Learning, Memory, and Sleep in Humans

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• Slow wave sleep • Memory • Hippocampus
• Rapid eye movement sleep

About one-third of a person's life is spent sleeping, yet in spite of the advances in understanding the processes that generate and maintain sleep, the functional significance of sleep remains a mystery. Numerous theories regarding the role of sleep have been proposed, including homeostatic restoration, thermoregulation, tissue repair, and immune control. A theory that has received enormous support in the last decade concerns sleep's role in processing and storing memories. This article reviews some of the evidence suggesting that sleep is critical for long-lasting memories. This body of evidence has grown impressively large and covers a range of studies at the molecular, cellular, physiologic, and behavioral levels of analysis.

DEFINING SLEEP AND MEMORY

Stages of Sleep

There are 2 main types of sleep. The first, rapid eye movement (REM) sleep, occurs in roughly 90-minute cycles throughout the night and alternates with 4 additional stages (stages 1–4) known collectively as non-REM (NREM) sleep, which comprises the second type of sleep.[1] Slow wave sleep (SWS) is the deepest of the NREM sleep phases and is characterized by high-amplitude, low-frequency oscillations seen in the electroencephalogram (EEG). REM sleep, on the other hand, is a lighter stage of sleep characterized by rapid eye movements (REMs), decreased muscle tone, and low-amplitude fast EEG oscillations. More than 80% of SWS is concentrated in the first half of the typical 8-hour night, whereas the second half of the night contains roughly twice as much REM sleep than the first half (**Fig. 1**).

This domination of early sleep by SWS and of late sleep by REM sleep not only has important functional consequences but also makes it difficult to know which distinction is critical for memory processing: NREM versus REM sleep or early versus late sleep.

Neurotransmitters, particularly the monoamines serotonin (5-HT) and norepinephrine (NE), and acetylcholine (ACh), play a critical role in switching the brain from one sleep stage to another. REM sleep occurs when activity in the aminergic system has decreased enough to allow the reticular system to escape its inhibitory influence.[1] The release from aminergic inhibition stimulates cholinergic reticular neurons in the brainstem and switches the sleeping brain into the highly active REM state, in which ACh levels are as high as in the waking state. Overall, REM sleep is also associated with higher levels of cortisol than NREM sleep. 5-HT and NE, on the other hand, are virtually absent during REM sleep. SWS, conversely, is associated with an absence of ACh and low levels of cortisol but detectable levels of 5-HT and NE.[2,3]

Stages of Memory Formation, and Different Memory Types

Memory consolidation is the process by which newly acquired information, initially fragile, is integrated and stabilized into long-term memory.[4] Evidence overwhelmingly suggests that sleep plays a role in the consolidation of a range of memory tasks, with the different stages of sleep selectively benefiting the consolidation of different types of memory.[2,5–10]

Like sleep, memory is also divided into several key stages and types.[11] First, there are various types of memories that can be recalled explicitly, including episodic memories, or memories of the

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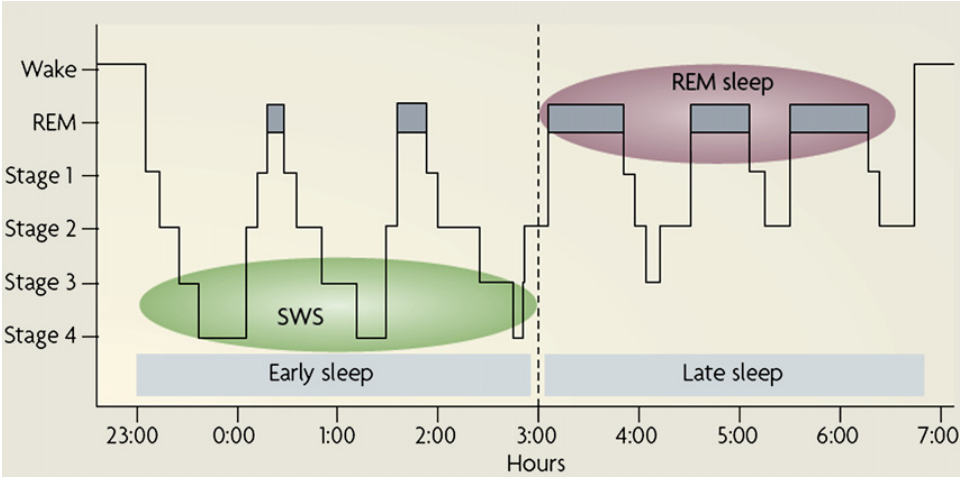

Fig. 1. A sleep histogram showing the typical distribution of SWS and REM sleep.

events in our lives. Retrieving an episodic memory from one's past requires access to defining contextual features of the event, such as specific details about the place and time of its occurrence. Because of this emphasis on spatial context, episodic memories and spatial memories are closely connected. Second, there are semantic memories, which are concerned with the knowledge one acquires during events but is itself separated from the specific event in question. Thus, our knowledge about the meaning of words and facts about the world, even though acquired in the context of some specific experience, appears to be stored in a context-independent format (eg, not bound to the originating context). Third, there are "how to" memories for the various skills, procedures, and habits that we acquire through experience. Because these memories are not so easily made explicit and are usually only evident in behavior, they are referred to as procedural or implicit memories. Finally, there are emotional memories for the positive and negative experiences in our lives. This class of memories is especially concerned with learning about fearful and negative stimuli, although evidence suggests it plays a role in learning about pleasant information as well.[12]

Evidence suggests that each of these memory types is subserved by distinct neural systems.[11–13] Whereas episodic and spatial memories are governed by the hippocampus and surrounding medial temporal areas, procedural or implicit memories are thought to be independent of the hippocampus and anatomically related regions, relying instead on various neocortical and subcortical structures. The emotional memory system is centered in the amygdala, a limbic structure that is richly connected to the hippocampus.[14] Importantly, evidence suggests that information dependent on each of these systems is processed differently during sleep. Although somewhat oversimplified,[15] there is a general consensus that NREM sleep, especially SWS, is important for the consolidation of explicit episodic and spatial memories, both of which rely on the hippocampus for their consolidation,[16] whereas REM sleep selectively benefits procedural and emotional memories.[17,18]

In addition to these distinct types, memory consolidation also consists of different stages. Although our experience of memory occurs at the moment of retrieval when information about the initial experience returns to conscious awareness, successful retrieval is contingent on the successful completion of at least 2 earlier stages of memory formation. First, the experience or information must be properly encoded. Encoding involves transforming new information into a representation capable of being stored in memory, just as the key presses that are made on a keyboard must be converted to a format that can be stored in a computer. Second, the information must be consolidated or durably stored in a manner that can withstand the passage of time. Only if these processes occur successfully will it be possible for information from the initial event to be retrieved later in time. Although this article mostly focuses on memory consolidation, it also briefly reviews new evidence that sleep is essential for effective memory encoding.

SLEEP BENEFITS IMPLICIT AND PROCEDURAL MEMORIES

Sleep seems to benefit the consolidation of both implicit and explicit forms of memory. Converging data suggest that most procedural skills and abilities (eg, performing a surgery, riding a bike) are acquired slowly and are not attained solely during the learning episode. While some learning certainly

develops quickly, performance on various procedural tasks improves further and without additional practice simply through the passage of time, particularly if these periods contain sleep. These slow off-line improvements occur as newly acquired information, initially fragile, is integrated and stabilized into long-term memory.

Early work investigating the effect of sleep on implicit learning used a visual texture discrimination task (VDT) originally developed by Karni and Sagi.[19] The task requires participants to determine the orientation (vertical or horizontal) of an array of diagonal bars that is embedded in one visual quadrant against a background of exclusively horizontal bars (**Fig. 2**). At the center of the screen is the fixation target, which is either the letter *T* or the letter *L*. This target screen is succeeded first by a blank screen for a variable interstimulus interval (ISI) and then by a mask (a screen covered with randomly oriented *V*'s with a superimposed *T* and *L* in the center). Subjects must determine the orientation of the array, and the performance is estimated by the ISI corresponding to 80% correct responses.[19,20]

Amnesic patients with damage to the hippocampal complex, who cannot acquire knowledge explicitly, show normal performance improvements on the VDT.[21] In neurologically normal subjects, improvement on the VDT develops slowly after training,[19,22] with no improvement when retesting occurs on the same day as training (**Fig. 3**A). Instead, improvement is only observed after a night of sleep (see **Fig. 3**A). This observation was true even for a group of subjects who were retested only 9 hours after training. Importantly, there was not even a trend to greater improvement when the training-retest interval was increased from 9.0 to 22.5 hours, suggesting that additional wake time after the night of sleep provided no additional benefit. Whereas further wake time provided no benefit, additional nights of sleep did produce incremental improvement. When subjects were retested 2 to 7 days after training rather than after a single night of sleep a 50% greater improvement was observed (see **Fig. 3**B). Critically, another group of subjects was sleep deprived on the first night after training. These subjects were allowed 2 full nights of recovery sleep before being retested 3 days later. The subjects failed to show any residual learning, suggesting that performance enhancements depend on a normal first night of sleep (see **Fig. 3**B). Time alone is clearly not enough to produce long-term benefits from VDT training. It seems that sleep is also required.[22]

Initially, improvement on this task seemed to depend solely on REM sleep, because subjects who underwent selective deprivation of REM sleep showed no improvement on the task.[20] Later studies, however, showed that optimal performance on this task requires both SWS and REM sleep.[23]

When subjects were trained and their subsequent sleep monitored in the sleep laboratory, the amount of improvement was proportional to the amount of SWS during the first quarter of the night (**Fig. 4**A), as well as to the amount of REM sleep in the last quarter (see **Fig. 4**B). Indeed, the product of these 2 sleep parameters explained more than 80% of the intersubject variance (see **Fig. 4**D). No significant correlations were found for sleep stage during other parts of the night (see **Fig. 4**C) or for the amount of stage 2 sleep at any time during the night.

Gais and colleagues[24] came to a similar conclusion by examining improvement after 3 hours of sleep either early or late in the night. They found that 3 hours of early night sleep, which was rich in SWS, produced an 8-millisecond improvement, but after a full night of sleep, which added REM-rich sleep late in the night, a 26-millisecond improvement was observed, 3 times that seen with early sleep alone. However, 3 hours of REM-rich, late night sleep actually produced deterioration in performance.[24] These results are further corroborated by daytime nap studies. Afternoon naps as short as 60 to 90 minutes also lead to

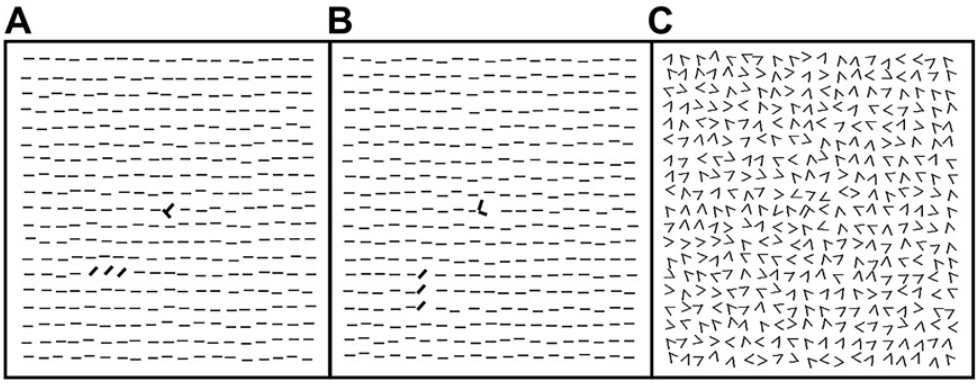

Fig. 2. (*A–C*) Sample screens from the VDT.

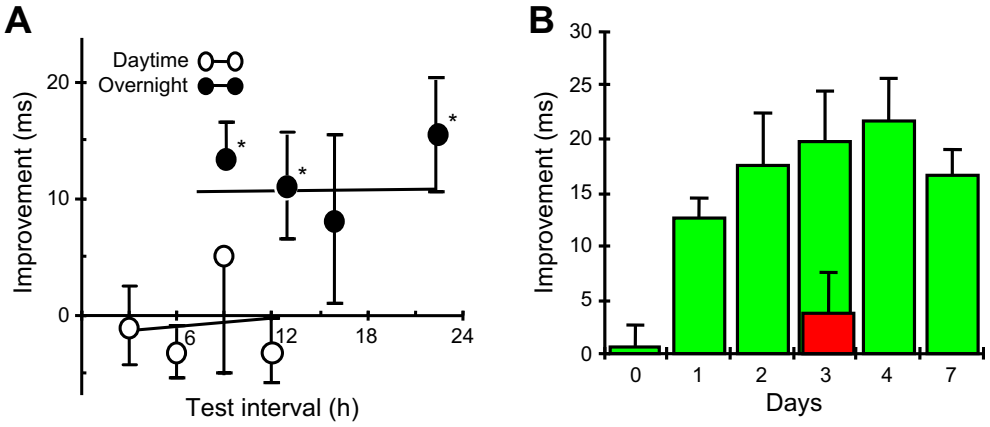

Fig. 3. Sleep-dependent improvement on the VDT. All subjects were trained and then retested only once. Each point in (*A*) and each green bar in (*B*) represents a separate group of subjects. Error bars in (*A*) and (*B*) are SEM. (*A*) There was no improvement when retesting occurred on the same day as training (*open circles*), but there was improvement after a night of sleep (*closed circles*). Asterisks indicate significant effects. (*B*) (*Green bars*) Improvement in performance of subjects when retested 2 to 7 days of training. (*Red bar*) No improvement in performance of subjects who were sleep deprived on the first night of training. ms, milliseconds. (*From* Stickgold R, James L, Hobson JA. Visual discrimination learning requires post-training sleep. Nat Neurosci 2000;2 (12):1237–8; with permission; and Stickgold R, Whidbee D, Schirmer B, et al. Visual discrimination task improvement: a multi-step process occurring during sleep. J Cognit Neurosci 2000;12:246–54; with permission.)

performance benefits on the VDT, especially when they contain REM and NREM sleep.[25,26]

At this point, sleep's role in visual discrimination learning (as measured by VDT performance) is clear. But the VDT represents a very specific type of sensory memory that may or may not share its sleep dependency with other procedural tasks. This specificity raises the question of whether the sleep effects observed with the VDT generalize to other forms of procedural memory. Studies of

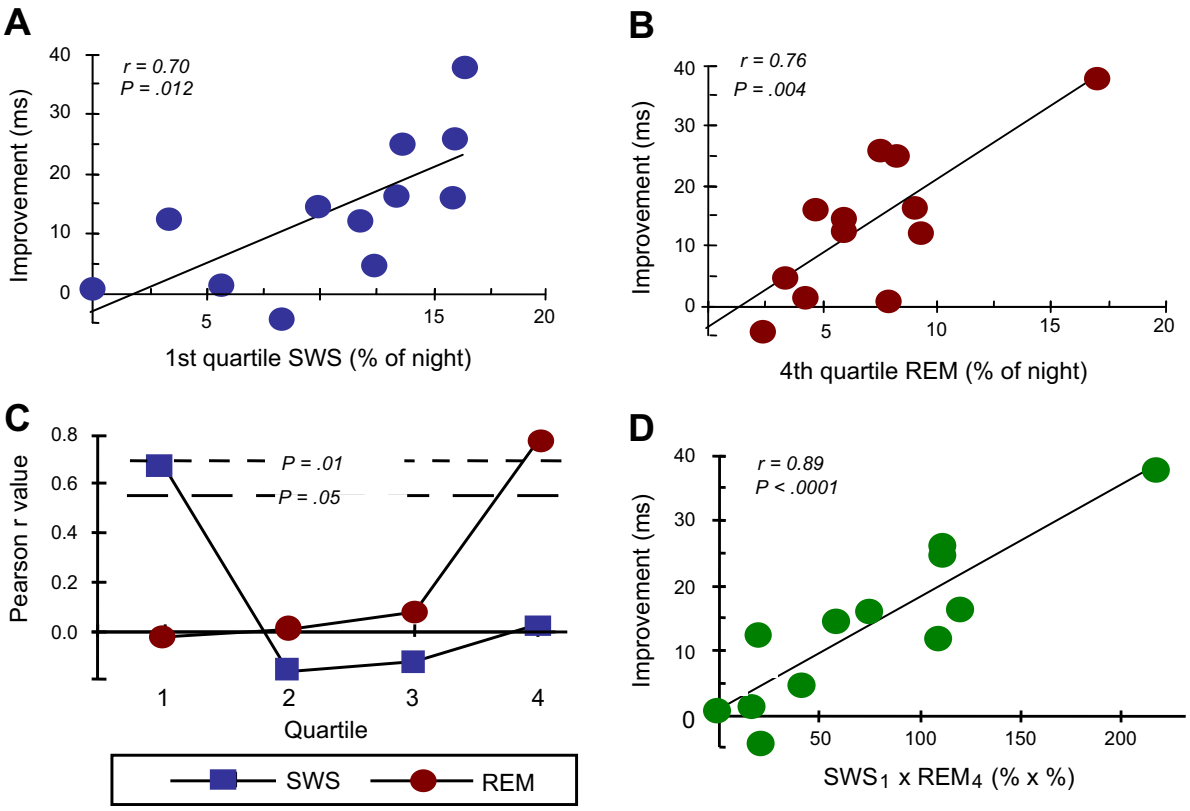

Fig. 4. (*A–D*) REM sleep and SWS dependence of VDT learning. ms, milliseconds; REM_4, 4th quartile of REM sleep; SWS_1, 1st quartile of SWS. (*From* Stickgold R, Whidbee D, Schirmer B, et al. Visual discrimination task improvement: a multi-step process occurring during sleep. J Cognit Neurosci 2000;12:246–54; with permission.)

sleep-dependent motor skill learning strongly suggest that they do.

As an example, Walker and colleagues[27] have demonstrated sleep-dependent improvements on a finger tapping task. The task requires subjects to repeatedly type the numeric sequence 4-1-3-2-4 as quickly and accurately as possible with the non-dominant hand. Training consisted of twelve 30-second trials separated by 30-second rest periods. All subjects show considerable improvement during the 12 trials of the training session (a fast learning component), but 12 hours later, the subjects performed differently depending on whether the 12-hour interval was spent sleeping or awake. When trained in the morning and retested 12 hours later, only an additional nonsignificant 4% improvement was seen in performance, but when tested again the next morning, a large and robust (14%) improvement was seen (**Fig. 5**A). The failure to improve during the daytime could not be caused by interference from related motor activity because subjects who were required to wear mittens and refrain from fine motor activities during this time showed a similar pattern of wake/sleep improvement (see **Fig. 5**B).

In contrast, when subjects were trained in the evening, improvement was observed the following morning (after sleep) but not across an additional 12 hours of wake (see **Fig. 5**C). Thus, improved performance resulted specifically from a night of sleep as opposed to the simple passage of time. Curiously, unlike the findings for the VDT, overnight improvement on this task correlated with the amount of stage 2 NREM sleep during the night, especially during the last quarter of the night.

These findings are in agreement with those of Fogel and colleagues,[28] Smith and MacNeill,[29] and Tweed and colleagues,[30] who have also shown that stage 2 sleep and possibly the sleep spindles that reach peak density during late night stage 2 sleep are critical for simple motor memory consolidation. This role of sleep spindles seems plausible because they have been proposed to trigger intracellular mechanisms that are required for synaptic plasticity.[31]

This motor sequence task has been examined to determine where precisely in the motor program this sleep-dependent improvement occurs.[32] In the sequence mentioned earlier (4-1-3-2-4), there are 4 unique key-press transitions: 4 to 1, 1 to 3, 3 to 2, and 2 to 4. When the speed between transitions was analyzed for individual subjects before sleep, "sticking points" emerged. Whereas some transitions were easy (ie, fast), others were problematic (ie, slow), as if the sequence was being parsed or chunked into smaller bits during presleep learning.[21] After a night of sleep, these problematic points were preferentially improved, whereas transitions that had already been mastered before sleep did not change. Subjects who were trained and retested after a daytime wake interval showed no such improvements.

These findings suggest that the sleep-dependent consolidation process involves the

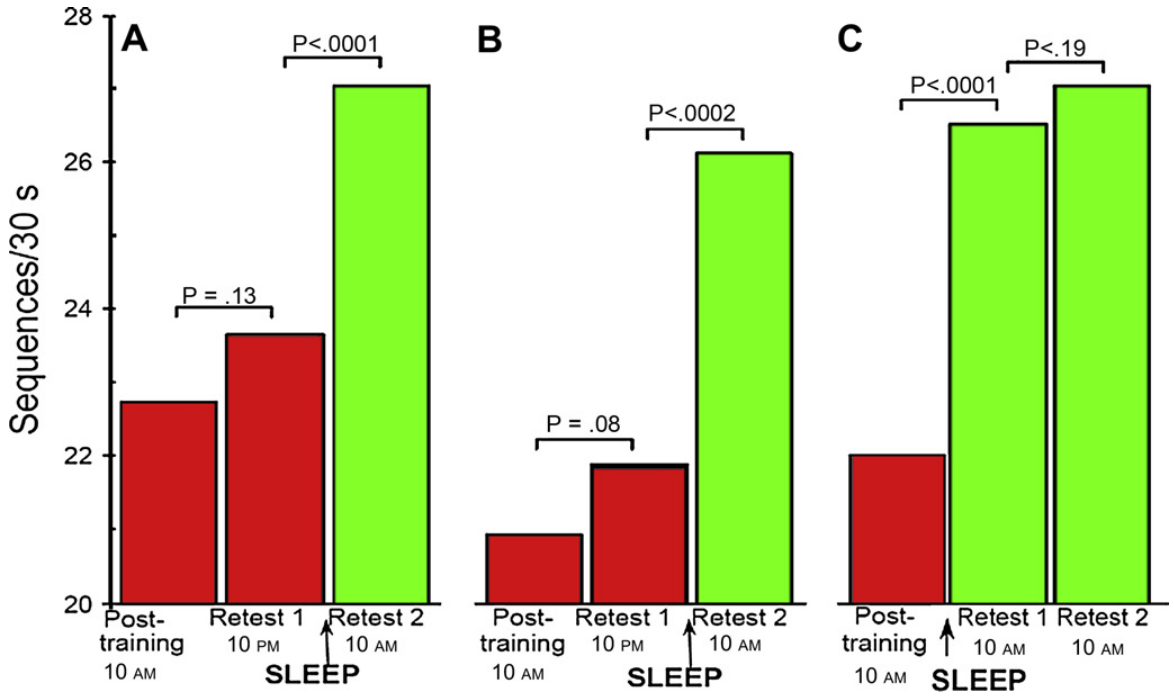

Fig. 5. (*A–C*) Sleep-dependent motor learning. Improvement in speed was seen in all 3 groups over a night of sleep but not over 12 hours of daytime wake. (*From* Walker M, Brakefield T, Morgan A, et al. Practice with sleep makes perfect: sleep dependent motor skill learning. Neuron 2002;35:205–11; with permission.)

unification of smaller motor memory units into a single motor memory representation, thereby improving problem points in the sequence. Importantly, this finding suggests that the role of sleep is subtle and complex and that sleep does more than simply strengthen memories; sleep may encourage the restructuring and reorganization of memories, an important and often-overlooked aspect of memory consolidation. The author returns to this idea later in the article.

Moving to another type of motor memory, motor adaptation, Maquet and colleagues[33] showed that sleep benefits performance on a motor pursuit task. Participants were trained to use a joystick to keep the cursor on a target when the target trajectory was predictable only on the horizontal axis, which meant that optimal performance could only be achieved by developing an implicit model of the motion characteristics of the learned trajectory. Half of the subjects were sleep deprived on the first posttraining night, whereas the other half were allowed to sleep normally. Three days later, after 2 full nights of recovery sleep, performance was superior in the sleep group compared with the sleep-deprived group, and functional magnetic resonance imaging (fMRI) revealed that that the superior temporal sulcus (STS) was differentially more active for the learned trajectory in subjects who slept than in the sleep-deprived subjects. Moreover, increased functional connectivity was observed between the STS and the cerebellum and between the supplementary and frontal eye fields, suggestive of sleep-related plastic changes during motor skill consolidation in areas involved in smooth pursuit and eye movements.

Admittedly, visual discrimination, finger tapping, and motor adaptation are all relatively basic low-level procedural tasks that may become automated fairly quickly. What about the more complex implicit and procedural tasks? Work on animals clearly demonstrates that complex tasks (eg, instrumental conditioning, avoidance, or maze learning) benefit from sleep, with rats showing increases in REM sleep that continue until the tasks are mastered.[34–36]

REM sleep has been implicated in complex procedural learning in humans as well. In a positron emission tomographic study of visuomotor skill memory using the serial reaction time task,[37] 6 spatially permanent position markers were shown on a computer screen and subjects watched for stimuli to appear below these markers. When a stimulus appeared in a particular position, subjects reacted as quickly as possible by pressing a corresponding key on the keyboard. Because the stimuli were generated in an order defined by a probabilistic finite-state grammar, improvement on the task (compared with randomly generated sequences) reflects implicitly acquired knowledge of this grammar.[37]

Neuroimaging was performed on 3 groups of subjects. One group was scanned while they were awake, both at rest and during performance of the task, providing information about which brain regions are typically activated by the task. A second group of subjects was trained on the task during the afternoon and then scanned the night after training, both while awake and during various sleep stages. Thus, group 2 was included to determine if similar brain regions were reactivated during sleep. A postsleep session was also conducted to verify that learning had indeed occurred. Finally, a third group, never trained on the task, was scanned while sleeping to ensure that the pattern of activation present in natural sleep was different from the pattern of activation present after training.

Results showed that during REM sleep, as compared with resting wakefulness, several brain areas used during task performance were more active in trained than in nontrained subjects. These areas included occipital, parietal, anterior cingulate, motor, and premotor cortices and the cerebellum, all activations that are consistent with the component processes involved in the visual and motor functioning involved in this task. Behavioral data confirmed that trained subjects improved significantly more across the night.

Peigneux and colleagues,[38] using the same task, showed that the level of acquisition of probabilistic rules attained before sleep was correlated with the increase in activation of task-related cortical areas during posttraining REM sleep. This observation suggests that cerebral reactivation is modulated by the strength of the memory traces developed during the learning episode, and as such, these data provide the first experimental evidence linking behavioral performance to reactivation during REM sleep.[38] Together with animal studies,[39,40] these findings suggest that it is not simply experiencing the task, but the process of memory consolidation associated with successful learning of the task that modifies sleep physiology.

These results support the idea that implicit/procedural memory traces in humans can be reactivated during REM sleep, and that this reactivation is linked to improved consolidation. Indeed, looking a bit more closely at the literature, human REM sleep has also been linked to memory for complex logic games, to foreign language acquisition, and to intensive studying.[41] It is interesting that these more-complex conceptual-procedural tasks often show REM sleep relationships, whereas more basic procedural tasks benefit

mainly from NREM sleep. The above-mentioned findings provide encouraging evidence that sleep-based processes can aid in procedural memory consolidation, not only for basic forms of sensory and motor memory in humans but also for complex procedural and conceptual knowledge. Moreover, these findings indicate that the consolidation of familiar skills, or those that are similar to other well-learned skills, may be reliant on NREM sleep stages (particularly stage 2 NREM sleep), whereas REM sleep may be required for the integration of new concepts or skills with preexisting information stored in memory.[42] This is an important concept that warrants future investigation.

Clearly, sleep is crucial to the consolidation of procedural memory. Although both the stabilization of explicitly learned motor skills and off-line improvements in pure implicit tasks may evolve over time spent awake,[43,44] the posttraining enhancement of motor skills seems to be exclusively dependent on sleep.[27] Participants with insomnia show impaired sleep-related procedural memory consolidation compared with participants with undisturbed sleep,[45] and schizophrenia, which is associated with changes in sleep, particularly in stage 2 NREM sleep spindles,[46,47] is also associated with procedural memory deficits.[48] More recently, Dresler and colleagues[49] demonstrated that off-line procedural memory consolidation is also disturbed in depression, another condition associated with changes in sleep architecture.

SLEEP BENEFITS EXPLICIT MEMORIES

This section describes the relationship between sleep and the consolidation of explicit memories. There is a general consensus that NREM sleep, especially SWS, is important for the consolidation of hippocampus-dependent episodic and spatial memories.[16] In a landmark study, Plihal and Born[50] assessed the recall of word pairs (an episodic memory task) and improvement in mirror tracing (a procedural memory task) after retention intervals of early sleep (the first 3–4 hours of the sleep cycle), which, as noted in the previous sections, is dominated by SWS, and late sleep (the last 3–4 hours of the sleep cycle), which is dominated by REM sleep. Recall of word pairs improved more significantly after a 3-hour sleep period rich in SWS than after a 3-hour sleep period rich in REM sleep or a 3-hour period of wakefulness. Mirror tracing, on the other hand, improved significantly more after a 3-hour sleep period rich in REM sleep than after 3 hours spent either in SWS or awake.

Similarly, using a nap paradigm, Tucker and colleagues[51] found that naps containing only NREM sleep enhanced memory for word pairs but did not benefit mirror tracing. After an afternoon training session, performance on these tasks was assessed after a 6-hour delay, either with or without an intervening nap. The subjects who were allowed a nap not only recalled more word pairs than the subjects who remained awake (**Fig. 6**) but also showed a weak correlation between improved recall and the amount of SWS in the nap.

These results are consistent with neurophysiological evidence derived from electrophysiological studies in rodents, which demonstrate that patterns of hippocampal place cell activity first seen during waking exploration are later reexpressed during postlearning SWS.[52–54] Similarly,

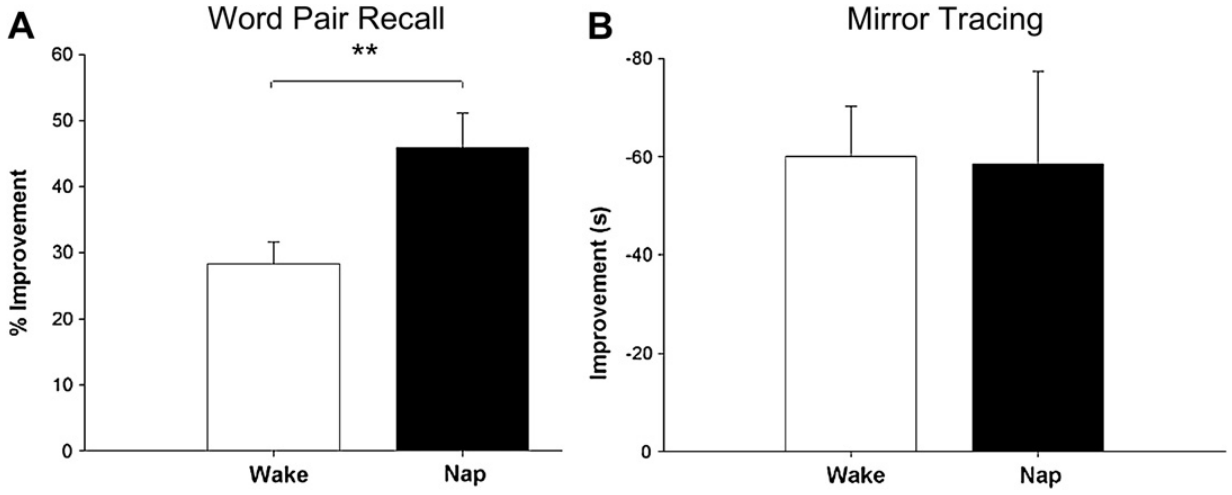

Fig. 6. (*A*, *B*) A brief daytime nap benefits episodic memory. Note that the nap (which did not contain REM sleep) benefited episodic, but not procedural memory. Asterisks indicate significant differences between groups. (*From* Tucker MA, Hirota Y, Wamsley EJ, et al. A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem 2006;86(2):241–7; with permission.)

several neuroimaging studies in humans have suggested an important role for SWS in hippocampus-dependent memory consolidation. The first of these studies investigated performance on a hippocampally-dependent virtual maze task.[55] Daytime learning of the task was associated with hippocampal activity. During posttraining sleep, there was a reemergence of hippocampal activation, and this activation occurred specifically during SWS. The most compelling finding, however, is that the increase in hippocampal activation seen during posttraining SWS was proportional to the amount of improvement seen the next day. This finding suggests that the reexpression of hippocampal activation during SWS reflects the off-line reprocessing of spatial episodic memory traces, which in turn leads to the plastic changes underlying the improvement in memory performance seen the next day. Similarly, Rasch and colleagues[56] exposed human subjects to an odor while they were learning object-location pairings in a task similar to the memory game "concentration;" subjects who were reexposed to the odor during SWS (but not REM sleep) showed enhanced hippocampal activity and enhanced memory for the memory pairings.

Another study[57] investigated the time course of episodic memory consolidation across 90 days. Subjects studied 360 photographs of landscapes and were then tested on subsets of the photographs either after a nap the same day or after 2, 30, or 90 days. Before each test, subjects studied 80 new pictures and then were tested on 80 of the original pictures and the 80 new ones as well as 80 pictures that they had never seen before. All memory retrieval sessions occurred during fMRI scanning. After the initial 90-minute nap, stage 2 sleep was positively correlated with successful recall of both remote and recent items, indicating a nonspecific benefit of stage 2 NREM sleep on episodic memory. This is an intriguing finding, given that stage 2 is when sleep spindles are most prominent (see section on neurophysiological and neurochemical evidence for sleep's role in memory consolidation later). SWS, on the other hand, was correlated only with memory for remote (but not recent) items. Because performance on remote items increased with longer SWS duration, but performance for recent items did not, the effect on memory performance for remote items cannot be explained by a general effect of SWS on memory retrieval processes. These findings strongly suggest that episodic memories can undergo initial consolidation within a rather short time frame and that this consolidation is promoted by SWS.

These observations suggest that learning triggers the reactivation of episodic memory traces during NREM SWS, a process that in turn enhances behavioral performance.

SLEEP BENEFITS EMOTIONAL MEMORY CONSOLIDATION

Sleep also contributes to the consolidation of emotional episodic memories. As noted in the previous section, sleep clearly benefits memory for neutral episodic memory materials across both verbal and spatial modalities.[5,16] However, when emotional (especially emotionally negative) episodic items are intermixed with neutral items in a study, sleep disproportionately benefits the consolidation of emotional memories relative to neutral memories. For example, Hu and colleagues[58] examined the effect of a full night's sleep on both axes of emotional affect, valence (positive/negative) and arousal (high/low), across both "remember" and "know" judgments of memory for pictures. Results showed that a night of sleep improved memory accuracy for emotionally arousing pictures relative to an equivalent period of daytime wakefulness, but only for know judgments. No differences were observed for remember judgments. Moreover, memory bias changed across a night of sleep relative to wake, such that subjects became more conservative when making remember judgments, especially for emotionally arousing pictures. No bias differences were observed for know judgments between sleep and wake.

REM sleep may be particularly important for the consolidation of emotional memories, which rely critically on the amygdala for their consolidation.[7,59] Wagner and colleagues[59] found that 3 hours of late night REM-rich sleep (but not 3 hours of early night slow wave–rich sleep or 3 hours of wakefulness) facilitated memory for negative arousing narratives, an effect that could still be observed years later when the subjects were recontacted for a follow-up memory test.[60] Consistent with these findings, the amygdala and hippocampus are among the most active brain regions during REM sleep, with some evidence suggesting that they are more active during REM sleep than during wakefulness.[61] This observation suggests that emotional memory processing may be a primary goal of REM sleep. Moreover, several studies have correlated features of REM sleep, including oscillatory activity in the theta frequency band range,[17] with enhanced emotional memory consolidation.[10,62] These findings strongly suggest a role for sleep, especially REM sleep, in the processing of memory for emotional experiences.

SLEEP TRANSFORMS MEMORIES IN USEFUL WAYS

The findings reviewed in the previous sections provide compelling evidence that sleep plays an important role in solidifying experience into long-term memory in a veridical manner, more or less true to its form at initial encoding.[63] However, it has long been known that memories change with the passage of time,[64] suggesting that the process of consolidation does not always yield exact representations of past experiences. On the face of it, this process may seem strikingly maladaptive, yet such flexibility in memory representation allows the emergence of key cognitive abilities, such as generalization and inference,[65] future thought,[66] and selective preservation of useful information extracted from a barrage of incoming stimulations and experiences.[67,68] Consistent with these ideas, growing evidence suggests that sleep does more than simply consolidating memories in a veridical form; it also transforms them in ways rendering the memories less accurate in some respects but more useful and adaptive in the long run. Sleep leads to flexible restructuring of memory traces so that insights can be made,[69] inferences can be drawn,[64] and both integration and abstraction can occur.[68] In each of these cases, sleep confers a flexibility to memory that may at times be more advantageous than a literal representation of experience.

As a specific example of such qualitative changes in memory representation, recent studies demonstrate that sleep transforms the emotional memory trace. Payne and colleagues[7,67] examined how the different components of complex negative arousing memories change across periods of sleep versus wakefulness. Emotional scenes could be stored as intact units, suffering some forgetting over time but retaining the same relative vividness for all components. Alternatively, the components of an experience could undergo differential memory processing, perhaps with a selective emphasis on what is most salient and worthy of remembering.

Participants viewed scenes depicting negative or neutral objects embedded on neutral backgrounds at 9 AM or 9 PM. Twelve hours later, after a day spent awake or a night including at least 6 hours of sleep, they were tested on their memory for objects and backgrounds separately to examine how these individual components of emotional memories change across periods of sleep and wake (see **Fig. 7** for example stimuli).

Daytime wakefulness led to forgetting of negative arousing scenes in their entirety, with both objects and backgrounds being forgotten at similar rates. Sleep, however, led to a selective preservation of negative objects but not their accompanying backgrounds, suggesting that the 2 components undergo differential processing during sleep. This finding suggests that rather than preserving intact representations of scenes the sleeping brain effectively unbinds scenes to consolidate only their most emotionally salient, and perhaps adaptive, elements (see[68,69] for additional examples of potential unbinding during sleep).

Paralleling these behavioral findings, a recent fMRI study provided evidence that a single night of sleep is sufficient to provoke changes in the emotional memory circuitry, leading to increased

Fig. 7. Example stimuli for emotional trade-off task, where a neutral (intact car, *A*) or negative (crashed car, *B*) object is embedded on a neutral background scene (street). (*From* Payne JD, Kensinger EA. Sleep's role in the consolidation of emotional episodic memories. Curr Dir Psychol Sci 2010;19(5):290–5; with permission.)

activity within the amygdala and the ventromedial prefrontal cortex and strengthened connectivity between the amygdala and both the hippocampus and ventromedial prefrontal cortex during retrieval.[70] These findings are consistent with a study by Sterpenich and colleagues[71] and suggest that sleep strengthens the modulatory effect of the amygdala on other regions of the emotional memory network as memories undergo consolidation.[14] Whether these selective effects of sleep on emotional memory consolidation depend on REM sleep is an interesting question for future research.

BEYOND SLEEP STAGES

The above-mentioned results should not be taken to mean that SWS strictly mediates the consolidation of episodic memories, whereas REM sleep only mediates the consolidation of procedural and emotional memories. Matters are clearly not so simple. As mentioned in the previous sections, improvement on a visual discrimination task depends on SWS as well as REM,[24] and improvement on a motor task correlates with stage 2 NREM sleep.[29] Moreover, emotionally charged episodic memories may rely on both REM sleep and SWS for their consolidation.[7,72]

There are 2 possible interpretations of these apparent contradictions. First, the sleep stage dependency of these various memory tasks may depend on aspects of the task other than simply whether they are episodic or procedural, perhaps depending more on the intensity of training, the emotional salience of the task, or even the manner in which information is encoded (eg, deep vs shallow encoding or implicit vs explicit). The second possibility involves an inherent oversimplification in correlating performance improvements with sleep stages as they are classically defined. Indeed, mounting evidence points to several electrophysiological, neurotransmitter, and neuroendocrine mechanisms that may underlie these effects and that do not necessarily correlate with any single sleep stage, and sleep staging, as it has been defined for 40 years, may not capture all the key elements that lead to memory consolidation enhanced by sleep.

NEUROPHYSIOLOGICAL AND NEUROCHEMICAL EVIDENCE FOR SLEEP'S ROLE IN MEMORY CONSOLIDATION

Each of the above-mentioned sleep stages is characterized by a unique collection of electrophysiological, neurotransmitter, and neuroendocrine properties that tend to overlap with the different sleep stages but are not perfectly correlated with them. For example, SWS is associated with cortical slow oscillations (slow, <1 Hz oscillatory activity during SWS), sleep spindles (faster, 11–16 Hz, bursts of coherent brain activity), and hippocampal sharp wave-ripple complexes (approximately 200 Hz), all of which have been associated with episodic memory consolidation. Indeed, the co-occurrence of these electrophysiological events may underlie the coordinated information flow back and forth between the hippocampus and neocortex as memories are integrated within neocortical long-term storage sites.[13]

For example, slow oscillations are intensified when SWS is preceded by a learning experience[73–75] and hippocampus-dependent memories are specifically enhanced when slow oscillations are induced during SWS by transcranial electrical stimulation at 0.75 Hz (but not 5 Hz).[76]

Several human studies have shown a correlation between hippocampus-dependent episodic learning and cortical sleep spindles. In one such study,[77] subjects studied a long list of unrelated word pairs 1 hour before sleep, on 2 separate occasions at least a week apart. In one case, they were instructed to imagine a relationship between the 2 nominally unrelated words, whereas in the other they were simply asked to count the number of letters containing curved lines in each word pair. Such instructions lead to deep hippocampally mediated encoding and shallow cortically mediated encoding, respectively. During the subsequent nights of sleep, subjects showed significantly higher spindle densities on the nights after deep encoding, averaging 34% more spindles in the first 90 minutes of sleep. Moreover, sleep spindle density was positively correlated both with immediate recall tested in the final stage of training and with recall the next morning, after sleep. Thus, those who learned better had more spindles the following night and those with more spindles showed a greater performance gain the next morning.[78–80]

Hippocampal network oscillations such as sharp wave-ripple complexes may also help promote the synaptic plasticity necessary for memory consolidation. Such events can accompany the reactivation of hippocampal neuron ensembles that were activated during prior waking training. Moreover, inducing long-term potentiation, a neurophysiological mechanism of learning and memory, can trigger the generation of sharp wave-ripple complexes in the rat hippocampus,[81] suggesting that strengthened synaptic coupling can lead to neurons firing synchronously during formation of sharp wave-ripples complexes. Connecting these events to behavior, Eschenko and

colleagues[82] demonstrated that rats learning odor-reward associations produced an increase in the number and size of ripple events for 2 hours during subsequent SWS. Moreover, episodic memory consolidation in human epileptic patients correlates with the number of ripples recorded from the major output regions of the hippocampus (perirhinal and entorhinal cortices),[83] and selective disruption of hippocampal ripples by electric stimulation during postlearning rest phases in rats impairs formation of long-lasting spatial memories, suggesting that ripples could have a causal role in sleep-based memory consolidation.[84]

Recent work also suggests that there is a close temporal relationship between the occurrence of slow oscillations, spindles, and sharp wave-ripple complexes during SWS that may coordinate bidirectional information flow between the hippocampus and neocortex as memories are integrated within long-term storage sites.

NEUROTRANSMITTERS AND NEUROHORMONES

There is also evidence to suggest that nocturnal changes in neurotransmitter and neurohormone levels contribute to memory consolidation. ACh, norepinephrine, 5-HT, and cortisol play important roles both in modulating sleep[85] and memory function.[86–88] Cortisol levels, for instance, follow a marked circadian rhythm, whereby the hormone is at its nadir during early-night slow wave–rich sleep and reaches its zenith during late-night REM-rich sleep. Indeed, the difference between the cortisol level in the blood at sleep onset and at awakening is so great that the interpretation of cortisol blood levels is meaningless without knowing exactly when the sample was taken.[89–91] Moreover, the secretion of cortisol is not continuous but composed of gradually increasing peaks that tend to coincide with REM sleep (**Fig. 8**). REM sleep thus tends to co-occur with cortisol elevations.[90,92]

The early night reduction in ACh and cortisol levels may be necessary for hippocampus-dependent memories to undergo effective consolidation because experimentally elevating the levels of either substance during early sleep impairs performance on episodic memory tasks. Gais and Born[93] trained subjects on word pair task and mirror tracing tasks before 3 hours of nocturnal sleep or wakefulness during which they received a placebo or an infusion of the cholinesterase inhibitor physostigmine (which increases cholinergic tone). When tested after 3 hours of early sleep rich in SWS, recall on the paired associates task was markedly impaired in the physostigmine group, while the procedural memory performance was unaffected. Using a similar design, Plihal and Born[94] showed that when cortisol was infused during the early SWS-rich interval, retention of episodic information that is

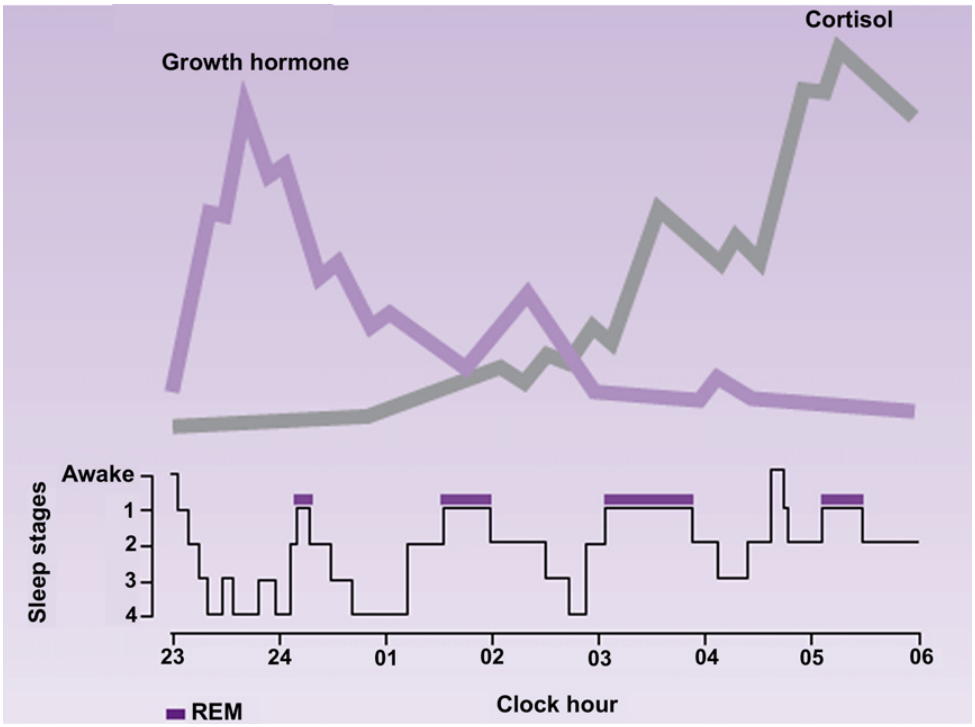

Fig. 8. The relationship between sleep stage architecture and circulating levels of growth hormone and cortisol. Note both the linear increase in cortisol levels across the night and also the cortisol peaks riding on top of the REM periods.

normally facilitated during this time was impaired. Thus, enhancing plasma cortisol concentrations during early sleep eradicated the benefit typically observed for episodic memory while leaving procedural memory unimpaired (**Fig. 9**).

Plihal and Born[94] concluded that because episodic, but not procedural, memory relies on hippocampal function, cortisol inhibition during early nocturnal sleep is necessary for episodic memory consolidation. Thus, because cortisol release is normally inhibited during early night periods dense in SWS, this time window may provide the ideal physiologic environment for episodic memory consolidation. REM sleep, on the other hand, is an inefficient time to consolidate episodes because of the deleterious effect of elevated cortisol on hippocampus-dependent memory processing. Thus, the neurobiological properties of early sleep and late sleep, as opposed to SWS and REM sleep per se, may be essential for the consolidation of different types of memory.

In line with the above-mentioned findings, elevation of cortisol levels during wakefulness can also impair performance on episodic memory.[89,95] The cortisol level in the Plihal and Born[94] study (15.2 + 0.68 mg/dL) was elevated just enough to mimic the late night peak of circadian cortisol activity and is proportionate to the amount of cortisol typically released in response to a mild to moderate stressor (approximately 10–30 mg/dL) and is a sufficient dose to disrupt episodic memory function during wakefulness,[89,92,96,97] particularly when administered prior to consolidation or at

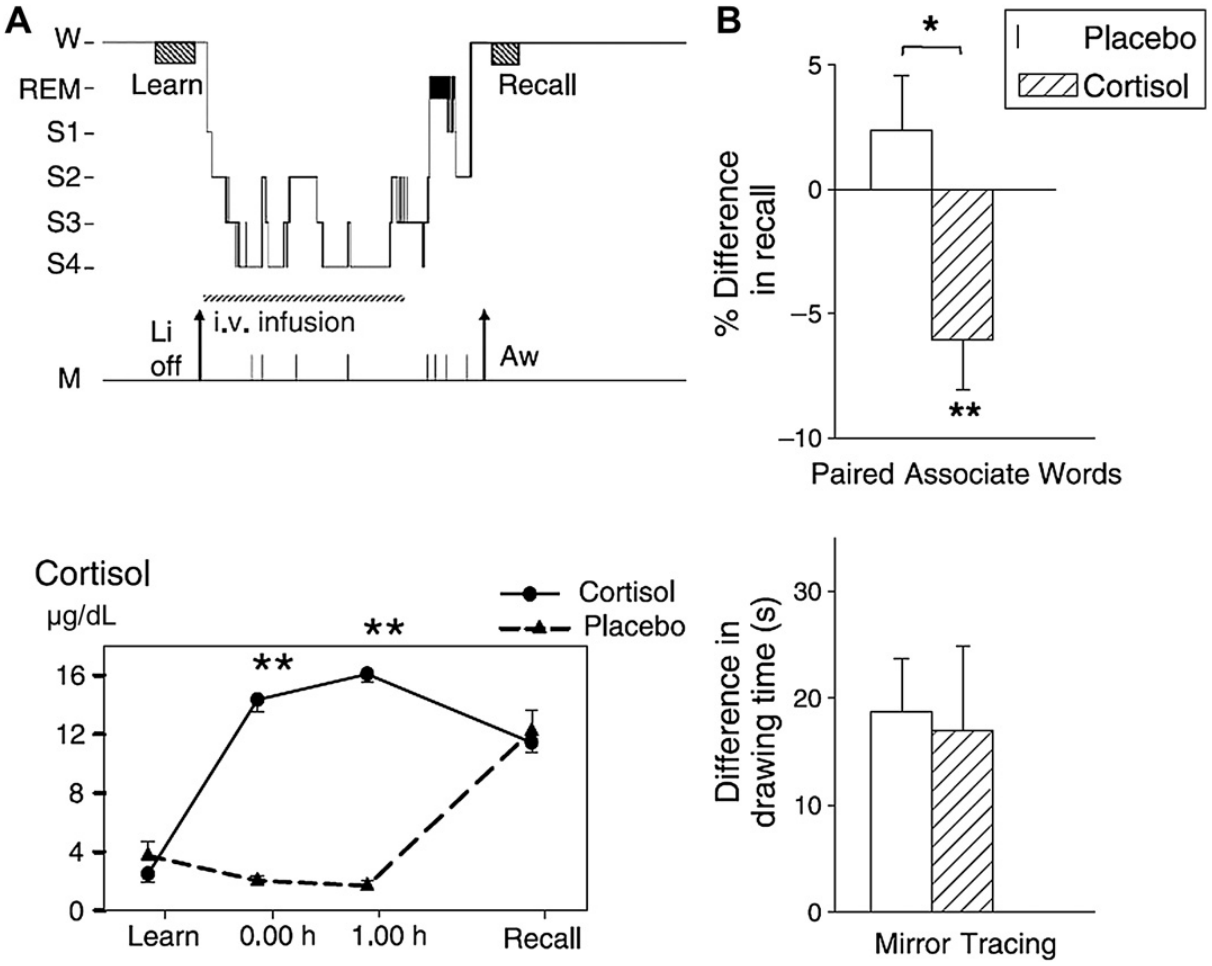

Fig. 9. (*A, top*) Experimental design for examining the effect of cortisol on memory consolidation during a 3-hour period of early nocturnal sleep rich in SWS, illustrated by an individual sleep profile. Before sleep, subjects learned episodic and procedural memory tasks to a criterion. Recall was tested 15 to 30 minutes after awakening. Infusion of cortisol or placebo began at 11 PM and was discontinued after 2.5 hours. (*Bottom*) Mean plasma cortisol concentrations during administration of placebo (*dotted line*) and cortisol (*solid line*). (*B*) Cortisol infusion during sleep, compared with placebo, impaired hippocampus-dependent episodic memories for word pairs across sleep (*top*), but did not affect hippocampus-independent procedural memory (speed in mirror tracing, *bottom*). N = 14, **P*<.05, ***P*<.01. Aw, awake; IV, intravenous, Li, lights; S, stage; W, wake. (*Data from* Plihal W, Born J. Memory consolidation in human sleep depends on inhibition of glucocorticoid release. Neuroreport 1999;10(13):2741–7.)

retrieval.[95,98] Elevations in cortisol levels seen during late night REM sleep may help explain why replay of episodic memories in REM sleep dreaming is so scarce[99] and perhaps also why dreams are difficult to remember on awakening.[87,100]

In addition to cortisol, other hormones (eg, growth hormone) are also known to affect memory function in the waking state and vary across sleep, suggesting that they might modulate sleep-based memory consolidation as well. Although initial studies of growth hormone have failed to find such an effect,[101] further investigation of the neurochemistry underlying the relationship between sleep and memory consolidation is a productive avenue for future research. Indeed, it seems especially important to forge ahead into precisely this neuromodulatory realm, in which the chemical basis of the sleep/memory consolidation connection can be examined.

FUTURE DIRECTIONS

Over the past 10 years, the field of sleep and memory has grown exponentially, with reports of sleep-memory interactions emerging from myriad disciplines and ranging from cellular and molecular studies in animals to behavioral and neuroimaging studies in humans. Correspondingly little is known, however, about sleep-dependent memory consolidation in diverse clinical conditions that are associated with sleep impairment. These conditions range from physical conditions, such as sleep apnea, to psychiatric conditions, such as depression, and each condition may affect sleep-dependent memory processing in profound but different ways.

For example, obstructive sleep apnea (OSA) is characterized by repetitive breathing cessations during sleep that can produce hundreds of short EEG arousals each night. Although the cognitive deficits associated with OSA are well documented[102] and the hypoxia associated with OSA is thought to alter brain regions (eg, hippocampus) that underlie the cognitive deficits,[103,104] very little research has directly assessed decrements to sleep-dependent memory consolidation in this population (see[105] for a notable exception). Similarly, depression and schizophrenia, both of which are associated with marked changes in sleep architecture,[106] have recently been associated with disrupted procedural memory consolidation,[48,49] yet a careful study of sleep-related episodic, and especially emotional, memory consolidation in these populations have yet to be conducted. These are but 3 examples of the vital and potentially fruitful questions that remain to be answered about sleep-dependent memory consolidation in the clinical realm. Future research in the field should thus target clinical conditions that are characterized by sleep deficits, assessing to what degree sleep dysfunction is associated with impaired memory consolidation, and, equally importantly, determining whether sleep treatment will yield cognitive, emotional, and physical benefits.

REFERENCES

1. Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 1975;189:55–8.
2. Walker MP, Stickgold R. Sleep, memory and plasticity. Annu Rev Psychol 2006;57:139–66.
3. Stickgold R, Hobson JA, Fosse R. Sleep, learning, and dreams: off-line memory reprocessing. Science 2001;294:1052–7.
4. McGaugh JL. Memory – a century of consolidation. Science 2000;287:248–51.
5. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci 2010;11:114–26.
6. Payne JD, Ellenbogen JM, Walker MP, et al. The role of sleep in memory consolidation. In: Byrne JH, editor. Concise learning and memory: the editor's selection. Oxford (UK): Elsevier Press; 2008. p. 547–69.
7. Payne JD, Kensinger EA. Sleep's role in the consolidation of emotional episodic memories. Curr Dir Psychol Sci 2010;19(5):290–5.
8. Stickgold R. Sleep-dependent memory consolidation. Nature 2005;437:1272–8.
9. Smith C. Sleep states, memory processes and synaptic plasticity. Behav Brain Res 1995;78:49–56.
10. Walker MP. The role of sleep in cognition and emotion. Ann N Y Acad Sci 2009;1156:168–97.
11. Schacter DL, Tulving E. Memory systems 1994. Cambridge (MA): MIT Press; 1994.
12. Hamann SB. Cognitive and neural mechanisms of emotional memory. Trends Cogn Sci 2001;5:394–400.
13. Moscovitch M, Rosenbaum RS, Gilboa A, et al. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 2005;207(1):35–66.
14. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 2004;27:1–28.
15. Giuditta A, Ambrosini MV, Montagnese P, et al. The sequential hypothesis of the function of sleep. Behav Brain Res 1995;69:157–66.

16. Marshall L, Born J. The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci 2007;11:442–50.
17. Nishida M, Pearsall J, Buckner RL, et al. REM sleep, prefrontal theta and the consolidation of human emotional memory. Cereb Cortex 2009;19: 1158–66.
18. Walker MP, Stickgold R. Overnight alchemy: sleep-dependent memory evolution. Nat Rev Neurosci 2010;11:218.
19. Karni A, Sagi D. The time course of learning a visual skill. Nature 1993;365:250–2.
20. Karni A, Tanne D, Rubenstein BS, et al. Dependence on REM sleep of overnight improvement of a perceptual skill. Science 1994;265(5172):679–82.
21. Stickgold R. Human studies of sleep and off-line memory reprocessing. In: Maquet P, Smith C, Stickgold R, editors. Sleep and plasticity. London: Oxford University Press; 2003. p. 41–65.
22. Stickgold R, James L, Hobson JA. Visual discrimination learning requires post-training sleep. Nat Neurosci 2000;2(12):1237–8.
23. Stickgold R, Whidbee D, Schirmer B, et al. Visual discrimination task improvement: a multi-step process occurring during sleep. J Cogn Neurosci 2000;12:246–54.
24. Gais S, Plihal W, Wagner U, et al. Early sleep triggers memory for early visual discrimination skills. Nat Neurosci 2000;3(12):1335–9.
25. Mednick S, Nakayama K, Stickgold R. Sleep dependent learning: a nap is as good as a night. Nat Neurosci 2003;6:697–8.
26. Mednick SC, Nakayama K, Cantero JL, et al. The restorative effect of naps on perceptual deterioration. Nat Neurosci 2002;5:677–81.
27. Walker M, Brakefield T, Morgan A, et al. Practice with sleep makes perfect: sleep dependent motor skill learning. Neuron 2002;35:205–11.
28. Fogel S, Jacob J, Smith C. Increased sleep spindle activity following simple motor procedural learning in humans. Actas de Fisiología 2001;7:123.
29. Smith C, MacNeill C. Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. J Sleep Res 1994;3:206–13.
30. Tweed S, Aubrey JB, Nader R, et al. Deprivation of REM sleep or stage 2 sleep differentially affects cognitive procedural and motor procedural memory. Sleep 1999;22:S241.
31. Sejnowski TJ, Destexhe A. Why do we sleep? Brain Res 2000;886(1–2):208–23.
32. Kuriyama K, Stickgold R, Walker MP. Sleep-dependent learning and motor-skill complexity. Learn Mem 2004;11(6):705–13.
33. Maquet P, Laureys S, Perrin F, et al. Festina lente: evidences for fast and slow learning processes and a role for sleep in human motor skill learning. Learn Mem 2003;10(4):237–9.
34. Hennevin E, Hars B, Maho C, et al. Processing of learned information in paradoxical sleep: relevance for memory. Behav Brain Res 1995;69:125–35.
35. Smith C, Wong PT. Paradoxical sleep increases predict successful learning in a complex operant task. Behav Neurosci 1991;105(2):282–8.
36. Smith C, Young J, Young W. Prolonged increases in paradoxical sleep during and after avoidance-task acquisition. Sleep 1980;3(1):67–81.
37. Maquet P, Laureys S, Peigneux P, et al. Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 2000; 3(8):831–6.
38. Peigneux P, Laureys S, Fuchs S, et al. Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. Neuroimage 2003;20(1): 125–34.
39. Datta S. Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. J Neurosci 2000; 20(22):8607–13.
40. Datta S, Mavanji V, Ulloor J, et al. Activation of phasic pontine-wave generator prevents rapid eye movement sleep deprivation-induced learning impairment in the rat: a mechanism for sleep-dependent plasticity. J Neurosci 2004;24(6):1416–27.
41. Smith C. Sleep states and memory processes in humans: procedural versus declarative memory systems. Sleep Med Rev 2001;5(6):491–506.
42. Greenberg R, Pearlman CA. Cutting the REM nerve: an approach to the adaptive function of REM sleep. Perspect Biol Med 1974;17:513–21.
43. Robertson EM, Cohen DA. Understanding consolidation through the architecture of memories. Neuroscientist 2006;12:261–71.
44. Robertson EM, Pascual-Leone A, Press DZ. Awareness modifies the skill-learning benefits of sleep. Curr Biol 2004;14:208–12.
45. Nissen C, Kloepfer C, Nofzinger EA, et al. Impaired sleep-related memory consolidation in primary insomnia – a pilot study. Sleep 2006;29: 1068–73.
46. Manoach D, Thakkar KN, Stroynowski E, et al. Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. J Psychiatr Res 2009;44(2):112–20.
47. Maquet P. The role of sleep in learning and memory. Science 2001;294(5544):1048–52.
48. Manoach DS, Cain MS, Vangel MG, et al. A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. Biol Psychiatry 2004;56: 951–6.
49. Dresler M, Kluge M, Genzel L, et al. Impaired off-line memory consolidation in depression. Eur Neuropsychopharmacol 2010;20:533–61.

50. Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 1997;9(4):534–47.
51. Tucker MA, Hirota Y, Wamsley EJ, et al. A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem 2006;86(2):241–7.
52. Ji D, Wilson MA. Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 2007;10:100–7.
53. Wilson MA, McNaughton BL. Reactivation of hippocampal ensemble memories during sleep. Science 1994;265:676–9.
54. O'Neil J, Pleydell-Bouverie B, Dupret D, et al. Play it again: reactivation of waking experience and memory. Trends Neurosci 2010;33(5):220–9.
55. Peigneux P, Laureys S, Fuchs S, et al. Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 2004; 44:535–45.
56. Rasch B, Buchel C, Gias S, et al. Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 2007;315:1426–9.
57. Takashima A, Petersson KM, Rutters F, et al. Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci U S A 2006; 103(3):756–61.
58. Hu P, Stylos-Allan M, Walker M. Sleep facilitates consolidation of emotional declarative memory. Psychol Sci 2006;17:891–8.
59. Wagner U, Gais S, Born J. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem 2001;8:112–9.
60. Wagner U, Hallschmid M, Rasch B, et al. Brief sleep after learning keeps emotional memories alive for years. Biol Psychiatry 2006;60:788–90.
61. Maquet P, Péters JM, Aerts J, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 1996;383:163–6.
62. Greenberg R, Pearlman C, Schwartz W, et al. Memory, emotion, and REM sleep. J Abnorm Psychol 1983;92:378–81.
63. Ellenbogen JM, Payne JD, Stickgold R. Sleep's role in declarative memory consolidation: passive, permissive, active or none? Curr Opin Neurobiol 2006;16:716–22.
64. Bartlett FC. Remembering: a study in experimental and social psychology. Cambridge (UK): Cambridge University Press; 1932.
65. Ellenbogen JM, Hu P, Payne JD, et al. Human relational memory requires time and sleep. Proc Natl Acad Sci U S A 2007;104:7723–8.
66. Schacter DL, Addis DR, Buckner RL. Episodic simulation of future events. Ann N Y Acad Sci 2008;1124:39–60.
67. Payne JD, Stickgold R, Swanberg K, et al. Sleep preferentially enhances memory for emotional components of scenes. Psychol Sci 2008;19:781–8.
68. Payne JD, Schacter DL, Tucker MA, et al. The role of sleep in false memory formation. Neurobiol Learn Mem 2009;92:327–34.
69. Wagner U, Gais S, Haider H, et al. Sleep inspires insight. Nature 2004;427:352–5.
70. Payne JD, Kensinger EA. Sleep leads to qualitative changes in the emotional memory trace: evidence from fMRI. J Cogn Neurosci 2010. DOI:10.1162/jocn.2010.21526.
71. Sterpenich V, Albouy G, Darsaud A, et al. Sleep promotes the neural reorganization of remote emotional memory. J Neurosci 2009;29:5143–52.
72. Payne JD, Nadel L. Sleep, dreams, and memory consolidation: the role of the stress hormone cortisol. Learn Mem 2004;11:671–8.
73. Huber R, Ghilardi MF, Massimini M, et al. Local sleep and learning. Nature 2004;430:78–81.
74. Molle M, Marshall L, Gais S, et al. Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. Proc Natl Acad Sci U S A 2004;101:13963–8.
75. Molle M, Eschenko O, Gais S, et al. The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur J Neurosci 2009;29:1071–81.
76. Marshall L, Helgadottir H, Molle M, et al. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444:610–3.
77. Gais S, Molle M, Helms K, et al. Learning-dependent increases in sleep spindle density. J Neurosci 2002;22(15):6830–4.
78. Schmidt C, Peigneux P, Muto V, et al. Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. J Neurosci 2006; 26:8976–82.
79. Clemens Z, Fabo D, Halasz P. Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. Neurosci Lett 2006;403:52–6.
80. Schabus M, Hodlmoser K, Gruber G, et al. Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. Eur J Neurosci 2006;23(7):1738–46.
81. Behrens CJ, van den Boom LP, et al. Induction of sharp wave-ripple complexes in vitro and reorganization of hippocampal networks. Nat Neurosci 2005;8:1560–7.
82. Eschenko O, Ramadan W, Molle M, et al. Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 2008;15:222–8.
83. Axmacher N, Elger CE, Fell J. Ripples in the medial temporal lobe are relevant for human memory consolidation. Brain 2008;131:1806–17.

84. Girardeau G, Benchenane K, Wiener SI, et al. Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 2009;12: 1222–3.
85. Hobson JA, Pace-Schott EF. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Nat Rev Neurosci 2002;3: 679–93.
86. Cahill L, McGaugh JL. Mechanisms of emotional arousal and lasting declarative memory. Trends Neurosci 1998;21:294–9.
87. Payne JD. Memory consolidation, the diurnal rhythm of cortisol, and the nature of dreams: a new hypothesis. Int Rev Neurobiol 2010;92: 101–36.
88. Hasselmo ME. Neuromodulation: acetylcholine and memory consolidation. Trends Cogn Sci 1999;3: 351–9.
89. Payne JD, Nadel L, Britton WB, et al. The biopsychology of trauma and memory. In: Reisberg D, Hertel P, editors. Emotion and memory. Oxford (UK): Oxford University Press; 2004. p. 76–127.
90. Lavie P. The enchanted world of sleep. New Haven (CT): Yale University Press; 1996.
91. Weitzman ED, Fukushima D, Nogeire C, et al. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab 1971;33:14–22.
92. Wagner U, Born J. Memory consolidation during sleep: interactive effects of sleep stages and HPA regulation. Stress 2008;11:28–41.
93. Gais S, Born J. Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. Proc Natl Acad Sci U S A 2004; 101(7):2140–4.
94. Plihal W, Born J. Memory consolidation in human sleep depends on inhibition of glucocorticoid release. Neuroreport 1999;10(13):2741–7.
95. de Quervain DJF, Aerni A, Schelling G, et al. Glucocorticoids and the regulation of memory in health and disease. Front Neuroendocrinol 2009; 30:358–70.
96. Kirschbaum C, Wolf OT, May M, et al. Stress and treatment induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci 1996;58:1475–83.
97. Kirschbaum C, Pirke K, Hellhammer D. The 'Trier Social Stress Test' - A tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993;28:76–81.
98. de Quervain DJF, Roozendaal B, Nitsch RM, et al. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci 2000;3:313–4.
99. Fosse MJ, Fosse R, Hobson JA, et al. Dreaming and episodic memory: a functional dissociation? J Cogn Neurosci 2003;15:1–9.
100. Hobson JA. The dreaming brain. New York: Basic Books; 1988.
101. Gais S, Hullemann P, Hallschmid M, et al. Sleep-dependent surges in growth hormones do not contribute to sleep-dependent memory consolidation. Psychoneuroendocrinology 2006;31(6):786–91.
102. Saunamaki T, Jehkonen M. A review of executive functions in obstructive sleep apnea syndrome. Acta Neurol Scand 2007;115:1–11.
103. Meerlo P, Mistlberger RE, Jacobs BL, et al. New neurons in the adult brain: the role of sleep and consequences of sleep loss. Sleep Med Rev 2009;13:187–94.
104. Row BW. Intermittent hypoxia and cognitive function: implications from chronic animal models. Adv Exp Med Biol 2007;618:51–67.
105. Kloepfer C, Riemann D, Nofzinger EA, et al. Memory before and after sleep in patients with moderate obstructive sleep apnea. J Clin Sleep Med 2009;5:540–8.
106. Armitage R. Sleep and circadian rhythms in mood disorders. Acta Psychiatr Scand 2007; 115(Suppl 433):104–15.