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SLEEP, MEMORY, AND PLASTICITY

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■ **Abstract** Although the functions of sleep remain largely unknown, one of the most exciting hypotheses is that sleep contributes importantly to processes of memory and brain plasticity. Over the past decade, a large body of work, spanning most of the neurosciences, has provided a substantive body of evidence supporting this role of sleep in what is becoming known as sleep-dependent memory processing. We review these findings, focusing specifically on the role of sleep in (*a*) memory encoding, (*b*) memory consolidation, (*c*) brain plasticity, and (*d*) memory reconsolidation; we finish with a summary of the field and its potential future directions.

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INTRODUCTION

An exciting renaissance is currently under way within the biological sciences, centered on the question of why we sleep, and focusing specifically on the dependence of memory and plasticity on sleep. 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 (Hartley 1801). Yet it was not until 1924 that Jenkins and Dallenbach performed the first systematic studies of sleep and memory to test Ebbinghaus's theory of memory decay (Jenkins & Dallenbach 1924). Their findings showed that memory retention was better following a night of sleep than after an equivalent amount of time awake. However, they concluded 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 (Aserinsky & Kleitman 1953), that research began testing the hypothesis that sleep, or even specific stages of sleep, actively participated in the process of memory development. This review explores this relationship between what has become known as sleep-dependent memory processing and its associated brain basis, sleep-dependent plasticity.

DELINEATIONS AND DEFINITIONS

We begin our discussion of interactions between sleep and memory by clarifying the complexities that these terms encompass.

Sleep States

To begin, it is important to note that the brain does not reside in one single physiological state across the 24-hour day, but instead cycles through periods of differing neural and metabolic activity, 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 1*A*). In primates and felines, NREM sleep has been further divided into substages 1 through 4, corresponding to increasingly deeper states of sleep (Rechtschaffen & Kales 1968) (Figure 1*A*). The deepest NREM stages, stages 3 and 4, are collectively referred to as "slow wave sleep" (SWS), based on a prevalence of low-frequency cortical oscillations in the electroencephalogram (EEG). 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 (Hobson & Pace-Schott 2002). 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 consolidation.

Memory Categories

In the same way that sleep cannot be considered homogeneous, the spectrum of memory categories believed to exist in the human brain, and the processes that create and sustain memory, appear 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 (Schacter & Tulving 1994, Squire & Zola 1996) (Figure 1*B*). Declarative memory can be considered as the 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) (Tulving 1985). Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, especially the hippocampus (Eichenbaum 2000), 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 regarded as nonconscious, 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 be less dependent on medial temporal lobe structures.

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 to articulate speech, to memory of grammatical rules and structure, and through to aspects of declarative memory for the source of word selection. This too 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 develops it. Instead, memory appears to develop in several unique stages over time (Figure 1*C*). 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. Following 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 (McGaugh 2000). That is to say, the memory becomes more stable. It should be noted, however, that although most forms of memory appear to require subsequent consolidation following encoding, not all tasks appear to be resistant to competitive interference

almost immediately, and hence do not demonstrate this characteristic of time-dependent consolidation (Goedert & Willingham 2002).

Recent findings have begun to extend the definition of consolidation. For example, consolidation can be thought of as not only stabilizing memories, but also as enhancing them—two processes that may be mechanistically distinct (Walker 2005). The stabilization phase of consolidation appears to occur largely during wake cycles (Brashers-Krug et al. 1996, Muellbacher et al. 2002, Walker et al. 2003a). The enhancement stage appears to occur primarily, if not exclusively, during sleep, either restoring previously lost memories (Fenn et al. 2003) or producing additional learning (Fischer et al. 2002; Gais et al. 2000; Karni et al. 1994; Korman et al. 2003; Stickgold et al. 2000a,b; Walker et al. 2002a,b), 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 postencoding memory processing, with each phase occurring in specific brain states such as wake or sleep, or even in specific stages of sleep (Brashers-Krug et al. 1996; Karni et al. 1994; Muellbacher et al. 2002; Smith & MacNeill 1994; Stickgold et al. 2000b; Walker 2005; Walker et al. 2002a, 2003a,b).

Following its initial stabilization, a memory can be retained for days to years, during which time it can be recalled. But the act of memory recall itself is now believed to destabilize the memory representation, making it again labile and subject to potential degradation. Reconsolidation therefore has been proposed to transform the now destabilized memory into a restabilized form (Nader 2003). When a destabilized memory is not reconsolidated, it can degrade relatively quickly.

Although this chapter focuses primarily on the effects of sleep on encoding, stabilization, enhancement, and reconsolidation, it is important to note that additional postencoding stages of memory processing should also be appreciated. These 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), 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 (Stickgold & Walker 2005), and may also be considered stages of memory consolidation. It is interesting to note that sleep has already been implicated in all of these steps (Crick & Mitchison 1983, Stickgold 2002, Stickgold et al. 1999, Walker et al. 2003a).

SLEEP AND MEMORY ENCODING

Some of the first studies to investigate the relationship between sleep and human memory examined the influence of sleep on posttraining consolidation (see sections below) rather than its influence on initial encoding. However, more recent data have described the detrimental consequence of inadequate pretraining sleep on successful memory encoding. The section below offers an overview of this

evidence that spans a range of phylogeny and is supported across a variety of descriptive levels, from molecules to behavior.

Sleep and Memory Encoding—Human Studies

One of the earliest studies to report the effects of sleep deprivation on declarative memory encoding in humans was by Morris et al. (1960), who found that "temporal memory" (memory for when events occur) was significantly disrupted by a night of pretraining deprivation. These findings have been revisited in a more rigorous study by Harrison & Horne (2000), again using the temporal memory paradigm. The task comprised photographs of unknown faces, with the temporal memory component involving recency discrimination, together with a confidence judgment. Significant impairments of temporal memory were evident in a group deprived of sleep for 36 hours, which scored significantly lower than did controls; significant impairment was evident even in a 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.

Based on data from studies indicating that memory encoding (as measured by the success of later recall) relies on the integrity of the prefrontal cortex (PFC) (e.g., Brewer et al. 1998, Canli et al. 2000, Henson et al. 1999, Wagner et al. 1998), and that baseline PFC reductions in cerebral metabolic rate are evident following one night of deprivation, the authors hypothesized that sleep deprivation impaired prefrontal function critical for effective memory encoding.

In similar studies, Drummond et al. (2000) directly examined this hypothesis by using functional magnetic resonance imaging (fMRI) to investigate the effects of 35-hour total sleep deprivation on encoding of a verbal memory task. As in previous studies, total sleep deprivation resulted in significantly worse acquisition of verbal learning. Surprisingly, however, subjects showed more PFC activation during encoding when sleep deprived than when not sleep deprived. In contrast, regions of the medial temporal lobe were significantly less activated during encoding 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 memory encoding, and suggest that these impairments 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 (Drummond & Brown 2001).

We recently investigated the impact of sleep deprivation on declarative memory encoding of both emotional and nonemotional material (M.P. Walker, unpublished results). Subjects were either sleep deprived for 36 hours or allowed to sleep normally prior to an incidental memory encoding session composed of sets of emotionally negative, positive, and neutral words. Following two subsequent nights of sleep, subjects returned for an unexpected recognition task. Overall, subjects in the sleep-deprived condition exhibited a 40% reduction in memory retention

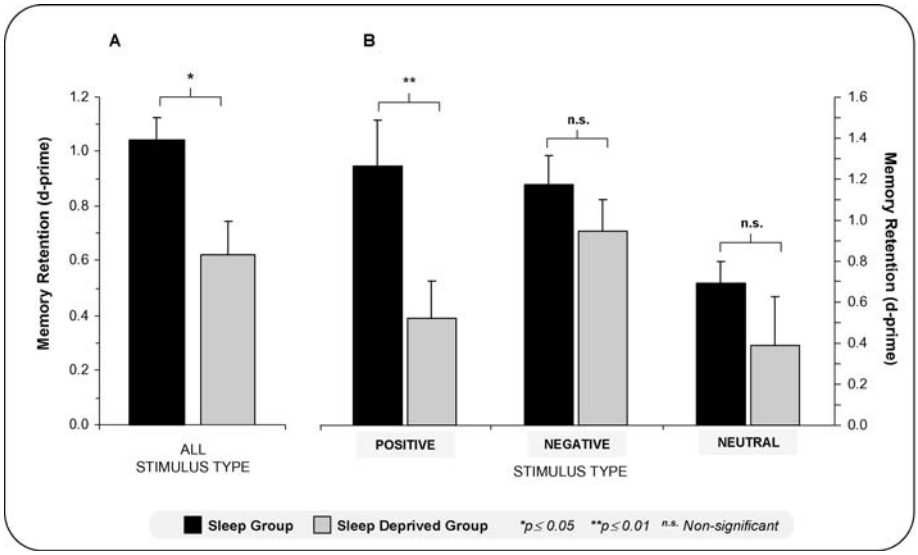

Figure 2 Sleep deprivation and encoding of emotional and nonemotional declarative memory. (*A*) Effects of 36 hours of total sleep deprivation on encoding of human declarative memory when combined across all emotional and nonemotional categories. (*B*) Effects when separated into emotional (positive and negative valence) and nonemotional (neutral valance) categories.

relative to subjects who had slept normally prior to encoding (Figure 2*A*); these results 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 2*B*). Within the sleep control group, both positive and negative stimuli were associated with superior retention levels relative the neutral condition, consonant with the notion that emotion facilitates memory encoding (Phelps 2004). However, there was severe disruption of encoding and hence later memory retention deficit for neutral and especially positive emotional memory in the sleep-deprived group, which exhibited a significant 59% retention deficit relative to the control condition for positive emotional words. Most interesting, however, was the resistance of negative emotional memory to sleep deprivation, showing a markedly smaller (19%) and nonsignificant impairment.

These data indicate that sleep deprivation severely impairs the encoding of declarative memories, resulting in significantly worse retention two days later. Although the effects of sleep deprivation are directionally consistent across subcategories, the most profound impact is on the encoding of positive emotional stimuli, and to a lesser degree, emotionally neutral stimuli, while the encoding of negative stimuli appears more resistant to the effects of prior sleep deprivation.

Sleep and Memory Encoding—Animal Studies

In animals, pretraining sleep deprivation has been demonstrated to impair the encoding of numerous memory tasks (Smith 1985, Stern 1971). For example, using the Morris water maze in a configuration that is hippocampally dependent (nonvisible platform), Guan et al. (2004) demonstrated that 6 hours of total sleep deprivation prior to training results in a severe disruption of encoding, as assessed by retention 24 hours later. In contrast, learning of the nonspatial task version (visible platform; hippocampally independent) was more resistant to prior sleep deprivation, suggesting first that the impairments for spatial memory were not a consequence of gross alternations in attention or stress, and second that sleep deprivation may selectively disrupt hippocampal-based encoding. Beaulieu & Godbout (2000) subsequently demonstrated that even selective deprivation of REM sleep for eight hours prior to training is sufficient to impair encoding on this task. Furthermore, in a more complex configuration of the task that requires increased frontal cortex involvement (continual switching of the platform location), prior REM sleep deprivation induced even greater retest deficits, which suggests that both basic hippocampal spatial memory and more complex spatial learning requiring additional frontal involvement are susceptible to a lack of prior REM.

REM sleep deprivation also has detrimental effects on the encoding of other hippocampally mediated tasks, including one-way and two-way avoidance learning, taste aversion, and passive avoidance tasks (see McGrath & Cohen 1978, Smith 1985). Even short (five-hour) bouts of pretraining REM sleep deprivation significantly impair encoding of two-way avoidance learning in rats, producing deficits that cannot be overcome by additional practice during training (Gruart-Masso et al. 1995).

An interesting dissociation of sleep deprivation effects is seen using a fear-conditioning task. The contextual versus cued memory paradigm in animals offers the ability to distinguish memory processing mediated primarily by the hippocampus (context) from that mediated primarily by the amygdala (cue). Using this task, Ruskin et al. (2004) demonstrated that pretraining sleep deprivation (predominantly REM) profoundly impaired contextual memory encoding ($>50\%$) measured 24 hours later, whereas cued learning was largely unaffected. These data suggest that pretraining sleep deprivation may affect memory encoding by neuroanatomically distinct systems, impairing hippocampal encoding processes while having only minor effects on encoding mediated by the amygdala (McDermott et al. 2003). These findings, which are strikingly similar to those described above in humans, suggest that encoding of both neutral and positive memory events are most severely impaired by sleep deprivation, while encoding of more negative stimuli, presumably in concert with the amygdala, exhibit greater immunity.

Building on these behavioral findings, a number of animal studies have gone on to explore the potential cellular and molecular underpinnings of sleep deprivation–induced encoding deficits; many of these studies have focused on the hippocampus. At the cellular level, REM sleep deprivation (ranging from of 24 to 72 hours) not

only reduces the basic excitability of hippocampal neurons, but also significantly impairs the formation of long-term potentiation [LTP; a foundational mechanism of memory formation (Kandel 2001)] within those neurons (Davis et al. 2003, McDermott et al. 2003). Furthermore, the LTP that does develop decays within 90 minutes, a finding that suggests that even in the event of successful LTP induction, hippocampal neurons are still unable to maintain these plastic changes after REM deprivation (Davis et al. 2003).

At the molecular level, nerve growth factor is significantly reduced in the hippocampus following six hours of REM sleep deprivation, and brain-derived neurotrophic factor is significantly decreased in the brain stem and cerebellum (Sei et al. 2000). This anatomically differentiated pattern of molecular disruption suggests a selective elimination of hippocampal nerve growth factor secretion, normally a key event in the regulation of neuronal plasticity (Kandel 2001). Finally, Guan et al. (2004) have explored the impact of prior sleep deprivation on levels of extracellular signal–regulated kinase (ERK)—a protein intimately linked to LTP formation and learning (Kelleher et al. 2004). When rats were trained on the hippocampally dependent Morris water maze following three or six hours of total sleep deprivation, behavioral encoding impairments were accompanied by significantly reduced levels of hippocampal ERK in the six-hour group (Figure 3), and to a lesser extent, in the three-hour group. Interestingly, when rats were allowed a short (two-hour) period of recovery sleep after the sleep deprivation, subsequent memory encoding and hippocampal ERK returned to normal levels (Figure 3).

SLEEP AND MEMORY CONSOLIDATION

In addition to the impact of prior sleep deprivation on memory encoding, a plethora of work also demonstrates the impact of sleep deprivation after learning on later memory consolidation. Through the use of 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.

Human Studies—Declarative Memory

Much of the early work investigating sleep and memory in humans focused on declarative learning tasks. These studies offered mixed conclusions, some in favor of sleep-dependent memory processing, and others against it. For example, De Koninck et al. (1989) demonstrated significant increases in posttraining REM sleep after intensive foreign language learning, with the degree of successful learning correlating with the extent of REM sleep increase. Such findings suggest that REM sleep plays an active role in memory consolidation, and that posttraining increases reflect a homeostatic response to the increased demands for such consolidation. However, Meienberg (1977) found no evidence of altered posttraining sleep architecture following learning of a verbal memory task. Similar inconsistencies have

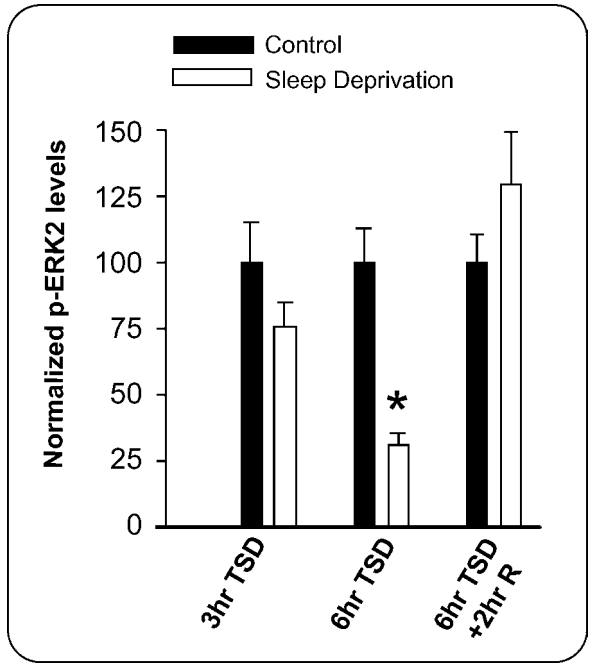

Figure 3 Phospho-extracellular signal-regulated kinase 2 (pERK2) in the rat hippocampus. pERK2 levels were significantly reduced after six hours total sleep deprivation (6 hr TSD), but returned to above control levels after two hours recovery (2 hr R) sleep following six hours sleep deprivation. Asterisk indicates significant difference between the control and sleep-deprived rats.

been reported both for the degree to which encoding of declarative memories alters subsequent sleep-stage properties and for the degree of learning impairment that follows selective sleep deprivation (e.g., Chernik 1972; Empson & Clarke 1970; Lewin & Glaubman 1975; Meienberg 1977; Plihal & Born 1997; Zimmerman et al. 1970, 1978). Recently, several studies by Born and his colleagues have shown actual improvement on a word-pair associates task after SWS-rich early night sleep (Gais & Born 2004), as well as modification of this posttraining sleep (Gais et al. 2002). These findings are striking in the face of earlier studies that showed no effect. However, the discrepancy may reflect the nature of the word pairs used. Whereas older studies used unrelated word pairs, such as dog–leaf, Born used related word pairs, such as dog–bone (Gais & Born 2004). 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, as with memory encoding, the role of sleep in declarative memory consolidation, rather than being absolute, might depend on more subtle aspects of

the information being learned. Indeed, several studies suggest that factors such as task difficulty (Empson & Clarke 1970, Tilley & Empson 1978) and emotional salience (Wagner et al. 2001) can strongly influence the degree of sleep dependency. Furthermore, a thorough examination of different declarative memory categories, including episodic and semantic forms, has not been completed (Cipolli & Salzarulo 1980), and such an investigation may further clarify the apparent contradictions regarding the roles of both SWS and REM sleep in declarative memory consolidation (Smith 2001).

Such studies have only begun to test sleep-related memory processes. Indeed, all of these studies have used tasks of recall and recognition as outcome measures, thereby focusing exclusively on processes of memory enhancement and resistance to normal decay, and no study has looked at such processes as memory stabilization, association, translocation, and reconsolidation, discussed above. More recent studies, however, have demonstrated that the strengths of associative memories are altered in a state-dependent manner. Two reports have shown that REM sleep provides a brain state in which access to weak associations is selectively facilitated (Stickgold et al. 1999), and flexible, creative processing of new information is enhanced (Walker et al. 2002b). It 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 (Wagner et al. 2004).

Taken as a whole, these studies suggest a rich and multifaceted role for sleep in the processing of human declarative memories. Although contradictory evidence is found for a role in the processing of simple, emotion-free declarative memories, such as the learning of unrelated word pairs, a substantial body of evidence indicates that both SWS and REM sleep contribute to the consolidation of complex, emotionally salient declarative memories, embedded in networks of previously existing associative memories. In light of this evidence, pronouncements of a lack of relationship between REM sleep and "memory" (e.g., Siegel 2001, Vertes & Eastman 2000) appear to be unfortunate overgeneralizations that disregard evidence that specific sleep stages play distinct roles in different stages of memory processing in separate memory systems.

Human Studies—Procedural Memory

The reliance of procedural, nondeclarative memory on sleep is now a robust and persistent finding. These data span a wide variety of functional domains, including both perceptual (visual and auditory) 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) (Doyon et al. 2003). Beginning with motor sequence learning, a night of sleep can trigger significant improvements in speed and accuracy on a sequential finger-tapping task, while equivalent periods of wake

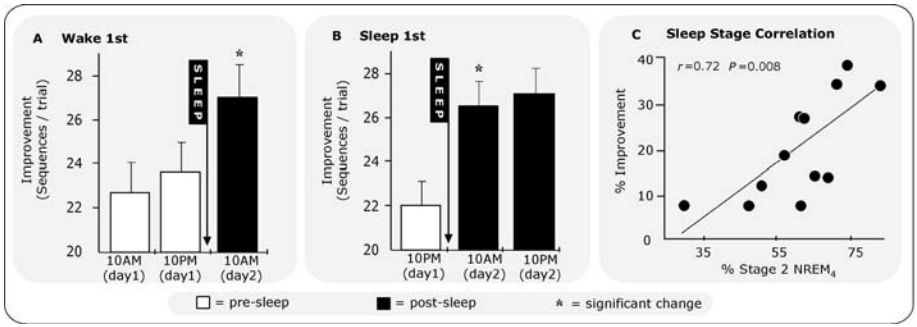

Figure 4 Sleep-dependent motor skill learning. (*A*) Wake first: After morning training (10 AM, *unfilled bar*), subjects showed no significant change in performance when tested after 12 hours of wake time (10 PM, *unfilled bar*). However, when tested again following a night of sleep (10 AM, *filled bar*), performance had improved significantly. (*B*) Sleep first: After evening training (10 PM, *unfilled bar*), subjects displayed significant performance improvements just 12 hours after training following a night of sleep (10 AM, *filled bar*), yet expressed no further significant change in performance following an additional 12 hours of wake time (10 PM, *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.

provide no significant benefit (Walker et al. 2002a). These sleep-dependent benefits appear to be specific to both the motor sequence learned and hand used to perform the task (Fischer et al. 2002, Korman et al. 2003). Furthermore, overnight learning gains correlate with the amount of stage 2 NREM sleep, particularly late in the night (Figure 4*A–C*) (Walker et al. 2002a). This sleep window corresponds to a time when sleep spindles—a defining electrophysiological characteristic of stage 2 NREM—reach peak density (De Gennaro et al. 2000). Spindles have been proposed to trigger intracellular mechanisms required for synaptic plasticity (Sejnowski & Destexhe 2000), and they increase following training on a motor task (Fogel et al. 2001). Thus, sleep spindles produced in late-night sleep may trigger key cellular events that in turn initiate mechanisms for neural plasticity.

At the behavioral level, the motor sequence task described above has been dissected to determine where in the motor program this sleep-dependent improvement occurs (Kuriyama et al. 2004). More specifically, differences in transition speeds between each of the separate key-press movements, before and after sleep, were analyzed. For example, in the sequence 4-1-3-2-4, there are four unique key-press transitions: (*a*) from 4 to 1, (*b*) from 1 to 3, (*c*) from 3 to 2, and (*d*) from 2 to 4. When individual subjects' transition-speed profiles were analyzed before sleep, the speed of individual key-press transitions within the sequence were not equal (Figure 5*A*, unfilled circles), with some transitions seemingly easy (fast) and others problematic (slow), as if the entire sequence was being parsed into smaller

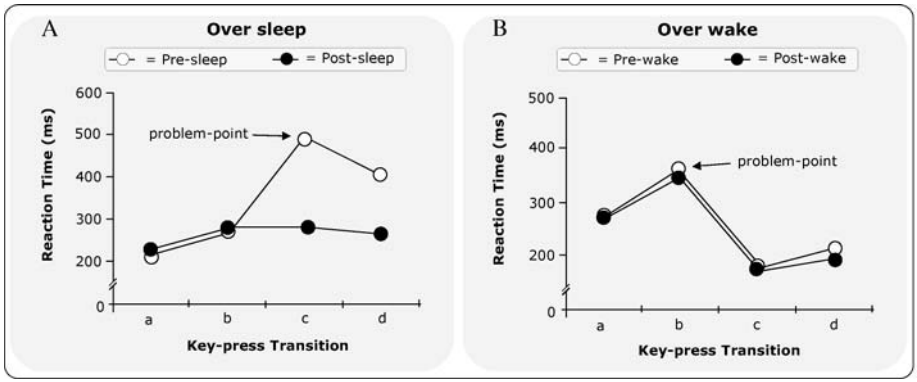

Figure 5 Single-subject examples of changes in transition speeds. Within a five-element motor sequence (e.g., 4-1-3-2-4), there are four unique key press transitions: (*a*) from 4 to 1, (*b*) from 1 to 3, (*c*) from 3 to 2, and (*d*) from 2 to 4. (*A*) The transition profile at the end of training before sleep (*unfilled circles*) demonstrated considerable variability, with certain transitions being particularly slow (most difficult; "problem points"), whereas other transitions appear to be relatively rapid (easy). Following a night of sleep (*filled circles*), there was a specific reduction (improvement) in the time required for the slowest problem point transition. (*B*) Similarly, at the end of training before a waking interval, transition profiles were uneven (*unfilled circles*), with some particularly slow transitions (problem points) and other relatively fast transitions (easy). However, in contrast to postsleep changes, no change in transition profile was observed following eight hours of wake (*filled circles*).

subsequences during initial learning [a phenomena termed "chunking" (Sakai et al. 2003)]. Surprisingly, after a night of sleep, the problematic slow transitions ("problem points") were preferentially improved, whereas transitions that had already been effectively mastered prior to sleep did not change (Figure 5*A*, filled circles). Most remarkable, however, in subjects who were trained and retested after an eight hour waking interval across the day, no such improvement was seen in the profile of key-press transitions at any location within the sequence (Figure 5*B*).

These findings suggest that the sleep-dependent consolidation process involves the unification of smaller motor memory units into one single memory element by selectively improving problem regions of the sequence. This overnight process would therefore offer a greater degree of performance automation, effectively optimizing speed across the motor program, and would explain the sleep-dependent improvements in speed and accuracy previously reported. But more importantly, it again suggests that the role of sleep is more subtle and complex than to simply increase the strength of existing memory representations.

Using a different sequential finger-tapping task (finger-to-thumb movements rather than keyboard typing), Fisher et al. (2002) have shown that sleep during the first day or night following training is critical for the delayed performance improvements. In their case, however, they described a correlation between overnight

improvement and amounts of REM sleep rather than stage 2 NREM. This discrepancy remains to be resolved, but it is possible that the more novel finger-to-thumb task requires REM sleep, whereas the keyboard typing version, a simple variant of a well-learned skill (i.e., typing), is consolidated during stage 2 NREM. A similarly subtle distinction has been reported by Robertson et al. (2004), who recently demonstrated sleep-dependent enhancement of performance on a perceptual-motor sequence task when there was explicit awareness of the presence of a repeating sequence, but not when awareness was only gained implicitly. In this study, delayed overnight learning with explicit awareness correlated with amounts of NREM sleep.

Moving from motor sequence learning to motor adaptation learning, Smith & MacNeill (1994) have shown that selective sleep deprivation impairs retention of a visuomotor adaptation task. All subjects were trained and tested on the task and were retested one week later. However, some subjects were either completely or selectively deprived of different sleep stages across the first night following memory acquisition. At later retest, subjects 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.

Huber et al. (2004) have similarly demonstrated that following initial memory acquisition of a motor reaching-adaptation task, delayed learning was observed exclusively across a night of sleep, and not across equivalent periods of wake. Furthermore, through the use of high-density EEG, they were able to show that daytime motor skill practice was 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 was proportional to the amount of delayed learning that developed 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.

Taken together, these reports build a convincing argument in support of sleep-dependent learning across several forms of motor skill memory. All these studies indicate that a night of sleep triggers delayed learning, without the need for further training. In addition, overnight motor skill improvements consistently display a strong relationship to NREM sleep, and, in some cases, to specific NREM sleep-stage windows at specific times in the night.

VISUAL PERCEPTUAL LEARNING Learning of a visual texture discrimination task, which does not benefit from 4–12 hours of wake following training (Stickgold et al. 2000b), improves significantly following a night of sleep (Karni et al. 1994) and appears to require both SWS and REM sleep. Selective disruption of REM sleep resulted in a loss of overnight improvement (Karni et al. 1994). Similarly, selective deprivation of either early sleep (normally dominated by SWS) or late-night sleep (normally dominated by REM and stage 2 NREM) impair overnight consolidation, a finding that suggests that consolidation is initiated by SWS-related processes, but that subsequent REM sleep then promotes additional enhancement (Gais et al.

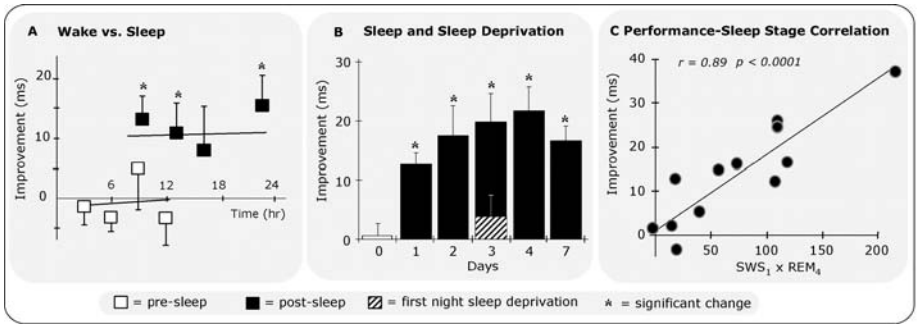

Figure 6 Sleep-dependent visual skill learning. Subjects were trained (during which time, baseline performance was measured) and then retested at a later time; improvement [ms (milliseconds)] in performance is illustrated across time. Each subject was retested only once, and each point represents a separate group of subjects. (*A*) Wake versus sleep: Subjects who were trained and then retested on the same day, after either 3, 6, 9, or 12 hours of subsequent wake (*unfilled squares*) showed no significant improvement as a consequence of the passage of waking time across at any of the four time points. In contrast, subjects who were trained and then retested 8, 12, 15, or 23 hours after one night of sleep (*filled squares*) showed a significant improvement occurring as a consequence of sleep. In total, $n = 57$, with $n = 7$ to 9 for individual points. (*B*) Sleep and sleep deprivation. Subjects ($n = 89$) who were trained and retested 1–7 days later (*filled bars*) continued to improve after the first night, without additional practice. Subjects ($n = 11$) sleep deprived the first night after training showed no improvement (*crosshatched bar*), even after two nights of recovery sleep. (*C*) Overnight improvement was correlated with the percent of slow-wave sleep (SWS) in the first quarter of the night (SWS_1) and rapid eye movement (REM) sleep in the last quarter of the night (REM_4). $^*p < 0.05$; error bars indicate standard error of the mean.

2000). Overnight improvement is specifically sleep dependent, not time dependent (Figure 6*A*) (Stickgold et al. 2000b), and correlates 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 (Figure 6*C*). In addition, these delayed performance benefits are absolutely dependent on the first night of sleep following acquisition (Figure 6*B*) (Stickgold et al. 2000a).

AUDITORY LEARNING Evidence of sleep-dependent auditory skill learning has also been reported. Using a pitch memory task, Gaab et al. (2004) have shown that delayed performance improvements develop only across a night of sleep and not across similar wake periods. Atienza and colleagues have also described evidence of both time- and sleep-dependent auditory memory consolidations, including sleep-dependent changes in brain-evoked response potentials (ERPs) (Atienza et al. 2002, 2004). Although posttraining sleep deprivation did not prevent continued behavioral improvements, ERP changes normally associated with the automatic shift of attention to relevant stimuli failed to develop following a posttraining night

of sleep deprivation. These findings make clear the danger of presuming that a lack of behavioral improvement is equivalent to an absence of beneficial plastic changes within the brain, and they highlight the importance of using combined behavioral and physiological analyses. Finally, Fenn et al. (2003) have shown periods of wake following training on a synthetic speech-recognition task result in a degradation of task performance that a subsequent night of sleep can restore, which suggests a process of sleep-dependent consolidation capable of reestablishing previously learned complex auditory skill memory.

It therefore appears that, as with motor skills, learning of perceptual skills, both visual and auditory, depends on sleep for the development of delayed learning, and several different sleep stages may be involved in producing this form of overnight consolidation.

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. Based on evidence that motor learning continues to develop overnight, the influence of daytime naps on the sequential finger-tapping task has been explored (Walker & Stickgold 2005). Two groups of subjects were trained on the task in the morning. One group subsequently obtained a 60- to 90-minute midday nap while the other group remained awake. When retested later that same day, those subjects who napped displayed a significant 16% learning enhancement, whereas those who did not nap showed no significant improvement (Figure 7). This nap-mediated improvement is, however, at the expense of subsequent overnight learning. Thus, although the control subjects showed 24% improvement overnight, the nap subjects showed only an additional 7%, for a total of 23%—essentially identical to that seen in the control group.

As with motor skill learning, daytime naps also appear to benefit visual skill learning, although the characteristics of these effects are subtly different. Mednick and colleagues have shown that if a visual skill task is repeatedly administered across the day, performance deteriorates rather than remaining stable or improving (Mednick et al. 2002). This may reflect a selective fatigue of brain regions recruited during task performance, a characteristic not observed in the motor system. However, if a 30- to 60-minute daytime nap is introduced among these repeated tests, the performance deterioration is ameliorated. 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 also is enhanced (Mednick et al. 2003). Furthermore, these benefits did not prevent additional significant improvements across the following night of sleep, in contrast to findings for motor skill task performance.

Together these studies build a cohesive argument that daytime naps confer a robust learning benefit to both visual and motor skills and, in the case of visual skill learning, are capable of restoring performance deterioration caused by repeated practice across the day.

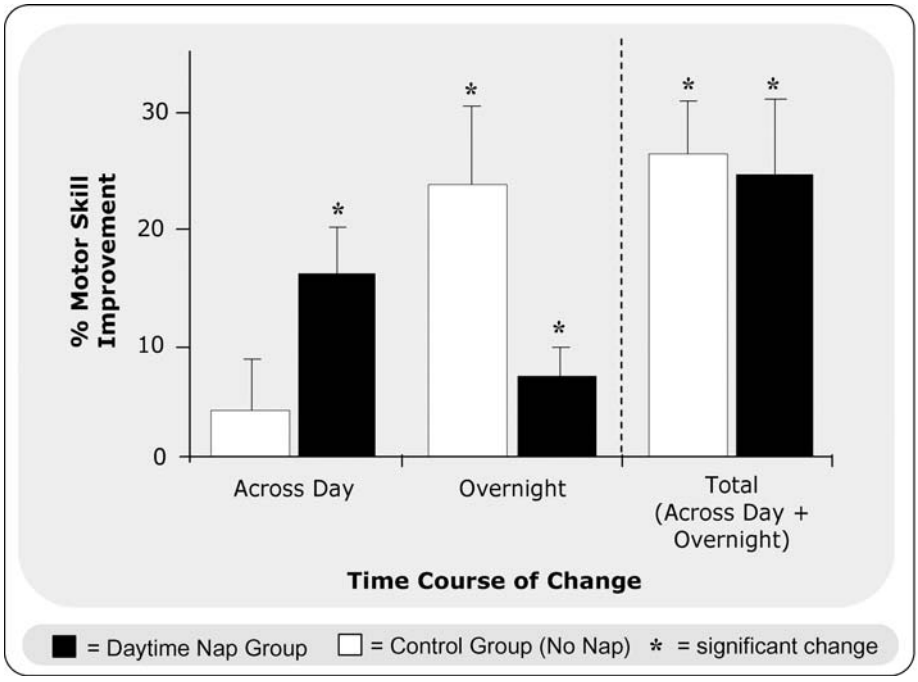

Figure 7 Daytime naps and motor skill learning. Subjects practiced the motor skill task in the morning, and either obtained a 60- to 90-minute midday nap or remained awake across the first day. When retested later that same day, subjects who experienced a 60- to 90-minute nap (*filled bar*, Across Day)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

SLEEP AND BRAIN PLASTICITY

Memory formation depends on brain plasticity—lasting structural and/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 section, we consider a mounting wealth of data describing sleep-dependent brain plasticity; our focus is on neuroimaging studies in humans (see Walker & Stickgold 2004 for a detailed discussion of cellular and molecular data).

Modification of Posttraining Sleep and Brain Activation

Several studies have investigated whether daytime training is capable of modifying functional brain activation during subsequent sleep. Based on animal studies, neuroimaging experiments have explored whether the signature pattern of brain activity elicited while practicing a memory task actually reemerges, i.e., is "replayed," during subsequent sleep. Using brain imaging, Maquet and colleagues have shown that patterns of brain activity expressed during training on a serial reaction time motor task reappear during subsequent REM sleep, whereas no such change in REM sleep brain activity occurs in subjects who received no daytime training (Maquet et al. 2000). Furthermore, the extent of learning during daytime practice exhibits a positive relationship to the amount of reactivation during REM sleep (Peigneux et al. 2003). As with previously described animal studies (Datta 2000), 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. Daytime task learning is initially associated with hippocampal activity. Then, during posttraining sleep, there was a reemergence of hippocampal activation, this time specifically during SWS. The most compelling finding, however, is that the amount of SWS reactivation in the hippocampus is proportional to the amount of next-day task improvement, which suggests that this reactivation leads to off-line memory improvement (Peigneux et al. 2004). 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 approach, which more directly examines sleep-dependent plasticity, compares 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 improved performance results from an overnight, sleep-dependent *restructuring* of the neural representation of the memory. Using the sleep-dependent motor skill task, differences between patterns of brain activation before and after sleep have recently been investigated using fMRI (Walker et al. 2005a). Following a night of sleep, and relative to an equivalent intervening period awake, increased activation was identified in motor control structures of the right primary motor cortex (Figure 8*A*) and left cerebellum (Figure 8*B*)—changes that allow more precise motor output (Ohyama et al. 2003) and faster mapping of intention to key-press (Ungerleider et al. 2002). There were also regions of increased activation in the medial prefrontal lobe and hippocampus (Figure 8*C*,*D*), structures recently identified as supporting improved sequencing of motor movements (Koechlin et al. 2000, 2002; Poldrack & Rodriguez 2003; Schendan et al. 2003). In contrast, decreased activity postsleep was identified bilaterally in the parietal cortices (Figure 8*E*), possibly reflecting a reduced need for conscious spatial monitoring (Muller et al. 2002,

Seitz et al. 1990, Toni et al. 1998) as a result of improved task automation (Kuriyama et al. 2004), together with regions of signal decrease throughout the limbic system (Figure 8*F–H*), which suggests a decreased emotional task burden. In total, these results 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. These findings hold important implications for understanding the brain basis of perfecting real-life skills and may signify a potential role for sleep in clinical rehabilitation following brain damage.

fMRI has also been used to investigate whether overnight reorganization similarly occurs in sensory-perceptual systems using the sleep-dependent visual texture discrimination task described earlier (Walker et al. 2005b). Subjects were trained with or without intervening sleep. Relative to the condition without sleep, retest following sleep was associated with significantly greater activation in an area of primary visual cortex corresponding to the visual target location. However, there were also several other regions of increased postsleep activity, throughout both the ventral object recognition (inferior parietal and occipital-temporal junction) and dorsal object location (superior parietal lobe) pathways (Ungerleider & Haxby 1994), together with corresponding decreases in the right temporal pole, a region involved in emotional visual processing. Thus, a night of sleep appears to reorganize the representation not only of procedural motor but also of visual skill memories, with greater activation throughout the visual processing streams offering improved identification of both the stimulus form and its location in space, and with signal decreases in the temporal pole reflecting a reduced emotional task burden resulting from the overnight learning benefits.

Maquet et al. (2003) have investigated the detrimental effects of sleep deprivation on underlying brain activity using a visuomotor adaptation task—the only such study to date. Subjects were trained on the task, tested, and retested three days later, with half the subjects deprived of sleep the first night. At retest, subjects performed both the previously learned motor task and a new, related task. Controls, who slept all three nights, showed both enhanced behavioral performance at retest 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 subjects, indicating that sleep deprivation had interfered with a latent process of plasticity and consolidation. This study indicates that sleep deprivation disrupts not only consolidation, but also the underlying neural mechanisms that support it.

SLEEP AND MEMORY RECONSOLIDATION

Reconsolidation

Recent studies (Nader 2003) suggest that upon recall of previously consolidated information, the memory returns to an unstable state, once more requiring

consolidation, or "reconsolidation." But we know much less about memory reconsolidation than we do about memory consolidation. Although originally reported in the 1960s (Misanin et al. 1968, Schneider & Sherman 1968), the details of memory reconsolidation have only recently come under intensive investigation (Nader 2003), and most of these more recent studies have focused on the degree to which the process of reconsolidation is the same as or different from the initial processes of encoding and stabilization (Alberini 2005). But additional questions have not been as widely addressed. Conceptually, a consolidated memory can undergo at least four processes: (*a*) reactivation, which leads to (*b*) destabilization, which in turn leads to either (*c*) degradation or (*d*) reconsolidation. Yet the temporal evolution of these individual steps, the mechanisms and brain states that produce them, and even their biological functions, remain unclear.

Time Course of Reconsolidation

Determining the time course over which destabilization develops is difficult since neither cellular-molecular nor behavioral correlates have been identified. But its duration has been studied extensively because, by definition, the destabilized state ends when reconsolidation is completed. For example, when reconsolidation of learning on a radial maze task was blocked with propanalol either 5 minutes, 2 hours, or 5 hours after reexposure to the maze (and, presumably, reactivation of the memory), error rates, measured 24 hours after reactivation, increased sixfold, threefold, or not at all, respectively (Przybyslawski et al. 1999), which suggests a half-life for the destabilized state of about 2 hours. Inhibition of reconsolidation for conditioned taste aversion showed a similar half-life for the destabilized state, on the order of 1 hour, with reconsolidation again apparently complete by 6 hours (Gruest et al. 2004). Similarly, protein synthesis inhibitors injected 6 hours after reexposure had no effect on destabilized fear-conditioned memories (Nader et al. 2000). Thus, reconsolidation would appear to be complete (and hence, destabilization ended) 6 hours after reexposure, at which time the memory trace is again resistant to interference.

Once destabilized, and in the absence of subsequent reconsolidation, degradation of a memory has generally been considered a passive process, perhaps based on molecular turnover. Alternatively, it may be that the memory is not degraded at all, but its recall blocked. The nature of this degradation currently remains unclear, and degradation is defined behaviorally as diminished performance of the learned task.

Little data is available on the time course over which degradation occurs. Following reactivation and blockade of reconsolidation, previously learned behaviors are still intact 2 hours (Suzuki et al. 2004) and 4 hours (Debiec et al. 2002, Duvarci & Nader 2004, Nader et al. 2000) later, with no sign that degradation has begun. This makes sense because reconsolidation appears to take at least this long and it would be counterproductive for memories to begin to degrade before reconsolidation normally has completed. At the other end of the process, any degradation of the memory appears to be complete 24 hours after reactivation (Boccia et al. 2004, Debiec & Ledoux 2004, Duvarci & Nader 2004; see also Myers & Davis 2002).

Hints of the complex mechanisms governing reconsolidation as well as its possible function come from studies showing that inhibitors of cholinergic (Boccia et al. 2004) and noradrenergic (Przybyslawski et al. 1999) neuromodulation can also block reconsolidation. In addition, N-methyl-D-aspartate antagonists reportedly can block the destabilization normally associated with reactivation (Nader et al. 2004). Thus, the reconsolidation process appears to be controlled by a number of neuromodulators and plasticity-related neurotransmitters. But perhaps the most direct evidence of a functional role for modulation of reconsolidation comes from human studies of sleep-dependent memory processing.

Sleep and Reconsolidation

As was described above for memory consolidation, it generally has been assumed that reconsolidation processes progress over a fixed time, independent of brain state. Yet as more and more phases of consolidation are found to be influenced by, and in some cases dependent on, sleep, it is important to ask what role sleep might play in reconsolidation and its associated processes. Although few data pertain directly to this question, we offer the hypothesis that both degradation and reconsolidation processes can, and in some circumstances must, occur during sleep. Indeed, most rodent studies of reconsolidation have been carried out during the light (sleep) phase of the circadian cycle, and it is likely that animals in these studies slept between reactivation and subsequent measurements of reconsolidation.

Evidence suggesting a role for sleep comes again from the human motor sequence task discussed above (Walker et al. 2003a). When retested 24 hours after training (on day 2), subjects showed overnight sleep-dependent enhancements of both speed and accuracy (Figure 9*A*, none). However, if subjects trained on a second, competing sequence 10 minutes after the first sequence on day 1, interference effects on sleep-dependent consolidation were observed the next day (Figure 9*A*, 10′); the normal delayed overnight improvement in accuracy was completely blocked (Walker et al. 2002a). When the time between learning the two sequences was increased from 10 minutes to either 6 hours or 24 hours, no significant interference was observed (Figure 9*A*, 6 hr and 24 hr). Thus, stabilization of the memory occurred over a period between 10 minutes and 6 hours, affording the original memory immunity from the interfering effects of a second competing memory, immunity that was still present 24 hours later, following sleep.

In contrast, when the original memory was reactivated at 24 hours (through 90 seconds of rehearsal), just prior to interference training on day 2, a 57% decrease in accuracy was seen across the subsequent night of sleep (Figure 9*B*, 48 hr), returning subjects' accuracy to slightly below the level seen at the end of the original training session. Thus, reactivation led to destabilization of the sleep-enhanced memory. Presumably, under normal conditions, in the absence of competing interference training, the memory would become restabilized over the next 6 hours, becoming once again resistant to interference, although such reconsolidation was not explicitly measured.

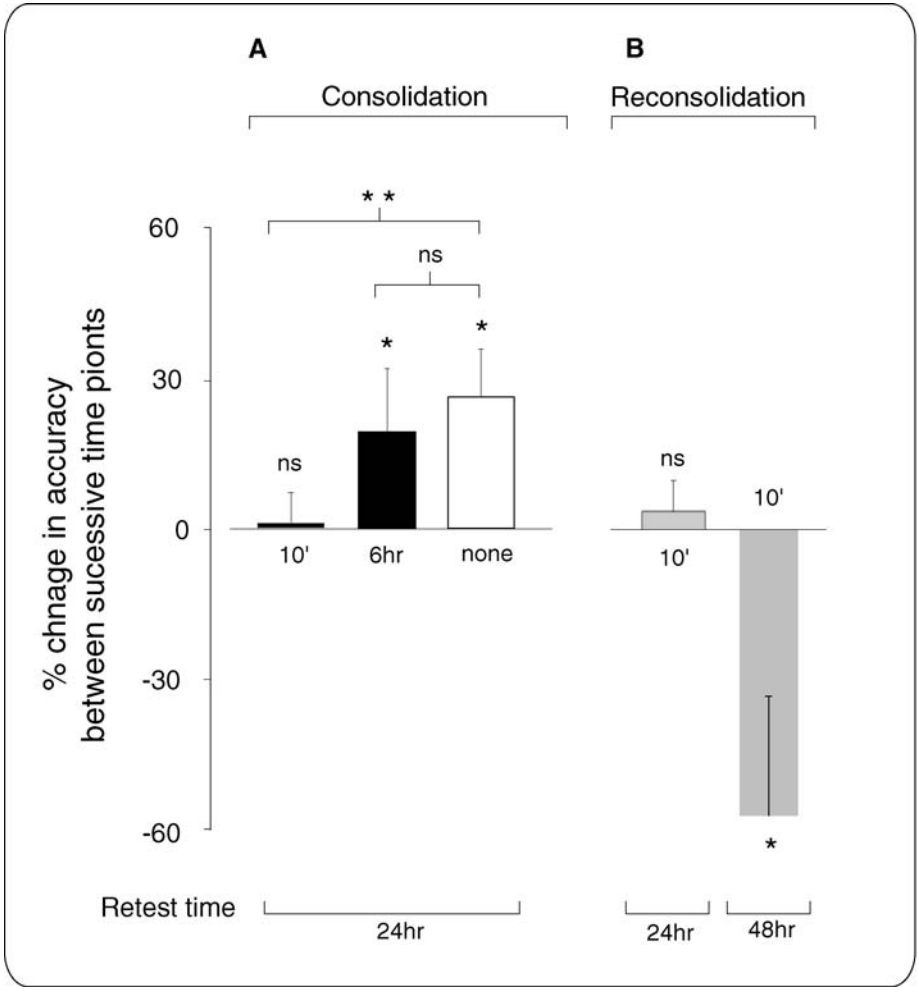

Figure 9 Reconsolidation of sleep-dependent learning. (*A*) Consolidation: Overnight improvement in accuracy was blocked by interference training (a second competing motor sequence, *filled bars*) at 10′, but not at 6 hours posttraining relative to controls without interference (none, *unfilled bar*). (*B*) Reconsolidation: Interference training 10′ after reactivation (retest time 24 hours, *gray bar*) did not cause an immediate deterioration in the overnight improvement, but 24 hours after reactivation and interference training, the initial overnight improvement was abolished (retest time 48 hours, *gray bar*). Asterisks indicate significant improvement; error bars indicate standard error of the mean; values are calculated as the percentage difference in accuracy between successive test-retest intervals.

These results lead to two conclusions. First, reconsolidation can be blocked by ecologically relevant stimuli, such as a competing learning experience, and without resorting to extreme electrical or chemical interventions (Walker et al. 2003a) previously used to prevent reconsolidation. Second, the deterioration in performance might be limited to a reversal of earlier sleep-dependent consolidation.

SUMMARY

Over the past 25 years, the field of sleep and memory has grown exponentially, with the number of publications per year doubling between the years 2000 and 2004. These reports, ranging from cellular and molecular studies in animals to behavioral studies in humans, have provided a wealth of converging evidence that sleep-dependent mechanisms of neural plasticity lead to the consolidation of learning and memory across a range of animal species.

At the molecular level, inadequate pretraining sleep appears to compromise hippocampally dependent modulation of molecules critically involved in memory formation, resulting in impaired memory encoding. Significant numbers of genes also appear to be up-regulated specifically in brain tissue during posttraining sleep, and at least one immediate early gene related to synaptic plasticity, *zif-286*, is up-regulated during REM sleep expressly in response to environmental or direct electrical stimulation of the hippocampus (for a review, see Walker & Stickgold 2004).

At the electrophysiological level, studies in rats have shown that retention of learning of a shuttle-box avoidance task increases subsequent P-wave density, and is strongly correlated with this increase, while in humans, spindle density increases following training on a declarative memory task and, again, this increase correlates with subsequent improvement on the task. In rats, patterns of neuronal activation expressed during waking exploration reappear during subsequent sleep; in humans, patterns of regional brain activation seen during daytime task training are repeated during subsequent REM sleep.

At the behavioral level, animal studies have found robust increases in REM sleep following task training, and decrements in performance after REM deprivation, even when retesting is delayed until one week after the period of deprivation. In contrast, several animal studies have failed to find evidence of either increased REM sleep or deterioration following deprivation. Most likely this reflects a combination of methodological problems and conditions under which consolidation is, in fact, not sleep dependent. Similarly, human studies have provided examples where increases in REM sleep are seen following training, where REM or stage 2 NREM deprivation diminishes subsequent performance, and where overnight improvement correlates with REM, SWS, or stage 2 NREM sleep. Furthermore, these overnight learning benefits are associated with a system-level reorganization of memory throughout the brain.

It is now clear that sleep mediates learning and memory processing, but the way in which it does so remains largely unknown. The future of the field is truly exciting,

and the challenge to neuroscience will be to uncover the mechanisms of brain plasticity that underlie sleep-dependent memory processing and to expand our understanding of sleep's role beyond encoding, consolidation, and reconsolidation, 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, the next decade should provide important advances in our understanding of this critical function of sleep. By way of this multidisciplinary approach, and with a measured appreciation of the fundamental role that sleep plays in consolidating and reforming memories, we can look forward to new advances in understanding memory and treating its disorder.

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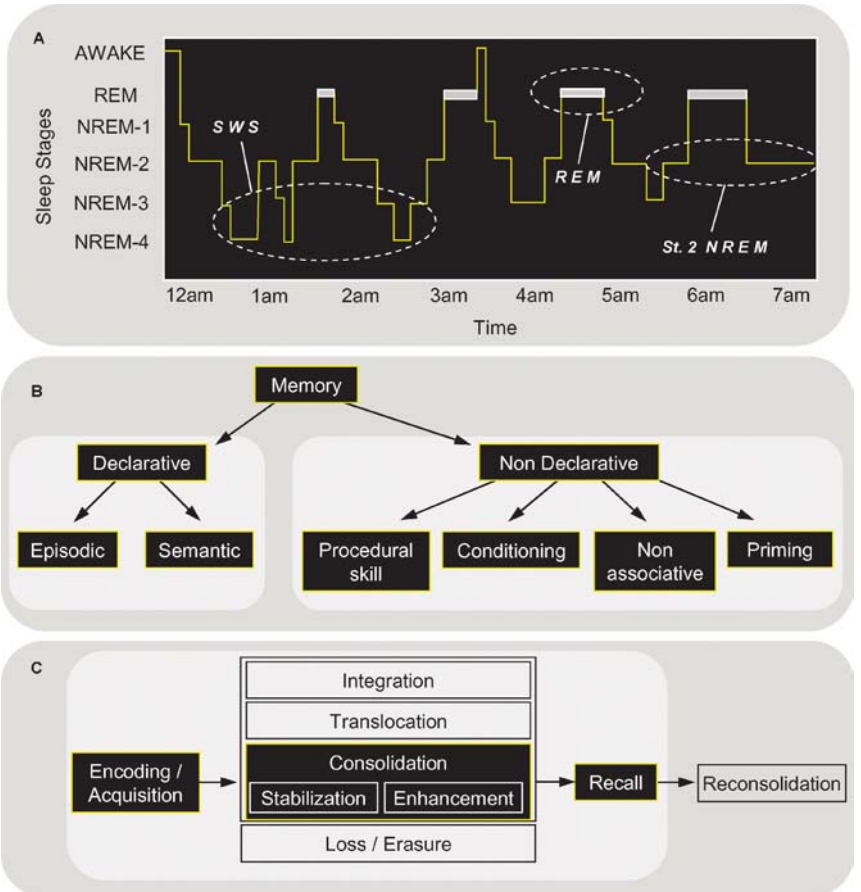

Figure 1 The sleep cycle, memory systems, and memory stages. (*A*) The human sleep cycle. Across the night, rapid eye movement (REM) and non-REM (NREM) sleep cycle every 90 minutes in an ultradian manner, while the ratio of NREM to REM sleep shifts. During the first half of the night, NREM stages 3 and 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.

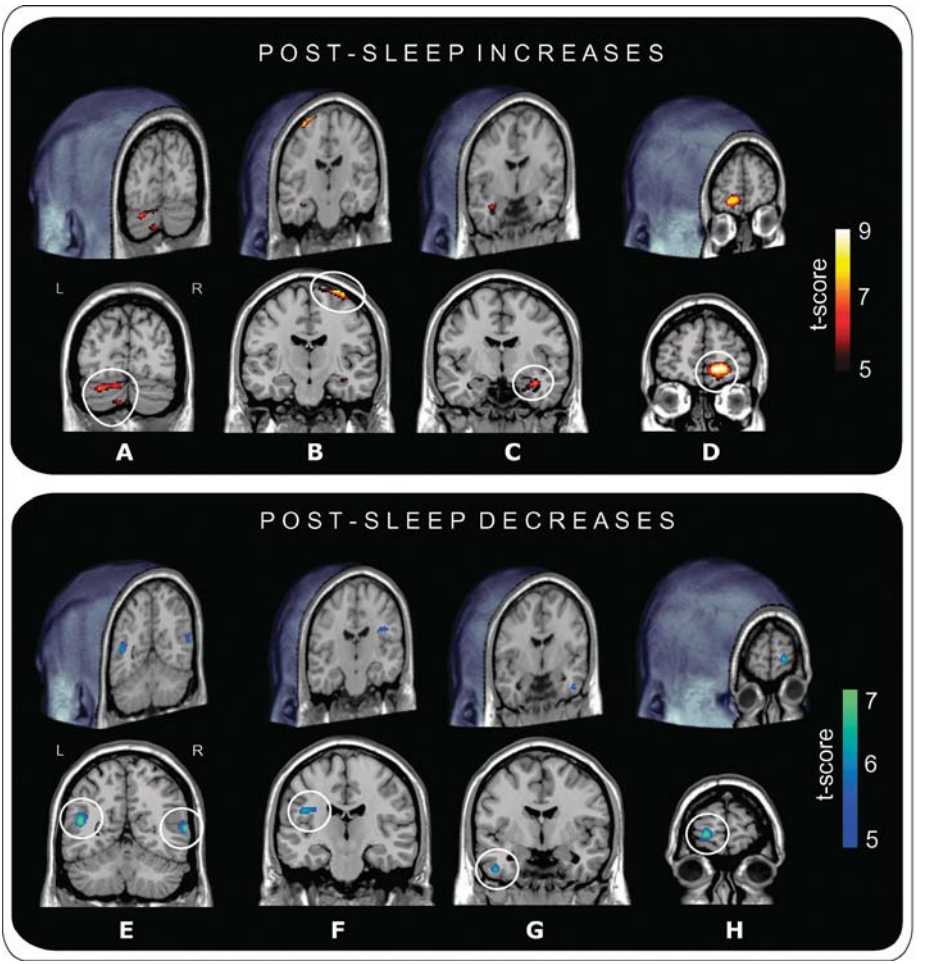

Figure 8 Sleep-dependent motor memory reorganization in the human brain. Subjects were trained on a sleep-dependent motor skill task and then tested 12 hours later, either following a night of sleep or following intervening wake, during a functional magnetic resonance imaging (fMRI) brain-scanning session. Scans after sleep and wake were compared (subtracted), resulting in regions showing increased fMRI activity postsleep (in red/yellow; *A–D*) or decreased signal activity (in blue; *E–H*) postsleep, relative to postwake. Activation patterns are displayed on three-dimensional rendered brains (*top panel* of each graphic), together with corresponding coronal sections (*bottom panel* of each graphic). 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 frontopolar 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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