■ REVIEW

Sleep to Remember

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Recently, compelling evidence has accumulated that links sleep to learning and memory. Sleep has been identified as a state that optimizes the consolidation of newly acquired information in memory. Consolidation is an active process that is presumed to rely on the covert reactivation and reorganization of newly encoded representations. Hippocampus-dependent memories benefit primarily from slow-wave sleep (SWS), whereas memories not depending on the hippocampus show greater gains over periods containing high amounts of rapid eye movement sleep. One way sleep does this is by establishing different patterns of neurotransmitters and neurohormone secretion between sleep stages. Another central role for consolidating memories is played by the slow oscillation, that is, the oscillating field potential change dominating SWS. The emergence of slow oscillations in neocortical networks depends on the prior use of these networks for encoding of information. Via efferent pathways, they synchronize the occurrence of sharp wave ripples accompanying memory reactivations in the hippocampus with thalamocortical spindle activity. Thus, hippocampal memories are fed back into neocortical networks at a time when these networks are depolarized and, because of concurrent spindle activity, can most sensitively react to these inputs with plastic changes underlying the formation of long-term memory representations. NEUROSCIENTIST 12(5):410–424, 2006. DOI: 10.1177/1073858406292647

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Perhaps the most impressive characteristic of sleep, aside from the state of general behavioral inactivity, is the loss of consciousness. Here, we will provide evidence that sleep facilitates the storage of newly encoded information into long-term memory. In the central nervous system, the same neuronal networks are used for the online processing of information and for long-term storage of this information. To separate these two functions and to prevent interference, it appears that the benefits of an evolutionary introduction of an offline state outweighed the dangers of temporary unconsciousness and immobility. We do not intend to argue here that sleep serves exclusively to form long-term memories. Sleep has multiple other functions like the saving of energy and restorative functions (Siegel 2005). However, the memory function of sleep might be the only one that eventually explains the lack of consciousness associated with sleep, which represents the greatest evolutionary risk in this state with the organism being a prey to predators (Kavanau 1997).

Memory Processes and Memory Systems

The investigation of memory differentiates three fundamental processes: acquisition, consolidation, and retrieval. Acquisition refers to the learning process whereby the new information is encoded into a neuronal trace. Consolidation refers to processes that continue after learning and stabilize, transform, or enhance the newly encoded memory trace, which is initially fragile and temporary. Thus, consolidation counteracts forgetting due to the decay of the fresh trace or retroactive interference from subsequently encoded material (Wixted 2004). Retrieval refers to the recall of stored memories. We concentrate here on the effects of sleep on the consolidation of memory.

The concept that fresh memories need to consolidate slowly over time to become resistant against interference and decay was put forward originally by Müller and Pilzecker (1900). Apart from strengthening memory traces, consolidation includes also processes that support an integration of newly encoded memories with preexisting long-term memories. With respect to the underlying neurophysiological mechanisms, two types of consolidation have been distinguished: a "synaptic consolidation," which is accomplished within minutes or hours after learning and involves mainly the stabilization of synaptic changes, and a "system consolidation," which can take days or months to complete. During system consolidation, neural memory representations undergo a reorganization so that they become represented by different neural networks in the course of this process (Dudai 2004; Frankland and Bontempi 2005).

Traditionally, declarative and nondeclarative memory systems are distinguished in human neuropsychology. The declarative memory system refers to the explicit memories for facts and events, and their encoding and short-term retrieval essentially rely on the hippocampus (Squire

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1992). However, over time their retrieval becomes independent of the hippocampus, presumably due to a gradual transfer to neocortical networks (Sutherland and McNaughton 2000). However, hints at a reorganization during consolidation have been likewise provided for procedural, nondeclarative memories, which primarily rely on striatocortical circuitry (Doyon and Benali 2005).

Sleep-Dependent Consolidation of Procedural Memory

First studies that aimed to test a beneficial effect of sleep on the consolidation of memory date back to the beginnings of the experimental investigations of memory (Heine 1914). However, only recently a beneficial effect of sleep on procedural memory consolidation could be shown for tasks such as visual texture discrimination and finger sequence tapping (Karni and others 1994; Gais and others 2000; Stickgold and others 2000a; Fischer and others 2002; Walker and others 2002; Walker 2005). A most interesting feature of such procedural types of memory tasks is a gain in performance that is seen only at delayed retesting several hours after training. This increase in performance indicates that the memory representation underlying the skill does not only stabilize across the retention interval but in fact becomes enhanced despite the absence of any further training during the retention interval (Fig. 1). Studies have provided converging evidence that for visual texture discrimination, this gain in skill performance at later retrieval testing emerges only if the training is followed by a period of sleep (Gais and others 2000; Stickgold and others 2000a; Mednick and others 2002, 2003).

Similar sleep-dependent gains at a later retrieval testing were observed for motor skills such as finger sequence tapping (Fischer and others 2002; Walker and others 2002). Retrieval testing after retention periods of wakefulness revealed that the quiet wake state can stabilize behavior, making it resistant to interference within shorter periods of six to eight hours (Brashers-Krug and others 1996; Walker and others 2003). However, a robust gain in performance was observed only when the training was followed by a period of sleep. Accordingly, Walker (2005) proposed to differentiate two stages of consolidation in procedural memory formation. The first involves a process of stabilization, which may take just a certain time after acquisition but does not require sleep. The second involves enhancement and does require sleep. However, the available data do not rule out a beneficial effect of sleep also on the stability of memories, for example, by increasing their resistance to interference.

On the other hand, significant enhancements in performance at retrieval testing have been observed on sequence finger tapping tasks also after wake retention periods, although these were weaker than those after retention periods including sleep (Fischer and others 2002; Korman and others 2003). Employing auditory verbal identification tasks, some studies revealed gains in performance that were dependent on sleep (Fenn and others 2003), whereas others pointed to a mere time dependence of the gains with comparable performance enhancements after retention periods of sleep and quiet wakefulness (Gottselig and others 2004; Roth and others 2005). Overall the emerging picture suggests that, depending on task characteristics, both processes of stabilization and enhancement are not exclusively confined to sleep, but they are clearly amplified by sleep.

The sleep-dependent gain of skill has been ascribed to a latent learning process that leads to a reactivation and reorganization of the neural representation of the skill. A sleep-specific reorganization of skill representations in the brain has in fact been demonstrated by studies using functional magnetic brain imaging (Maquet and others 2003; Fischer and others 2005; Walker and others 2005). Trained on a finger sequence tapping task, at a retesting after retention sleep, in comparison with wake retention control conditions, participants showed distinctly less involvement of prefrontal, premotor, and primary motor cortical areas, along with a stronger involvement of left parietal cortical regions and the basal ganglia, suggesting overall a more automatized performance after sleep (Fig. 2) (Fischer and others 2005).

Sleep-Dependent Consolidation of Declarative Memory

There is a body of data indicating that sleep likewise benefits declarative memory consolidation. In fact, the first experimental trials to examine the role of sleep for memory all employed declarative tasks like the learning of word lists and nonsense syllables (eg, Heine 1914; Jenkins and Dallenbach 1924; Van Ormer 1933). Although these early studies were done in only a few individuals, often including the authors themselves, results were confirmed subsequently in greater participant samples and with other learning materials (eg, Newman 1939; Lovatt and Warr 1968; Benson and Feinberg 1975, 1977; Ekstrand and others 1977; Idzikowski 1984; Schoen and Badia 1984; Nesca and Koulack 1994).

The most frequently used approach in these studies relied on a comparison of retrieval performance tested shortly after retention intervals of nocturnal sleep and daytime wakefulness, with the learning phase directly preceding the retention periods. This approach bears two basic problems. First, effects of circadian rhythm may confound recall performance after sleep and wakefulness, when retention intervals cover different periods of the day. Second, recall may be selectively hampered by fatigue when taking place after prolonged periods of wakefulness. To avoid these confounds, several recent studies used a design in which participants either slept or remained awake in the first night after learning and recall was tested not until after a second night, which enabled recovery sleep after the wake retention period (Drosopoulos and others 2006; Gais and others 2006). These studies employing word recognition and word pair association tasks indicated that sleep after learning improves declarative memory consolidation, in the absence of circadian confounds or differences in fatigue at recall testing. In addition, they showed that participants forgot more words when these were learned in the morning than in the evening before nocturnal sleep

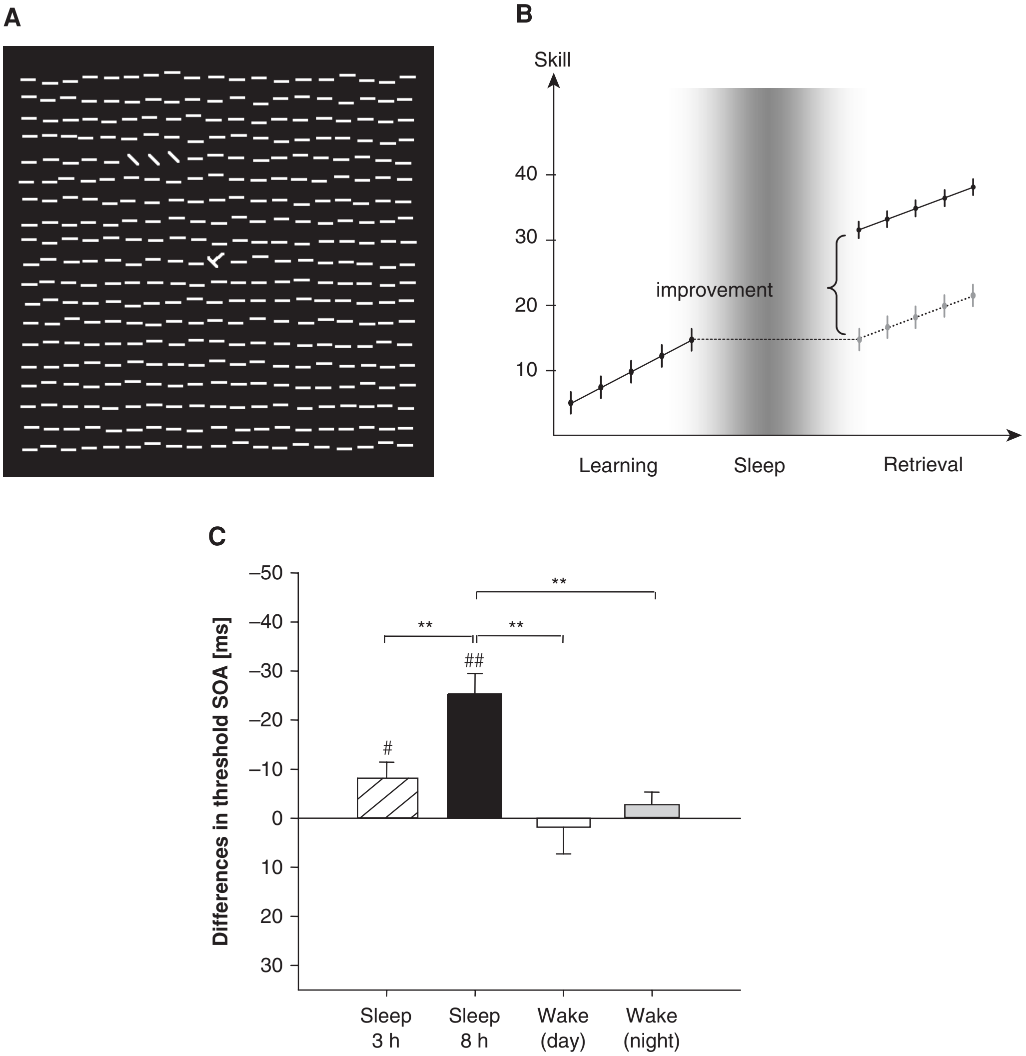

Fig. 1. Sleep-dependent memory consolidation of visual texture discrimination skill. *A*, Example of a stimulus display with the fixation point (rotated T) and the target stimulus (three oblique lines in the *upper-left* quadrant). The stimulus display is presented with progressively shorter exposure times (360–60 millisecond). Participants have to report the fixation stimulus letter (T or L) and the alignment of the target stimulus (ie, whether horizontal, as in this example, or vertical). *B*, Schematic illustration of skill improvement within and between learning and retrieval sessions that are separated by nocturnal sleep. *C*, Change in discrimination threshold at retrieval testing, relative to performance at learning. "Stimulus to mask onset asynchrony" (SOA) defines the exposure time of the display at which 80% of the target textures are discriminated correctly. An improved discrimination performance at retrieval testing (ie, a gain of skill as a consequence of memory consolidation) was only seen when participants had at least three hours of sleep (hatched bar). Performance further increased when participants were allowed to sleep for eight hours (black bar). There was no improvement at a retrieval testing in the evening, when participants had learned in the morning and stayed awake during the day (white bar) or at a retrieval testing, after participants had stayed awake the night after training (gray bar). $^{**}P < 0.01$ for comparisons between conditions; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ for difference from zero. Modified after Gais and others (2000).

(Gais and others 2006). Studies, in which retrieval testing was delayed by more than one night of recovery sleep and up to one week after learning, revealed less consistent results, with some studies failing to find a beneficial effect of sleep following learning (Graves 1937; Richardson and Gough 1963; Smith 2001). This might be because consolidation of declarative memory is not restricted to the first night after learning, so that sleep in later nights partly compensates and eventually masks the effects of lacking sleep on the first night.

Sleep Reorganizes Memory Representations

In contrast to procedural memories, which require repeated trials for learning but fade slowly, acquisition of declarative memories is faster and often relies on just

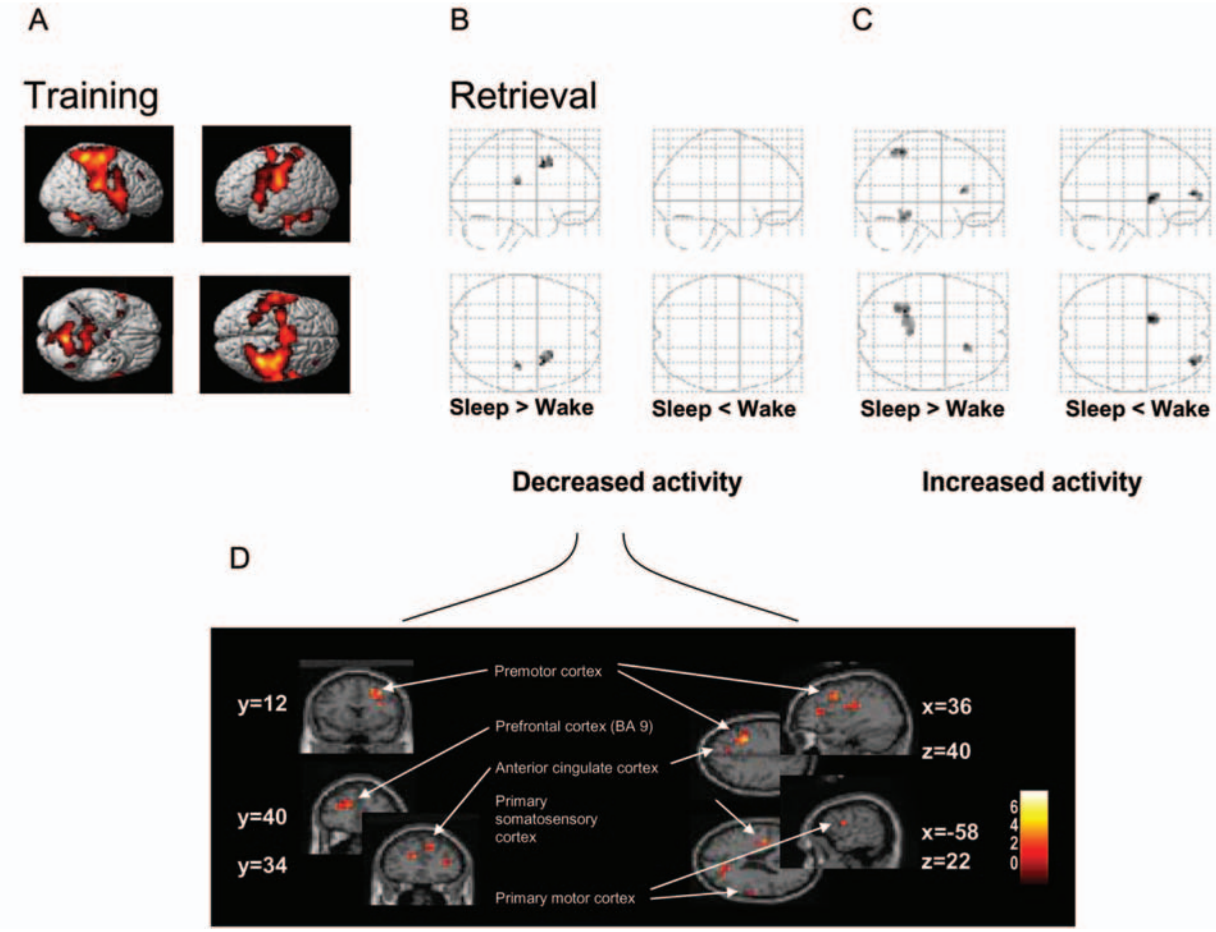

Fig. 2. Sleep-specific reorganization of skill representations in the brain as demonstrated by functional magnetic brain imaging performed in healthy students twice, that is, at initial training of a finger sequence tapping task and at retrieval testing two days later. Training was followed either by regular nocturnal sleep (posttraining sleep condition) or a night of sleep deprivation followed by recovery sleep on the second night (posttraining wake condition). *A*, Brain regions activated during initial training, in comparison with rest. *B*, Brain regions, where at retrieval testing, the *decrease* in activation (with reference to training) was greater in the posttraining sleep than in the posttraining wake condition and vice versa, in which this decrease was larger in the posttraining wake than in the posttraining sleep condition (which never happened). *C*, Brain regions in which the *increase* in retrieval-related activation across the retention interval was larger in the posttraining sleep than posttraining wake condition and vice versa in which this increase was larger in the posttraining wake than posttraining sleep condition. Statistical parametric maps are thresholded at $P < 0.005$ (uncorrected) and displayed as sagittal and horizontal projections. *D*, Brain regions of significant sleep-dependent decreases compared to initial training (as depicted in panel *B*) are displayed here superimposed on the Montreal Neurological Institute standard brain with corresponding labels of brain regions. Data adapted from Fischer and others (2005).

a single but salient event. However, declarative memories after encoding are sensitive to interference and decay rapidly. It might be this fast rate of forgetting in the declarative memory system that has prompted the traditional view that sleep benefits memory consolidation mainly by protecting the newly encoded and still fragile representations from interference that results from the encoding of other events during the critical period of consolidation (Wixted 2004). However, there is evidence that sleep plays an active role in the consolidation of declarative memory leading to a reorganization of newly acquired representations. For example, brain activity related to a spatial memory task was shifted from the hippocampus to the striatum after participants slept, which did not happen when participants were sleep deprived (Orban and others 2006).

There is also evidence that sleep after learning can provide a qualitative change to memories. Wagner and others (2004) showed this using a number reduction task originally developed by Thurstone and Thurstone (1941) for testing intelligence. In this task, participants are shown strings of digits and are instructed to process each string as fast as possible and name the final result as soon as they know it. They are taught how to reach the solution by sequentially processing the digits according to a set of rules. However, there is a hidden structure in the sequences, such that the participant, once gaining insight into this hidden structure, can give the correct answer

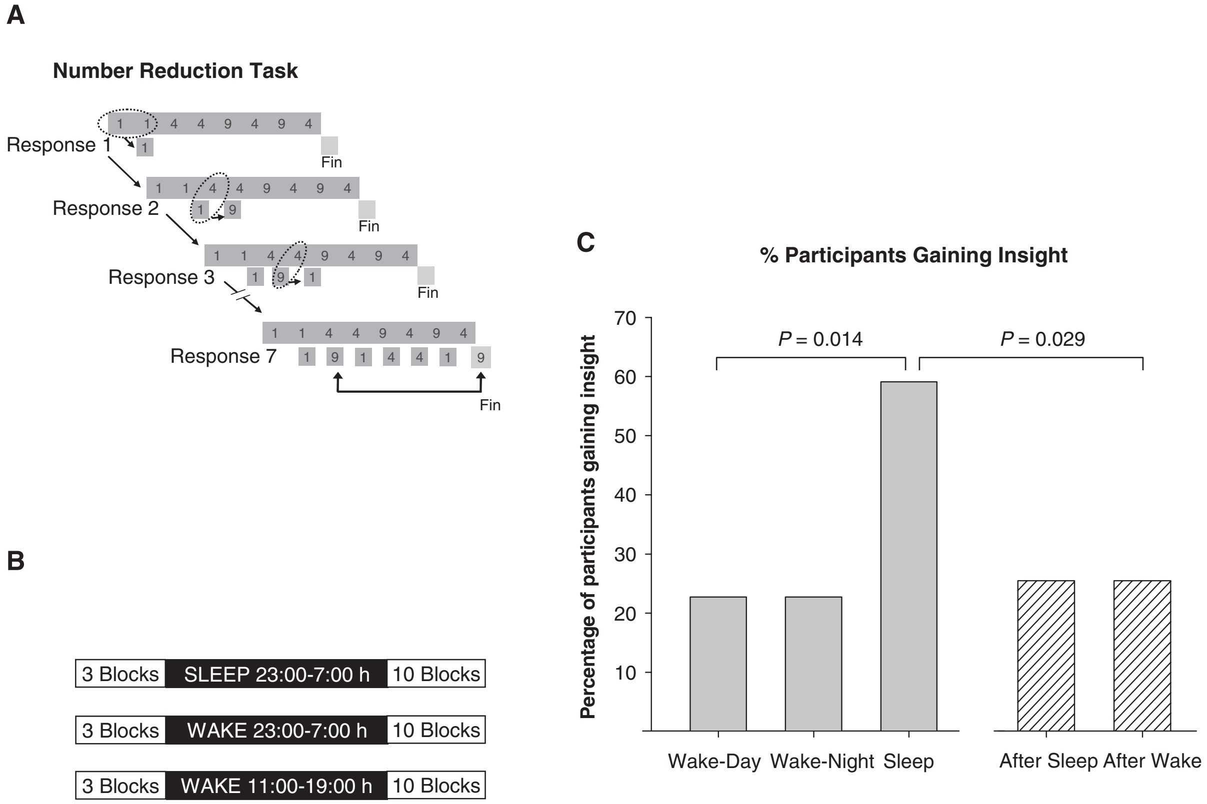

Fig. 3. Sleep facilitates gain of explicit knowledge. *A*, Number reduction task, illustrated by an example trial. On each trial, a different string of eight digits was presented. Each string was composed of the digits 1, 4, and 9. For each string, participants had to determine a digit defined as the "final solution" of the task trial. This could be achieved by sequentially processing the digits pairwise from left to right according to two simple rules. One, the "same rule," states that the result of two identical digits is just this digit (for example, 1 and 1 results in 1, as in response 1 here). The other rule, the "different rule," states that the result of two nonidentical digits is the remaining third digit of this three-digit system (for example, 1 and 4 results in 9, as in response 2 here). After the first response, comparisons are made between the preceding result and the next digit. The seventh response indicates the final solution (Fin), to be confirmed by pressing a separate key. Instructions stated that only this final solution was to be determined and this could be done at any time. Not mentioned to the participants, the strings were generated in such a way that the last three responses always mirrored the previous three responses. This implies that in each trial the second response coincided with the final solution (arrow). Participants who gain insight into this hidden structure abruptly cut short sequential responding by pressing the solution key immediately after the second response. *B*, Experimental design: An eight-hour period of nocturnal sleep, nocturnal wakefulness, or daytime wakefulness separated an initial training phase (three blocks) from later retesting (10 blocks). *C*, Effects of sleep and wakefulness on the occurrence of insight. Columns indicate percentage of participants gaining insight into the hidden structure in the three conditions of the main experiment (gray), in which participants either slept (at night) or remained awake (at night or during daytime) between initial training and retesting, and in two supplementary conditions (hatched), where participants were tested after nocturnal sleep or daytime wakefulness in the absence of initial training before these periods. Modified from Wagner and others (2004).

without having to go through the whole sequence (Fig. 3). In the experiment, the participants first practiced 3 blocks each containing 30 sequences, which was not sufficient to produce insight into the hidden structure but still induced a memory representation of the task. Then, an eight-hour interval followed that covered a period of overnight sleep or wakefulness or a wake period during daytime, before participants were retested on another 10 blocks. At retesting, more than twice as many participants of the sleep group gained insight into the hidden structure as compared to both wake-control groups. Importantly, additional controls showed that sleep did not facilitate insight when the participants had not practiced the tasks before sleep, that is, when no representation of the task was encoded beforehand.

A similar sleep-dependent gain of explicit knowledge was shown in another study using a serial reaction time task (SRTT), which requires the participant to respond as quickly as possible with different button press responses to a cue appearing at different positions (Fischer and others 2006). Unknown to the participant, the position of the cue varies according to an underlying grammar, which in that study followed a probabilistic rule. By training, participants gain an implicit knowledge of the sequence. This implicit sequence knowledge manifests itself in faster reaction times to grammatically correct target positions in comparison with reaction times to grammatically incorrect target positions that are occasionally introduced in test blocks. After training, a generation task was used to assess whether participants had also gained an explicit knowledge of the sequence. In this task, participants were explicitly instructed to predict the sequential target positions. At learning, participants displayed implicit but no explicit sequence knowledge. However, when retested after sleep, participants had gained significant explicit knowledge of the sequence, whereas responses after a wake retention interval remained at chance level. It is of note that the sleep-dependent gain of explicit knowledge about the sequence of the SRTT as well as about the hidden structure in the number reduction task arose from a procedural type of performance.

In sum, these behavioral studies support the conclusion that in comparison with wakefulness, sleep is a brain state particularly enforcing the consolidation of memories. The memory effect of sleep is enduring, as impressively demonstrated in a recent experiment in which the enhancing effect of only a three-hour period of sleep after encoding on memory for emotional texts was still detectable four years later (Wagner and others 2006). Moreover, it is clear from these studies that consolidation during sleep involves a reorganization of memory representations.

Is Sleep-Related Memory Consolidation Dependent on Intention?

A central question has emerged from this research: Does sleep indiscriminately enhance all memories encoded during the wake phase? Recently, a synaptic homeostasis hypothesis has been proposed by Tononi and Cirelli (2003, 2006) according to which encoding activity during wakefulness results in a net increase in synaptic strength in many brain circuits. Sleep, and particularly slow-wave sleep, downscales synaptic strength to a baseline level to maintain homeostatic balance in the total synaptic weights. The beneficial effect on memory in this view is a consequence of synaptic downscaling that reduces noise and removes weak memory traces. However, this view is at odds with findings indicating a greater benefit from sleep for associations that were only weakly associated (Kuriyama and others 2004; Drosopoulos and others 2006) as well as findings indicating that memory representations undergo a reorganization during retention sleep (Wagner and others 2004; Fischer and others 2005, 2006; Orban and others 2006).

Nevertheless, newly encoded memories may not benefit from sleep under all circumstances, which leads to another central issue: What are the factors that make a newly encoded memory susceptible to sleep-dependent consolidation? In this regard, findings by Robertson and others (2004) suggest that some kind of "intentionality" has to be present at learning for later consolidation of the memories during sleep. Using an SRTT, these authors found a sleep-dependent gain in skill only under intentional learning conditions, that is, when participants were aware of a grammar in the sequence. When participants were unaware of the grammar, performance gains at retesting did not differ between wake and sleep conditions. In another study by this group (Cohen and others 2005), goal- and movement-based aspects of performance on an SRTT were dissociated by switching hands during test performance. Retention of goal-based representations (ie, knowledge of the sequence of response button positions, independent of the fingers used) selectively benefited from sleep, whereas movement-based aspects (ie, knowledge of the specific finger movements, independent of the sequence of response button positions) benefited equally from sleep and wake periods. Thus, the extent to which learning is intentional might eventually determine whether memories gain from sleep or not (Born and Wagner 2004).

Which Sleep Stages Are Involved in Memory Consolidation?

Human sleep consists of the cyclic occurrence of periods of non-REM (rapid eye movement) and REM sleep. The deepest form of non-REM sleep, that is, sleep stages 3 and 4, is termed slow-wave sleep (SWS). There is an ongoing debate whether memories are consolidated mainly during SWS or REM sleep. Because REM sleep is linked to vivid dreams and obvious cognitive processing, this sleep stage has been traditionally believed to be more important for memory formation. Tests of the "REM sleep memory hypothesis," however, were based mainly on investigations of the effects of selective REM sleep deprivation, which revealed mixed results indicating impaired recall in some cases (eg Empson and Clarke 1970; Grieser and others 1972; Lewin and Glaubman 1975; Tilley and Empson 1978; Karni and others 1994) and unchanged performance in others (eg, Feldman and Dement 1968; Muzio and others 1972; Castaldo and others 1974; Tilley and Empson 1981; Greenberg and others 1983). Findings after selective REM sleep deprivation have been criticized based on the stress the deprivation procedure imposes on the participant, which contaminates later recall performance (Born and Gais 2000). A strategy that appears more appropriate to compare effects of REM sleep with those of SWS was adopted by Ekstrand and coworkers (Yaroush and others 1971; Barrett and Ekstrand 1972; Fowler and others 1973; Ekstrand and others 1977). They compared retention following undisturbed periods of early and late nocturnal sleep. Due to an underlying circadian rhythm, early nocturnal sleep in humans is dominated by SWS and contains only little amounts of REM sleep, whereas this relationship is reversed during the late part of sleep when REM sleep is predominant. The work of Ekstrand's group showed that declarative memory for word pairs is distinctly better if learning is followed by a four-hour retention interval placed in the early, SWS-rich period of nocturnal sleep than after a four-hour retention interval placed in the late, REM sleep–rich part of nocturnal sleep. In more recent studies, we extended these experiments to other memory systems, that is, procedural and emotional memories. The studies confirmed a greater benefit of different types of declarative memories (word pairs, spatial locations, word recognition) from early SWS-rich periods of sleep (Plihal and Born 1997; Drosopoulos and others 2005). On the other hand, procedural memories (eg, a mirror tracing skill) improved particularly from periods of late sleep (Fig. 4). Word-stem priming, another type of nondeclarative memory, and amygdala-dependent emotional memories benefited selectively from late REM sleep–rich sleep as well (Plihal and Born 1999a; Wagner and others 2001, 2003). Because in these experiments the time spent in the lighter sleep stages as well as time awake was closely comparable between the early and late periods of retention sleep, a contribution of these states to the differential effect on procedural and declarative memory consolidation was excluded. Retention tests across corresponding wake intervals covering the early and late night excluded any effects of circadian rhythm. These experiments can also rule out that higher retention after sleep results from a lack of interference. Because participants were sleeping in both early and late night conditions, external interference was present in neither condition.

In conclusion, this series of studies supports the concept that declarative, hippocampus-dependent memory is strengthened particularly by SWS, whereas nondeclarative, procedural memories benefit to a greater extent from REM sleep. However, at first glance, this general rule does not hold for every specific task (Rauchs and others 2005). Rauchs and others (2004) reported a particular improvement from late, REM sleep–rich sleep for strictly episodic declarative memories. Gais and others (2000) showed a distinct improvement in procedural visual texture discrimination skill across an early SWS-rich period of sleep, and Stickgold and others (2000b) found the overnight gain of skill on the same task to be correlated to the amount of SWS in the first quarter of the night and to the amount of REM sleep in the last quarter. Especially for nondeclarative memory, tasks using very different memory systems located in different brain areas (visual cortex, motor cortex, cerebellum) can be affected by sleep in very different manners. Importantly, memory tasks are never purely declarative or procedural, and both systems interact during sleep-dependent consolidation (Peigneux and others 2001; Poldrack and Rodriguez 2003, 2004; Born and Wagner 2004; Fischer and others 2006). Thus, declarative aspects of explicitly training a skill might subsequently contribute to consolidation during sleep. Conversely, strengthening of procedural associations can impact declarative task aspects (Wagner and others 2004).

Memory Consolidation by Reactivation of Representations during Sleep

A central hypothesis held by many researchers is that the consolidation of memories during sleep relies on a covert reactivation of the networks that have been implicated in encoding information during the wake phase (Buzsáki 1996, 1998; McNaughton and others 2003). The reactivation during sleep is covert because it is not associated with conscious re-experience of memories. A reactivation of single neurons and neuron assemblies during sleep after a learning period was first demonstrated in rats using hippocampus-dependent tasks such as maze learning (Pavlides and Winson 1989; Wilson and McNaughton 1994; Sutherland and McNaughton 2000). Reactivation was identified mostly during SWS but, in some cases, also during REM sleep (Louie and Wilson 2001). In the case of hippocampus-dependent tasks, they appeared not to be limited to hippocampal networks but extended to striatal and neocortical circuitry (Qin and others 1997; Pennartz and others 2004). Reactivation during REM sleep after exploration of novel stimuli was observed in the hippocampus, neocortex, putamen, and thalamus of rats (Ribeiro and others 2004). This replay co-occurring in neocortical and hippocampal regions has been proposed to support a transfer of memory representations between hippocampal and neocortical networks, which leads eventually to permanent storage in neocortical regions.

Importantly, hippocampal reactivation is suggested to occur mainly during bursts of activity known as sharp wave–ripple events (Buzsáki 1998; Kudrimoti and others 1999). The sharp waves are fast, depolarizing potentials generated in CA3. They are superimposed upon ripple activity, which is a high-frequency local field potential oscillation (100–300 Hz) originating in CA1 (Buzsáki 1986; Chrobak and Buzsáki 1994, 1996). Ripple activity occurs with increased probability in temporal association with spindle activity in thalamo-neocortical circuitry and affects also neuronal reactivation in striatal circuitry (Siapas and Wilson 1998; Pennartz and others 2004; Mölle and others 2006). In humans, support for a reactivation of newly acquired memory representations has been provided by studies using positron emission tomography. Maquet and others (2000) found reactivations in the cuneus and left premotor cortex that occurred during REM sleep in the night following training on a procedural SRTT. On the other hand, hippocampal areas that were activated during route learning in a virtual town were found to be reactivated during subsequent SWS (Peigneux and others 2004). The amount of hippocampal activity expressed during SWS positively correlated with the improvement in route retrieval on the next day. Although these correlations speak strongly for an involvement of reactivations in the consolidation of neurobehavioral memories during sleep, a causative role of these reactivations still needs to be proved. Yet the imaging findings on reactivations during sleep do corroborate the concept of a differential influence of sleep stages on different memory systems in that they show reactivation for hippocampus-dependent tasks mainly during SWS but procedural reactivation during REM sleep.

Based on the observation that recently acquired memories are reactivated during sleep, the process of consolidation for hippocampus-dependent memories can be conceptualized as an interaction between neocortical and hippocampal networks (Fig. 5) (Buzsáki 1998; Gais and Born 2004a). According to this concept, apart from neocortical encoding, new materials are encoded predominantly into hippocampal networks, where they are

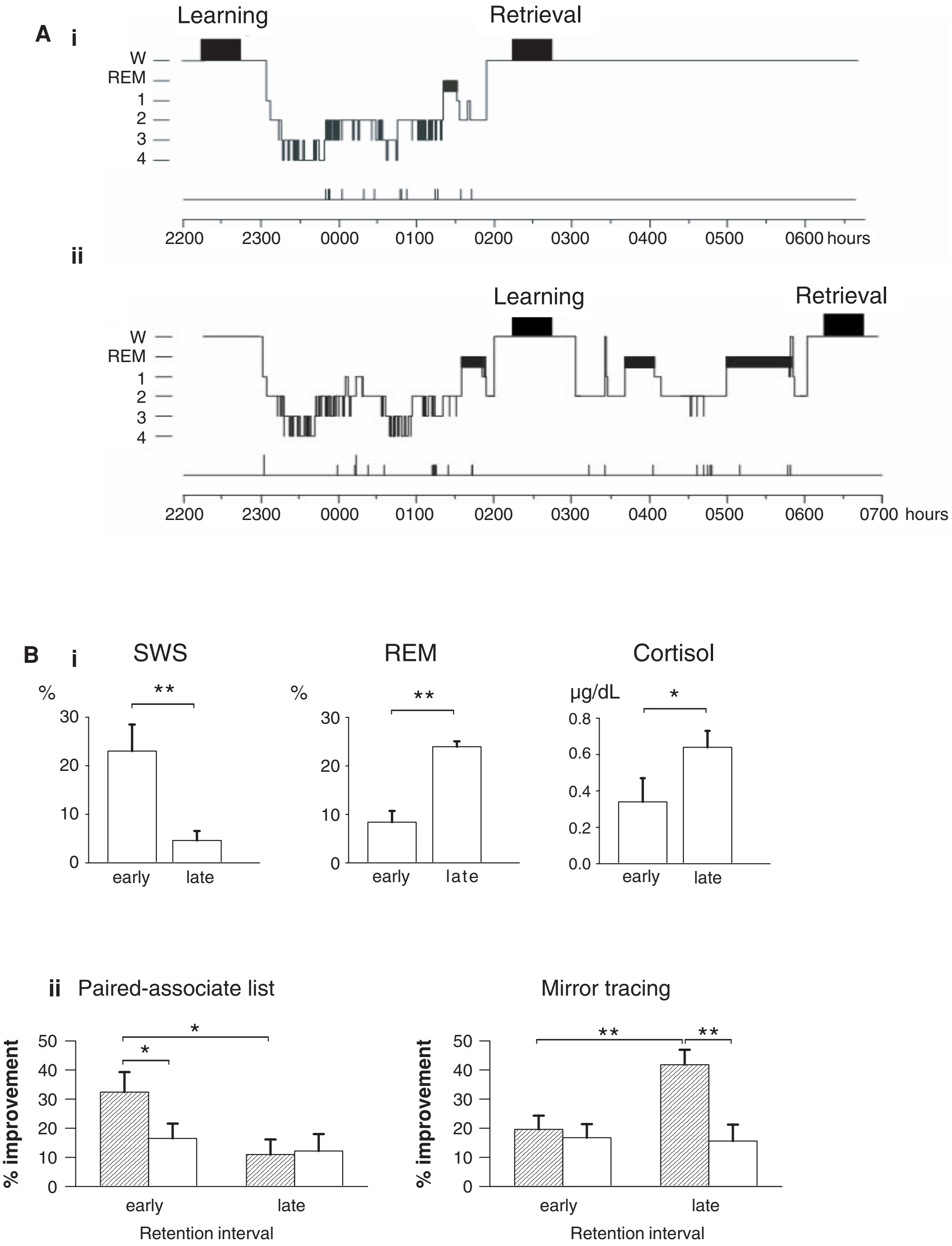

Fig. 4. *A*, Representative hypnograms from two nights in an experimental design used to study the influence of early and late sleep on memory consolidation. Sleep and wake groups were tested both on early and late nights, with the order of nights balanced across participants. *i*, *Early night:* Participants learned the tasks to a criterion at 2215 hours and were tested at ~0215 hours. Between 2300 hours and 0200 hours, the sleep group was allowed to sleep, while the wake control group stayed awake. *ii*, *Late night:* All participants slept during the first half of the night to reduce propensity for slow-wave sleep (SWS). They learned the tasks to the criterion at 0215 hours and were retested at ~0615 hours. From 0300 hours to 0600 hours, the sleep group was allowed to sleep. Note the high amount of SWS (ie, stages 3 and 4) during early sleep and the high amount of rapid eye movement (REM) sleep during late sleep. *B*, *i*, Mean (±SEM) percentage of time in SWS and REM sleep and blood cortisol concentrations for the early and late sleep retention condition. *ii*, Mean improvement (±SEM) in performance after early and late sleep (hatched bars) and respective wake control conditions (empty bars) for a declarative (paired-associate word list) and a procedural (mirror tracing) memory task. There is a double dissociation between memory system and time of night. Whereas declarative memory benefits from early SWS-rich sleep, procedural memory is enhanced after late REM-rich sleep. W = wake. $^*P < 0.05$, $^{**}P < 0.01$ for comparisons between conditions. Data are from Plihal and Born (1997).

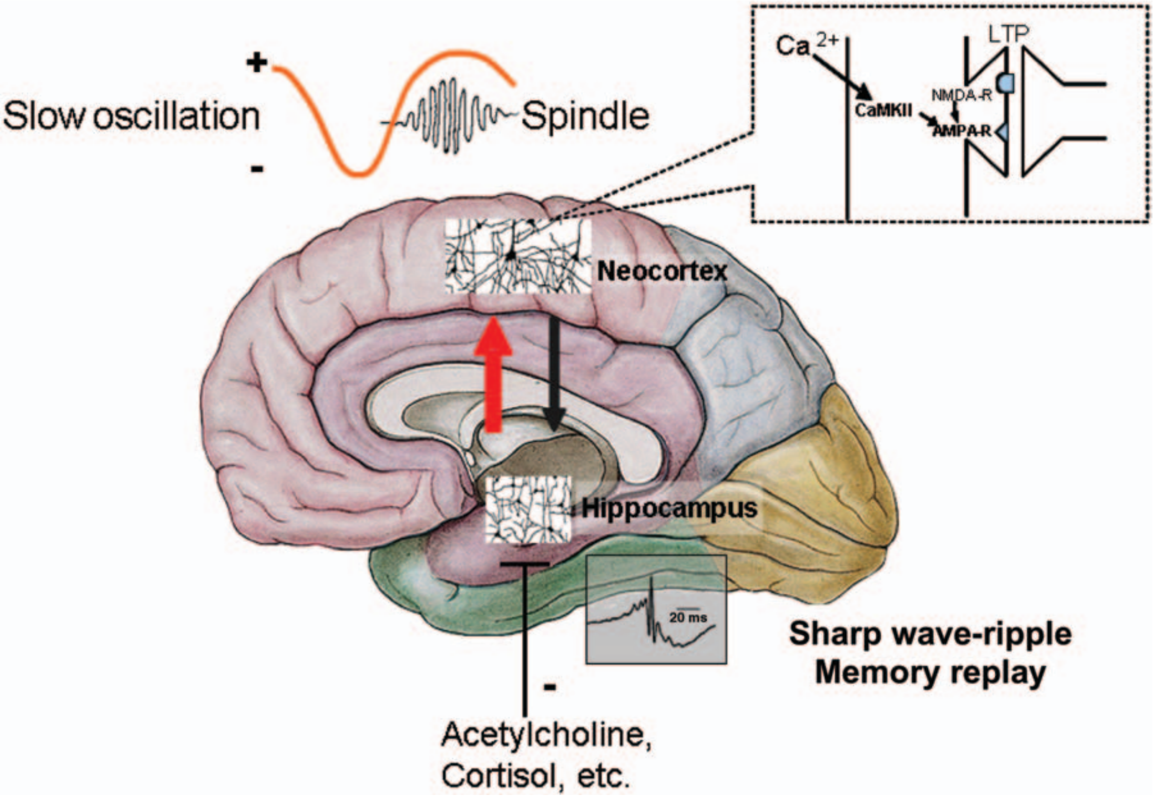

Fig. 5. Concept of declarative memory consolidation during sleep. During wakefulness, the information to be stored is encoded into neocortical networks and parts of it, simultaneously, in hippocampal networks serving as an intermediate buffer in this system (black arrow). During slow-wave sleep, the newly encoded information in the hippocampus is repeatedly reactivated. Reactivations are associated with sharp wave–ripple activity in the hippocampus. They are driven by slow oscillations, which originate in neocortical networks (preferentially those that were used during encoding) and synchronize hippocampal memory reactivation with the occurrence of spindle activity in thalamocortical circuitry. Hippocampal reactivations stimulate a transfer of the newly encoded information back to neocortical networks (red arrow). The hippocampal input arriving in synchrony with spindle input at the neocortical circuitry leads to long-term plastic changes selectively at those synapses previously used for encoding, that is, a long-term memory of the information in neocortical networks. The plastic changes are enabled by concurrent spindle input, which stimulates massive calcium influx into the dendrites of cortical pyramidal cells and, via calcium-sensitive kinases (like CaMK II), enhances expression of immediate early genes and glutamate receptors (AMPA), with the latter effects supporting the maintenance of long-term potentiation (LTP) in these synapses (see insert). High levels of acetylcholine or cortisol activity in the hippocampus suppress reactivations of memories in hippocampal networks and flow of information to the neocortex.

stored only temporarily. During subsequent periods of SWS, driven by the slow oscillations that dominate SWS, the newly encoded representations are repeatedly reactivated in the hippocampus. These reactivations, which are accompanied by sharp wave–ripple activity and occur in association with thalamocortical spindle activity, stimulate a transfer of information from hippocampal to neocortical networks. Spindle activity refers to 10 to 16 Hz oscillatory activity that is generated in the reticular nucleus of the thalamus and propagates via thalamocortical fibers to the entire neocortex (Steriade 2003). Together, these concerted activations could achieve a transfer of information as well as a strengthening of weak memory traces by providing repeated activation of memory traces without further training.

Neurotransmitters and Hormones

The neurotransmitter acetylcholine (ACh) is supposed to play a key role in the regulation of the dialogue between the neocortex and hippocampus. Cholinergic activation in the central nervous system mainly stems from two regions: the mesopontine tegmentum and the nucleus basalis of Meynert. The tegmental cells are genuinely involved in the regulation of sleep/wake states, which is described in the reciprocal-interaction model of REM–non-REM alternation (Pace-Schott and Hobson 2002). During wakefulness and REM sleep, these cells provide cholinergic input to thalamocortical neurons, which in turn activate the cortex via glutamatergic projections (Steriade 2003). Other projections from the

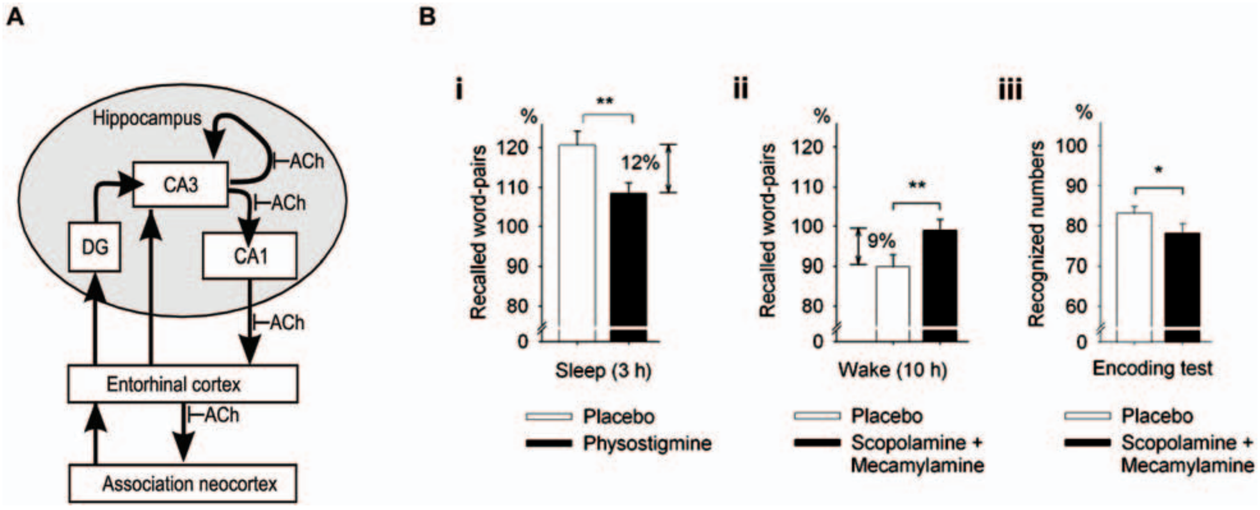

Fig. 6. *A*, According to a widely held model, the hippocampus temporarily stores new memories and transfers them gradually to the neocortex. Hasselmo (1999) reviewed evidence that feedback pathways within the hippocampal CA3 region and from CA3 to CA1 and further to the neocortex are inhibited during wakefulness and rapid eye movement sleep by acetylcholine (ACh). During slow-wave sleep (SWS), these synapses become disinhibited because of the low cholinergic tone, and information can flow back to the neocortex. *B*, Effects of manipulating cholinergic activity on memory retention (assessed by retrieval performance relative to performance at learning). *i*, Compared to placebo conditions, declarative memory was impaired after increasing ACh levels by administration of physostigmine during a 3-hour retention interval of mainly SWS and (*ii*) enhanced after combined blockade of cholinergic receptors with scopolamine and mecamylamine during a 10-hour retention interval of wakefulness. *iii*, Encoding of a list of numbers (assessed by recognition one minute after presentation) was impaired under combined nicotinic and muscarinic blockade. Means (±SEMs) are indicated. $^*P \leq 0.05$; $^{**}P \leq 0.01$. Data are adapted from Rasch and others (2006) and Gais and Born (2004b).

tegmentum, also using glutamate, activate the nucleus basalis of Meynert, which in turn provides cholinergic activation throughout the cortex.

According to a model of cholinergic memory modulation by Buzsáki (1989, 1996) and Hasselmo (1999), high cholinergic activity during wakefulness is inhibiting feedback synapses within the hippocampal CA3 region and efferent projections from CA3 to CA1, the entorhinal cortex, and the neocortex, thus leading to a reduced flow of information from the hippocampus to the neocortex (Fig. 6*A*). Consequently, during wakefulness, the primary direction of information flow is from the neocortex to the hippocampus, which allows encoding of new memories. In contrast, minimal cholinergic activity during SWS enables a feedback of information from the hippocampus to neocortical networks. To test this model and to examine whether low ACh during SWS is critical for hippocampus-dependent memory consolidation, we experimentally enhanced cholinergic activity by infusion of the cholinesterase inhibitor physostigmine in healthy participants during a period of SWS-rich early nocturnal sleep (Gais and Born 2004b). In the evening before, participants learned paired-associate word lists. As hypothesized, recall tested after retention sleep revealed a significantly impaired recall when cholinergic tone was enhanced during sleep (Fig. 6*B(i)*). In fact, physostigmine blocked declarative memory consolidation to a level found in the wake control condition. Notably, the effect of physostigmine did not depend on changes of SWS or spindle activity, as it occurred also in participants whose sleep architecture remained unchanged during infusion of physostigmine. Because slow-wave and spindle activities arise from thalamocortical networks, this finding further supports the view that physostigmine led primarily to inhibition of hippocampal feedback synapses. Conversely, blocking high cholinergic activity in waking participants by combined administration of the muscarinic antagonist scopolamine and the nicotinic antagonist mecamylamine improved retention of declarative memories (Fig. 6*B(ii)*) (Rasch and others 2006). Concurrently, the blockade of cholinergic transmission impaired acquisition of new memories (Fig. 6*B(iii)*), which is consistent with previous findings (Bartus and others 1982; Sherman and others 2003). In combination, these findings corroborate the notion that ACh acts as a regulator of the neocortico-hippocampal dialogue by switching between modes of acquisition and consolidation. In this way, the natural shift in brain cholinergic tone from high levels during wakefulness to minimal levels during SWS optimizes declarative memory consolidation.

The adrenal stress hormone cortisol (corticosterone in the rat) represents another factor that suppresses hippocampal output from CA1 and possibly also activity of excitatory feedback loops within CA3, which are needed for spontaneous reactivation of newly acquired memories (De Kloet and others 1998). The release of cortisol is mainly controlled by the hypothalamic-pituitary-adrenocortical (HPA) system. Cortisol serves multiple functions in the body periphery and feeds back to the central nervous system. In the brain, it acts mainly in the hypothalamus and limbic regions such as the hippocampus and amygdala, which express high amounts of corticosteroid receptors. Cortisol enhances the acquisition of new and interferes with retrieval of old memories during wakefulness (DeQuervain and others 2000; Roozendaal 2000; Wolf 2003). Sleep and circadian oscillators exert a synergistic control over HPA secretory activity. Early sleep, and in particular SWS, inhibits HPA activity and thereby contributes to the circadian minimum of cortisol during the first hours of the night (Bierwolf and others 1997; Born and Fehm 1998), (see also Fig. 4*B*). During the late REM sleep–rich period of nocturnal sleep, HPA secretory activity distinctly increases to reach a maximum at about the time of morning awakening (Born and others 1999). The suppression of cortisol during early SWS-rich sleep was shown to be a critical factor for the formation of hippocampus-dependent declarative memory during sleep (Plihal and Born 1999b; Plihal and others 1999). Apart from reducing ACh availability, low levels of cortisol therefore are the second means by which sleep actively provides an environment that favors memory reactivation and consolidation.

Slow Oscillations Coordinating Memory Consolidation

Sleep stages are characterized by unique patterns of electroencephalographic (EEG) activity. During the passage into SWS in humans, slow oscillations (<1 Hz) and classic delta activity (1–4 Hz) as well as oscillatory activity in the spindle frequency (10–16 Hz) prevail (Steriade 2003). During SWS, power in all of these frequency bands is maintained at a high level and only gradually decreases over time. These changes in oscillatory activity are paralleled by distinct changes in the direct current potential, which over frontocortical sites shifts steeply toward negativity at the transition into SWS (Marshall and others 1998, 2003). During REM sleep, fast desynchronized activity and θ waves (~5 Hz) predominate.

Recent research has ascribed to the slow oscillation a central role in memory consolidation. Slow oscillations, which have been discovered by Mircea Steriade's group in cats, appear during SWS with a peak frequency of about 0.75 Hz in the human EEG (Steriade and others 1993a, 1993b, 1993c; Achermann and Borbely 1998; Mölle and others 2002; Massimini and others 2004). The oscillations reflect widespread alternating "up" and "down" states of neocortical network activity that originate mainly from prefrontal cortical areas and, as traveling waves, grasp all parts of the neocortex. The up state associated with global neocortical neuronal depolarization and excitation is manifested in a depth-negative, surface-positive field potential in the EEG. Conversely, the down state reflecting widespread neuronal hyperpolarization and neuronal silence is accompanied by a depth-positive, surface-negative field potential (Contreras and Steriade 1995; Steriade and Timofeev 2003). Slow oscillations are generated in the neocortex, in that they survive thalamectomy and are present in the isolated cortex (Sanchez-Vives and McCormick 2000; Timofeev and others 2000). A major function of slow oscillations is that they drive neurons to fire in a synchronous manner. The synchronization is not restricted to the neocortex but extends via efferent pathways also to other structures such as the thalamus, where spindles are generated, and the hippocampus, where sharp wave–ripple activity originates (Steriade 1999; Buzsaki and Draguhn 2004). The generation of slow oscillations within neocortical networks depends partly on the prior use of the networks for encoding of information during wakefulness. Participants who had trained intensely on a motor skill or a declarative word pair task showed during subsequent SWS, respectively, increased amplitude and coherence of slow-waves (Huber and others 2004; Mölle and others 2004). This increase in slow-wave activity was restricted to the cortical areas that were primarily involved in training and was correlated with the overnight gain in the skill.

Recent studies inducing slowly oscillating potential fields by electrical brain stimulation provided a direct proof of a causative role of slow oscillations for memory formation (Marshall and others 2004, 2006). In these experiments, healthy participants received stimulation via electrodes attached over the frontal cortex and to the mastoids. The frequency of the oscillating stimulation was <1 Hz, and the amplitude was chosen such that the estimated potential fields induced in the underlying cortex closely resembled that accompanying endogenously generated slow oscillations. Applied during early SWS-rich sleep, the stimulation improved memory for word pairs that the participants had learned in the evening before. Notably, the stimulation was found also to increase endogenous slow oscillations and spindle activity directly after stimulation, suggesting that the slowly oscillating potential fields induced a resonance in cortical networks. A stimulation of 5-Hz θ frequency reduced rather than increased endogenous slow oscillations and spindle activity.

Slow oscillations have been demonstrated to temporally group fast oscillatory activity arising from the neocortex as well as spindle activity originating from the thalamic nucleus reticularis from where spindles spread to the entire cortex (Contreras and Steriade 1995; Destexhe and others 1999). Specifically, in the human EEG, the negative half-wave of the slow oscillation is associated with cortical disfacilitation and suppressed spindle activity, which is followed by a pronounced rebound increase in spindle activity during the subsequent positive half-wave reflecting a widespread depolarization in cortical networks (Mölle and others 2002). Intense learning increases spindle activity during subsequent sleep, and this relationship has been demonstrated in animals and humans and for declarative as well as procedural memory tasks (Meier-Koll and others 1999; Fogel and others 2002; Gais and others 2002; Schiffelholz and Aldenhoff 2002; Schabus and others 2004; Clemens and others 2005, 2006). In some of these studies, spindle activity correlated positively with overnight retention of the learned materials (Schabus and others 2004; Clemens and others 2006). The learning-dependent increase in spindle activity is clearly restricted to the depolarizing up phase of the slow oscillation, but is virtually absent during the hyperpolarizing down phase (Mölle and others, in preparation). There is also evidence suggesting that synchronous spindle activity occurs preferentially at synapses previously potentiated during encoding of information (Werk and others 2005) and that repeated spindle-associated spike discharges can efficiently trigger long-term potentiation in neocortical synapses (Rosanova and Ulrich 2005). Thus, spindle activity might specifically enhance plasticity in neuronal networks previously involved in encoding.

In addition to the effect on spindle activity, slow oscillations exert a grouping influence also on sharp wave–ripple activity accompanying memory reactivation in hippocampal neuronal networks (Sirota and others 2003; Battaglia and others 2004; Mölle and others 2006). The temporal association of sharp wave–ripple events to the slow oscillation is even stronger than that of spindle activity (Mölle and others 2006). Like spindles, the occurrence of hippocampal sharp wave–ripple events is distinctly decreased during the hyperpolarizing negative phase of slow oscillations, whereas their occurrence distinctly increases during the depolarizing positive phase of the slow oscillation (Fig. 7). A fine-grained analysis of the temporal dynamics indicated that slow oscillation–associated changes in prefrontal multiunit activity precede changes in hippocampal sharp wave–ripple activity by about 30 milliseconds, which is consonant with a driving influence of the cortical slow oscillation and associated multiunit activity on the hippocampal memory readout (Sirota and others 2003; Mölle and others 2006). Cross-correlating ripple and spindle activity revealed that the increased occurrence of sharp wave ripples during the positive phase of the slow oscillation coincides also with an increased spindle activity, whereby hippocampal neuronal firing tends to precede the onset of spindles and thus could feed excitation to subsequent spindle cycles (Siapas and Wilson 1998). However, the association between ripple and spindle activity is only of modest size, in comparison with that of both phenomena to the slow oscillations. Therefore, this pattern speaks for a synchronizing influence of slow oscillations on both phenomena.

It can be hypothesized that slow oscillations have the function to promote a coordinated reactivation of memory representations and bind together different neocortical networks, thalamic, hippocampal, and even brainstem structures, like the locus coeruleus (Lestienne and others 1997). According to this concept, slow oscillations originate preferentially in those neocortical networks that have been previously involved in the acquisition of information (Huber and others 2004; Mölle and others 2004). During sleep after learning, the slow oscillation drives in parallel 1) the generation of spindle activity via corticothalamic efferents and simulataneously 2) the reactivation of recently acquired memories in hippocampal circuitry via entorhinal pathways (manifesting in grouped hippocampal sharp wave–ripple activity). This enables the feedback activity from these structures, that is, thalamocortical spindle activity and hippocampo-neocortical replay activity, to arrive synchronously at the neocortex. The disfacilitation of hippocampal sharp wave ripple and thalamic spindle activity during the slow oscillation down states appears to serve a synchronizing role in the hippocampal-neocortical interplay, whereby succeeding rebound depolarization effectively drives the reactivation of hippocampal memories at a time when corticothalamic networks are most excitable. Depolarization of cortical pyramidal cells during the up state would make these cells most sensitive to specific inputs from hippocampal networks and in this way ease long-lasting plastic change in the respective neocortical networks.

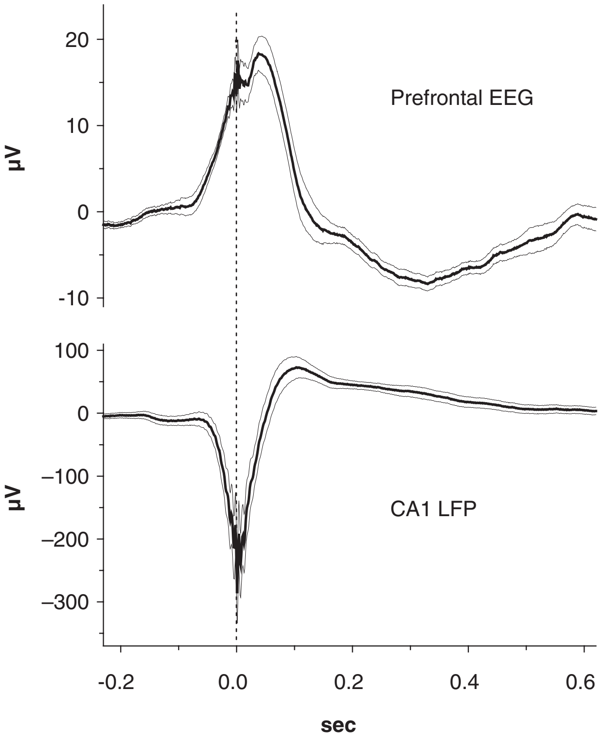

Fig. 7. Temporal relationship between neocortical slow oscillation and hippocampal sharp wave–ripple complex in rats. Averages of unfiltered prefrontal electroencephalographic (EEG) activity (*top*) and of unfiltered hippocampal activity in CA1 local field potentials (LFPs, *bottom*) across sharp wave–ripple events detected during slow-wave sleep. Averaging was performed with reference to the deepest ripple trough of sharp wave–ripple events (dotted line, average includes >2500 sharp wave–ripple events per session). Means (thick lines) ± SEMs (thin lines) are shown. Note sharp wave–ripple occurrence during the positive going phase of the slow oscillation consistent with a driving influence of the depolarizing phase of slow oscillations on hippocampal sharp wave–ripple generation. Adapted from Mölle and others (2006).

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