SLEEP

The memory function of sleep

Susanne Diekelmann and Jan Born

Abstract | Sleep has been identified as a state that optimizes the consolidation of newly acquired information in memory, depending on the specific conditions of learning and the timing of sleep. Consolidation during sleep promotes both quantitative and qualitative changes of memory representations. Through specific patterns of neuromodulatory activity and electric field potential oscillations, slow-wave sleep (SWS) and rapid eye movement (REM) sleep support system consolidation and synaptic consolidation, respectively. During SWS, slow oscillations, spindles and ripples — at minimum cholinergic activity — coordinate the re-activation and redistribution of hippocampus-dependent memories to neocortical sites, whereas during REM sleep, local increases in plasticity-related immediate-early gene activity — at high cholinergic and theta activity — might favour the subsequent synaptic consolidation of memories in the cortex.

Declarative memory
Memories that are accessible to conscious recollection including memories for facts and episodes, for example, learning vocabulary or remembering events. Declarative memories rely on the hippocampus and associated medial temporal lobe structures, together with neocortical regions for long-term storage.

Procedural memory
Memories for skills that result from repeated practice and are not necessarily available for conscious recollection, for example, riding a bike or playing the piano. Procedural memories rely on the striatum and cerebellum, although recent studies indicate that the hippocampus can also be implicated in procedural learning.

University of Lübeck, Department of Neuroendocrinology, Haus 50, 2. OG, Ratzeburger Allee 160, 23538 Lübeck, Germany.
Correspondence to J. B.
e-mail:
born@kfg.uni-luebeck.de
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Although sleep is a systems-level process that affects the whole organism, its most distinctive features are the loss of behavioural control and consciousness. Among the multiple functions of sleep[1], its role in the establishment of memories seems to be particularly important: as it seems to be incompatible with the brain's normal processing of stimuli during waking, it might explain the loss of consciousness in sleep. Sleep promotes primarily the consolidation of memory, whereas memory encoding and retrieval take place most effectively during waking. Consolidation refers to a process that transforms new and initially labile memories encoded in the awake state into more stable representations that become integrated into the network of pre-existing long-term memories. Consolidation involves the active re-processing of 'fresh' memories within the neuronal networks that were used for encoding them. It seems to occur most effectively off-line, i.e. during sleep, so that encoding and consolidation cannot disturb each other and the brain does not 'hallucinate' during consolidation[2].

The hypothesis that sleep favours memory consolidation has been around for a long time[3]. Recent research in this field has provided important insights into the underlying mechanisms through which sleep serves memory consolidation[4–7]. In this Review, we first discuss findings from behavioural studies regarding the specific conditions that determine the access of a freshly encoded memory to sleep-dependent consolidation, and regarding the way in which sleep quantitatively and qualitatively changes new memory representations. We then consider the role of slow-wave sleep (SWS) and rapid eye movement (REM) sleep in memory consolidation (BOX 1). We finish by comparing two hypotheses that might explain sleep-dependent memory consolidation on a mechanistic level, that is, the synaptic homeostasis hypothesis and the active system consolidation hypothesis.

Behavioural studies

Numerous studies have confirmed the beneficial effect of sleep on declarative and procedural memory in various tasks[8–10], with practically no evidence for the opposite effect (sleep promoting forgetting)[11]. Compared with a wake interval of equal length, a period of post-learning sleep enhances retention of declarative information[3,12–16] and improves performance in procedural skills[13,17–24]. Sleep likewise supports the consolidation of emotional information[25–27]. Effects of a 3-hour period of sleep on emotional memory were even detectable 4 years later[28]. However, the consolidating effect of sleep is not revealed under all circumstances and seems to be associated with specific conditions[29] (see below).

Sleep duration and timing. Significant sleep benefits on memory are observed after an 8-hour night of sleep, but also after shorter naps of 1–2 hours[14,19,23,30], and even an ultra-short nap of 6 minutes can improve memory retention[16]. However, longer sleep durations yield greater improvements, particularly for procedural memories[18,21,31]. The optimal amount of sleep needed to benefit memory and how this might generalize across species showing different sleep durations is unclear at present.

Some data suggest that a short delay between learning and sleep optimizes the benefits of sleep on memory consolidation. For example, for declarative

Serial reaction time task
A task in which subjects are required to rapidly respond to different spatial cues by pressing corresponding buttons. This task can be performed implicitly (that is, without knowledge that there is a regularity underlying the sequence of cue positions) or explicitly (by informing the subject about this underlying regularity).

information, sleep occurring 3 hours after learning was more effective than sleep delayed by more than 10 hours[32,33]. However, these studies did not control for the confounding effects of forgetting during the wake interval before the onset of sleep. For optimal benefit on procedural memory consolidation, sleep does not need to occur immediately[18,19] but should happen on the same day as initial training[17,22,24].

Explicit versus implicit encoding. Whether memories gain access to sleep-dependent consolidation depends on the conditions of encoding. Encoding of declarative memories is typically explicit, whereas procedural memory encoding can involve both implicit and explicit processes. Most robust and reliable sleep-dependent gains in speed have been revealed for the finger sequence tapping task, which involves explicit procedural memory[17–19,24]. For the serial reaction time task (SRTT), which can be learnt implicitly or explicitly, the sleep-induced speeding of performance was more robust when people learnt the task explicitly than after implicit learning[34]. These observations suggest that explicit encoding of a memory favours access to sleep-dependent consolidation.

The benefit of sleep is greater for memories formed from explicitly encoded information that was more difficult to encode or that was only weakly encoded[35,36], and it is greater for memories that were behaviourally relevant. Thus, sleep enhances the consolidation of memories for intended future actions and plans (D. S., I. Wilhelm, U. Wagner, J. B., unpublished observations). Notably, this enhancement could be nullified by letting the subject

Box 1 | **Sleep architecture and neurophysiological characteristics of sleep stages**

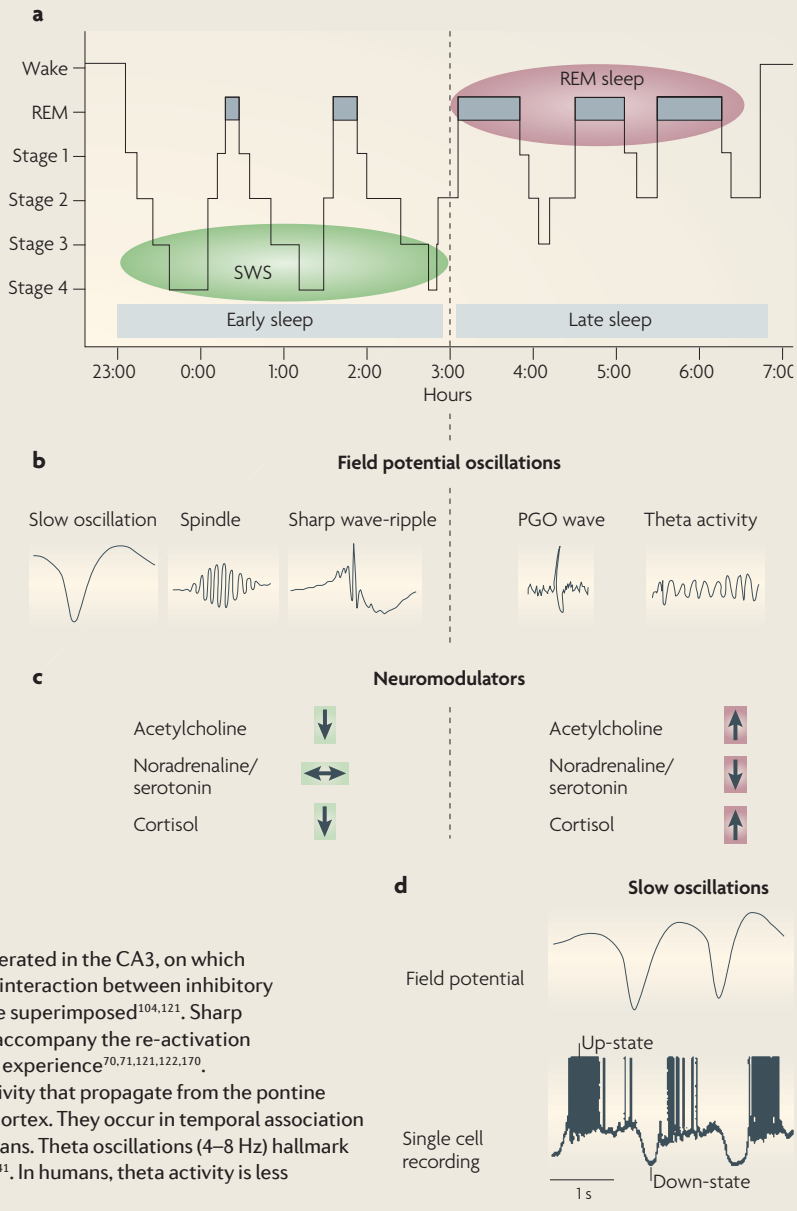
Sleep is characterized by the cyclic occurrence of rapid eye movement (REM) sleep and non-REM sleep, which includes slow wave sleep (SWS, stages 3 and 4) and lighter sleep stages 1 and 2 (see the figure, part **a**). In humans, the first part of the night (early sleep) is characterized by high amounts of SWS, whereas REM sleep prevails during the second half (late sleep). SWS and REM sleep are characterized by specific patterns of electrical field potential oscillations (part **b**) and neuromodulator activity (part **c**, BOX 3).

The most prominent field potential oscillations during SWS are the slow oscillations, spindles and sharp wave-ripples, whereas REM sleep is characterized by ponto-geniculo-occipital (PGO) waves and theta activity. The slow oscillations originate in the neocortex with a peak frequency (in humans) of ~0.8 Hz[130,164]. They synchronize neuronal activity into down-states of widespread hyperpolarization and neuronal silence and subsequent up-states, which are associated with depolarization and strongly increased, wake-like neuronal firing[132,165,166] (part **d**). The hyperpolarization results from activation of a Ca^{2+}-dependent K^+ current and inactivation of a persistent Na^+ current, which dampens excitability[165,167,168]. The depolarizing up-state might be triggered by summation of miniature EPSPs (from residual activity from encoding information) and is formed by activation of T-type Ca^{2+} and persistent Na^+ currents.

Spindle activity refers to regular electroencephalographic oscillations of ~10–15 Hz, which are observed in human sleep stage 2 as discrete waxing and waning spindles, but are present at a similar level during SWS (although here they form less discrete spindles)[169]. Spindles originate in the thalamus from an interaction between GABAergic neurons of the nucleus reticularis, which function as pacemakers, and glutamatergic thalamo-cortical projections that mediate their synchronized and widespread propagation to cortical regions[132,168,169].

Hippocampal sharp waves are fast depolarizing events, generated in the CA3, on which high-frequency oscillations (100–300 Hz) originating from an interaction between inhibitory interneurons and pyramidal cells in CA1 (so-called ripples) are superimposed[104,121]. Sharp wave-ripples occur during SWS and also during waking, and accompany the re-activation of neuron ensembles that are active during a preceding wake experience[70,71,121,122,170].

PGO-waves are driven by intense bursts of synchronized activity that propagate from the pontine brainstem mainly to the lateral geniculate nucleus and visual cortex. They occur in temporal association with REM in rats and cats but are not reliably identified in humans. Theta oscillations (4–8 Hz) hallmark tonic REM sleep in rats and predominate in the hippocampus[141]. In humans, theta activity is less coherent[144,145].



execute the intended behaviour before sleep. Similarly, subjects who had been trained on two different finger-tapping sequences showed greater sleep-dependent gains in performance for the sequence for which they expected to be rewarded for optimal performance at re-testing after sleep[37]. Thus, a motivational tagging of memories, which probably relies on the function of the prefrontal cortex[38], might signal behavioural effort and relevance and mediate the preferential consolidation of these memories.

In summary, a great number of studies indicate that sleep supports the consolidation of memory in all major memory systems, but preferentially those that are explicitly encoded and that have behavioural relevance to the individual. There is growing evidence that explicit encoding, even in procedural tasks, involves a dialogue between the prefrontal cortex and the hippocampus[38–40], which also integrates intentional and motivational aspects of the task. Activity of this circuit may be crucial in making a memory susceptible to sleep-dependent memory consolidation.

Sleep changes memory representations quantitatively and qualitatively. Consolidation of memory during sleep can produce a strengthening of associations as well as qualitative changes in memory representations. Strengthening of a memory behaviourally expresses itself as resistance to interference from another similar task ('stabilization') and as an improvement of performance ('enhancement') that occurs at re-testing, in the absence of additional practice during the retention interval. The stabilizing effects of sleep have been observed in declarative[41] and procedural[19] memory tasks. Similarly, enhancements in performance after sleep have been shown for declarative information[13,14,20] and in procedural tasks[13,17,18,21,22,31]. However, it is still controversial to what extent these improvements reflect actual performance 'gains' induced by sleep, because the measured gains depend on the pre-sleep performance used as a reference, which itself can be subject to rapid changes after training[42,43].

There is a long-standing debate about whether sleep passively protects memories from decay and interference or actively consolidates fresh memory representations[44] (for a review see REF. 45). Importantly, a lack of enhancement of memory performance after sleep does not preclude an active role of sleep in memory consolidation. There is strong evidence for an active consolidating influence of sleep from behavioural studies, which indicate that sleep can lead to qualitative changes in memory[46–48]. For example, in one study, subjects learned single relations between different objects which, unknown to the subject, relied on an embedded hierarchy[47]. When learning was followed by sleep, subjects at a re-test were better at inferring the relationship between the most distant objects, which had not been learned before. Likewise, after sleep subjects more easily solved a logical calculus problem that they were unable to solve before sleep or after corresponding intervals of wakefulness[46]. Of note, sleep facilitated the gain of insight into the problem only if adequate encoding of the task was ensured before sleep.

Interacting or competing memory systems? The behavioural findings described above show that sleep can 're-organize' newly encoded memory representations, enabling the generation of new associations and the extraction of invariant features from complex stimuli, and thereby eventually easing novel inferences and insights. Re-organization of memory representations during sleep also promotes the transformation of implicit into explicit knowledge, as was shown in an SRTT which was implicitly trained but in which explicit knowledge about the underlying sequence was examined during the re-test[48]. Following post-training sleep, subjects were better at explicitly generating the SRTT sequence. Interestingly, subjects who developed explicit sequence knowledge no longer showed the improvement in implicit procedural skill (that is, faster reaction times) that is normally observed after sleep, suggesting that procedural and declarative memory systems interact during sleep-dependent consolidation.

Contrasting with this view of interacting memory systems, it has also been proposed that disengagement of memory systems is an essential characteristic of sleep-dependent consolidation[49]. This idea derives mainly from experiments showing that declarative learning of words immediately after training of a procedural skill can block off-line improvement in that skill if the subject does not sleep between learning and re-testing, but not if the subject sleeps between learning and re-testing[50]. This suggests that memory systems compete and reciprocally interfere during waking, but disengage during sleep, allowing for the independent consolidation of memories in different systems. The two views might be reconciled by assuming a sequential contribution of interaction and disengagement processes to consolidation, which might be associated with different sleep stages (REM sleep and SWS), as discussed below.

Influence of sleep stages on consolidation

Early studies in rats and humans investigating whether different sleep stages have different roles in memory consolidation mainly focused on REM sleep and the consequences of REM sleep deprivation (REMD) by repeatedly waking subjects at the first signs of REM sleep. However, this approach is of limited value for logical reasons and because the repeated awakenings cause stress, which itself influences memory function[51,52]. Overall, these studies have provided mixed results[52–55]. Of note is a recent study showing that pharmacological suppression of REM sleep by administration of antidepressant drugs (selective noradrenaline or serotonin re-uptake inhibitors) did not impair consolidation of procedural memory[56], which is in agreement with clinical observations that antidepressant treatment does not affect memory function[57]. However, such substances also exert direct effects on synaptic plasticity and synaptic forms of consolidation that could compensate for a loss of REM sleep[58].

Some studies performed in rats showed that REMD is only effective during specific periods after learning — the so-called 'REM sleep windows'[54]. During post-learning sleep, increases in the amount and intensity

Implicit learning
Learning without being aware that something is being learned.

Explicit learning
Learning while being aware that something is being learned.

Memory systems
Different types of memory, such as declarative and non-declarative memory, are thought to be mediated by distinct neural systems, the organization of which is still a topic of debate.

of REM sleep occur several hours or even days after learning, depending on the kind of task and amount of initial training[54], and memory is particularly impaired if REMD coincides with these periods. Of note, the memory tasks used in rats are typically emotionally loaded. As there is evidence that REM sleep preferentially benefits the consolidation of emotional aspects of a memory[25,27], this could partly account for the strong REMD effect observed in many animal studies[53,55].

Studies in humans have compared the effects on consolidation between sleep periods with different proportions of SWS and REM sleep. In humans, SWS and REM sleep dominate the early and late part of nocturnal sleep, respectively (BOX 1). SWS-rich, early sleep consistently benefits the consolidation of declarative memories[12,13,59], whereas REM-rich sleep benefits non-declarative types of memory (that is, procedural and emotional aspects of memory)[13,25,59]. These results are consistent with the 'dual-process hypothesis', which assumes that SWS facilitates declarative, hippocampus-dependent memory and REM sleep supports non-declarative, hippocampus-independent memory[6].

Other studies have shown that SWS can also improve procedural skill (that is, non-declarative) memories[31,60,61] and that REM sleep can also improve declarative memory[62,63]. Although these divergent findings could reflect that stimuli used in memory tasks are often not of one type of memory system, they agree with the 'sequential hypothesis', which argues that the optimum benefits of sleep on the consolidation of both declarative and non-declarative memory occur when SWS and REM sleep take place in succession[31,64]. Thus, overnight improvements in visual texture discrimination correlated with both the amount of SWS in the first quarter of sleep and the amount of REM sleep in the last quarter[21]. Texture discrimination also improved following a short midday nap of 60–90 minutes containing solely SWS, but more so if the nap included both SWS and REM sleep[23]. Also, memory consolidation seems to be impaired by disruptions of the natural SWS–REM sleep cycle that left the time spent in these sleep stages unchanged[65].

Intermediate sleep stages (non-REM sleep stage 2 in humans, transitory sleep in rats) can also contribute to memory consolidation[66,67]. For example, pharmacological suppression of REM sleep in humans produced an unexpected overnight improvement in procedural skill that was correlated with increased non-REM sleep stage 2 spindle activity (see below)[56]. Such findings highlight the fact that it is not a particular sleep stage *per se* that mediates memory consolidation, but rather the neurophysiological mechanisms associated with those sleep stages, and that some of these mechanisms are shared by different sleep stages.

Transitory sleep
Short transitory periods of sleep in rats that, based on EEG criteria, can neither be classified as REM sleep or SWS.

Core features of off-line consolidation

Since the publication of Hebb's seminal book[68], memory formation has been conceptualized as a process in which neuronal activity reverberating in specific circuits promotes enduring synaptic changes. Building on this, it is widely accepted that the consolidation process that takes place off-line after encoding relies on the re-activation of neuronal circuits that were implicated in the encoding of the information. This would promote both the gradual redistribution and re-organization of memory representations to sites for long-term storage (that is, system consolidation; BOX 2) and the enduring synaptic changes that are necessary to stabilize memories (synaptic consolidation). The conditions that enable these two processes during sleep differ strongly between SWS and REM sleep.

Re-activation of memory traces during sleep. The finding that in rats the spatio-temporal patterns of neuronal firing that occur in the hippocampus during exploration of a novel environment or simple spatial tasks are re-activated in the same order during subsequent sleep was an important breakthrough in memory research[69–74] (FIG. 1a, see REF. 75 for methodological considerations on the identification of neuronal re-activations). Such neuronal re-activation of ensemble activity mostly occurs during SWS (it is rarely observed during REM sleep[76,77]) and during the first hours after learning (but see REF. 78), and typically only in a minority of recorded neurons[69–74]. Moreover, unlike re-activations that occur during wakefulness, re-activations during SWS almost always occur in the order in which they were experienced[79]. Compared with activity during encoding phases, re-activations during SWS seem to be noisier, less accurate and often happen at a faster firing rate[71]. They are also observed in the thalamus, the striatum and the neocortex[72–74,78]. Sleep-dependent signs of re-activation in brain regions implicated in prior learning were also shown in human neuroimaging studies[80,81].

The first evidence for a causal role of re-activation during SWS in memory consolidation came from a study in humans learning spatial locations in the presence of an odour[15]. Re-exposure to the odour during SWS, but not REM sleep, enhanced the spatial memories (FIG. 1b) and induced stronger hippocampal activation than during wakefulness, indicating that during SWS hippocampal networks are particularly sensitive to inputs that can re-activate memories (FIG. 1c). It is assumed that the re-activations during system consolidation stimulate the redistribution of hippocampal memories to neocortical storage sites, although this has not been directly demonstrated yet[82,83].

Synaptic consolidation. In addition to system consolidation (BOX 2), consolidation involves the strengthening of memory representations at the synaptic level (synaptic consolidation)[84,85]. Long-term potentiation (LTP) is considered a key mechanism of synaptic consolidation, but it is unclear whether memory re-activation during sleep promotes the redistribution of memories by inducing new LTP (at long-term storage sites not involved at encoding) or whether re-activation merely enhances the maintenance of LTP that was induced during encoding.

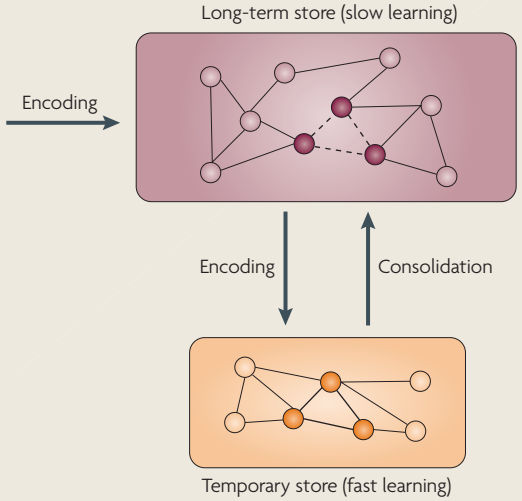
LTP can be induced in the hippocampus during REM sleep but less reliably so during SWS[86]. LTP induction in the hippocampus or neocortex during SWS is

Immediate early genes
Genes that encode transcription factors that are induced within minutes of raised neuronal activity without requiring a protein signal. Immediate-early gene activation is, therefore, used as an indirect marker of neuronal activation. The immediate early genes *Arc* and *Egr1* (*zif268*) are associated with synaptic plasticity.

Hebbian plasticity
Refers to the functional changes at synapses that increase the efficacy of synaptic transmission and occurs when the presynaptic neuron repeatedly and persistently stimulates the postsynaptic neuron.

Spike-time dependent plasticity
Refers to the functional changes at synapses that alter the efficacy of synaptic transmission depending on the relative timing of pre- and postsynaptic firing ('spiking'). The synaptic connection is strengthened if the presynaptic neuron fires shortly before the postsynaptic neuron, but is weakened if the sequence of firing is reversed.

Box 2 | **The two-stage model of memory consolidation**



A key issue of long-term memory formation, the so-called stability–plasticity dilemma, is the problem of how the brain's neuronal networks can acquire new information (plasticity) without overriding older knowledge (stability). Many aspects of events experienced during waking represent unique and irrelevant information that does not need to be stored long term. The two-stage model of memory offers a widely accepted solution to this dilemma[2,7,85,152] (see the figure). The model assumes two separate memory stores: one store allows learning at a fast rate and serves as an intermediate buffer that holds the information only temporarily; the other store learns at a slower rate and serves as the long-term store. Initially, new events are encoded in parallel in both stores. In subsequent periods of consolidation, the newly encoded memory traces are repeatedly re-activated in the fast-learning store, which drives concurrent re-activation in the slow-learning store, and thereby new memories become gradually redistributed such that representations in the slow-learning, long-term store are strengthened. Through the repeated re-activation of new memories, in conjunction with related and similar older memories, the fast-learning store acts like an internal 'trainer' of the slow-learning store to gradually adapt the new memories to the pre-existing network of long-term memories. This process also promotes the extraction of invariant repeating features from the new memories. As both stores are used for encoding information, in order to prevent interference, the re-activation and redistribution of memories take place off-line (during sleep) when no encoding occurs. Because in this model consolidation involves the redistribution of representations between different neuronal systems that is, the fast- and slow-learning stores, it has been termed 'system consolidation'. For declarative memories, the fast- and slow-learning stores are represented by the hippocampus and neocortex, respectively.

probably temporally restricted to the up-states of the slow oscillation and its concurrent phenomena of ripples and spindles[87,88] (see BOX 1 and below). Indeed, in neocortical slices, stimulation that mimicked neuronal activity during SWS could induce long-term depression (LTD)[89] or LTP[87] depending on the pattern of stimulation (rhythmic bursts or spindle-like trains, respectively). LTP maintenance in the rat hippocampus, but not in the medial prefrontal cortex, was impaired if induction was followed by REMD[90]. In humans, sleep strengthened LTP-like plasticity that had been induced in the neocortex by transcranial magnetic stimulation (TMS) prior to sleeping[91].

Globally (meaning measured in whole-brain or large cortical samples) sleep suppresses the molecular signals that mediate LTP-related synaptic remodelling but enhances LTD-related signalling, and this effect seems to be mediated by SWS[92–95]. This observation, however, does not preclude that LTP occurs during sleep (during SWS or REM sleep) in specific regions, for example in those that were engaged in memory encoding prior to sleeping. In rats, both induction of hippocampal LTP and exposure to a novel tactile experience during waking increased the expression of the plasticity-related immediate early genes (IEGs) *Arc* and *Egr1* (which are implicated in LTP) during subsequent sleep, mainly in cortical areas that were the most activated by the novel experience, and this effect seemed to be mediated by REM sleep[96–98]. Investigations in visual cortex in cats and humans have demonstrated that sleep-dependent plasticity depends on the activation of glutamatergic NMDA (*N*-methyl-D-aspartate) receptors and associated cAMP-dependent protein kinase A (PKA), and on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor activation, that is, the postsynaptic machinery that is crucial for the induction and maintenance of LTP[99–102]. These findings indicate that local, off-line re-activation of specific glutamatergic circuits supports both LTP induction and maintenance, and the molecular processes underlying synaptic consolidation. Moreover, these processes probably occur preferentially during REM sleep, although they are likely to be triggered by the re-activations that occur during prior SWS (see below). Evidence about how LTP induction and maintenance is linked to specific sleep stages is presently scarce, but based on the available data it is tempting to speculate that SWS supports the re-activation of new memories (system consolidation) and thus, could initialize LTP and prime the relevant networks for synaptic consolidation during subsequent REM sleep. This idea seems to be supported by electroencephalographic (EEG) rhythms that characterize these sleep stages.

Sleep-specific field potential oscillations

Sleep stages are characterized by specific electrical field potential rhythms that temporally coordinate information transfer between brain regions and might support Hebbian and spike-time-dependent plasticity[103,104].

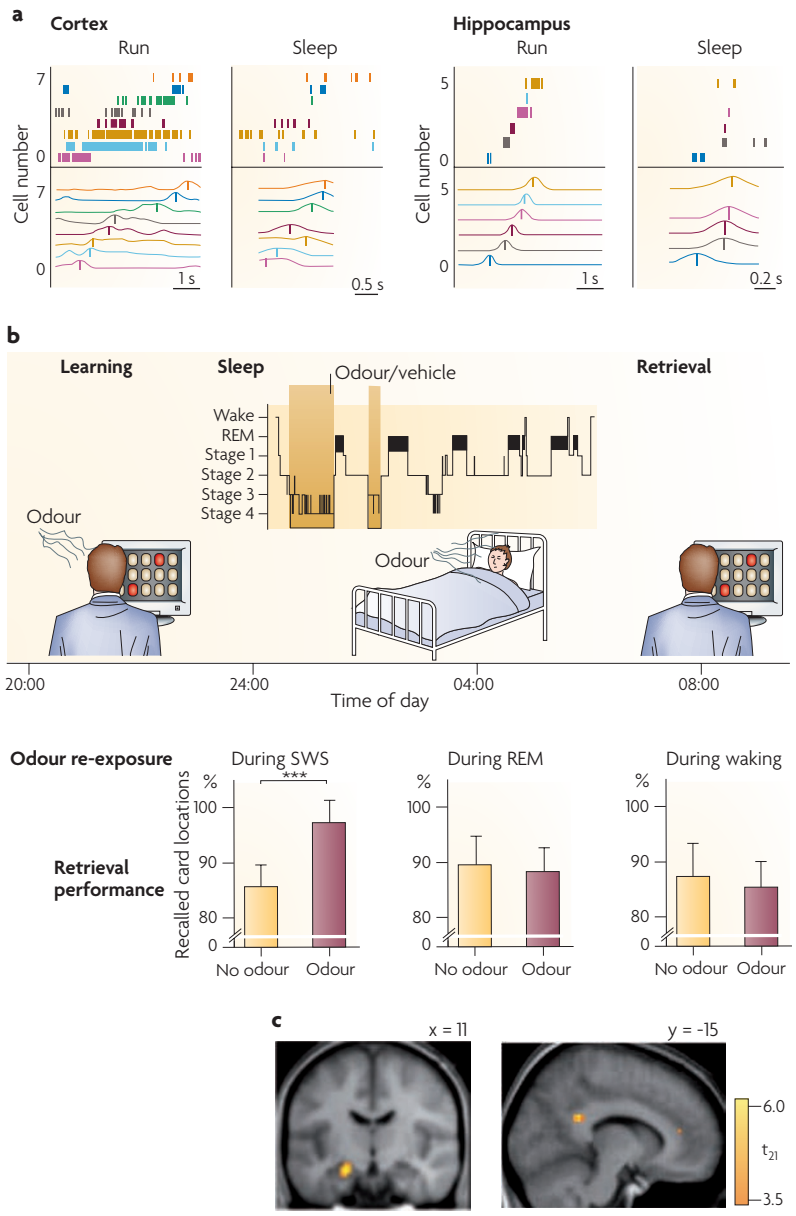


Figure 1 | **Memory re-activation during slow wave sleep (SWS). a** | In awake rats running on a circular track (Run), neurons in the sensory cortex and hippocampus fire in a characteristic sequential pattern. Each row represents an individual cell and each mark in the upper parts of the diagrams indicates a spike; the curves in the lower parts indicate the respective average firing patterns of the cells. During subsequent slow wave sleep (SWS) (Sleep), temporal firing sequences observed in the cell assemblies during running re-appear both in the cortex and in the hippocampus[72]. **b** | Human subjects learned a two-dimensional object location task on a computer while an odour was presented as a context stimulus. Re-exposure to the odour specifically during subsequent SWS enhanced retention performance (recalled card locations) when tested the next day. There was no enhancement in retention when no association was formed between object locations and odour (that is, odour presentation during SWS but not during learning) or when odour re-exposure occurred during rapid eye movement (REM) sleep or waking[15]. **c** | When participants slept in an fMRI scanner after learning in the presence of odour, re-exposure to the odour during SWS activated the left anterior hippocampus (left) and neocortical regions like the retrosplenial cortex (right), which was not observed without odour presentation during prior learning[7]. Part **a** is modified, with permission, from REF. 72 © 2007 Macmillan Publishers Ltd. All rights reserved; part **b** is modified, with permission, from REF. 15 © 2007 American Association for the Advancement of Science; part **c** modified, with permission, from REF. 7 © 2007 Elsevier.

Field potentials associated with SWS. Neocortical slow oscillations, thalamo-cortical spindles and hippocampal ripples have been associated with memory consolidation during SWS (BOX 1). The neocortical slow oscillations (of <1 Hz), by globally inducing up- and down-states of neuronal activity, are thought to provide a supra-ordinate temporal frame for the dialogue between the neocortex and subcortical structures that is necessary for redistributing memories for long-term storage[8,105,106]. The amplitude and slope of the slow oscillations are increased when SWS is preceded by specific learning experiences[60,107,108] and decreased when the encoding of information was prevented[109]. These changes occur locally, in the cortical regions that were involved in encoding, and can also be induced in humans by potentiating synaptic circuits through TMS[91,110,111]. Inducing slow oscillations during non-REM sleep by transcranial electrical stimulation using slow (0.75 Hz) but not fast (5 Hz) oscillating potential fields improved the consolidation of hippocampus-dependent but not hippocampus-independent (procedural) memories[112], indicating that slow oscillations have a causal role in the consolidation of hippocampus-dependent memories.

Thalamo-cortical spindles seem to prime cortical networks for the long-term storage of memory representations. Repeated spindle-associated spike discharges can trigger LTP[87] and synchronous spindle activity occurs preferentially at synapses that were potentiated during encoding[113]. Studies in rats and humans showed increases in spindle density and activity during non-REM sleep and SWS after learning of both declarative tasks and procedural motor skills[20,108,114–118]. In some studies these increases correlated with the post-sleep memory improvement[30,119,120] and were localized to the cortical areas that were activated during encoding, for example, in the prefrontal cortex after encoding of difficult word pairs[117,119], the parietal cortex after a visuo-spatial task[120] and the contralateral motor cortex after finger motor-skill learning[30].

Hippocampal sharp wave-ripples accompany the sleep-associated re-activation of hippocampal neuron ensembles that were active during the preceding awake experience[70,71,121,122]. The occurrence of sharp wave-ripples is facilitated in previously potentiated synaptic circuits[123] and sharp wave-ripples might promote synaptic potentiation[88,124]. During an individual ripple event only a small subpopulation of pyramidal cells fire — the subpopulation varies between successive ripples, indicating modulation of select neuronal circuits[121,125]. In rats, learning of odour–reward associations produced a robust increase in the number and size of ripple events for up to two hours during subsequent SWS[126]. In humans (epileptic patients) the consolidation of picture memories that were acquired before a nap correlated with the number of ripples recorded from the peri- and entorhinal cortex, which are important output regions of the hippocampus[127]. Selective disruption of ripples by electrical stimulation during the post-learning rest periods in rats impaired formation of long-lasting spatial memories[128], suggesting that ripples have a causal role in sleep-associated memory consolidation.

Interestingly, there is a fine-tuned temporal relationship between the occurrence of slow oscillations, spindles and sharp wave-ripples during SWS that coordinates the bidirectional information flow between the neocortex and the hippocampus. With some exceptions (which are probably due to methodological differences[129]) a consistent finding in humans, cats, rats and mice is that spindle activity and ripples increase during the up-state and become suppressed during the down-state of a slow oscillation[105,129–132]. The top–down control of neuronal activity by neocortical slow oscillations probably extends to activity in other brain regions that are also relevant to memory consolidation, such as the noradrenergic burst activity of the locus coeruleus[133,134]. Sharp wave-ripple complexes are also temporally coupled to sleep spindles[105,135,136], with individual ripple events becoming nested in individual spindle troughs[135]. It has been suggested that such ripple-spindle events provide a mechanism for a fined-tuned hippocampal-neocortical information transfer, whereby ripples and associated hippocampal memory re-activations feed exactly into the excitatory phases of the spindle cycle[8,105,137,138]. In this scenario, the feed-forward control of slow oscillations over ripples and spindles enables transferred information to reach the neocortex during widespread depolarization (during the up-state), that is, a state that favours the induction of persistent synaptic changes, eventually resulting in the storage of the information in the cortex. The extent to which the grouping effect of the slow oscillation on hippocampal activity is associated with transfer of memory-specific information in the opposite direction (from cortex to hippocampus), is currently unclear.

Field potentials associated with REM sleep. Ponto-geniculo-occipital (PGO) waves and the EEG theta rhythm seem to support REM sleep-dependent consolidation processes (BOX 1). The significance of PGO-waves for memory consolidation is indicated by findings in rats of a robust increase in REM sleep PGO-wave density for 3–4 hours following training on an active avoidance task[67,139,140]. The increase was proportional to the improvement in post-sleep task performance, and was associated with increased activity of plasticity-related IEGs and brain-derived neurotrophic factor (Bdnf) in the dorsal hippocampus within 3 hours following training[140].

The theta (4–8 Hz) oscillations that characterize REM sleep in rats are also thought to contribute to consolidation, based mainly on the finding that theta activity during waking occurs during the encoding of hippocampus-dependent memories[141]. However, evidence for this assumption is scarce. There is evidence of neuronal re-play of memories in the hippocampus during REM sleep-associated theta activity[76,77]. Place cells encoding a familiar route were re-activated preferentially during the troughs of theta oscillations during post-training REM sleep, whereas cells encoding novel sites fired during the peaks[77]. As LTP induction in hippocampal CA1 cells during theta activity depends on the phase of burst activity[142], this finding is consistent with the idea that REM sleep de-potentiates synaptic circuits that encode familiar events but potentiates synaptic circuits that encode novel episodes[77]. In humans, neocortical theta activity was enhanced during REM sleep following learning of word pairs[62]. Theta activity specifically over the right prefrontal cortex was correlated with the consolidation of emotional memories[27]. By contrast, mice exhibited reduced REM sleep theta activity after fear conditioning[143]. Thus, although overall there is some evidence for an involvement of theta activity in memory processing during sleep, its specific contribution to consolidation is obscure at present.

Theta activity occurring in conjunction with activity in other EEG frequencies points to another important feature that is relevant to memory processing: during REM sleep, EEG activity in a wide range of frequencies, including theta, shows reduced coherence between limbic-hippocampal and thalamo-cortical circuits than during SWS or waking[144,145]. Likewise, >40 Hz gamma band activity shows reduced coherence between CA3 and CA1 during tonic REM sleep[146]. These findings suggest that memory systems become disengaged during REM sleep[49], possibly as a pre-requisite for establishing effective local processes of synaptic consolidation in these systems (see below).

Synaptic homeostasis versus system consolidation

There are currently two hypotheses for the mechanisms underlying the consolidation of memory during sleep (FIG. 2). The synaptic homeostasis hypothesis[11,147] assumes that consolidation is a by-product of the global synaptic downscaling that occurs during sleep. The active system consolidation hypothesis proposes that an active consolidation process results from selective re-activation of memories during sleep[2,8]. The two models are not mutually exclusive; indeed, the hypothesized processes probably act in concert to optimize the memory function of sleep.

Synaptic homeostasis. According to the synaptic homeostasis hypothesis, information encoding during wakefulness leads to a net increase in synaptic strength in the brain. Sleep would serve to globally downscale synaptic strength to a level that is sustainable in terms of energy and tissue volume demands and that allows for the re-use of synapses for future encoding[92,94]. Slow oscillations are associated with downscaling: they show maximum amplitudes at the beginning of sleep when overall synaptic strength is high, due to information uptake during encoding prior to sleep, and decrease in amplitude across SWS cycles as a result of the gradual synaptic depotentiation. Memories become relatively enhanced as downscaling is assumed to be proportional in all synapses, nullifying weak potentiation and thus improving the signal-to-noise ratio for the synapses that were strongly potentiated during prior waking[147] (FIG. 2a).

However, there is no clear evidence on how slow oscillations might induce synaptic downscaling. The low levels of excitatory neurotransmitters during SWS (BOX 3) and the sequence of depolarization (up-states) and hyperpolarization (down-states) of slow oscillations

Up- and down-states
The slow oscillations that predominate EEG activity during SWS are characterized by alternating states of neuronal silence with an absence of spiking activity and membrane hyperpolarization in all cortical neurons ('down-state') and strongly increased wake-like firing of large neuronal populations and membrane depolarization ('up-state').

at a frequency of <1 Hz might specifically promote the de-potentiation of synapses[148]. Indeed, slow oscillations and the associated activation of T-type Ca^{2+} channels seem to favour LTD over LTP[89]; however, thalamo-cortical spindles and hippocampal ripples nesting in depolarizing up-states of slow oscillations support LTP[87,88,124].

In addition, although the expression of markers of synaptic potentiation (such as plasticity-related IEGs) is globally reduced after a period of sleep, it is increased in specific regions, particularly if sleep was preceded by a learning experience[78,96,98], indicating that synaptic potentiation might still take place during sleep. Consistent with downscaling, some neuroimaging studies (which measure relative changes in brain activation) have shown reduced task-related activity in cortical regions after sleep (e.g. REF. 149), but these reductions were accompanied by increases in activity in other regions[82,83,149,150]. Also, global synaptic downscaling implicates that weakly encoded memories are forgotten, which contrasts with behavioural evidence indicating either no or, under certain conditions, a greater benefit from sleep for weakly than strongly encoded memories[35,36]. Therefore, downscaling *per se* does not explain key features of sleep-dependent consolidation. However, the synaptic downscaling model explains a second memory-related function of sleep, namely that sleep pro-actively facilitates the encoding of new information during subsequent wakefulness through the de-potentiation of synapses that had become saturated during preceding wakefulness (this topic is beyond the scope of this Review)[151].

Active system consolidation. This concept originated from the standard two-stage model of consolidation proposed for declarative memory[2,7,85,121,152] (BOX 2; FIG. 2b), but might also account for consolidation in other memory systems[8]. It is assumed that in the waking brain events are initially encoded in parallel in neocortical networks and in the hippocampus. During subsequent periods of SWS the newly acquired memory traces are repeatedly re-activated and thereby become gradually redistributed such that connections within the neocortex are strengthened, forming more persistent memory representations. Re-activation of the new representations gradually adapt them to pre-existing neocortical 'knowledge networks',

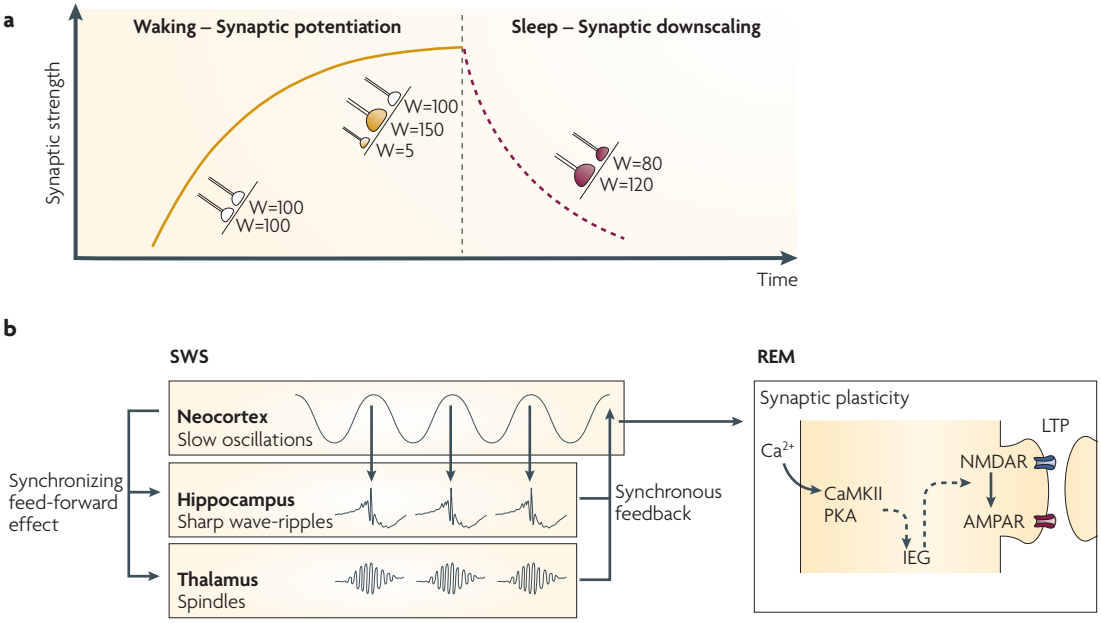


Figure 2 | **Synaptic homeostasis versus active system consolidation.** The synaptic homeostasis hypothesis (**a**) proposes that due to encoding of information during waking, synapses become widely potentiated (large yellow nerve ending), resulting in a net increase in synaptic strength (W = synaptic weight). The small nerve ending represents a new synapse and the unfilled nerve ending is not activated and therefore does not increase in weight. The slow oscillations during subsequent SWS serve to globally downscale synaptic strength (burgundy nerve endings). Thereby, weak connections are eliminated, whereas the relative strength of the remaining connections is preserved. Thus, a memory is enhanced as a consequence of an improved signal-to-noise ratio after downscaling. The active system consolidation model (**b**) assumes that events during waking are encoded in both neocortical and hippocampal networks. During subsequent slow wave sleep (SWS), slow oscillations drive the repeated re-activation of these representations in the hippocampus, in synchrony with sharp wave-ripples and thalamo-cortical spindles (synchronizing feed-forward effect of the slow oscillation up-state). By synchronizing these events the slow oscillations support the formation of ripple-spindle events, which enable an effective hippocampus-to-neocortex transfer of the re-activated information. Arrival of the hippocampal memory output at cortical networks, coinciding with spindle activity during the depolarizing slow oscillation up-state predisposes these networks to persisting synaptic plastic changes (for example, expression of immediate early genes (IEG) through Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase A (PKA) activation) that are supported primarily by subsequent rapid eye movement (REM) sleep. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; LTP, long-term potentiation; NMDAR, *N*-methyl-D-aspartate receptor. Part **a** is modified, with permission, from REF. 147 © 2006 Elsevier; part **b** is modified, with permission, from REF. 5 © 2006 Sage publications.

thereby promoting the extraction of invariant repeating features and qualitative changes in the memory representations[2,7].

Corroborating this concept, studies showed that memory re-activation during post-learning SWS and hippocampal ripples accompanying this re-activation have a causal role in consolidation[15,128]. Re-activation in hippocampal networks seems to be enabled by the low cholinergic tone that characterizes SWS[153–155] (BOX 3). Moreover, there is evidence that the re-activation and redistribution of memories during SWS is regulated by a dialogue between the neocortex and the hippocampus that is essentially under feed-forward control of the slow oscillations, which provide a temporal frame. The depolarizing cortical up-states repetitively drive the re-activation of memory traces in hippocampal circuits in parallel with thalamo-cortical spindles and activity from other regions (for example, noradrenergic locus coeruleus bursts, see BOX 3). This enables synchronous feedback from these structures to the neocortex during the slow oscillation up-state, which is probably a prerequisite for the formation of more persistent traces in neocortical networks[8,106]. Consistent with this concept, neuronal re-activations in the timeframe of cortical slow oscillations have been demonstrated, in which hippocampal re-play leads re-activation in the neocortex[72,122] (and also in other structures like the striatum[156]). Moreover, slow oscillations drive the ripples that accompany hippocampal re-activation, thus allowing for the formation of spindle-ripple events as a mechanism for effective hippocampus-to-neocortex information transfer[105,137,138] (FIG. 2b). Spindles reaching the neocortex during slow oscillation up-states probably act to prime specific neuronal networks, for example, by stimulating Ca^{2+} influx, for subsequent synaptic plastic processes[87,157].

The concept of active system consolidation during SWS integrates a central finding from behavioural studies, namely that post-learning sleep not only strengthens memories but also induces qualitative changes in their representations and so enables the extraction of invariant features from complex stimulus materials, the forming of new associations and, eventually, insights into hidden rules[46–48]. The concept of a redistribution of memories during sleep has been corroborated by human brain imaging studies[82,83,149,150,158]. Interestingly, in these studies, hippocampus-dependent memories were particularly redistributed to medial prefrontal cortex regions[82,83,122] that also contribute to the generation of slow oscillations[159,160]. These regions not only have a key role in the recall and binding of these memories once they are stored for the long term[85], but also, together with the hippocampus, form a loop that supports the explicit encoding of information. As mentioned above, behavioural data indicate that sleep does not benefit all memories equally, but seems to preferentially consolidate explicitly encoded information[34]. In this context, the prefrontal–hippocampal system might provide a selection mechanism that determines which memory enters sleep-dependent consolidation.

A role for REM sleep in synaptic consolidation

The active system consolidation hypothesis leaves open one challenging issue: although it explains a re-activation-dependent temporary enhancement and integration of newly encoded memories into the network of pre-existing long-term memories, active system consolidation alone does not explain how post-learning sleep strengthens memory traces and stabilizes underlying synaptic connections in the long term. Hence, sleep presumably also supports a synaptic form of consolidation for stabilizing memories and this could be the function of REM sleep.

The view that synaptic consolidation is promoted by REM sleep is supported by the molecular and electrophysiological events that characterize this stage.

Box 3 | **Neuromodulators**

The specific neurochemical milieu of neurotransmitters and hormones differs strongly between slow wave sleep (SWS) and rapid eye movement (REM) sleep. Some of these neuromodulators contribute to memory consolidation. Interestingly, the most prominent contributions to memory processing seem to originate from the cholinergic and monoaminergic brainstem systems that are also involved in the basic regulation of sleep[171].

SWS

Cholinergic activity is at a minimum during SWS; this is thought to enable the spontaneous re-activation of hippocampal memory traces and information transfer to the neocortex by reducing the tonic inhibition of hippocampal CA3 and CA1 feedback neurons[8,154,155]. Accordingly, increasing cholinergic tone during SWS-rich sleep (using physostigmine) blocked the sleep-dependent consolidation of hippocampus-dependent word-pair memories[153]. Conversely, blocking the high cholinergic tone in awake subjects improved consolidation but impaired the encoding of new information[172], suggesting that acetylcholine serves as a switch between modes of brain activity, from encoding during wakefulness to consolidation during SWS[154,155]. This dual function of acetylcholine seems to be complemented by glucocorticoids (cortisol in humans), the release of which is also at a minimum during SWS. Glucocorticoids block the hippocampal information flow to the neocortex, and if the level of glucocorticoids is artificially increased during SWS, the consolidation of declarative memories is blocked[173,174].

Noradrenergic activity is at an intermediate level during SWS, and seems to be related to slow oscillations. In rats, phasic burst firing in the locus coeruleus (the brain's main source of noradrenaline) can be entrained by slow oscillations in the frontal cortex, with a phase-delay of ~300 ms[133]. It is possible that such bursts enforce plasticity-related immediate early gene (IEG) activity in the neocortex[93,95], and thereby support at the synaptic level the stabilization of newly formed memory representations. In humans, the consolidation of odour memories was impaired after pharmacological suppression of noradrenergic activity during SWS-rich sleep and improved after increasing noradrenaline availability (S. Gais, B. Rasch, J.C. Dahmen, S.J. Sara and J. B., unpublished observations).

REM sleep

Cholinergic activity during REM sleep is similar or higher than during waking. This high cholinergic activity might promote synaptic consolidation by supporting plasticity-related IEG activity[162] and the maintenance of long-term potentiation[163]. Accordingly, blocking muscarinic receptors in rats by scopolamine during REM sleep impaired memory in a radial arm maze task[175]. In humans, blocking cholinergic transmission during REM-rich sleep prevented gains in finger motor skill[176]. Conversely, enhancing cholinergic tone during post-training REM-rich sleep improved consolidation of a visuo-motor skill[177].

Noradrenergic and serotonergic activity reaches a minimum during REM sleep, but it is unclear whether this contributes to consolidation. It has been proposed that the release from inhibitory noradrenergic activity during REM sleep enables the re-activation of procedural and emotional aspects of memory (in cortico-striatal and amygdalar networks, respectively), thus supporting memory consolidation[154,178]. However, enhancing noradrenergic activity during post-learning REM sleep in humans failed to impair procedural memory consolidation[56].

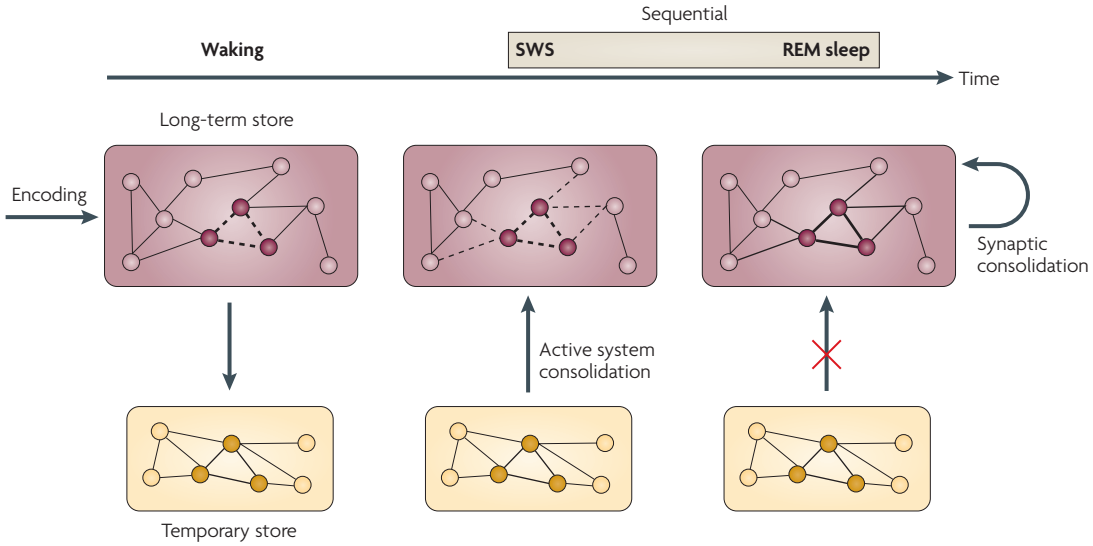


Figure 3 | **Sequential contributions of SWS and REM sleep to memory consolidation in a two-stage memory system.** During waking, memory traces are encoded in both the fast-learning, temporary store and the slow-learning, long-term store (in the case of declarative memory these are represented by the hippocampus and neocortex, respectively). During subsequent slow wave sleep (SWS), active system consolidation involves the repeated re-activation of the memories newly encoded in the temporary store, which drives concurrent re-activation of respective representations in the long-term store together with similar associated representations (dotted lines). This process promotes the re-organization and integration of the new memories in the network of pre-existing long-term memories. System consolidation during SWS acts on the background of a global synaptic downscaling process (not illustrated) that prevents saturation of synapses during re-activation (or during encoding in the subsequent wake-phase). During ensuing rapid eye movement (REM) sleep, brain systems act in a 'disentangled' mode that is also associated with a disconnection between long-term and temporary stores. This allows for locally encapsulated processes of synaptic consolidation, which strengthen the memory representations that underwent system consolidation (that is, re-organization) during prior SWS (thicker lines). In general, memory benefits optimally from the sequence of SWS and REM sleep. However, declarative memory, because of its integrative nature (it binds features from different memories in different memory systems), benefits more from SWS-associated system consolidation, whereas procedural memories, because of their specificity and discrete nature, might benefit more from REM sleep-associated synaptic consolidation in localized brain circuits. Figure modified, with permission, from REF. 85

Although any links between sleep phases of short duration and gene expression are difficult to demonstrate for methodological reasons, several studies suggest that REM sleep, unlike SWS, is associated with an upregulation of plasticity-related IEG activity (REFS 97,98,139). The upregulation depends on learning experience during prior wakefulness and is localized to brain regions involved in prior learning[97,98,139]. Interestingly, this IEG activity is correlated with EEG spindle activity during preceding SWS[98]. Spindles (which, as discussed above, represent a candidate mechanism that tags networks for the neocortical storage of memories during system consolidation) *per se* do not induce IEG activity, but might prime particular brain areas for it, possibly by enhancing Ca^{2+} concentrations in select subgroups of cortical neurons[87,157]. The activity of plasticity-related early genes depends on cholinergic tone[161,162], which is enhanced to wake-like levels during REM sleep (BOX 3). Cholinergic activation strengthens the maintenance of LTP in the hippocampus-medial prefrontal cortex pathway[163], a main route for transferring memories during SWS-dependent system consolidation[82,83,122,136]. Electrophysiological signatures of REM sleep, such as PGO waves, are increased during post-learning sleep and might promote IEG activity and memory consolidation[140]. EEG recordings indicate that during REM sleep brain activation is as high as during waking, but less coherent between different regions and noisier[144–146]. This high level of activation could act non-specifically to amplify local synaptic plasticity in an environment that, compared with the awake state, is almost entirely unbiased by external stimulus inputs. The disentangled, localized nature of synaptic consolidation might also explain why REM sleep alone fails to improve declarative memory consolidation: this process essentially relies on the integration of features from different memories in different memory systems and corresponding information transfer between widespread brain areas, that is, SWS-dependent system consolidation.

Conclusions and future directions

SWS and REM sleep have complementary functions to optimize memory consolidation (FIG. 3). During SWS — characterized by slow oscillation-induced widespread synchronization of neuronal activity — active system consolidation integrates newly encoded memories with pre-existing long-term memories, thereby inducing conformational changes in the respective representations. System consolidation (which preferentially affects explicitly encoded, behaviourally relevant information) acts in

concert with global synaptic downscaling, which serves mainly to preclude the saturation of synaptic networks. Ensuing REM sleep — characterized by de-synchronization of neuronal networks, which possibly reflects a disengagement of memory systems — might act to stabilize the transformed memories by enabling undisturbed synaptic consolidation. Although REM sleep has been suspected for a long time to have a key role in memory consolidation, research has paid little attention to the fact that REM sleep naturally follows SWS. This points to complementing contributions of sequential SWS and REM sleep to memory consolidation — an idea that was originally proposed in the sequential hypothesis[64]. This Review revives this idea by indicating an essential role of SWS in system consolidation that might be complemented by the synaptic consolidation taking place during REM sleep. However, direct evidence of this is scarce at present[65]. Specifying the role of REM sleep, as an integral part of this sequence, in synaptic consolidation will undoubtedly pose a particular challenge to future research.

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