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The contribution of sleep to hippocampus-dependent memory consolidation

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There is now compelling evidence that sleep promotes the long-term consolidation of declarative and procedural memories. Behavioral studies suggest that sleep preferentially consolidates explicit aspects of these memories, which during encoding are possibly associated with activation in prefrontal–hippocampal circuitry. Hippocampus-dependent declarative memory benefits particularly from slow-wave sleep (SWS), whereas rapid-eye-movement (REM) sleep seems to benefit procedural aspects of memory. Consolidation of hippocampus-dependent memories relies on a dialog between the neocortex and hippocampus. Crucial features of this dialog are the neuronal reactivation of new memories in the hippocampus during SWS, which stimulates the redistribution of memory representations to neocortical networks; and the neocortical slow (<1 Hz) oscillation that synchronizes hippocampal-to-neocortical information transfer to activity in other brain structures.

Sleep and consolidation of memory

Sleep in mammals is characterized primarily by behavioral inactivity together with distinct electrophysiological changes in brain activity. Despite some ongoing fundamental controversy about the function of sleep in general and the specific link of sleep to memory function, the last two decades have seen an upsurge in literature supporting the importance of sleep for memory consolidation and brain plasticity [1–4]. Eventually memory consolidation could turn out to be the essential function that explains the loss of consciousness during sleep, because the brain uses the same limited neuronal network capacities for the immediate processing and long-term storage of huge amounts of information – mutually exclusive functions that cannot take place simultaneously in these networks [2,5].

Memory encompasses the stages of acquisition, consolidation and retrieval. Acquisition refers to the uptake of (new) information during learning and its encoding into a vulnerable memory trace. Subsequent consolidation stabilizes the newly encoded memory, and also includes processes of enhancement and integration with pre-existing long-term memories. Retrieval refers to the recall of stored memories. Sleep seems to support specifically the consolidation of memories, although the underlying mechanisms are elusive. Here we review evidence suggesting a particular role for the hippocampus in encoding and consolidating memories that is enhanced by sleep.

Memory systems and explicitness in memory

In recent years there has accumulated strong evidence that sleep supports consolidation of both procedural and declarative memories (reviewed elsewhere, e.g. refs [1,2,4,6–9]; see also Box 1). The consolidating effect of sleep was demonstrated principally in two ways. On the one hand, it was shown that compared with wakefulness, sleep after learning stabilizes newly encoded representations by increasing their resistance to interfering inputs. Thus, sleep after acquisition of declarative memories for word-pairs made those memories resistant to an interfering list of word-pairs encoded shortly before retrieval was tested [9]. An equivalent finding was revealed when sleep followed training on a procedural finger sequence tapping task, with interpolated training on a different sequence used for testing effects of interference [10]. On the other hand, it was shown that delayed retrieval is improved relative to that of post-learning wakefulness if acquisition is followed by a period of sleep. Thus, perceptual and motor skills, like visual texture discrimination and finger sequence tapping, are enhanced at delayed retrieval when sleep occurs within a certain time window (of less than ~16 h) after training compared with a corresponding wake retention interval [11–14]. Because the sleep-dependent improvement in skill at delayed retesting is usually also significant compared with the performance level at the end of initial training, sleep induces an actual gain in skill. For some tasks, like the visual texture discrimination task, sleep after training seems to be mandatory for this type of gain [13,14]. In the declarative memory system, as a result of prevailing processes of decay and forgetting, the memory-enhancing effect of post-learning sleep typically expresses itself in a relatively diminished forgetting of the materials learned before a sleep period. Nevertheless, sleep-dependent improvements were consistently revealed [7,15,16], and in the case of emotional declarative texts were found to persist for as long as 4 years after a brief 3-h period of post-learning sleep [17]. Possible confounding influences of the circadian rhythm or tiredness at retrieval testing (after wake retention intervals) on the sleep-associated memory enhancement were excluded in these studies by showing similar effects for daytime sleep and when

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Box 1. Declarative, procedural and explicit memories

A common distinction in neuropsychology is between declarative and nondeclarative memory systems [71]. Declarative memory refers to the retention of facts (semantic) and events (episodic), and is neuroanatomically defined by its crucial dependence on hippocampal function. Declarative memories are rapidly encoded but, thereafter, highly susceptible to decay, interference and forgetting. Procedural memory represents the type of nondeclarative memory that has been most extensively studied in conjunction with sleep. Procedural memory refers to memories for perceptual and motor skills with the latter essentially relying on cortico-striatal and cortico-cerebellar loops. Skills are acquired gradually by repeated practice but, once automated remain fairly stable.

Encoding and retrieval of memories can be explicit or implicit (i.e. with or without awareness) although both processes normally occur in parallel [71,72]. Encoding and retrieval are thought to be always explicit for declarative memories, but both modes are possible for procedural memories. In learning a skill, initially explicit processing guided by attention to task rules can dominate whereas with continuous training the skill becomes automated and implicit processes become predominant. Importantly, although procedural memory is considered not to depend on hippocampal function, studies using fMRI have indicated hippocampal activation during explicit and implicit motor skill learning on a serial reaction time task [73] indicating that at least initially skill acquisition normally involves hippocampal function. It is still a matter of debate whether explicit or implicit modes of encoding and retrieval are connected to different types of memories or just describe different pathways to the same memory. Studies in patients with brain lesions and fMRI studies remain inconclusive in this regard because of their inability to dissociate processes of encoding and retrieval from the memory representation itself. However, findings that sleep following acquisition can influence a memory such that explicit recall is selectively facilitated at delayed retrieval, strongly supports the notion that memory representations encompass distinct explicit and implicit aspects, with the former probably related to hippocampal function.

additional recovery sleep was allowed before retrieval testing.

Preferential consolidation of explicit aspects of memory

It seems that sleep does not benefit memory consolidation under all circumstances. In some instances, failure to demonstrate memory benefits by post-learning sleep might primarily reflect problems of measurement. Findings of sleep-induced changes in neuronal representations not accompanied by changes in overt retrieval, indicate that behavioral assessment itself can be insufficient to characterize sleep-dependent consolidation [18]. Yet, whether a memory benefits from sleep depends also on several other factors. Amongst these, the 'explicitness' of memory seems to be of particular relevance (Box 1). Robertson *et al.* [19] trained subjects on a procedural serial reaction time task (SRTT) either under explicit or implicit conditions – that is, subjects during training were aware or remained unaware of the underlying sequence of cue positions throughout training. Skill acquisition is measured by the difference in reaction times to sequential versus random positioning of cues. Interestingly, and partly diverging from other studies [20,21], a gain in skill at delayed retesting specific to post-training sleep was revealed only when subjects were aware of the sequence. In the implicit task, delayed performance gains were also observed in the sleep condition, but these did not differ from those of the wake condition. Once explicitly encoded, the consolidating effect of sleep is greater for weakly than strongly encoded associations [22,23] and, in episodic memories, selective for the forward temporal sequence [24]. A preferential consolidation of explicit aspects of a memory during sleep was likewise revealed by investigations of recognition memory, in which post-learning sleep selectively enhanced explicit recollection whereas estimates of familiarity remained unaffected [25].

Indeed, in an SRTT, consolidation during sleep strengthened explicit aspects of a memory representation at the expense of implicit aspects [26]. Although subjects in this study remained unaware of the underlying sequence structure of the task during training before sleep, only after post-learning sleep did they develop explicit sequence knowledge as assessed in a generation task where subjects were explicitly instructed to predict the sequential cue positions. However, when retested on the original SRTT, reaction times did not indicate the expected sleep-dependent improvement in implicit skill. Similarly, in a number reduction task, sleep facilitated the gain of (explicit) insight into the hidden sequence structure underlying the task, but only subjects who failed to gain insight improved in cognitive skill (i.e. speed of number processing) across sleep [27].

To summarize, sleep supports the consolidation of both declarative and procedural memories. In conditions of competition between explicit and implicit moments, explicit aspects of memory representations seem to be preferentially strengthened by sleep. Explicitness at encoding predisposes a memory for sleep-dependent consolidation and probably also directs how implicit aspects of a memory representation are bound into the sleep-dependent consolidation process [28,29]. This view, however, is in need of detailed investigation. Explicit encoding involves a network of brain structures fundamentally relying on coordinated activation of prefrontal cortical and hippocampal circuitry [30–32]. We hypothesize that only activation of this prefrontal–hippocampal circuitry during encoding enables access of a memory, whether procedural or declarative, to sleep-dependent consolidation.

What is the role of specific sleep stages?

Sleep is a complex phenomenon hallmarked by the cyclic occurrence of non-REM (non-rapid eye movement) and REM sleep stages (Box 2). Essentially the significance of sleep states for memory consolidation has been investigated through two general approaches: by investigating (i) the impact of partial or selective post-learning sleep deprivation on delayed retrieval, and (ii) modifications in sleep architecture and sleep stage-associated electrophysiological phenomena immediately following training. In recent studies more fine-grained manipulations were applied: rather than abolishing an entire sleep stage, specific processes of brain activity during a certain sleep stage were modified after learning either by pharmacological or electrophysiological intervention.

Partial sleep deprivation: the slow-wave sleep–REM sleep dichotomy

In human research, both types of experimental approaches are common. Because of an underlying circadian rhythm the first half of nocturnal sleep in humans is dominated by

Box 2. Sleep electroencephalographic activity and a slow-oscillation theory

Sleep consists of approximately 90-minute cycles of non-REM and REM sleep (Figure I), with the EEG during REM sleep characterized by theta (4–8 Hz) and wake-like faster frequencies. Light non-REM stage 2 sleep is characterized by the presence of spindle activity (~10–15 Hz) and K-complexes (a sharp-wave followed by a large positive wave). Around the onset of slow-wave sleep (SWS, equivalent to deep non-REM sleep stages 3 and 4), spindle and slow-wave (traditionally termed 'delta') activity (<4 Hz), including the <1 Hz slow oscillations, reaches a maximum. The transition into SWS is linked to a distinct surface negative direct current (DC) potential shift whereas the shift is of opposite polarity during REM sleep.

Thalamically generated spindles are widely distributed over the neocortex, showing a slower frequency over the frontal than parietal cortex. Spindle activity is increased after periods of intense learning [40,41]. Differential cortical distributions subsequent to learning a verbal versus visuospatial task have been reported [42,74].

Slow oscillations are generated in the neocortex, predominantly prefrontally, and consist of a depolarizing up phase of massive neuronal activity, and a hyperpolarizing down phase of neuronal silence. The down to up transitions drive, through efferent pathways, thalamic spindles and, in parallel, hippocampal sharp wave-ripples presumed to accompany neuronal reactivation of memories [46,59,60,65]. The traditional delta waves of SWS probably represent faster, though less potent, equivalents of the slow oscillation, particularly in regard to the negative (hyperpolarizing) phase [46].

Slow oscillations are under homeostatic control, showing a reciprocal relation to theta EEG activity during wakefulness [75]. It has been proposed that the rhythmic activity of neurons in the <1 Hz frequency of the slow oscillation serves primarily a global synaptic downscaling [70] by supporting long-term depression and depotentiation of synaptic transmission. Because synaptic strength becomes widely upregulated by encoding throughout wakefulness, maintaining homeostasis requires general downscaling of synaptic strength, which is optimally achieved during the absence of encoding during sleep. Sleep-dependent enhancement in memory is thereby considered an indirect consequence of the proportional downscaling of all synaptic weights thus leading to an improved signal-to-noise ratio for strongly potentiated synapses. In the framework we presented here, it is conceivable that within the neocortex synaptic downscaling acts in concert with processes of neuronal reactivation to consolidate memories.

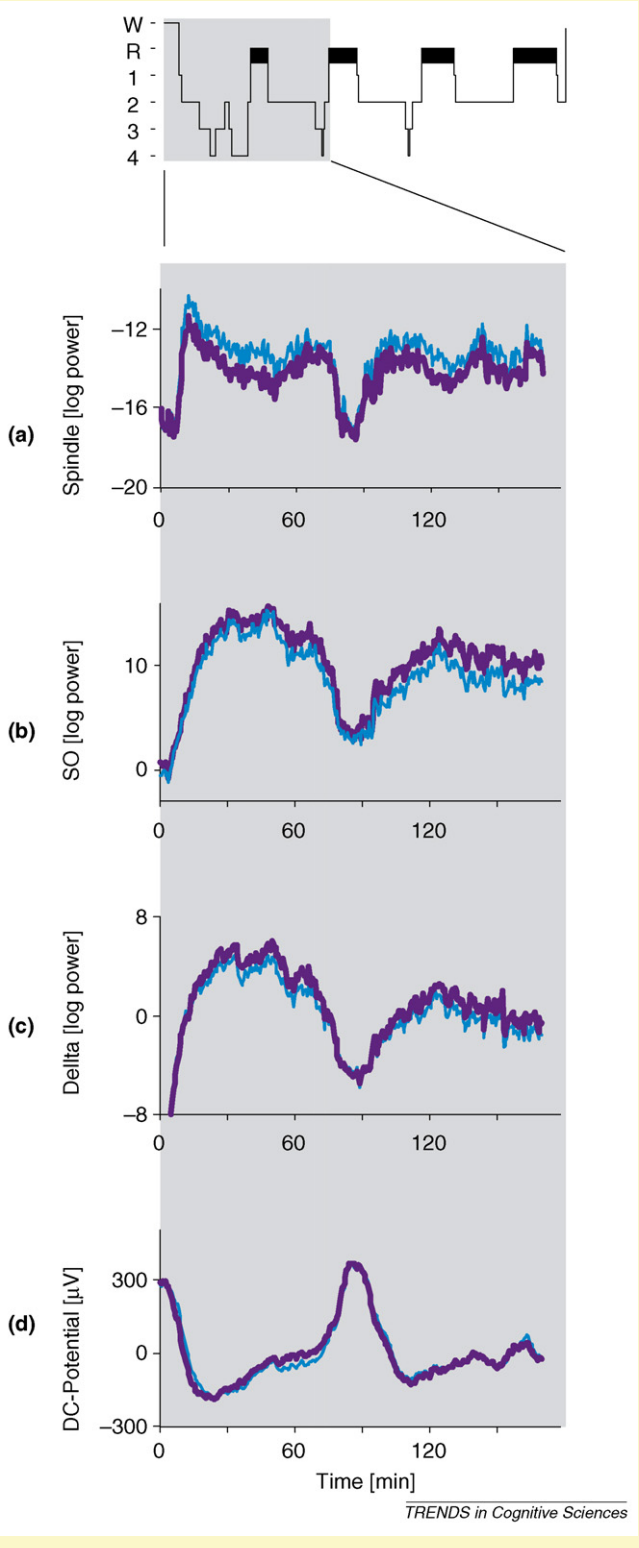

Figure I. Changes in the EEG signal during a non-REM–REM sleep cycle. Uppermost panel illustrates cyclic structure of sleep with an individual sleep profile for the whole night (W, wakefulness; R, REM sleep; 1–4, non-REM sleep stages 1 to 4). Lower panels indicate, for the first non-REM–REM–non-REM sleep period, alterations in: **(a)** EEG spindle activity (12–15 Hz); **(b)** slow oscillation (<1 Hz, SO) activity; **(c)** delta activity (representing the upper frequencies, i.e. 1–4 Hz of the slow-wave activity band); and **(d)** the transcortical direct current (DC) potential. Time courses represent averages from nine nights. Spindle, slow oscillation and delta activity were derived from spectral analysis of the EEG signal at a frontal (Fz, thick lines) and central (Cz, thin lines) electrode over the midline. Adapted with permission from ref. [76].

slow-wave sleep (SWS) whereas REM sleep predominates during the second half (Box 2). On this background, an attractive design for investigating the predominant involvement of non-REM versus REM sleep on consolidation without disturbing the cyclic pattern is to compare memory across retention intervals spanning either the early or late part of nocturnal sleep. Undisturbed sleep in the complementary early night-half is permitted when late sleep is examined. Effects of circadian rhythm are excluded by examining memory across corresponding nocturnal wake retention intervals. Along this line different types of declarative memories (word-pairs, spatial locations, word recognition) benefited from early SWS-rich periods of sleep [7,16,33,34]. By contrast, nondeclarative types of mem-

ories, including procedural memory (e.g. mirror tracing) and the amygdala-dependent enhancement of emotional declarative memories, benefited particularly from periods of REM sleep-rich late sleep. But deviations from this dichotomy indicate that more features need consideration: for instance, in one study declarative episodic memory benefitted from late REM-rich sleep [35], and procedural visual texture discrimination was improved also after SWS-rich early sleep [2,13].

Post-learning sleep modifications in sleep architecture

When examining post-training modifications in sleep, increases in electroencephalogram (EEG) coherence during SWS have been observed following intense learning of declarative word-pairs [36], whereas increases in the duration of REM sleep or increases in the number of REMs (or both) occurred after acquisition of procedural tasks requiring implicit visuo-motor adaptation and cognitive skills [8,37]. Again, this SWS–REM sleep dichotomy does not fit all findings. Regional increases in slow-wave activity were observed following acquisition of a procedural rotation adaptation task, and arm immobilization caused a decrease in slow-wave activity [38,39]. Learning word-pairs was followed by increased EEG-theta activity during REM sleep [40].

Changes in non-REM sleep stage 2 are probably also relevant. Intensive learning of declarative visuospatial and verbal tasks and of simple motor skills were all associated with increased time in sleep stage 2 or spindle density (or both) during this sleep stage [8,41–43]. Moreover, improvement in performance of nondeclarative tasks was found to correlate with an increased amount of stage 2 sleep or spindle density [6,40].

To summarize, sleep stages differentially affect memory consolidation. Whereas SWS supports in particular, but not exclusively, the consolidation of hippocampus-dependent declarative memories, REM sleep seems to benefit preferentially, but not exclusively, consolidation of memory aspects not directly mediated by hippocampal function (procedural, emotional enhancement). Considering the strong evidence for post-learning changes in spindles and non-REM sleep stage 2, this sleep stage probably acts *per se* or cooperatively with SWS and REM sleep to enhance consolidation. Learning a task does not lead to isolated activation of a single memory system. This, in conjunction with interactions between explicit and implicit memory processes during encoding and consolidation, could be responsible not only for divergent findings about the role of SWS and REM sleep for consolidation, but could also explain findings suggesting that optimum retention performance after sleep is achieved only through the regular cyclic sequence of SWS and REM sleep bound by transitional sleep periods [44].

Reactivation of memories

A leading concept assumes that consolidation during sleep evolves from repeated covert reactivation of the neuronal networks that were previously used to encode the information, although alternative views have been proposed (Box 2). Reactivations are covert in the sense that they are not consciously experienced as during wake retrieval. Reactivation is supposed to support both synaptic consolidation and systems consolidation, the latter involving transfer of memory representations to other neuronal networks for long-term storage.

Unit recordings and neuroimaging studies

Following the discovery of place cells in the rodent hippocampus came the revelation of temporal patterns of neuronal reactivation and neuronal coactivation after exploration of a novel environment and spatial tasks, such as maze learning, mostly during SWS but occasionally also during REM sleep [45–48]. Reactivations during SWS are not limited to the hippocampus but are seen also in the striatum, thalamus and neocortex. Experience-dependent coactivation of hippocampal cell-pairs during sleep is most pronounced within the first hour but can remain greatly correlated during sleep periods for up to 24 h.

Neuroimaging studies in humans corroborated the concept of reactivation. Subsequent to learning a declarative task involving navigation in a virtual town, hippocampal activity was found to be reactivated during SWS, and the amount of reactivation was also correlated with route recall performance the following day [49]. Following intense training of a procedural skill (SRTT), reactivations were observed during REM sleep in the cuneus and left motor cortex [50]. However, whereas evidence for an association of neuronal activity during learning and reactivations during post-learning sleep is compelling, only recently has a causative role of reactivation during sleep for memory consolidation been demonstrated [51] (Figure 1). Cuing new memories by odor re-exposure during SWS was associated with distinct hippocampal activation and increased retention performance, in contrast to re-exposure during wakefulness or REM sleep, indicating that hippocampal networks are particularly sensitive in SWS to stimuli capable of memory reactivation.

Neurochemical studies

Pharmacological studies add support to the relevance of reactivations for memory consolidation during sleep. The neurotransmitter acetylcholine is a key regulator of hippocampal neuronal activity. Forebrain cholinergic activity is greatest during active wakefulness and REM sleep, and shows a marked minimum during SWS. Studies in humans have lent support to the model of cholinergic memory modulation [52] according to which elevated cholinergic activity in hippocampal circuitry during wakefulness facilitates input to and encoding of information in the hippocampus, whereas minimal cholinergic activity during SWS enables the emergence of reactivations of hippocampal memories and their transfer to neocortex. Enhancement of cholinergic tone by infusion of physostigmine during a period of SWS-rich sleep blocked declarative memory consolidation usually benefiting from this period of sleep [53]. By contrast, consolidation of declarative memories was enhanced in wake persons after blocking cholinergic activity by a combined administration of muscarinic (scopolamine) and nicotinic (mecamylamine) antagonists [54]. The suppression of cortisol during early SWS-rich sleep, which corresponds to the normal physiological state at the beginning of nocturnal sleep, was likewise shown to be a

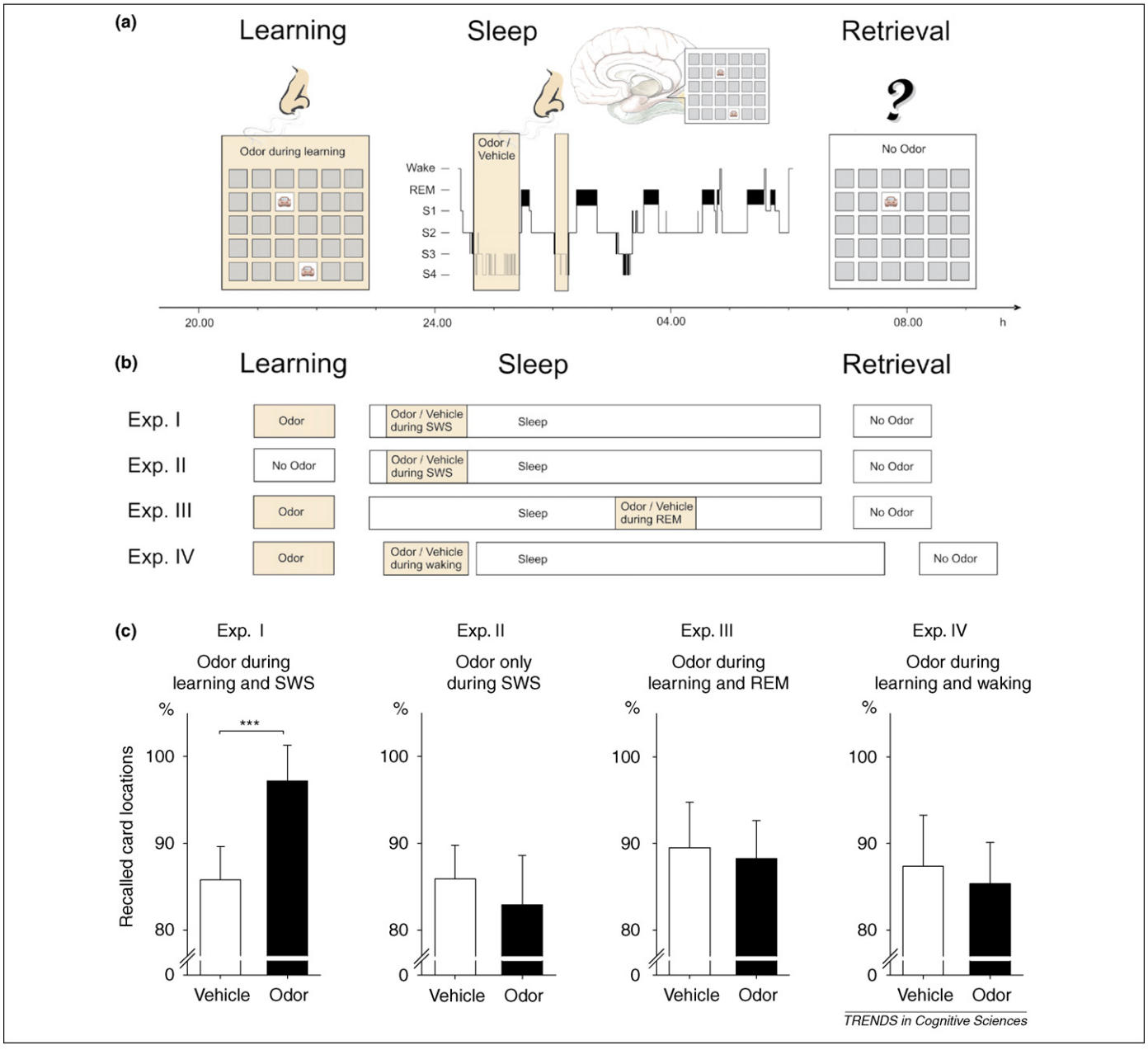

Figure 1. Reactivation of memory by olfactory context cue during SWS. **(a)** Experimental procedure. Subjects learned a two-dimensional (2D) object spatial location task (known as the game 'Concentration') requiring memorization of the location of card-pairs showing the same object. The set consisted of 15 card-pairs. Learning was followed by nocturnal sleep and recall was tested on the next day. **(b)** Design and **(c)** results (mean ± SEM); ***: P = 0.001). In the main experiment (Exp. I), an odor ('rose') was presented repeatedly while the subject learned the card-pair locations, to form a context association. When the same odor was presented again during subsequent SWS, memory for the spatial locations was distinctly enhanced at later retrieval, compared with a control night without odor re-exposure during SWS after learning (vehicle). To produce the memory enhancement, an association between the odor and the card-pair locations formed during learning was crucial, because when the odor had not been presented at learning but was only presented during SWS (Exp. II) memory consolidation remained unchanged. Re-exposure of odor after learning during REM sleep (Exp. III) or waking (Exp. IV) also proved ineffective. In combination with fMRI data (not depicted) showing that cuing the memories by odor re-exposure during SWS was associated with distinct hippocampal activation, the results corroborate the notion that hippocampal reactivation of newly encoded memories during SWS has a causative role for the consolidation of these memories. Adapted with permission from reference [51].

crucial factor for declarative memory consolidation. Corticosteroids are supposed to inhibit hippocampal CA1 activity through glucocorticoid receptors. Infusion of cortisol in addition to the glucocorticoid receptor agonist dexamethasone blocked sleep-associated consolidation of declarative memories [7,55].

A dialog between neocortex and hippocampus to consolidate memory

Modeling of memory has shown that two complementing stages are required in a memory system to enable it to store information for the long term and to incorporate new material within long-term memory without compromising pre-existing memories [5,56]. It is assumed that, to prevent interference with pre-existing long-term memories during incorporation of new memories, information is encoded temporarily into an intermediate buffer from where in an offline process it is gradually transferred to the long-term store. Much evidence exists that the medial temporal lobe including hippocampus is essential for the retention of recent memories whereas the neocortex stores remote memories [57]. Sleep provides an offline mode of

processing that leads to gradual incorporation of newly acquired memories into neocortical networks for long-term storage. The offline mode comprises a dialog between neocortex and hippocampus during non-REM and SWS in which the neocortex, presumably through slow (<1 Hz) oscillations, drives and organizes in time the hippocampal-to-neocortical transfer of recent memories (Box 2) [2].

Evidence from unit activity and field potentials

At the level of unit activity, in both hippocampus and neocortex, the replay of recent memories during SWS was found to be organized into temporal frames of generally increased firing corresponding to the up state (phase) of the slow oscillation. Cortical frames led hippocampal frames by ~50 ms, consistent with the concept of neocortical control over frames of activity in the hippocampus. However, with regard to actual replay, activity in the hippocampus seemed to lead reactivation in visual cortex suggesting a hippocampal-to-neocortical direction of underlying information flow [48].

At the level of field potentials, replay of sequence firing in the hippocampus during SWS is accompanied by hippocampal sharp-wave ripple events originating from strong depolarization of CA3 collaterals. At the cortical level, sharp-wave ripples are associated with sleep spindles arising from thalamo-cortical circuitry [58–61] but also with bursts of activity originating from the locus coeruleus [62]. That ripple events were found to be temporally nested in individual spindle troughs stimulated the idea that within such spindle-ripple events the hippocampal output message becomes temporally sandwiched between the cyclic discharges of spindle-activated neocortical neurons [46,60]. The specificity of this network mechanism would lie in the sharp wave-ripple event biasing spindle activity towards modifying the synaptic inputs of only a subset of neocortical cell assemblies involved in memory representation. There is evidence suggesting that synchronous spindle activity occurs preferentially at synapses previously potentiated during encoding of information [63] and that repeated spindle-associated spike discharges can efficiently trigger long-term potentiation in neocortical synapses [64]. Moreover, spindle activity provokes massive influx of Ca^{2+} into cortical pyramidal cells that in concert with noradrenergic inputs from locus coeruleus, could predispose the cells to plastic synaptic changes underlying long-term storage [65].

Slow oscillations

Hippocampal-to-neocortical information transfer during SWS is under feed-forward control of the neocortical slow oscillation occurring in humans at a peak frequency of ~0.75 Hz. The slow oscillation is generated within neocortical networks [65] at least partially depending on the previous use of these networks for encoding [38]. It synchronizes neuronal activity into generalized up (depolarizing) and down (hyperpolarizing) states not only in neocortex but also through efferent pathways in other brain regions. A grouping influence of the slow oscillation has been established in cats, rodents and humans on thalamo-cortical spindles such that periods of cortical hyperpolarization are followed by strong rebound spindle activity [59,60]. In parallel, neocortical slow oscillations impact through entorhinal cortex activity in the hippocampus, which does not seem to develop slowly oscillating up and down states on its own [61,66,67]. Sharp wave-ripple events and CA1 interneuron activity become suppressed during slow oscillation down states and show a rebound during development of up states, with cortical up and down states leading the temporal dynamics in hippocampal activity by 30–50 ms. Thus, by repeatedly resetting networks during the down phase, the neocortical slow oscillation provides a global temporal frame for offline memory processing. The co-occurrence during the up state of inputs to neocortical networks from different regions including thalamus and locus coeruleus, aside from hippocampal input, could be crucial for promoting the formation of persisting memories in neocortical networks.

Evidence supporting the idea that the cortical slow oscillation is involved in consolidation is derived from a study in humans in which stimulating the brain electrically with slow oscillations during SWS increased not only subsequent memory for declarative word-pair associates learned before, but also endogenous slow oscillation and spindle activity [34] (Figure 2). The stimulation did not enhance finger sequence tapping skill. Stimulation in the theta range was also not effective, suggesting that stimulation with slow oscillation frequency induced resonance in underlying cortex.

A sleep-dependent transfer of recent memories from hippocampus to neocortex is supported by recent studies of hippocampal lesions in rats [68]. After the acquisition of an 'associative schema' of different spatial locations that was represented in neocortical networks, rats were able rapidly to assimilate new locations into this schema within 48 h after training. However, the rapid integration of the new spatial memories into the neocortical representation was disrupted when the hippocampus was lesioned within 3 h after learning and no sleep had occurred during this interval. In humans, functional magnetic resonance imaging (fMRI) studies revealed first indications of a sleep-specific reorganization of declarative memories (for a virtual maze) involving increased striatal activity at later retrieval testing [18]. Similar sleep-specific reorganization was observed for other types of memory, including finger tapping skill [69].

In sum, available evidence supports the notion that consolidation of hippocampus-dependent memories crucially relies on a reactivation and redistribution of memories taking place during SWS. Reactivation and redistribution of memories might represent a general mechanism of systems consolidation that is active during sleep in other memory systems. Its characterization represents the most intriguing issue of future research in this field.

Questions for future research

An intriguing puzzle that remains is to dissociate more clearly those aspects of memory and underlying neuronal systems that do and do not access the sleep-dependent consolidating process. Explicit aspects of a memory seem to

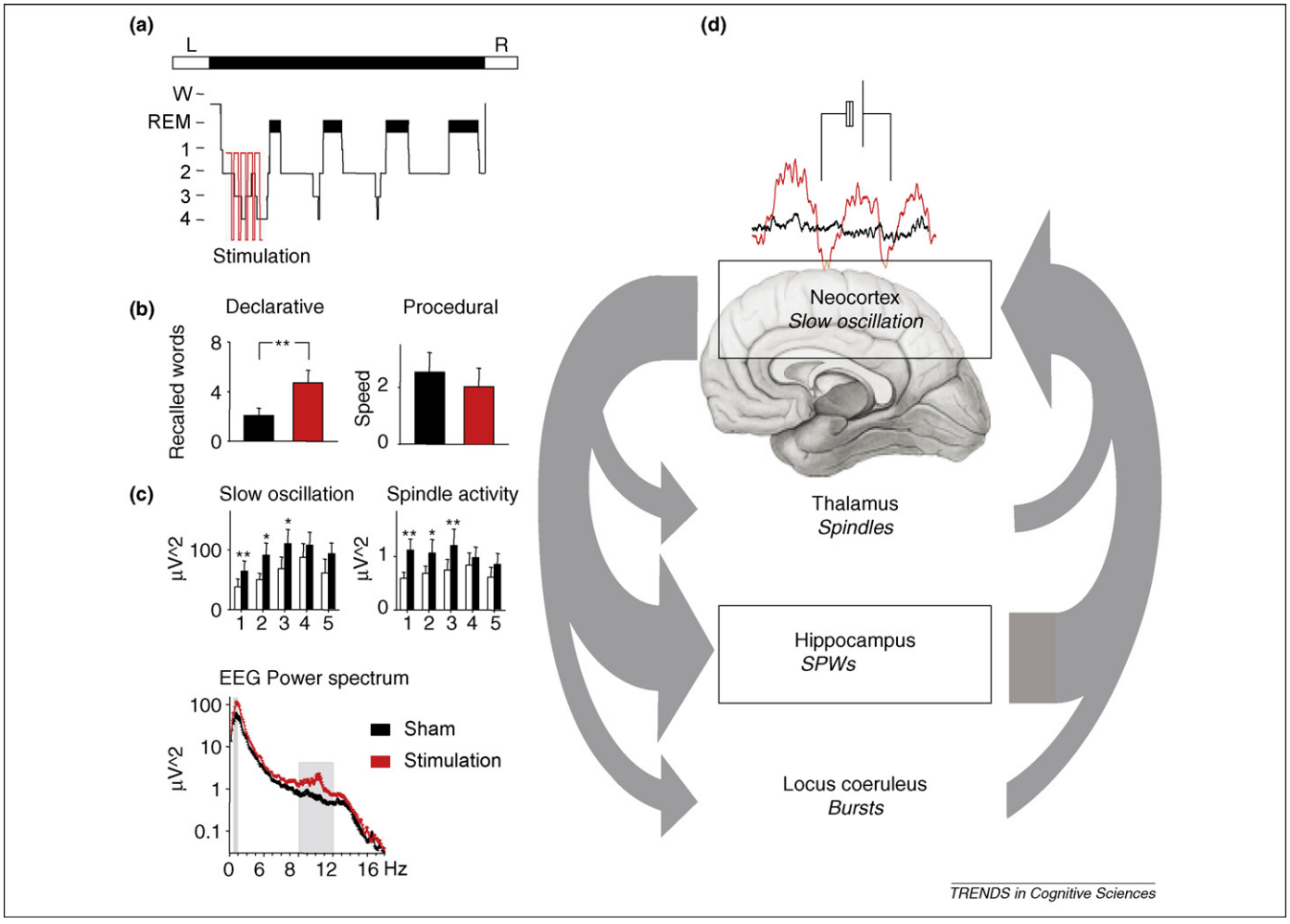

Figure 2. Transcranial slow oscillation stimulation boosts declarative memory consolidation. **(a)** Experimental design. Before nocturnal sleep, subjects learned (L) a declarative (word-pair associates) and a procedural (finger-sequence tapping) task. Retrieval (R) on both tasks was tested the next morning. Subjects were tested on two experimental nights in which either slowly oscillating potential stimulation (frequency ~0.75 Hz) or sham stimulation was applied by electrodes attached bilaterally over the prefrontal cortex and the mastoids. Stimulation was applied during early SWS-rich sleep for five 5-minute intervals separated by 1-minute breaks. **(b)** Retrieval performance (mean ± SEM). Slow oscillation stimulation specifically enhanced (**: $P < 0.01$) retention of declarative word-pairs (number of words recalled minus words learned) whereas speed and accuracy of finger tapping remained unaffected, indicating that stimulation boosted network mechanisms underlying consolidation of hippocampus-dependent declarative memory. **(c)** EEG activity. Slow oscillation stimulation (filled bars), compared with sham stimulation (unfilled bars), significantly enhanced the endogenous slow oscillation of the brain (<1 Hz) and frontal spindle activity (8–12 Hz; see shaded areas in EEG spectrum underneath) during the 1-minute breaks between periods of stimulation, particularly during the first three of the five stimulation periods, suggesting that transcranial stimulation enhanced physiological oscillating activity in underlying cortex by inducing resonance. Because the stimulation induced an estimated potential field in extracellular space closely resembling that accompanying endogenously generated neocortical slow oscillations, the findings point to field effects contributing to synchronizing influences of slow oscillations in neocortex (*: $P < 0.05$; **: $P < 0.01$). **(d)** Hypothetical dialog underlying consolidation of hippocampus-dependent memory during sleep. The depolarizing 'up' phase of slow oscillations (whether endogenous or induced by stimulation) drives the replay of newly encoded memories in hippocampal circuitry (which is accompanied by sharp wave-ripples - SPW) and, in parallel, the generation of thalamic spindles and of burst activity in the locus coeruleus. This enables feedback activity from these structures, that is, hippocampal-to-neocortical replay activity, thalamo-cortical spindles and noradrenergic locus coeruleus bursts, to arrive at about the same time at the neocortex, where the co-occurrence of these inputs is probably essential for the formation of long-term memories in neocortical networks. Adapted with permission from ref. [34].

be crucial here. It is presently unclear how explicitness influences the consolidation of concurrent implicit aspects. Also the link between awareness and involvement of prefrontal–hippocampal circuitry during encoding and subsequent consolidation needs elaboration.

Neuroimaging methods have revealed sleep-dependent changes in memory representations, even in the absence of modified recall performance. An important step in researching the effect of sleep on memory will be to establish clearer associations between sleep-dependent changes in the neuronal representation and behavioral output measures of memory consolidation.

Does sleep induce forgetting of certain memories? This is predicted by the 'synaptic downscaling' concept' [70]. However, evidence from behavioral experiments is scarce. Forgetting might rather be a ubiquitous process of decay not specifically linked to sleep.

Sleep stages (SWS, REM sleep, stage 2 sleep) are complex phenomena with only some of the underlying processes (e.g. slow oscillations) specifically linked to memory processing. Rather than manipulating sleep stages as a whole, researchers need to identify the specific electrophysiological and neurochemical events that are involved. A causative role of memory reactivation during SWS for memory consolidation has been demonstrated. Reactivations are assumed to stimulate the redistribution of memory representations to other mainly neocortical circuitry. The redistribution itself and the question of subsequent reconsolidation of redistributed memories will be at the centre of future research.

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References

1 Stickgold, R. (2005) Sleep-dependent memory consolidation. *Nature* 437, 1272–1278
2 Born, J. *et al.* (2006) Sleep to remember. *Neuroscientist* 12, 410–424
3 Walker, M.P. and Stickgold, R. (2004) Sleep-dependent learning and memory consolidation. *Neuron* 44, 121–133
4 Maquet, P. (2001) The role of sleep in learning and memory. *Science* 294, 1048–1052
5 McClelland, J.L. *et al.* (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457
6 Walker, M.P. (2005) A refined model of sleep and the time course of memory formation. *Behav. Brain Sci.* 28, 51–64
7 Gais, S. and Born, J. (2004) Declarative memory consolidation: mechanisms acting during human sleep. *Learn. Mem.* 11, 679–685
8 Smith, C. (2001) Sleep states and memory processes in humans: procedural versus declarative memory systems. *Sleep Med. Rev.* 5, 491–506
9 Ellenbogen, J.M. *et al.* (2006) Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. *Curr. Biol.* 16, 1290–1294
10 Korman, M. *et al.* (2007) Daytime sleep condenses the time-course of motor memory consolidation. *Nat. Neurosci.* 10, 1206–1213
11 Fischer, S. *et al.* (2002) Sleep forms memory for finger skills. *Proc. Natl. Acad. Sci. U. S. A.* 99, 11987–11991
12 Walker, M.P. *et al.* (2003) Dissociable stages of human memory consolidation and reconsolidation. *Nature* 425, 616–620
13 Gais, S. *et al.* (2000) Early sleep triggers memory for early visual discrimination skills. *Nat. Neurosci.* 3, 1335–1339
14 Stickgold, R. *et al.* (2000) Visual discrimination learning requires sleep after training. *Nat. Neurosci.* 3, 1237–1238
15 Gais, S. *et al.* (2006) Sleep after learning aids memory recall. *Learn. Mem.* 13, 259–262
16 Plihal, W. and Born, J. (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. *J. Cogn. Neurosci.* 9, 534–547
17 Wagner, U. *et al.* (2006) Brief sleep after learning keeps emotional memories alive for years. *Biol. Psychiatry* 60, 788–790
18 Orban, P. *et al.* (2006) Sleep after spatial learning promotes covert reorganization of brain activity. *Proc. Natl. Acad. Sci. U. S. A.* 103, 7124–7129
19 Robertson, E.M. *et al.* (2004) Awareness modifies the skill-learning benefits of sleep. *Curr. Biol.* 14, 208–212
20 Cajochen, C. *et al.* (2004) Circadian modulation of sequence learning under high and low sleep pressure conditions. *Behav. Brain Res.* 151, 167–176
21 Fischer, S. *et al.* (2007) Developmental differences in sleep's role for implicit off-line learning: comparing children with adults. *J. Cogn. Neurosci.* 19, 214–227
22 Kuriyama, K. *et al.* (2004) Sleep-dependent learning and motor-skill complexity. *Learn. Mem.* 11, 705–713
23 Drosopoulos, S. *et al.* (2007) Sleep's function in the spontaneous recovery and consolidation of memories. *J. Exp. Psychol. Gen.* 136, 169–183
24 Drosopoulos, S. *et al.* (2007) Sleep enforces the temporal order in memory. *PLoS. ONE* 2, E376
25 Drosopoulos, S. *et al.* (2005) Sleep enhances explicit recollection in recognition memory. *Learn. Mem.* 12, 44–51
26 Fischer, S. *et al.* (2006) Implicit learning–explicit knowing: a role for sleep in memory system interaction. *J. Cogn. Neurosci.* 18, 311–319
27 Wagner, U. *et al.* (2004) Sleep inspires insight. *Nature* 427, 352–355
28 Spencer, R.M. *et al.* (2006) Sleep-dependent consolidation of contextual learning. *Curr. Biol.* 16, 1001–1005
29 Brown, R.M. and Robertson, E.M. (2007) Inducing motor skill improvements with a declarative task. *Nat. Neurosci.* 10, 148–149
30 Jensen, O. (2005) Reading the hippocampal code by theta phase-locking. *Trends Cogn. Sci.* 9, 551–553
31 Wagner, A.D. *et al.* (1998) Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* 281, 1188–1191
32 Mölle, M. *et al.* (2002) EEG theta synchronization conjoined with alpha desynchronization indicate intentional encoding. *Eur. J. Neurosci.* 15, 923–928
33 Wagner, U. and Born, J. Memory consolidation during sleep: Interactive effects of sleep stages and HPA regulation. *Stress* (in press)
34 Marshall, L. *et al.* (2006) Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613
35 Rauchs, G. *et al.* (2004) Consolidation of strictly episodic memories mainly requires rapid eye movement sleep. *Sleep* 27, 395–401
36 Mölle, M. *et al.* (2004) Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. *Proc. Natl. Acad. Sci. U. S. A.* 101, 13963–13968
37 Smith, C.T. *et al.* (2004) Posttraining increases in REM sleep intensity implicate REM sleep in memory processing and provide a biological marker of learning potential. *Learn. Mem.* 11, 714–719
38 Huber, R. *et al.* (2004) Local sleep and learning. *Nature* 430, 78–81
39 Huber, R. *et al.* (2006) Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat. Neurosci.* 9, 1169–1176
40 Fogel, S.M. *et al.* (2007) Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. *Behav. Brain Res.* 180, 48–61
41 Gais, S. *et al.* (2002) Learning-dependent increases in sleep spindle density. *J. Neurosci.* 22, 6830–6834
42 Clemens, Z. *et al.* (2006) Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. *Neurosci. Lett.* 403, 52–56
43 Schmidt, C. *et al.* (2006) Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. *J. Neurosci.* 26, 8976–8982
44 Giuditta, A. *et al.* (1995) The sequential hypothesis of the function of sleep. *Behav. Brain Res.* 69, 157–166
45 Pennartz, C.M.A. *et al.* (2002) Memory reactivation and consolidation during sleep: from cellular mechanisms to human performance. *Prog.Brain. Res.* 138, 143–166
46 Buzsáki, G. (2006) *Rhythms of the Brain,* Oxford University Press
47 Ribeiro, S. *et al.* (2004) Long-lasting novelty-induced neuronal reverberation during slow-wave sleep in multiple forebrain areas. *PLoS Biol.* 2, E24
48 Ji, D. and Wilson, M.A. (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat. Neurosci.* 10, 100–107
49 Peigneux, P. *et al.* (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron* 44, 535–545
50 Maquet, P. *et al.* (2000) Experience-dependent changes in cerebral activation during human REM sleep. *Nat. Neurosci.* 3, 831–836
51 Rasch, B. *et al.* (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science* 315, 1426–1429
52 Hasselmo, M.E. (2006) The role of acetylcholine in learning and memory. *Curr. Opin. Neurobiol.* 16, 710–715
53 Gais, S. and Born, J. (2004) Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proc. Natl. Acad. Sci. U. S. A.* 101, 2140–2144
54 Rasch, B.H. *et al.* (2006) Combined blockade of cholinergic receptors shifts the brain from stimulus encoding to memory consolidation. *J. Cogn. Neurosci.* 18, 793–802
55 Plihal, W. and Born, J. (1999) Memory consolidation in human sleep depends on inhibition of glucocorticoid release. *Neuroreport* 10, 2741–2747
56 Kali, S. and Dayan, P. (2004) Off-line replay maintains declarative memories in a model of hippocampal-neocortical interactions. *Nat. Neurosci.* 7, 286–294
57 Frankland, P.W. and Bontempi, B. (2005) The organization of recent and remote memories. *Nat. Rev. Neurosci.* 6, 119–130
58 Siapas, A.G. and Wilson, M.A. (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* 21, 1123–1128
59 Mölle, M. *et al.* (2002) Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *J. Neurosci.* 22, 10941–10947

60 Sirota, A. *et al.* (2003) Communication between neocortex and hippocampus during sleep in rodents. *Proc. Natl. Acad. Sci. U. S. A.* 100, 2065–2069
61 Clemens, Z. *et al.* (2007) Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. *Brain.* DOI: 10.1093/brain/awm146
62 Yeshenko, O. *et al.* (2006) Locus coeruleus firing during SWS is time-locked to slow oscillations: possible contribution of the noradrenergic system to off-line information processing in rats. *J. Sleep. Res.* 15 (suppl. 1), 11
63 Werk, C.M. *et al.* (2005) Induction of long-term potentiation leads to increased reliability of evoked neocortical spindles *in vivo*. *Neuroscience* 131, 793–800
64 Rosanova, M. and Ulrich, D. (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *J. Neurosci.* 25, 9398–9405
65 Steriade, M. (2006) Grouping of brain rhythms in corticothalamic systems. *Neuroscience* 137, 1087–1106
66 Mölle, M. *et al.* (2006) Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *J. Neurophysiol.* 96, 62–70
67 Isomura, Y. *et al.* (2006) Integration and segregation of activity in entorhinal-hippocampal subregions by neocortical slow oscillations. *Neuron* 52, 871–882
68 Tse, D. *et al.* (2007) Schemas and memory consolidation. *Science* 316, 76–82
69 Fischer, S. *et al.* (2005) Motor memory consolidation in sleep shapes more effective neuronal representations. *J. Neurosci.* 25, 11248–11255
70 Tononi, G. and Cirelli, C. (2006) Sleep function and synaptic homeostasis. *Sleep Med. Rev.* 10, 49–62
71 Squire, L.R. (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* 99, 195–231
72 Forkstam, C. and Petersson, K.M. (2005) Towards an explicit account of implicit learning. *Curr. Opin. Neurol.* 18, 435–441
73 Schendan, H.E. *et al.* (2003) An fMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron* 37, 1013–1025
74 Nishida, M. and Walker, M.P. (2007) Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS ONE* 2, e341
75 Finelli, L.A. *et al.* (2000) Dual electroencephalogram markers of human sleep homeostasis: correlation between theta activity in waking and slow-wave activity in sleep. *Neuroscience* 101, 523–529
76 Marshall, L. *et al.* (2003) Spindle and slow wave rhythms at slow wave sleep transitions are linked to strong shifts in the cortical direct current potential. *Neuroscience* 121, 1047–1053