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REVIEW

Memory processes during sleep: beyond the standard consolidation theory

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Abstract Two-step theories of memory formation suggest that an initial encoding stage, during which transient neural assemblies are formed in the hippocampus, is followed by a second step called consolidation, which involves re-processing of activity patterns and is associated with an increasing involvement of the neocortex. Several studies in human subjects as well as in animals suggest that memory consolidation occurs predominantly during sleep (standard consolidation model). Alternatively, it has been suggested that consolidation may occur during waking state as well and that the role of sleep is rather to restore encoding capabilities of synaptic connections (synaptic downscaling theory). Here, we review the experimental evidence favoring and challenging these two views and suggest an integrative model of memory consolidation.

Keywords Memory consolidation · Sleep · Hippocampus · Replay · Ripples

The standard model of long-term memory formation

Although we spend about one-third of our life sleeping, the function of sleep is still a matter of intense debate. Obviously, sleep is an "offline" mode of the organism when it is mostly devoid of sensory information processing and goal-directed behavior. It has long been suggested that sleep contributes to memory formation by consolidating new information and by integrating it with previously stored contents [1, 2]. More specifically, both declarative and non-declarative forms of memory formation appear to benefit from sleep. Declarative (hippocampus-dependent) memory formation occurs in at least two subsequent stages [3–9]. Initial encoding of declarative memories depends on the integrity of the hippocampus [10, 11] and is probably linked to fast synaptic plasticity which leads to the formation of transient neuronal assemblies. The temporal coupling of activity between these selected neurons constitutes an early representation of experience. Encoding of new information occurs mainly during waking state and, more specifically, during exploratory behavior. The second, subsequent step of memory formation is called consolidation. During this phase, activity patterns of previously formed assemblies are reverberated and propagated into neocortical areas, probably leading to a gradually increasing contribution of the neocortex to long-term information storage. It should be noted that it is still an open question whether remote episodic memories become independent of the hippocampus, as proposed by some studies [12], or whether the hippocampus remains important for episodic aspects of memories, as suggested by the multiple trace theory [13]. This question is beyond the scope of the current review. In both cases, as a result of consolidation, memories are embedded into the network of previous knowledge and become resistant to interference [14].

In this review, we will follow the general concept of two-step memory formation. We will, however, challenge its close connection to sleep. According to the "standard model" of sleep-related memory formation which we will

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discuss here, consolidation occurs predominantly during sleep. For example, David Marr [15] states that during memory consolidation, "[…] ordinary sensory information must be rigorously excluded. The only time when this exclusion condition is satisfied is during certain phases of sleep." (p. 215). Later, Gyorgy Buzsaki proposed a specific neuronal pathway for information transfer from the hippocampus to the neocortex: "In the awake brain, information about the external world reaches the hippocampus via the entorhinal cortex, whereas during sleep the direction of information flow is reversed: population bursts initiated in the hippocampus invade the neocortex." ([4], p. 17). This model prompts three major hypotheses: (1) sleep facilitates memory consolidation on a behavioral level. As memory consolidation is operationally defined in terms of experimental psychology, the role of sleep for memory consolidation should be behaviorally measurable as increased or altered recall functions after relevant periods of sleep. (2) The second statement concerns the neural representations of experience. Because memory consolidation is related to a reactivation of experience-specific activity patterns, the standard consolidation model claims that this reactivation should occur predominantly during sleep. (3) During sleep, information should be transferred from the hippocampus to the neocortex. Thus, activity should start within the hippocampus and should be systematically followed by subsequent specific activity patterns in neocortical circuits.

Here, we will review the evidence for each of these three hypotheses. It will be shown that the first and second hypotheses are supported by some studies, while there is currently no firm evidence for the third hypothesis. Available data do, rather, support a reciprocal dialogue between the neocortex and the hippocampus during sleep-related memory consolidation, consistent with parallel processing of memory in and between both structures.

An alternative view to the standard model of sleep-related consolidation proposes that sleep serves predominantly to reduce synaptic weights and to allow for "fresh" encoding of new information after sleep [16]. This "synaptic downscaling" theory is consistent with several experimental findings: Memory consolidation is not strictly bound to sleep, but occurs constantly, also during waking state (modified hypothesis 1*); newly acquired, specific patterns of activity are not only re-played during sleep, but also during waking state (modified hypothesis 2*); and the predominant direction of propagating activity during sleep is actually from the neocortex to the hippocampus and not vice versa (modified hypothesis 3*). Importantly, however, we do not claim that the "standard model" of sleep-related memory consolidation is incorrect, but rather that it requires combination with the synaptic downscaling theory to account for the full range of available data.

Why do we need multiple long-term memory systems?

Two-step theories of memory formation suggest that an initial learning phase results in transient and labile neural representations, and is then followed by a subsequent step of memory consolidation. The function of consolidation is to stabilize engrams and to integrate freshly acquired information with previous experiences. This theory addresses the fundamental challenge that memory should both reliably store information and be plastic to allow for the modification of existing memories by new experiences. One of the first metaphorical descriptions of these requirements was given in Freud's model of the "Wunderblock" [17]. This apparatus consists of a superficial wax layer, in which new information can be rapidly inscribed but which can also be easily overwritten, followed by an intermediate layer and a deep layer in which all events leave their enduring traces. As a result, recent experiences are immediately visible but may still be erased; their transformation into permanent representations protects them, but impedes direct access. Later, two-step memory theories have been grounded in theoretical and experimental research on specialized memory systems. David Marr [1] was one of the first to postulate an intermediate memory storage system (between short-term retention and permanent storage) on theoretical grounds. He suggested that the main function of the neocortex is to classify events based on their similarity in order to represent statistical properties of the external world, such that the connections between neocortical cells map the probability space of the environment [15]. This map should allow for the incorporation of novel experiences. However, these novel experiences need to be properly related to previous knowledge. Marr argued that assigning new experiences to their correct location within the overall probability map is computationally very complex. Integration, therefore, cannot be performed on-line, but requires an intermediate buffer which transiently stores information and relates it to previous experiences. The properties of this intermediate storage system matched what was known about the hippocampus at that time (e.g., the association network in the CA3 region) and correctly predicted some of its physiological properties which were only confirmed many years later (e.g., that the CA3 region corresponds to a random connectivity matrix). Later, this theoretical model was complemented by connectionist accounts (most prominently: [5]) which aimed at explaining the pattern of neuropsychological findings in patients with hippocampal lesions [10, 11]. In these models, rapid learning of novel associations (e.g., A–C) in the presence of existing associations (A–B) may lead to catastrophic interference, resulting in degradation of the previous connections. This effect can most easily be avoided "if new information is added gradually, interleaved with ongoing

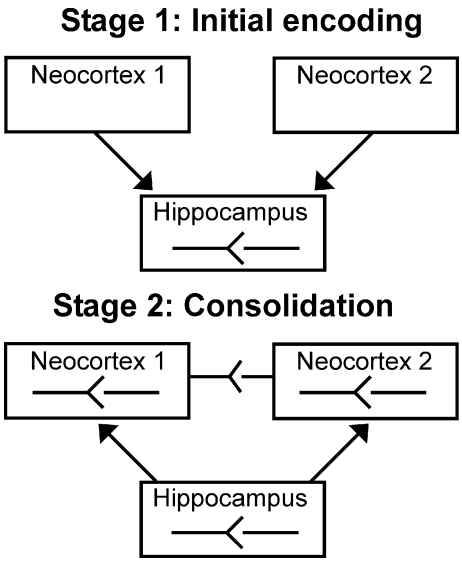

Fig. 1 Two-stage theory of memory consolidation. *Top* during initial encoding, new information is processed (via sensory neocortex) to the hippocampus, where it is transiently stored via fast synaptic plasticity. *Bottom* during consolidation, the neocortex receives information from the hippocampus for permanent storage of information (figure similar to [9]). Schematic synapses depict learning-related plasticity

exposure to other examples from the same domain of knowledge ([5], p. 433)". More generally, these models show that slow learning rates optimize the representation of statistical relationships by graded incorporation of new data and previous experiences. This hypothesis is highly compatible with the two-step model of memory formation where the hippocampus acquires environmental data online, while the neocortex receives information offline from the hippocampus at later stages (Fig. 1).

In the following, we will discuss the three major hypotheses derived from the standard model of memory consolidation (see above) and review the available evidence about the role of different sleep phases and of the cortico-hippocampal dialogue.

Standard hypothesis 1: memory consolidation occurs predominantly during sleep

The first hypothesis characterizing the "standard consolidation model" states that with regard to behavioral measures, memory consolidation occurs predominantly during sleep. Indeed, there is ample evidence that sleep supports both consciously accessible (declarative) and implicit memory consolidation. Moreover, some studies suggest that different stages of sleep support memory consolidation for different types of memory: while REM sleep appears to be particularly relevant for the consolidation of procedural and other non-declarative forms of memory, NREM sleep is rather beneficial for declarative memory consolidation. However, other studies question this seemingly clear distinction.

Procedural learning results in accelerated and more accurate conduction of perceptual and motor tasks. Execution of these tasks usually improves during a period of several hours following practice [18]. If subjects sleep during this period, there is an additional boost of performance in, for example, mirror-tracing [19], visual discrimination [20, 21], and execution of motor sequences (e.g., finger tapping; [22, 23]). Also other non-declarative kinds of memory have been shown to benefit from sleep (e.g., word-stem priming; [24]). It has been suggested that the consolidation of perceptual learning depends specifically on REM sleep [25]. On the other hand, some studies question the view that REM sleep is specifically related to consolidation of non-declarative memories. First, consolidation in a visual discrimination task depends not only on the second part of the night, which is dominated by REM sleep, but even more strongly on sleep in the first part of the night, which is dominated by slow wave sleep [19, 26]. Second, pharmacological suppression of REM sleep by antidepressant drugs actually enhanced the accuracy of finger tapping [27], consistent with clinical observations of preserved procedural memory in depressed patients receiving these substances over a long time period [28].

Besides procedural learning, declarative memory formation does also benefit from subsequent sleep. For example, the ability to recall vocabulary was improved by sleep after learning [29], and it was shown that sleep facilitates associative spatial learning [30]. The specific influence of different sleep states on declarative memory consolidation can be tested due to the dominance of NREM sleep during early night phases and REM sleep during later phases (reviewed in [31]). As a result, NREM sleep has been found to be particularly important for declarative memory [19, 24, 32] while procedural (implicit) memory consolidation benefits mostly from REM sleep [19, 24, 26, 33]. Furthermore, a brief day-time nap containing only NREM periods selectively enhanced memory in a paired associate task, but not in procedural learning paradigms [34]. If, in contrast, similar naps contained periods of REM sleep as well, procedural memory was enhanced [35]. Even "ultra-short" naps of only six minutes duration showed an improvement on recall of word lists [36]. On the other hand, it was found that consolidation of strictly episodic memories (located in space and time and associated with autonoetic consciousness) is more susceptible to deprivation of REM sleep than of slow wave sleep (SWS: deep stages of NREM, i.e., stages 3 and 4) [37]. Even more complicated, several studies suggest that procedural learning is improved together by SWS in the first quartile

of the night and by REM sleep in the 4th quartile of the night [38].

Several mechanisms have been suggested which might account for the beneficial effect of NREM sleep on memory consolidation. During waking states and REM sleep, levels of acetylcholine are high, impairing the output from the hippocampus to the neocortex [39]. At the same time, recurrent excitatory connections within hippocampal and neocortical circuits are suppressed, favoring the processing of afferent information. During SWS, acetylcholine levels are low, thus reducing the impact of afferent synapses and facilitating internal re-play of pre-established sequences [40]. Consistent with this hypothesis, declarative memory consolidation was suppressed when healthy human subjects received cholinesterase blockers during early night [41]. An additional mechanism facilitating memory consolidation during deep stages of NREM sleep may be constituted by sleep spindles of 10–16 Hz [42] which are generated in thalamocortical circuits and promote synaptic plasticity [43]. Interestingly, sleep spindle activity is enhanced by learning [44, 45] and correlates with the formation of associations in the sensory cortex [46]. Lastly, slow oscillations <1 Hz defining responsive "up"- and silent "down"-states of the neocortex during SWS [47] may organize the bi-directional cortico-hippocampal dialogue during SWS. Artificial application of such slow alternating voltage shifts to the brain during early sleep phases can indeed facilitate declarative memory consolidation [48]. Hippocampal activity patterns involved in spatial memory formation and the cortico-hippocampal dialogue during memory consolidation will be discussed in the next section on the Standard hypothesis 2.

Taken together, these data provide ample evidence for the facilitating role of sleep in memory consolidation. However, memory processing may be improved not only by subsequent sleep, but also by sleeping prior to learning. Yoo et al. [49] observed that one night of sleep deprivation significantly impaired the encoding of new episodic memories and was associated with reduced hippocampal activation during encoding. Similarly, Van der Werf et al. [50] found that even a reduction of sleep depth deteriorated subsequent hippocampus-dependent memory formation. We recently tested this idea using a recognition memory paradigm in epilepsy patients with intracranial EEG electrodes in bilateral hippocampi and rhinal cortices [51]. Subjects were presented pictures of buildings and landscapes on each of two subsequent days; on each day, a recognition memory test followed. One day contained a nap of 1 h duration between the first and second learning session, while the other day contained a period of the same duration without sleep. A schematic depiction of this paradigm and the main results is provided in Fig. 2. While we did not observe an effect of sleep on retrieval of information acquired before sleep, retrieval of the items learned

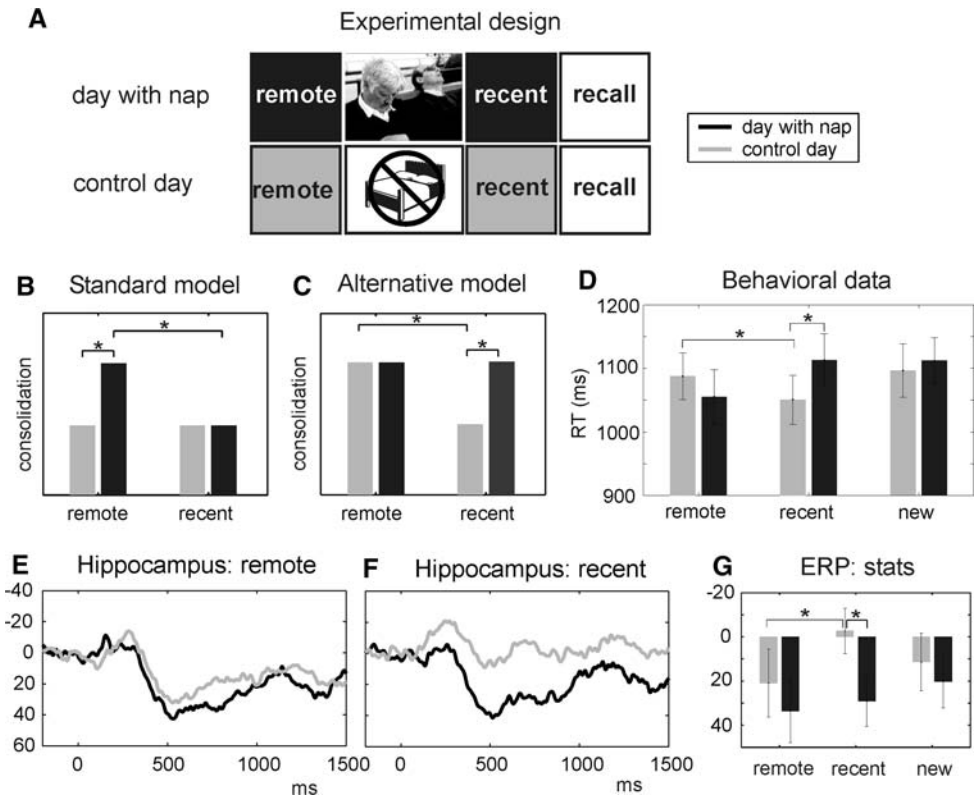

Fig. 2 Experimental design and results from a study of memory consolidation during a brief afternoon nap. **a** Experimental paradigm. **b** According to the Standard model of memory consolidation, consolidation occurs predominantly during sleep. **c** According to the alternative view, consolidation may also occur during waking state, but is facilitated after sleep. **d–g** Reaction times and intracranial event-related potentials (ERPs) within the hippocampus are consistent with the alternative model (modified from [51])

after sleep was significantly improved. It should be noted that the same paradigm has been conducted using fMRI [52]. In this study, naps affected memory for items encoded prior to sleep, consistent with the standard consolidation theory. This apparent discrepancy might, however, be explained by different recording modalities and experimental parameters (e.g., testing after different time intervals in the study by Takashima et al. [52] as compared to our study [51]). Both studies report increased reaction times for remote as compared to recent items (Fig. 2d). Such an increase in reaction times following sleep might seem to indicate less consolidation, but this is not necessarily the case: at least for declarative memory, consolidation implies that memories are embedded into larger networks of previous experiences, which might slow down rapid access to these memories [53]. Using intracranial EEG, we found that event-related hippocampal potentials on the control day were more negative during retrieval of recent than remote items (Fig. 2e, f). Such an increased negative potential likely corresponds to an enhanced activation of this region (e.g., [54]), which in turn indicates that these memories have undergone consolidation to a lesser degree at the time of retrieval. On the day with nap, in contrast, there was no difference in event-related potentials during retrieval of recent and remote items, suggesting that the nap facilitates at least early stages of memory consolidation of the recently learned items. These findings indicate that sleep can prepare the brain for better memory consolidation which can, however, itself occur in wake states (modified hypothesis 1*, see above). They are also consistent with the suggestion that one function of sleep is to reduce synaptic weights and thereby to restore the brain's encoding capacities [16], but move beyond it by suggesting that not only memory encoding, but also consolidation is facilitated by prior sleep. Before we describe this theory in greater detail, we will turn to the evidence for and against the two other hypotheses derived from the standard consolidation theory.

Standard hypothesis 2: memory representations are predominantly reactivated during sleep

The second hypothesis claims that the re-activation of neuronal assemblies (the proposed neuronal substrates of memory representations) occurs mainly during sleep. Before reviewing the respective literature, we will briefly describe how such sequences arise and how they may be related to memory. In rodents, individual cells in different subregions of the hippocampus increase their firing rate if the animal is located at a specific spatial location and have thus been termed "place cells" [55, 56]. During spatial exploration, action potentials of these neurons are entrained by the underlying theta network rhythm [57–60]. When the animal crosses the respective place field of a given place cell, the phase-relationship to the theta oscillations systematically proceeds, thereby generating a sequential activation of place cells with overlapping place fields. In principal, these sequences allow for the reconstruction of the animal's trajectory through the explored territory. Thus, by definition, they form a temporal representation of the navigated space. Later, Wilson and McNaughton [61] discovered that sequences of action potentials in place cells with overlapping place fields are re-played, in a temporally condensed manner, during sleep. They occur on top of hippocampal sharp wave-ripple complexes [62]. Sharp waves are field potential waves of 30–200 ms duration which are generated in the hippocampal subfield CA3 and propagate through the hippocampal output loop into the entorhinal cortex [63]. In CA1, they are superimposed by very fast network oscillations, reaching more than 200 Hz in rodents, termed ripples [62]. Together, theta-phase precession during spatial exploration forms temporal sequences of activity and sharp wave-ripple complexes provide a scaffold for their re-play during sleep. Indeed, sequence replay was observed both during SWS periods [61, 64–66] and during REM sleep [67]. Even sequences of three spikes fired by three different place cells during wheel-running are repeated in subsequent slow wave sleep [68], and information about the order in which the cells were activated is maintained [69]. These findings support the idea of temporal coding in transiently formed neuronal assemblies as a mechanism of experience-dependent learning [70]. The occurrence of sharp wave-ripple complexes during sleep or awake immobility [62] and their propagation into the adjacent entorhinal cortex [63] does also lend strong support to the two-stage model of spatial memory formation.

Replay of sequences is not restricted to the hippocampus, but has been observed in other regions as well: Behavior-related correlations between hippocampal and neocortical activity again occur during subsequent SWS [71, 72]. Correlations of cell-pair activity in the medial prefrontal cortex which were established during waking state were also observed in the subsequent night [73]. Ribeiro et al. [74] even described replay-related activity patterns during SWS in hippocampus, neocortex, putamen and thalamus, although this study was later criticized for methodological reasons [75].

Taken together, these studies provide good evidence for a re-activation of both hippocampal and neocortical activity patterns during sleep. However, in contrast to the canonical two-stage model of memory formation, ripples and ripple-coordinated neuronal discharges are not restricted to sleep (modified hypothesis 2*). During exploratory behavior, theta oscillations are not continuous,

leaving room for the occurrence of sharp wave-ripple complexes [76]. During such ripples, place cells with similar or overlapping place fields increase their correlated firing during sharp waves and maintain this coupling during subsequent sleep-related sharp wave-ripple complexes. Ripples occurring during exploratory behavior may indeed be involved in the generation of strong and persistent temporal coupling between hippocampal pyramidal neurons. These cells show an increased amount and temporal precision of coupling during ripples which occur in unfamiliar environments as compared to familiar environments [77]. Conversely, repeated activation of assemblies during behavioral repetitions in rats potentiates the occurrence of sharp waves and re-activated assemblies [78]. It is therefore quite feasible that fast ripple oscillations play an active role in the induction of plasticity processes which stabilize place-encoding neuronal assemblies. Indeed, sharp waves are prone to induce long-term potentiation in hippocampal CA1 pyramidal neurons [79] and sharp wave-ripple complexes in brain slices in vitro can be generated by plasticity-inducing stimulation paradigms [80].

Thus, the formation of assemblies by sharp wave-associated co-activation does already take place during wakefulness. Sequential activation of place cells on top of high-frequency oscillations has also been found during brief resting periods in rats running back and forth on a linear track. These sequences resembled the activation of place cells along the track but, surprisingly, occurred in reverse order [81]. Again, the underlying field activity consisted of sharp wave-ripple events. During subsequent sleep periods, re-activation was forward with respect to previous experience on the track. Later, this finding has been confirmed but replay occurred more frequently in the forward direction than in reverse order [82]. The inverted order of place cell discharges was mostly present immediately after a run through the track whereas forward replay was found before running. It is feasible that these different modes of re-play are related to the influence of recent experiences and anticipations of future activities, respectively [83, 84]. While these findings demonstrate that replay may also occur during waking state, they do not exclude the possibility that replay which is important for consolidation (i.e., which supports transfer of a memory trace from the hippocampus to the neocortex; see next section) predominantly occurs during sleep.

Although hippocampal ripple activity during SWS increases after learning [85], it should be noted that we are still lacking a proof for a causal link between sequence replay during sleep and memory consolidation. One way to tackle this question is to correlate the time and quantity of sequence replay with behavioral recall after sleep. The subsequent memory tasks can be most easily performed in human subjects; however, identification of stimulus-specific neural activity in humans is difficult. Single-unit recordings from the hippocampus of epilepsy patients revealed that individual cells represent specific items [86], but the apparent lack of a topographical organization of these representations suggests that field potentials (which can be recorded with standard macroelectrodes in these patients) are not stimulus-specific [87, 88]; for review, see [89].

However, several studies on humans describe a reactivation of memory-related brain regions during sleep following learning periods (hypothesis 2). Using PET, Maquet et al. [90] found that brain regions which were activated during a serial reaction time task show enhanced metabolism during REM sleep in the consecutive night. After declarative learning, the hippocampus is increasingly activated during periods of SWS, as shown by fMRI [91, 92]. Again, however, there is also evidence that replay is not restricted to sleep, but can occur during waking states as well (modified hypothesis 2*). In one study, Peigneux et al. [93] investigated BOLD activity in fMRI immediately after a hippocampus-dependent declarative learning task or a hippocampus-independent serial reaction time task and observed task-specific offline reactivation of the respective memory systems during waking state. In a second study, Gelbard-Sagiv [94] recorded single neurons within the hippocampus of epilepsy patients. These cells responded selectively to a specific famous person during a learning session and were again active prior to free recall of this person. However, in both studies it is unknown whether the observed reactivation patterns actually correspond to memory consolidation; especially in the study by Gelbard-Sagiv where replay did not occur spontaneously but was triggered by retrieval effort.

Do ripples occur in human subjects, and are they closely linked to sleep? In general, data from the human hippocampus are difficult to obtain because of its deep location and specific field properties. Therefore, it is not possible to record hippocampal ripples via scalp EEG. However, epilepsy patients with intracranial electrodes implanted during presurgical investigations allow studying human hippocampal activity. Ripples with a maximum power between 80 and 140 Hz were detected in the human hippocampus and rhinal cortex using microelectrodes with a diameter of 40 μm [95–97]. In addition, faster oscillations with a power maximum between 250 and 500 Hz (termed "fast ripples") were observed in close proximity to the epileptic focus and thus appear to be related to pathological processes [95–98]. Ripples with a slightly lower frequency maximum were also observed with macroelectrodes, which are routinely used for clinical purposes [99, 100]. Furthermore, Clemens et al. [101] recorded ripples using foramen ovale electrodes with a tip located in the subdural space close to the parahippocampal gyrus.

Interestingly, in several of these studies ripples were observed not only during sleep, but occurred during waking state as well: while Staba et al. [102] found that the rate of ripples during NREM sleep was twice as high as during waking state, Clemens et al. [101] observed that more ripples occurred during stage 1 and 2 of NREM sleep as compared to waking state, but that the incidence of ripples during SWS and waking state was comparable. Similarly, Bagshaw et al. [103] reported hippocampal ripples and fast ripples during all states of vigilance, including REM and wakefulness. Again, the occurrence of the fast events was most pronounced during stage 1–2 of NREM sleep. We found that the rate of ripples during waking state was even significantly higher as compared to all sleep stages [100]. It should be noted that the term "waking state" usually corresponds to normal awake behavior, whereas in our study, it referred to periods before or between sleep phases when subjects lay in a quiet dark room with their eyes closed. Thus, this state is more closely related to a resting state of the brain than to awake exploratory behavior. Possibly, replay during this awake resting state plays a similar role for memory consolidation (i.e., supports transfer of information from the hippocampus to the neocortex) as replay during sleep, although there is currently no direct evidence for hippocampal-neocortical cross-talk during this state. Together, these data strongly support the idea that not only reactivation of memory systems, but also ripple activity is not restricted to sleep, but occurs during waking states as well (modified hypothesis 2*).

Standard hypothesis 3: during sleep, information is transferred from the hippocampus to the neocortex

The third hypothesis proposes that during sleep, hippocampal markers of reactivation occur time-locked to, but briefly earlier than, neocortical activity patterns related to information encoding. This temporal order would be indicative of information transfer from hippocampus to the neocortex. It should be noted that thus far, the neural mechanisms supporting permanent storage of information are still unclear (see next section). However, several studies observed that neocortical sleep spindles, which occur with the highest incidence during stage 2 sleep, and slow waves depend on previous learning episodes. Again, this issue was investigated both in animals and humans. In humans, performance of a declarative memory task enhanced the density of sleep spindles in the subsequent night [104]. Parahippocampal ripples recorded with foramen ovale electrodes were locked to sleep spindles in surface EEG recordings [101]. These studies are, in principle, consistent with information transfer from the hippocampus to the neocortex, although the direction of coupling was not investigated.

The coupling of hippocampal ripples to neocortical sleep spindles and slow waves has also been studied in rats. Indeed, hippocampal ripples are temporally linked and mostly precede neocortical sleep spindles [105]. Furthermore, hippocampal ripples occurred time-locked to neocortical sleep spindles [106, 107]. In vivo recordings also revealed that hippocampal sharp waves are locked to the depolarizing phase of neocortical delta waves/slow rhythm, which is associated with enhanced cortical activity [106–109]. Likewise, sleep spindles and ripples are concentrated on the depolarizing phase of neocortical slow activity [110], suggesting that these coordinated patterns of activity take place during a highly responsive and plastic state of the neocortex [42, 111].

Again, while these studies show that hippocampal ripples, neocortical sleep spindles and up-states are locked in time, they do not reveal the direction of the hippocampo-cortical or cortico-hippocampal information transfer. Indeed, during SWS, hippocampal activity is influenced by neocortical transitions between up- and down-states, while an impact of the hippocampus on neocortical activity has not been observed [109]. Up to now, there is no clear evidence that the hippocampus specifically influences the neocortex during sleep (see the comment by Tononi et al. [112]). While Siapas and Wilson [105] had established a correlation between hippocampal ripples and neocortical sharp waves, a closer investigation of action potential timing revealed that neocortical spikes related to spindle and delta activity precede ripple-related discharges in the hippocampus by about 50 ms [106]. These findings are consistent with information transfer from the neocortex to the hippocampus, but not in the reverse direction. It may be argued that hippocampal activity always follows activity in the neocortex, but this is not true either: during waking state, prefrontal activity is locked to hippocampal theta oscillations [113], suggesting that the hippocampus actually exerts an influence on neocortical activity.

We recently investigated this question in human intracranial EEG recordings (unpublished observations). A directional coupling analysis [114] was used to study interactions of rhinal cortex, hippocampus and neocortex during waking state and during different sleep stages. While in general the predominant coupling direction was from the anterior hippocampus to the rhinal cortex and neocortex, the neocortex exerted an increasing influence on the hippocampus during sleep. Taken together, several studies indicate that hippocampus and neocortex interact closely and specifically during sleep. The predominant direction of influence, however, appears to be from the neocortex to the hippocampus and not vice versa (modified hypothesis 3*).

Synaptic potentiation or depression during sleep?

If, according to the standard consolidation theory, consolidation occurs predominantly during sleep, this state should also facilitate the cellular correlates of learning. One of the most important candidates for such a correlate is long-term potentiation (LTP), although this relation still remains disputed (see below). Such an "extended" standard consolidation theory would also predict a link between sleep and LTP. On the other hand, one of the most specific predictions of the synaptic downscaling theory is that sleep corresponds to a net depression of synaptic weights. In this section, we will review studies attempting to relate synaptic plasticity and sleep. Several studies linked sleep spindles with LTP. First, using computer simulations, Sejnowski and Destexhe [115] suggest that sleep spindles play a crucial role for the induction of long-term plasticity in the neocortex by triggering Ca^{2+} entry through dendritic depolarisations. Second, the local spindle density correlates with efficacy of TMS-induced spike-timing dependent plasticity (as measured by motor-evoked potentials after stimulation of both the median nerve and the hand region in the primary motor cortex; [46]). Finally, hippocampal ripples were related to LTP as well [79, 80]. However, there is also evidence relating sleep-related activity and synaptic depression. First, Colgin et al. [116] found that the induction of LTP was impaired in slices which showed spontaneous ripples. Second, Vyazovskiy et al. [117] observed a net synaptic potentiation during waking state and a depression during sleep. Third, sleep deprivation was found to impair LTP induction, possibly due to saturation [118, 119]. These observations support the synaptic downscaling theory, which suggests that the function of sleep for memory formation is to restore synaptic weights to allow for the efficient encoding of new information after sleep. This reduction of synaptic weights should improve the signal-to-noise ratio of cortical information processing because weakly potentiated synapses corresponding to interfering noise are completely silenced and only strongly potentiated synapses corresponding to the signal survive. More specifically, the synaptic downscaling theory (or "synaptic homeostasis hypothesis"; [16, 120]) is based on two observations: First, that the intensity of slow waves depends on the amount of accumulated prior waking time [121]; and second, that acquisition of new information during waking state is linked to sub-cellular modifications which eventually lead to an increase of synaptic weights, i.e., to synaptic potentiation [122].

Despite its role for learning in simple organisms such as aplysia and its existence in the mammalian neocortex (e.g., [123]), the exact functional role of LTP for learning and memory in mammals has still not been identified. One important form of LTP, which may serve as an implementation of the Hebbian learning rule of coordinated pre- and postsynaptic neuronal activity [124], depends on activation of *N*-methyl-D-aspartate (NMDA) receptors and a subsequent cascade of molecular and genetic changes [125, 126]. For example, it was shown that hippocampus-dependent spatial learning in mice is impaired after spatially selective deletion of the NMDA receptor in the CA1 region of the hippocampus ([127]; mice completely lacking the NMDA receptor die postnatally), or in mice lacking the alpha-calcium-calmodulin kinase II (alpha-CaM-Kinase II; [128]). Similar deficits were induced by pharmacological blockade of NMDA receptors via intra-hippocampal infusion of APV [129]. These and other putative molecular correlates of learning (such as BDNF, CREB, and Arc) are up-regulated during waking state, e.g., due to an increased activity of noradrenergic neurons [130, 131]. The synaptic downscaling theory predicts that the net synaptic potentiation during waking state is balanced by slow wave activity during sleep. Indeed, animals with lesions of the noradrenergic system and a subsequent reduction of LTP-related gene expression show a decrease in slow wave activity [130, 131]. In humans, putative induction of regionally-specific neural plasticity is associated with a subsequent enhancement of slow wave activity in the same brain area [132], while arm immobilization causes a reduction of local slow wave activity within the sensorimotor cortex [133]. Several results suggest that slow wave activity actually promotes a depression of synaptic weights. First, a frequency of $\sim$1 Hz is ideal to reverse the effect of NMDA receptor dependent LTP by removing AMPA receptors from the postsynaptic membrane (e.g., [134]). Second, the reduced concentration of neuromodulators such as acetylcholine (e.g., [135, 136]) and noradrenaline [137] is favorable for a reduction of synaptic weights. In addition, substances such as insulin and calcineurin which promote synaptic depression are up-regulated during sleep [138, 139].

It is less clear whether neocortical information storage depends on similar neural mechanisms. Some studies indicate that retrieval of remote memories enhances the expression of immediate early genes [140, 141] and depends on the alpha-CaM-Kinase II [142], which is closely linked to induction of LTP. Furthermore, it was shown that NMDA receptor expression is required for retrieval of old memories [143], although the neocortical localization of these receptors was not directly demonstrated in that study. Based on these studies, it has been suggested that long-term storage of information in the neocortex actually depends on LTP [9]. Importantly, however, these studies did not investigate the circadian effects on neocortical plasticity. Furthermore, several alternative plasticity mechanisms may account for long-term memory encoding as well. For example, long-term depression (LTD) was

Table 1 Overview of the experimental evidence for the "Standard consolidation theory"

	Standard consolidation theory	Alternative theory
Function of sleep	Consolidation of previous experiences	Synaptic downscaling for consecutive learning
Memory consolidation	*NREM: Declarative memory* *REM: Procedural memory*	*Continuous (during resting states immediately after encoding)*
Memory replay	*During sleep*	*During sleep and waking state*
Neocortical LTP during sleep	Increase (if encoding is related to LTP)	*Decrease*
Hippocampal–neocortical interactions during sleep (memory transfer)	**Hippocampus → neocortex**	No predictions

Predictions supported by experimental evidence are given in italics. Predictions with opposing experimental evidence are given in bold

associated with exploration of novel environments in rats [144] and may also be important in the neocortex to sharpen activity in neural assemblies during learning [88, 145]. In addition, non-synaptic plasticity mechanisms (for reviews, see [146, 147]) might also play a role during neocortical memory formation, in particular because spindle-related activity was shown to control dendritic excitability [148].

Conclusion

Above, we have evaluated three major hypotheses underlying the standard model of memory consolidation (see Table 1). Indeed, a large amount of data indicate that memory replay and consolidation take place during sleep, in particular during NREM sleep. However, several studies have also provided evidence that reactivation of memory representations and consolidation occur during waking states, contributing to the formation of neuronal assemblies. In contrast to common concepts of memory formation, sleep is associated rather with neocortical LTD than with LTP. Furthermore, studies investigating the interaction between hippocampus and neocortex do not support the idea of a hippocampal–neocortical information transfer during sleep, but rather suggest a co-activation or even a neocortical driving influence on the hippocampus.

To conclude, we think that an integrative view of the role of sleep for memory consolidation, which combines (slightly modified) elements from the standard theory of memory consolidation with ideas from the synaptic downscaling theory, is most consistent with the experimental evidence at hand: Such an integrative view comprises the idea that replay of activity sequences and memory consolidation occur during resting states characterized by decreased sensory and cognitive processing. Although NREM sleep is particularly suited for memory replay and consolidation, those processes, in principle, may start immediately after memory encoding. Furthermore, this view implies that sleep causes a downscaling of neocortical synapses. This downscaling promotes memory consolidation by refinement and sharpening of previously acquired memories and an increase of the signal-to-noise ratio. Finally, synaptic downscaling improves learning after sleep by preventing saturation of synaptic weights.

References

1. Marr D (1971) Simple memory: a theory for archicortex. Philos Trans R Soc Lond B 262:23–81
2. Crick F, Mitchison G (1983) The function of dream sleep. Nature 304:111–114
3. Buzsaki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31:551–570
4. Buzsaki G (1998) Memory consolidation during sleep: a neurophysiological perspective. J Sleep Res 7:17–23
5. McClelland JL, McNaughton BL, O'Reilly RC (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. Squire LR, Alvarez P (1995) Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 5:169–177
7. Hasselmo ME (1999) Neuromodulation: acetylcholine and memory consolidation. Trends Cogn Sci 3:351–359
8. Stickgold R, Hobson JA, Fosse R, Fosse M (2001) Sleep, learning, and dreams: off-line memory reprocessing. Science 294:1052–1057
9. Wiltgen BJ, Brown RA, Talton LE, Silva AJ (2004) New circuits for old memories: the role of the neocortex in consolidation. Neuron 44:101–108
10. Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21
11. Penfield W, Milner B (1958) Memory deficit produced by bilateral lesions in the hippocampal zone. AMA Arch Neurol Psychiatry 79:475–497
12. Alvarez P, Squire LR (1994) Memory consolidation and the medial temporal lobe: a simple network model. Proc Natl Acad Sci USA 91:7041–7045
13. Nadel L, Moscovitch M (1997) Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 7:217–227
14. Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL (2006) Interfering with theories of sleep and

memory: sleep, declarative memory, and associative interference. Curr Biol 16:1290–1294
15. Marr D (1970) A theory for cerebral neocortex. Proc Roy Soc Lond B 176:161–234
16. Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62
17. Freud S (1969) Gesammelte Werke Bd. II/III
18. Karni A, Sagi D (1993) The time course of learning a visual skill. Nature 365:250–252
19. Plihal W, Born J (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 9:534–547
20. Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA (2000) Visual discrimination task improvement: a multi-step process occurring during sleep. J Cogn Neurosci 12:246–254
21. Stickgold R, James L, Hobson JA (2000) Visual discrimination learning requires sleep after training. Nat Neurosci 3:1237–1238
22. Fischer S, Hallschmid M, Elsner AL, Born J (2002) Sleep forms memory for finger skills. Proc Natl Acad Sci USA 99:11987–11991
23. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205–211
24. Plihal W, Born J (1999) Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology 36:571–582
25. Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D (1994) Dependence on REM sleep of overnight improvement of a perceptual skill. Science 265:679–682
26. Gais S, Plihal W, Wagner U, Born J (2000) Early sleep triggers memory for early visual discrimination skills. Nat Neurosci 3:1335–1339
27. Rasch B, Pommer J, Diekelmann S and Born J (2008) Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat Neurosci (Epub ahead of print)
28. Amado-Boccara I, Gougoulis N, Poirier Littré MF, Galinowski A, Lôo H (1995) Effects of antidepressants on cognitive functions: a review. Neurosci Biobehav Rev 19:479–493
29. Gais S, Lucas B, Born J (2006) Sleep after learning aids memory recall. Learn Mem 13:259–262
30. Talamini LM, Nieuwenhuis IL, Takashima A, Jensen O (2008) Sleep directly following learning benefits consolidation of spatial associative memory. Learn Mem 15:233–237
31. Born J, Rasch B, Gais S (2006) Sleep to remember. Neuroscientist 12:410–424
32. Drosopoulos S, Wagner U, Born J (2005) Sleep enhances explicit recollection in recognition memory. Learn Mem 12:44–51
33. Wagner U, Hallschmid M, Verleger R, Born J (2003) Signs of REM sleep dependent enhancement of implicit face memory: a repetition priming study. Biol Psychol 62:197–210
34. Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, Fishbein W (2006) A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem 86:241–247
35. Backhaus J, Junghanns K (2006) Daytime naps improve procedural motor memory. Sleep Med 7:508–512
36. Lahl O, Wispel C, Willigens B, Pietrowsky R (2008) An ultra short episode of sleep is sufficient to promote declarative memory performance. J Sleep Res 17:3–10
37. Rauchs G, Bertran F, Guillery-Girard B, Desgranges B, Kerrouche N, Denise P, Foret J, Eustache F (2004) Consolidation of strictly episodic memories mainly requires rapid eye movement sleep. Sleep 27:395–401
38. Stickgold R, Walker MP (2007) Sleep-dependent memory consolidation and reconsolidation. Sleep Med 8:331–343
39. Buzsaki G (1996) The hippocampo-neocortical dialogue. Cereb Cortex 6:81–92
40. Giocomo LM, Hasselmo ME (2007) Neuromodulation by glutamate and acetylcholine can change circuit dynamics by regulating the relative influence of afferent input and excitatory feedback. Mol Neurobiol 36:184–200
41. Gais S, Born J (2004) Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. Proc Natl Acad Sci USA 101:2140–2144
42. Steriade M (2003) The corticothalamic system in sleep. Front Biosci 8:d878–d899
43. Timofeev I, Grenier F, Bazhenov M, Houweling AR, Sejnowski TJ, Steriade M (2002) Short- and medium-term plasticity associated with augmenting responses in cortical slabs and spindles in intact cortex of cats in vivo. J Physiol 542:583–598
44. Schabus M, Gruber G, Parapatics S, Sauter C, Klösch G, Anderer P, Klimesch W, Saletu B, Zeitlhofer J (2004) Sleep spindles and their significance for declarative memory consolidation. Sleep 27:1479–1485
45. Clemens Z, Fabo D, Halasz P (2006) Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. Neurosci Lett 403:52–56
46. Bergmann TO, Mölle M, Marshall L, Kaya-Yildiz L, Born J, Roman Siebner H (2008) A local signature of LTP- and LTD-like plasticity in human NREM sleep. Eur J Neurosci 27:2241–2249
47. Steriade M, Nuñez A, Amzica F (1993) A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J Neurosci 13:3252–3265
48. Marshall L, Helgadottir H, Mölle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444:610–613
49. Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP (2007) A deficit in the ability to form new human memories without sleep. Nat Neurosci 10:385–392
50. Van Der Werf YD, Altena E, Schoonheim MM, Sanz-Arigita EJ, Vis JC, De Rijke W, Van Someren EJ (2009) Sleep benefits subsequent hippocampal functioning. Nat Neurosci 12:122–123
51. Axmacher N, Haupt S, Fernandez G, Elger CE, Fell J (2008) The role of sleep in declarative memory consolidation—direct evidence by intracranial EEG. Cereb Cortex 18:500–507
52. Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, McNaughton BL, Fernandez G (2006) Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci USA 103:756–761
53. Nadel L, Moscovitch M (2001) The hippocampal complex and long-term memory revisited. Trends Cogn Sci 5:228–230
54. Speckmann EJ, Elger CE (1999) Introduction to the neurophysiological basis of the EEG and DC potentials. In: Niedermeyer E, Lopes da Silva F (eds) Electroencephalography, 4th edn. Lippincott, Williams and Wilkins, Baltimore, pp 15–27
55. O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34:171–175
56. O'Keefe J (1976) Place units in the hippocampus of the freely moving rat. Exp Neurol 51:78–109
57. O'Keefe J, Recce ML (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3:317–330
58. Skaggs WE, McNaughton BL, Wilson MA, Barnes CA (1996) Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. Hippocampus 6:149–172
59. Harris KD, Henze DA, Hirase H, Leinekugel X, Dragoi G, Czurko A, Buzsaki G (2002) Spike train dynamics predicts

theta-related phase precession in hippocampal pyramidal cells. Nature 417:738–741
60. Huxter J, Burgess N, O'Keefe J (2003) Independent rate and temporal coding in hippocampal pyramidal cells. Nature 425:828–832
61. Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676–679
62. Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K (1992) High-frequency network oscillation in the hippocampus. Science 256:1025–1027
63. Chrobak JJ, Buzsaki G (1996) High-frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat. J Neurosci 16:3056–3066
64. Pavlides C, Winson J (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. J Neurosci 9:2907–2918
65. Kudrimoti HS, Barnes CA, McNaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J Neurosci 19:4090–4101
66. Lee AK, Wilson MA (2002) Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36:1183–1194
67. Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29:145–156
68. Nadasdy Z, Hirase H, Czurko A, Csicsvari J, Buzsaki G (1999) Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci 19:9497–9507
69. Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271:1870–1873
70. Mehta MR, Lee AK, Wilson MA (2002) Role of experience and oscillations in transforming a rate code into a temporal code. Nature 417:741–746
71. Qin YL, McNaughton BL, Skaggs WE, Barnes CA (1997) Memory reprocessing in corticocortical and hippocampocortical neuronal ensembles. Philos Trans R Soc Lond B 352:1525–1533
72. Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10:100–107
73. Euston DR, Tatsuno M, McNaughton BL (2007) Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. Science 318:1147–1150
74. Ribeiro S, Gervasoni D, Soares ES, Zhou Y, Lin S-C, Pantoja J, Lavine M, Nicolelis MAL (2004) Long-lasting novelty-induced neuronal reverberation during slow-wave sleep in multiple forebrain areas. PLoS Biol 2:126–137
75. Tatsuno M, Lipa P, McNaughton BL (2006) Methodological considerations on the use of template matching to study long-lasting memory trace replay. J Neurosci 26:10727–10742
76. O'Neill J, Senior T, Csicsvari J (2006) Place-selective firing of CA1 pyramidal cells during sharp wave/ripple network patterns in exploratory behavior. Neuron 49:143–155
77. Cheng S, Frank LM (2008) New experiences enhance coordinated neural activity in the hippocampus. Neuron 57:303–313
78. Jackson JC, Johnson A, Redish AD (2006) Hippocampal sharp waves and reactivation during awake states depend on repeated sequential experience. J Neurosci 26:12415–12426
79. King C, Henze DA, Leinekugel X, Buzsaki G (1999) Hebbian modification of a hippocampal population pattern in the rat. J Physiol 521:159–167
80. Behrens CJ, van den Boom LP, de Hoz L, Friedman A, Heinemann U (2005) Induction of sharp wave-ripple complexes in vitro and reorganization of hippocampal networks. Nat Neurosci 8:1560–1567
81. Foster DJ, Wilson MA (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature 440:680–683
82. Diba K, Buzsaki G (2007) Forward and reverse hippocampal place-cell sequences during ripples. Nat Neurosci 10:1241–1242
83. Ferbinteanu J, Shapiro ML (2003) Prospective and retrospective memory coding in the hippocampus. Neuron 40:1227–1239
84. Shapiro ML, Ferbinteanu J (2006) Relative spike timing in pairs of hippocampal neurons distinguishes the beginning and end of journeys. Proc Natl Acad Sci USA 103:4287–4292
85. Eschenko O, Ramadan W, Mölle M, Born J, Sara SJ (2008) Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 15:222–228
86. Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I (2005) Invariant visual representation by single neurons in the human brain. Nature 435:1102–1107
87. Redish AD, Battaglia FP, Chawla MK, Ekstrom AD, Gerrard JL, Lipa P, Rosenzweig ES, Worley PF, Guzowski JF, McNaughton BL, Barnes CA (2001) Independence of firing correlates of anatomically proximate hippocampal pyramidal cells. J Neurosci 21:RC134
88. Quiroga RQ, Reddy L, Koch C, Fried I (2007) Decoding visual inputs from multiple neurons in the human temporal lobe. J Neurophysiol 98:1997–2007
89. Axmacher N, Elger CE, Fell J (2008) Memory formation by refinement of neural representations: the inhibition hypothesis. Behav Brain Res 189:1–8
90. Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C, Aerts J, Del Fiore G, Degueldre C, Meulemans T, Luxen A, Franck G, Van Der Linden M, Smith C, Cleeremans A (2000) Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 3:831–836
91. Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Fiore G, Aerts J, Luxen A, Maquet P (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 44:535–545
92. Rasch B, Büchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315:1426–1429
93. Peigneux P, Orban P, Balteau E, Degueldre C, Luxen A, Laureys S, Maquet P (2006) Offline persistence of memory-related cerebral activity during active wakefulness. PLoS Biol 4:e100
94. Gelbard-Sagiv H, Mukamel R, Harel M, Malach R, Fried I (2008) Internally generated reactivation of single neurons in human hippocampus during free recall. Science 322:96–101
95. Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsaki G (1999) High-frequency oscillations in human brain. Hippocampus 9:137–142
96. Bragin A, Engel J Jr, Wilson CL, Fried I, Mathern GW (1999) Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. Epilepsia 40:127–137
97. Staba RJ, Wilson CL, Bragin A, Fried I, Engel J Jr (2002) Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. J Neurophysiol 88:1743–1752
98. Foffani G, Uzcategui YG, Gal B, Menendez de la Prida L (2007) Reduced spike-timing reliability correlates with the emergence of fast ripples in the rat epileptic hippocampus. Neuron 55:930–941
99. Urrestarazu E, Chander R, Dubeau F, Gotman J (2007) Interictal high-frequency oscillations (100–500 Hz) in the intracerebral EEG of epileptic patients. Brain 130:2354–2366
100. Axmacher N, Elger CE, Fell J (2008) Ripples in the medial temporal lobe are relevant for human memory consolidation. Brain 131:1806–1817

101. Clemens Z, Mölle M, Eross L, Barsi P, Halasz P, Born J (2007) Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. Brain 130:2868–2878
102. Staba RJ, Wilson CL, Bragin A, Jhung D, Fried I, Engel J Jr (2004) High-frequency oscillations recorded in human medial temporal lobe during sleep. Ann Neurol 56:108–115
103. Bagshaw AP, Jacobs J, Levan P, Dubeau F and Gotman J (2008) Effect of sleep stage on interictal high-frequency oscillations recorded from depth macroelectrodes in patients with focal epilepsy. Epilepsia (Epub ahead of print)
104. Gais S, Mölle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22:6830–6834
105. Siapas AG, Wilson MA (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21:1123–1128
106. Sirota A, Csicsvari J, Buhl D, Buzsaki G (2003) Communication between neocortex and hippocampus during sleep in rodents. Proc Natl Acad Sci USA 100:2065–2069
107. Mölle M, Yeshenko O, Marshall L, Sara SJ, Born J (2006) Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. J Neurophysiol 96:62–70
108. Battaglia FP, Sutherland GR, McNaughton BL (2004) Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. Learn Mem 11:697–704
109. Isomura Y, Sirota A, Ozen S, Montgomery S, Mizuseki K, Henze DA, Buzsaki G (2006) Integration and segregation of activity in entorhinal-hippocampal subregions by neocortical slow oscillations. Neuron 52:871–882
110. Mölle M, Marshall L, Gais S, Born J (2002) Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. J Neurosci 22:10941–10947
111. Steriade M, Timofeev I (2003) Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 37:563–576
112. Tononi G, Massimini M, Riedner BA (2006) Sleepy dialogues between cortex and hippocampus: who talks to whom? Neuron 52:748–749
113. Siapas AG, Lubenov EV, Wilson MA (2005) Prefrontal phase locking to hippocampal theta oscillations. Neuron 46:141–151
114. Rosenblum MG and Pikovsky AS (2001) Detecting direction of coupling in interacting oscillators. Phys Rev E 64, 045202(R)
115. Sejnowski TJ, Destexhe A (2000) Why do we sleep? Brain Res 886:208–223
116. Colgin LL, Kubota D, Jia Y, Rex CS, Lynch G (2004) Long-term potentiation is impaired in rat hippocampal slices that produce spontaneous sharp waves. J Physiol 558:953–961
117. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 11:200–208
118. Davis CJ, Harding JW, Wright JW (2003) REM sleep deprivation-induced deficits in the latency-to-peak induction and maintenance of long-term potentiation within the CA1 region of the hippocampus. Brain Res 973:293–297
119. McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC (2003) Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 23:9687–9695
120. Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150
121. Borbely AA, Achermann P (2000) Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. Raven Press, New York, pp 377–390
122. Silva AJ (2003) Molecular and cellular cognitive studies of the role of synaptic plasticity in memory. J Neurobiol 54:224–237
123. Trepel C, Racine RJ (1998) Long-term potentiation in the neocortex of the adult, freely moving rat. Cereb Cortex 8:719–729
124. Hebb DO (1949) The organization of behavior. John Wiley, New York
125. Nowak L, Bregestovski P, Ascher P, Herbert A, Prochiantz A (1984) Magnesium gates glutamate-activated channels in mouse central neurones. Nature 307:462–465
126. McBain C, Mayer M (1994) *N*-methyl-D-aspartic acid receptor structure and function. Physiol Rev 74:723–760
127. Tsien JZ, Huerta PT, Tonegawa S (1996) The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 87:1327–1338
128. Silva AJ, Paylor R, Wehner JM, Tonegawa S (1992) Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. Science 257:206–211
129. Morris RGM, Anderson E, Lynch G, Baudry M (1986) Selective impairment of learning and blockade of long-term potentiation by an *N*-methyl-D-aspartate receptor antagonist, AP5. Nature 319:774–776
130. Cirelli C, Pompeiano M, Tononi G (1996) Neuronal gene expression in the waking state: a role for the locus coeruleus. Science 274:1211–1215
131. Cirelli C, Tononi G (2000) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. J Neurosci 20:9187–9194
132. Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430:78–81
133. Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, Tononi G (2006) Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. Nat Neurosci 9:1169–1176
134. Kemp N, Bashir ZI (2001) Long-term depression: a cascade of induction and expression mechanisms. Prog Neurobiol 65:339–365
135. Blitzer RD, Orlando G, Landau EM (1990) Cholinergic stimulation enhances long-term potentiation in the CA1 region of rat hippocampus. Neurosci Lett 119:207–210
136. Huerta PT, Lisman JE (1993) Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 364:723–725
137. Bliss TVP, Goddard GV, Riives M (1983) Reduction of long-term potentiation in the dentate gyrus of the rat following selective depletion of monoamines. J Physiol (Lond) 334:475–491
138. Simon C, Brandenberger G, Saini J, Ehrhart J, Follenius M (1994) Slow oscillations of plasma glucose and insulin secretion rate are amplified during sleep in humans under continuous enteral nutrition. Sleep 17:333–338
139. Cirelli C, Gutierrez CM, Tononi G (2004) Extensive and divergent effects of sleep and wakefulness on brain gene expression. Neuron 41:35–43
140. Frankland PW, Bontempi B, Talton LE, Kaczmarek L, Silva AJ (2004) The involvement of the cortex in remote contextual fear memory. Science 304:881–883
141. Maviel T, Durkin TP, Menzaghi F, Bontempi B (2004) Sites of neocortical reorganization critical for remote spatial memory. Science 305:96–99
142. Frankland PW, O'Brien C, Ohno M, Kirkwood A, Silva AJ (2001) Alpha-CaMKII-dependent plasticity in the cortex is required for permanent memory. Nature 411:309–313
143. Cui Z, Wang H, Tan Y, Zaia KA, Zhang S, Tsien JZ (2004) Inducible and reversible NR1 knockout reveals crucial role of the NMDA receptor in preserving remote memories in the brain. Neuron 41:781–793
144. Kemp A, Manahan-Vaughan D (2004) Hippocampal long-term depression and long-term potentiation encode different aspects of novelty acquisition. Proc Natl Acad Sci USA 101:8192–8197

145. Gruber T, Müller MM (2002) Effects of picture repetition on induced gamma band responses, evoked potentials, and phase synchrony in the human EEG. Brain Res Cogn Brain Res 13:377–392
146. Daoudal G, Debanne D (2003) Long-term plasticity of intrinsic excitability: learning rules and mechanisms. Learn Mem 10:456–465
147. Zhang W, Linden DJ (2003) The other side of the engram: experience-driven changes in neuronal intrinsic excitability. Nat Rev Neurosci 4:885–900
148. Contreras D, Dürmüller N, Steriade M (1997) Plateau potentials in cat neocortical association cells in vivo: synaptic control of dendritic excitability. Eur J Neurosci 9:2588–2595