkable dissociation

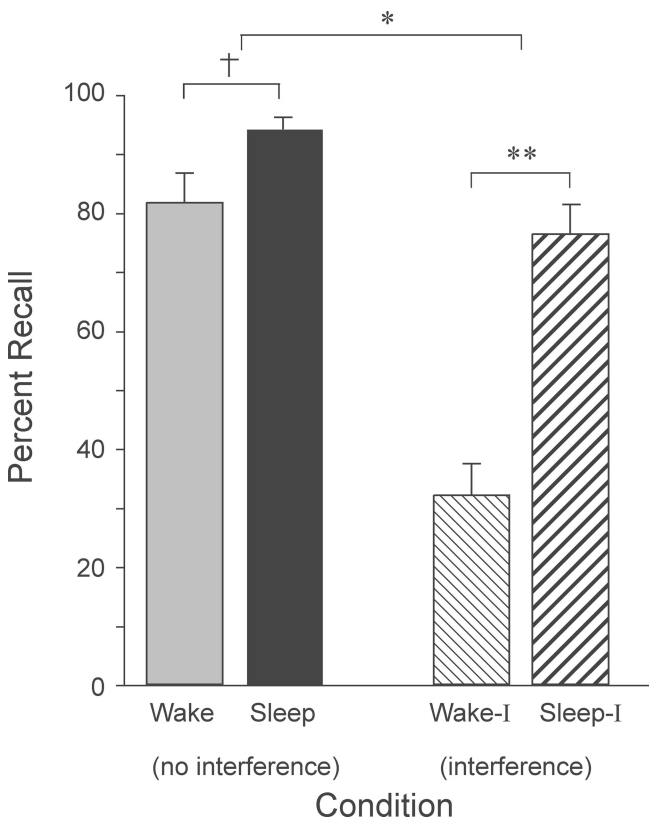

FIGURE 4. Percentage correct recall for B words from the original A-B pair after a 12-hour retention interval of either wake or sleep following no interference or interference learning (list A-C). The bar indicates one standard error of the mean. $^{\dagger}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.001$.

was evident (Figure 5B–C). While memory recognition was consistently superior following sleep, consolidation effects were especially strong for emotional rather than neutral stimuli, with recognition accuracy for emotional pictures improving by 42% overnight relative to the 12-hour waking period. Indeed, emotional memory performance following the wake period was no different than for neutral memory in either the wake or sleep conditions. These data indicate the selective facilitation of emotional declarative memory consolidation across sleep, rather than simply across time per se, resulting in the enhancement of memory retrieval.

It is important to note that such findings have only begun to test sleep-related effects at the most basic of memory levels—recognizing and recalling individual memories. Several recent studies have now explored more varied measures of memory, demonstrating that the strength and degree of associative memories are altered in a sleep-dependent manner. For example, it has been shown that REM sleep provides a brain state in which access to weak associations is selectively facilitated and in which flexible, creative processing of new information is enhanced.[30,31] It

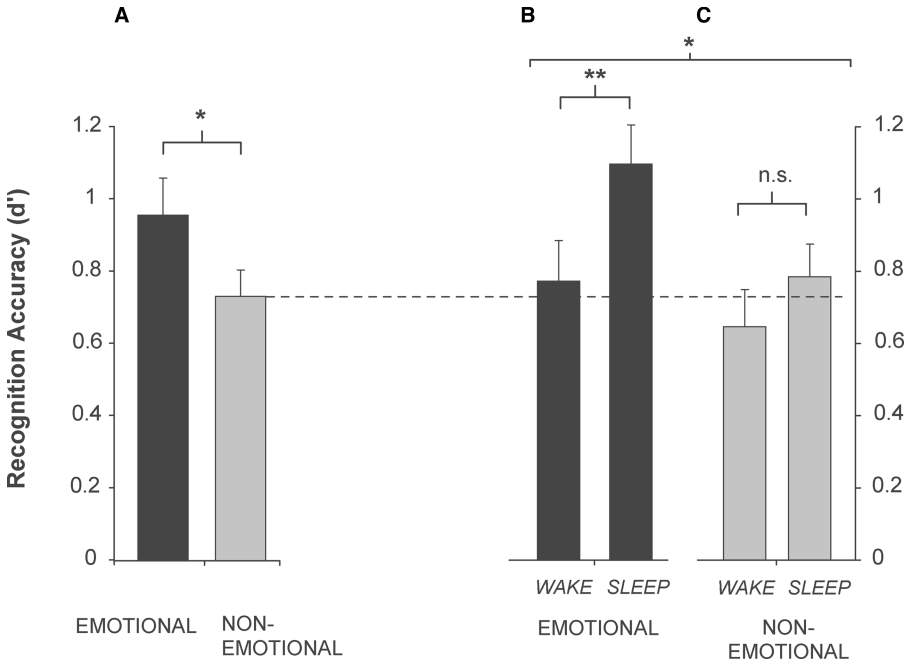

FIGURE 5. Sleep-dependent emotional memory consolidation. (*A*) Results for emotional and non-emotional memory recognition (d′) across 12 hours for sleep and wake conditions combined. (*B-C*) Results for the wake and sleep conditions separately, showing the significant facilitation of emotional memory following sleep and wake conditions separately. The dashed line is for comparison with non-emotional memory level in the sleep and wake conditions combined. Error bars indicate standard errors of the means. Significant differences between conditions and stimulus types are indicated by asterisks: $^{*}p < 0.05$; $^{**}p < 0.01$.

has also been demonstrated that, following initial practice on a numeric-sequence problem-solving task, a night of sleep can trigger insight into a hidden rule that can enhance performance strategy the following morning.[32] Moreover, a recent report demonstrated that a night of sleep not only strengthens individual item memories, but can actually build relational associations between them.[33] Indeed, the end goal of sleep-dependent memory processing may be not simply to enhance individual memories in isolation, but to integrate these memories into a common schema and, by doing so, facilitate the extraction of universal rules—a process that forms the basis of generalized knowledge. Considering the omnipresent co-occurrence of sleep disruption and memory impairment in affective and psychosocial clinical conditions, we should now start to consider such relationships as more causal, rather than simply co-occurring—an important future challenge in psychiatry.

Nondeclarative Procedural Memory

The reliance of procedural, nondeclarative memory on sleep is now a robust finding. These data span a wide variety of functional domains, including both perceptual and motor skills.

Motor learning. Motor skills have been broadly classified into two forms—motor adaptation (e.g., learning to use a computer mouse) and motor sequence learning (e.g., learning a piano scale). Beginning with motor sequence learning, we have shown that a night of sleep can trigger significant improvements in speed and accuracy on a sequential finger-tapping task, whereas equivalent periods of wake provide no significant benefit.[5,34,35] These sleep-dependent benefits appear to be specific to both the motor sequence learned and the hand used to perform the task. Furthermore, the gains from overnight learning correlate with the amount of stage 2 NREM sleep, particularly late in the night (Figure 6A–C); it is during this time window that sleep spindles—a defining electrophysiological characteristic of stage 2 NREM—reach peak density. Considering that sleep spindles have been proposed to trigger intracellular mechanisms required for synaptic plasticity, this late-night correlation may represent a time when sleep spindles may trigger key cellular events that, in turn, initiate mechanisms for neural plasticity.

Of particular clinical relevance have been recent attempts aimed at investigating impaired or abnormal sleep-dependent learning in different psychiatric cohorts. Using the sleep-dependent motor skill task, Manoach and colleagues[36] have shown that in chronic, medicated schizophrenics, initial practice-dependent learning during

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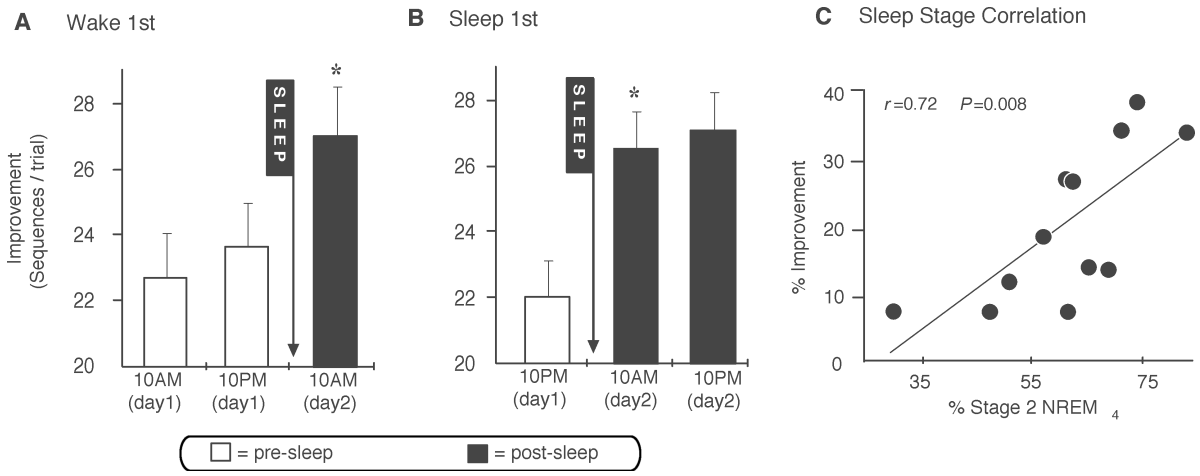

FIGURE 6. Sleep-dependent motor skill learning. (*A*) Wake first: After morning training (10 a.m., clear bar) subjects showed no significant change in performance when tested after 12 hours of wake time (10 p.m., clear bar). However, when tested again following a night of sleep (10 a.m., filled bar), performance had improved significantly. (*B*) Sleep first: After evening training (10 p.m., clear bar), subjects displayed significant performance improvements just 12 hours after training following a night of sleep (10 a.m., filled bar), yet expressed no further significant change in performance following an additional 12 hours of wake time (10 p.m., filled bar). (*C*) The amount of overnight improvement on the motor skill task correlated with the percentage of stage 2 non–rapid eye movement (NREM) sleep in the last (fourth) quarter of the night (stage 2 $NREM_4$). Asterisks indicate significant improvement relative to training, and error bars indicate standard error of the mean.

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training is remarkably similar to that of age-matched control subjects. When retested following a night of sleep, however, schizophrenic patients showed a total absence of normal overnight-learning improvements and, in fact, displayed a nonsignificant deterioration of performance, whereas age-matched controls express highly significant overnight improvement on day 2. While this study is not able to dissociate whether these overnight impairments are caused primarily by the disease, the medication, or a combination of both, they attest to a disruption of normal sleep-dependent procedural memory consolidation in a psychiatric population with known micro and macro impairments in sleep architecture.[37]

It has also been demonstrated that selective sleep deprivation impairs retention of a visuomotor adaptation task.[38] All subjects were trained and tested on the task and were retested one week later. Some subjects, however, were either completely or selectively deprived of different sleep stages across the first night following memory acquisition. At later retest, those deprived of stage 2 NREM sleep showed the most pronounced deficits in motor performance, which again suggests that stage 2 NREM is a crucial determinant of successful motor memory enhancement. Using high-density EEG, more recent studies have been able to show that daytime motor skill practice on a similar task is accompanied by a discrete increase in the subsequent amount of NREM slow-wave EEG activity over the parietal cortex at the start of the night, and that this increase in slow-wave activity is proportional to the amount of delayed learning that develops overnight; subjects showing the greatest increase in slow-wave activity in the parietal cortex that night produced the largest motor skill enhancement the next day.[39]

Visual perceptual learning. Learning of a visual texture discrimination task, which does not benefit from 4–12 hours of wake following training, has similarly been shown to improve significantly following a night of sleep and appears to require both SWS and REM sleep.[40,41] For example, overnight improvement has been shown to be specifically sleep dependent, not time dependent, and to correlate positively with the amount of both early-night SWS and late-night REM sleep. Indeed, the product of these two sleep parameters explains more than 80% of intersubject variance. Selective disruption of REM sleep or of either early sleep (normally dominated by SWS) or late-night sleep (normally dominated by REM and stage 2 NREM) results in a loss of overnight improvement, suggesting that consolidation of such memories is initiated by SWS-related processes but that subsequent REM sleep then promotes additional enhancement.[42] In addition, these delayed performance benefits have been shown to dependent on the first night of sleep following acquisition.

Procedural memory and daytime naps. Although the majority of sleep-dependent studies have investigated learning across a night of sleep, several reports have begun to examine the benefits of daytime naps on perceptual and motor skill tasks.[43] Based on evidence that motor learning continues to

develop overnight, we have explored the influence of daytime naps on motor sequence learning. Two groups of subjects trained on the task in the morning. One group took a 60–90 minute midday nap, while the other group remained awake.[10] When retested later that same day, subjects who had taken a 60–90 minute nap displayed a significant learning enhancement of nearly 16%, whereas the other subjects failed to show any significant improvement in performance speed across the day (Figure 7). Interestingly, however, when subjects were retested a second time following a subsequent full night of sleep, those subjects in the nap group showed only an additional 7% overnight increase in speed, whereas subjects in the control group, who had not napped the previous day, displayed speed enhancements of nearly 24% following the night of sleep. These results demonstrate that as little as 60–90 minutes of midday sleep is sufficient to produce large significant improvements in motor skill performance, whereas equivalent periods of wake produce no such enhancement. In addition, these data suggest there may be a limit to how much sleep-dependent motor skill improvement can occur over the course of 24 hours, such that napping changes the time course of when learning occurs, but not how much total delayed learning ultimately accrues. Thus, while both groups improved by approximately the same total amount 24 hours later (Figure 7), the temporal evolution of this enhancement was modified by a daytime nap.

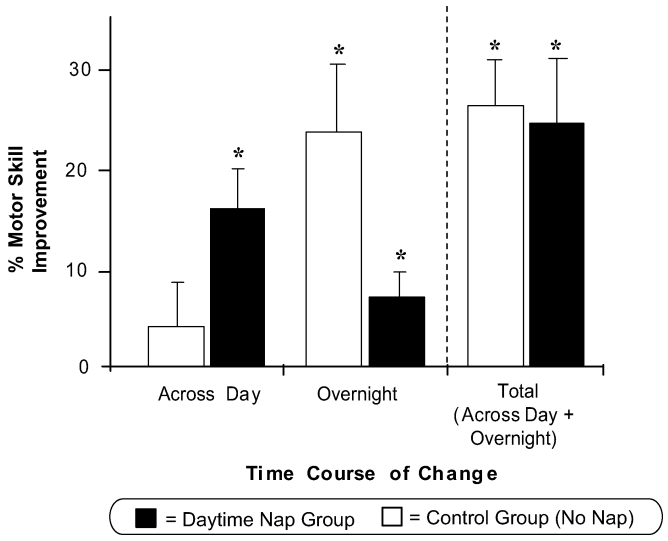

FIGURE 7. Daytime naps and motor skill learning. Subjects practiced the motor skill task in the morning and either obtained a 60- to 90-minute midday nap or remained awake across the first day. When retested later that same day, subjects who experienced a 60- to 90-minute nap (*filled bar*; Across Day) displayed significant performance speed improvements of 16%, whereas subjects who did not nap showed no significant enhancements (*clear bar*; Across Day). When retested a second time after a full night of sleep, subjects in the nap group showed only an additional 7% increase in speed overnight (*filled bar*; Overnight), whereas subjects in the control group showed a significant 24% overnight improvement following sleep (*clear bar*; Overnight). Therefore, 24 hours later, the groups averaged nearly the same total amount of delayed learning (*filled* and *clear bars*; Total). Asterisks indicate significant improvement and error bars indicate standard error of the mean.

As with motor skill learning, daytime naps also appear to benefit visual skill learning, although the characteristics of these effects are subtly different. For example, if a visual skill task is repeatedly administered across the day, performance deteriorates rather than remaining stable or improving. This deterioration may reflect a selective fatigue of brain regions recruited during task performance. However, if a 30- to 60-minute daytime nap is introduced among these repeated tests, the performance deterioration is decreased. If a longer nap period is introduced, ranging from 60 to 90 minutes and containing both SWS and REM sleep, performance not only returns to baseline, but is enhanced. Furthermore, these benefits did not prevent additional significant improvements across the following night of sleep, in contrast to findings for motor skill task performance.

SLEEP AND BRAIN PLASTICITY

Memory depends on brain plasticity—lasting structural or functional neural changes in response to stimuli (such as experiences). If sleep is to be considered a critical mediator of memory consolidation, then evidence of sleep-dependent plasticity would greatly strengthen this claim. In this final section, we consider a mounting wealth of data describing sleep-dependent brain plasticity; our focus here is on neuroimaging studies in humans.

Modification of Posttraining Sleep and Brain Activation

Several studies have investigated whether daytime learning is capable of modifying functional brain activation during subsequent sleep at night. Based on animal studies, neuroimaging experiments have explored whether the signature pattern of brain activity elicited while practicing a memory task actually reemerges—that is, is "replayed"—during subsequent sleep. Using positron emission tomography (PET), it has been shown that patterns of brain activity expressed during training on a motor sequence task reappear during subsequent REM sleep, whereas no such change in REM sleep brain activity occurs in subjects who received no daytime training.[44] Furthermore, the extent of learning during daytime practice exhibited a positive relationship to the amount of reactivation during REM sleep.[45] As with previously described animal studies, these findings suggest that it is not simply experiencing the task that modifies subsequent sleep physiology, but the process of learning itself. Similar findings have been reported using a virtual maze task.[46] Daytime task learning was initially

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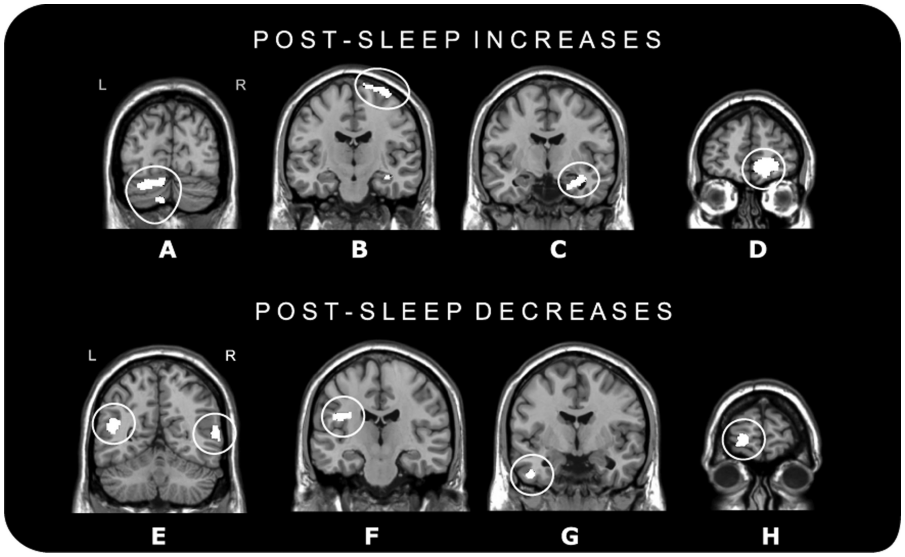

FIGURE 8. Sleep-dependent motor memory reorganization in the human brain. Subjects were trained on a sleep-dependent motor skill task and then tested 12 hours later, either following a night of sleep or following intervening wake, during a functional magnetic resonance imaging (fMRI) brain-scanning session. Scans after sleep and wake were compared (subtracted), resulting in regions showing increased fMRI activity postsleep (in circled white; $A - D$) or decreased signal activity (circled white; $E - H$) postsleep, relative to postwake. Activation patterns are displayed on coronal sections. Following sleep, regions of increased activation were identified in the right primary motor cortex (A), the left cerebellum (B), the right hippocampus (C), and the right medial prefrontal cortex (D). Regions of decreased activity postsleep were expressed bilaterally in the parietal lobes (E), together with the left insula cortex (F), left temporal pole (G), and left fronto-polar area (H), all regions of the extended limbic system. All data are displayed at a corrected threshold of $p < 0.05$.

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associated with hippocampal activity. Then, during post-training sleep, there was a reemergence of hippocampal activation, this time specifically during SWS. The most compelling finding, however, was that the amount of SWS reactivation in the hippocampus was proportional to the amount of next-day task improvement, which suggests that this reactivation is functional and leads to delayed memory improvement. Such sleep-dependent replay may potentially modify synaptic connections established within specific brain networks during practice, strengthening some synaptic circuits while potentially weakening others in the endeavor of refining the memory.

Overnight Reorganization of Memory Representations

A second research approach examines sleep-dependent plasticity by comparing patterns of brain activation before and after a night of sleep. In contrast to approaches that measure changes in functional activity during sleep, this technique aims to determine whether next-day learning improvements are associated with an overnight, sleep-dependent restructuring of the neural representation of the memory. Using a sleep-dependent motor skill task, we have recently investigated differences between patterns of brain activation before and after sleep using fMRI.[47] Following a night of sleep, and relative to an equivalent intervening period of wake, increased activation was identified in motor control structures of the right primary motor cortex (Figure 8A) and left cerebellum (Figure 8B)—changes that may allow more precise motor output and faster mapping of intention to key-press. There were also regions of increased activation in the medial prefrontal lobe and hippocampus (Figure 8C–D), structures recently identified as supporting improved sequencing of motor movements. In contrast, decreased postsleep activity was identified bilaterally in the parietal cortices (Figure 8E), possibly reflecting a reduced need for conscious spatial monitoring as a result of improved task automation, and regions of signal decrease throughout the limbic system were also observed (Figure 8F–H), indicating a decreased emotional task burden. Taken together, these findings suggest that sleep-dependent motor learning is associated with a large-scale plastic reorganization of memory throughout several brain regions, allowing skilled motor movements to be executed more quickly, more accurately, and more automatically following sleep.

Overnight reorganization of memory has similarly been demonstrated in sensory-perceptual systems using the sleep-dependent visual texture discrimination task, described earlier.[48] Testing after sleep, relative to without sleep, was associated with significantly greater activation in an area of primary visual cortex corresponding to the visual target location. Several other regions of increased postsleep

activity were also observed, however—throughout both the ventral object recognition (inferior parietal and occipital-temporal junction) and dorsal object location (superior parietal lobe) pathways—as were corresponding decreases in the right temporal pole, a region involved in emotional visual processing. Thus, a night of sleep also appears to reorganize the representation of visual skill memories; these changes seem to facilitate improved identification of both the stimulus form and its location in space.

While the above studies examined the benefit of a night of sleep, reports have also used a visuomotor adaptation task to investigate the detrimental effects of a lack of sleep on brain plasticity.[49] Subjects were trained on the task and tested three days later, with half the subjects deprived of sleep the first night. Controls, who slept all three nights, showed both enhanced behavioral performance at testing and a selective increase in activation in the superior temporal sulcus (a region involved in the evaluation of complex motion patterns), relative to subjects deprived of sleep the first night. In contrast, no such enhancement of either performance or brain activity was observed in these latter subjects, indicating that sleep deprivation had interfered with a latent process of plasticity and consolidation.

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SUMMARY

Over the last 25 years, the field of sleep and memory has grown exponentially, with the number of publications per year doubling every decade, faster than the growth for either sleep or memory alone. These reports, ranging from studies of cellular and molecular processes in animals to behavioral studies in humans, have provided converging evidence that pretraining sleep plays a critical role in preparing the brain for initial learning, while posttraining sleep is important in triggering memory consolidation and associated neural plasticity. In the end, the question appears to be not whether sleep mediates memory processing, but how it does so. The challenge to basic and clinical neuroscience will be both to further uncover the mechanisms of brain plasticity that underlie sleep-dependent memory consolidation, and to expand our understanding of sleep's role in memory processes beyond simple encoding and consolidation, and into the constellation of additional processes that are critical for efficient memory development. Work across the neurosciences will be necessary to answer these questions, but with the current rate of growth of research in the field, we can expect important advances in our understanding of this critical function of sleep. By way of such a multidisciplinary approach, and with a measured appreciation that sleep plays a fundamental role in forming, consolidating, integrating, and reforming memories, the most important tasks are to begin translating these basic findings into the clinical domain and, in turn, to understand how disease and pathology stemming from mental disorders can be understood through the lens of sleep-dependent memory failure.

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