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Review

Sleep—A brain-state serving systems memory consolidation

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SUMMARY

Although long-term memory consolidation is supported by sleep, it is unclear how it differs from that during wakefulness. Our review, focusing on recent advances in the field, identifies the repeated replay of neuronal firing patterns as a basic mechanism triggering consolidation during sleep and wakefulness. During sleep, memory replay occurs during slow-wave sleep (SWS) in hippocampal assemblies together with ripples, thalamic spindles, neocortical slow oscillations, and noradrenergic activity. Here, hippocampal replay likely favors the transformation of hippocampus-dependent episodic memory into schema-like neocortical memory. REM sleep following SWS might balance local synaptic rescaling accompanying memory transformation with a sleep-dependent homeostatic process of global synaptic renormalization. Sleep-dependent memory transformation is intensified during early development despite the immaturity of the hippocampus. Overall, beyond its greater efficacy, sleep consolidation differs from wake consolidation mainly in that it is supported, rather than impaired, by spontaneous hippocampal replay activity possibly gating memory formation in neocortex.

INTRODUCTION

Memory, in the broadest sense, is information that is kept by a substrate over an extended period of time. In the brain, networks of neurons and glial cells distributed across multiple regions encode information from experienced episodes into representations that are partly maintained as long-term memories to regulate future behaviors in similar contexts. It is generally assumed that freshly encoded memory engrams rapidly decay unless they are consolidated. This stabilization process takes place as synaptic consolidation by locally strengthening the synaptic connections between neurons coding the representation. However, it can also entail a systems consolidation process that involves the reorganization of the neural substrate hosting the representation and potentially a qualitative transformation of the representation.[1]

Sleep has been known to support the formation of long-term memory since the first experimental evidence was provided about a century ago.[2] Since then, hundreds of studies in humans and animals have shown that in comparison with wakefulness, sleep following the encoding of experimental stimuli, produces more long-lasting and stable memories (for reviews, see Rasch and Born,[3] Klinzing et al.,[4] and Girardeau et al.[5]). However, recently, there has been a growing number of experiments failing to reveal superior retrieval of memory for post-encoding sleep compared with wake conditions, and a few studies even suggesting enhanced forgetting of memory by sleep.[6,7] These findings call for a reassessment of the precise conditions mediating the sleep consolidation effect.

Sleep is a brain state that is characterized by a large-scale organization of neuronal activity that captures virtually all brain regions, the neocortex as well as hippocampus, thalamus, hypothalamus, and brainstem regions.[8] During sleep, the sub-states of slow-wave sleep (SWS) and rapid eye movement (REM) sleep alternate, SWS characterized by the presence of slow waves and slow oscillations (SOs) in EEG and local field potential (LFP) recordings, and REM by the prevalence of (4–8 Hz) theta activity in rodents, and of a wake-like mixture of low-amplitude "desynchronized" EEG oscillation in humans and non-human primates. SWS and REM sleep greatly differ also in global activity of neuromodulators, with SWS mainly characterized by strongly reduced cholinergic activity, and REM sleep characterized by minimum noradrenergic (NA) activity but wake-like cholinergic activity. However, SWS and REM sleep cannot always be considered as clearly separated entities. For example, the hippocampus often enters REM sleep while cortical areas still remain in SWS,[9,10] and slow-wave activity (SWA) can occasionally intrude into ongoing REM sleep.[11,12] Furthermore, SWS and REM sleep themselves comprise microstates associated with the occurrence of phasic events, such as SOs, spindles, and ripples associated with SWS and theta bursts, ponto-geniculo-occipital (PGO) waves, and REMs associated with REM sleep. It is still an open question how the precise interplay of these phenomena occurring across multiple spatiotemporal scales

impacts specific memories and their underlying neural representations such that they remain retrievable for a longer period of time.

Whereas the research on the mechanisms of memory consolidation during sleep has also been reviewed previously (e.g., see Girardeau and Lopes-Dos-Santos[5]), here, we focus on research topics that most rapidly advanced in recent years. Accordingly, following a brief update of the current state in the field of sleep and memory, we will discuss three major mechanisms by which sleep-dependent memory consolidation is affected: (1) memory reactivation, (2) the coupling of non-REM oscillatory phenomena in combination with specific neuromodulatory conditions, and (3) mechanisms of synaptic consolidation and how they might combine with the renormalization of synaptic connections evidenced on a large scale in brain synaptic networks. We will finally (4) go into early development as a condition where sleep is particularly important for the formation of persisting memory and (5) address the question about the unique contribution of sleep as a brain state consolidating memory, in comparison with the wake state.

AN UPDATE OF THE CURRENT STATE

Human behavioral studies

The starting point of research on sleep-dependent memory consolidation are studies in humans using behavioral measures of memory recall in combination with variations of standard experimental procedures comprising (1) an encoding phase in which participants performed a specific memory task, followed by a (2) post-encoding consolidation phase during which the participant either slept or remained awake, and (3) a retrieval test of the previously encoded information. These experiments can entail different sleep conditions (nocturnal sleep vs. midday naps), control conditions (sleep deprivation vs. daytime wakefulness), retrieval delays (immediately vs. several days after the consolidation phase) and memory domains. Across experimental designs, post-encoding sleep has been consistently found to enhance memory retrieval on non-verbal (e.g., object-location associations) and verbal (e.g., lists of word pairs) tasks assumed to assess hippocampus-dependent episodic types of memories.[3,13,14] Benefits of sleep have likewise been observed for procedural memories for perceptual and motor skills[15–17] which, in theory, represent memories that do not require hippocampal function.[18] Here, tasks requiring motor adaptation (such as pursuit rotor task) might represent an exception as they do not seem to benefit from sleep.[19] Enhancing effects of sleep were also revealed for various types of emotional memories including classical fear conditioning (e.g., Menz et al.[20]; but see Pavlov et al.[21]) and memory for aversive pictures, with sleep exerting a more gradual ameliorating effect on the affective response.[22,23]

A matter of controversy concerns the question whether sleep preferentially consolidates certain aspects of an experienced episode over others. This question roots in the idea that, to be considered during sleep-dependent consolidation, an information needs to be somehow tagged already during or shortly after encoding. In this context, sleep has been proposed to prioritize consolidation of emotional stimuli. For example, when asked to remember picture scenes comprising neutral as well as aversive features, post-encoding sleep produced a greater memory benefit for the aversive than neutral features of the scene.[24,25] However, other studies revealed comparable benefits from sleep for neutral over emotional stimuli.[26,27] To be noted, emotional stimuli are already more strongly encoded than neutral stimuli, with encoding strength well known to confound consolidating effects of sleep (e.g., Denis et al.[28]). On a more general level, it has been argued that sleep preferentially enhances salient memories that are relevant for future adaptation. Thus, sleep had a greater effect on the retention of newly encoded declarative (word pairs) or procedural (finger tapping) memories when the participants were informed (before sleep) that these memories were going to be tested at a later time, compared with misinformed participants.[29] Also, enhancing effects of sleep appeared to be particularly pronounced for prospective memories of plans in some cases,[30,31] whereas other studies on salient prospective memory failed to demonstrate similar effects.[27]

A related and currently open question is whether sleep-dependent consolidation favors the formation of abstracted, schema-like memories containing only the gist of previous experiences.[32] The proposal is based on the assumption that consolidation during sleep leads to a reorganization of the memory representation, as it has been evidenced in humans using functional magnetic resonance imaging (fMRI): in comparison with post-encoding wakefulness, sleep increased the recruitment of neocortical networks and functional connectivity between prefrontal cortex and hippocampus at a later retrieval test, especially with declarative types of memory.[33,34] Behaviorally, a number of studies revealed signs of an improved abstraction of rules and regularities at a later test session when participants had slept after encoding of the stimulus materials, in comparison with a wake control condition.[35–38] However, there is also a number of studies that failed to demonstrate such effects,[39,40] indicating the existence of specific boundary conditions for sleep-dependent memory abstraction to occur. For one, hippocampal tasks comprising temporal sequence regularities might be particularly sensitive to these effects. The verbal vs. non-verbal nature of the task may also play a role, as verbal tasks invoke representations at a rather abstract level already at encoding that might impede the demonstration of further abstraction processes during subsequent consolidation. Moreover, depending on the task, abstraction of generalized schema-like memories is considered a rather slow process that may lead to behavioral changes only with a certain delay. For example, using visual patterns, Lutz et al.[41] found that post-encoding sleep enhanced generalization of memory recall to a category prototype not presented during encoding, at a recall test 1 year but not 1 day after encoding. Finally, it is currently unclear what exactly the presumed gist is that is abstracted during sleep consolidation. Besides the differential generalizability of the stimulus material employed in these studies, the abstraction process may as well be strongly biased by other factors, most importantly the individual's prior knowledge.[42]

SWS vs. REM sleep

Substantial research efforts were made to dissociate contributions of specific sleep stages to memory consolidation, using the selective deprivation of REM sleep or comparing effects of REM-rich periods of sleep (naturally occurring in the morning

hours in humans) with SWS-rich sleep (occurring in the late evening hours). Across a great variety of tasks, these studies revealed stronger influences of SWS than REM sleep on memory consolidation. However, contributions of REM sleep appear to be particularly strong for the consolidation of emotional materials.[25,43] The minimal NA tone in which memories are processed during this sleep stage has been proposed to dismantle and depotentiate the autonomic charge of these memories.[44] REM sleep has also been proposed to be implicated in creative problem solving by promoting novel associations.[45] Contributions of SWS to memory consolidation have been further substantiated by findings indicating a close link between the hallmarking EEG signatures of this sleep stage, i.e., slow 0.5–4-Hz SWA, including SOs <1 Hz, and sleep spindle activity. (As this activity occurs also in the lighter form of non-REM sleep stage 2, which is specific to human sleep, most of these studies refer to "non-REM sleep" including both stage 2 sleep and SWS.) Measures of SO and slow-wave activity during post-encoding non-REM sleep were found to be positively correlated with later recall of the target memories in some studies (e.g., Wilhelm et al.[46] and Qian et al.[47]), but there were also exceptions showing negative correlations.[48,49] Studies experimentally enhancing or suppressing SO activity through closed-loop auditory or electrical stimulation support the view of a causal role of SOs in enhancing the consolidation process.[50–52] The link between sleep spindle activity during post-encoding sleep and later memory performance is even more consistent than that for measures of SWA (e.g., Alger et al.,[53] Peyrache and Seibt,[54] and Lutz et al.[55]). Sleep spindles originate from thalamocortical circuitry and are waxing and waning oscillatory EEG events in the 12–16 Hz frequency that dominate over central and parietal cortical areas. Selective manipulations of spindle activity, via closed-loop stimulation or pharmacological interventions, are difficult to achieve in humans.[56,57] However in mice, the optogenetic induction of spindles has confirmed their causal contribution to memory consolidation.[58] While generated in GABAergic loops comprising the reticular thalamic nucleus, spindles are driven by the depolarizing flank of the SO[59] which explains that they often occur in conjunction with the upstate of the SO in the surface EEG. Growing evidence points toward the strength of the coupling between SO and spindles as a critical factor determining the strength of the memories consolidated during sleep.[60,61] No robust associations have been found between the EEG signatures of REM sleep and memory consolidation in humans, probably owed to the fact that unlike in rodents, the EEG in primates is not hallmarked by a prominent 4–7-Hz theta rhythm.

Cross-species translation and the active systems consolidation model

Whereas rodents and fruit flies have been most often used as models for the study of the mechanisms underlying memory consolidation during sleep, relatively little efforts have been spent to directly translate and validate the major findings of human studies. Nevertheless, such research overall confirmed an enhancing effect of post-encoding sleep and sleep-like states on memory for all species examined in this regard, including not only rodents and drosophilae, but also honey bees, snails, and may even hold for worms like *C. elegans*.[62] However, the core sleep stages of SWS and REM sleep have been clearly discriminated only in mammals and birds, and some evolutionary older reptilian ancestors such as lizards.[63] Therefore, mainly rodent models were used to validate the respective contributions of SWS and associated SO and spindle activity to memory consolidation. Importantly, converging with the findings in humans, these studies showed benefits from SWS for both hippocampus-dependent spatial and episodic-like memory as well as for memories considered non-hippocampus dependent, similar to novel object recognition and motor skill memory.[63–69] These studies extended the body of findings in humans, mainly by indicating the critical involvement of hippocampal ripples and the replay of neuronal ensemble activity during SWS in the consolidation process. REM sleep and associated theta activity was most consistently found to be involved in the consolidation of emotional memories (e.g., fear conditioning[70,71]) including social memory for a conspecific mouse.[72]

Essentially referring to findings in rodent models the active systems consolidation concept has been proposed, which advances standard consolidation theory to explain memory consolidation during sleep.[4,73] The concept assumes that sleep-dependent consolidation is established in the hippocampus-dependent episodic memory system. At the core of this process is the neuronal replay of memory, i.e., repeated reactivations of firing patterns in neuron ensembles that were activated and used for encoding of the episodes during prior wake phases, and which re-occur in hippocampal networks during post-encoding SWS in coordination with hippocampal sharp wave-ripples (SPW-Rs). The coupling of hippocampal replay to the depolarizing upstates of SOs emerging from neocortical networks and to thalamic spindles represents a mechanism that supports the transmission of the reactivated memory information and its storage, through synaptic consolidation mechanisms, into respective neocortical networks serving as long-term store. The repeated replay in conjunction with the triple coupling of SOs, spindles, and ripples, thereby, facilitates a gradual redistribution of the representation toward neocortical networks, which at the psychological level, presumably, is accompanied by the formation of more abstract and schema-like memory. Although this concept focuses on the hippocampus-dependent episodic memory system, it also explains sleep benefits for non-hippocampus-dependent kinds of memory (e.g., procedural skills), as such memories are naturally experienced in the context of specific episodes implicating that they are always embedded into hippocampus-dependent episodic representations. Indeed, sleep-dependent gains in memories originally classified as "non-hippocampus dependent" can be abolished by suppressing hippocampal function during sleep.[66,74] While the active systems consolidation concept has proven a useful model integrating a wide range of research in humans and animals, it also helps to identify the gaps and unanswered questions in the field—which are the focus here.

MEMORY REPLAY AS A KEY MECHANISM PROMOTING CONSOLIDATION DURING SLEEP

Replay in rodents

The phenomenon of memory reactivation has mostly been investigated in rodents, but it occurs also in other species such as

zebra finch and fruit fly[75,76] underlining the universality of the phenomenon. In general, the term "reactivation" is used in a broader sense describing the re-emergence of any neuronal activity pattern representing a specific prior experience, whereas the term "replay" implicates a reactivation of neuronal ensemble firing patterns in the same sequential order.[77] We adopt this nomenclature in this manuscript. Most studies in rodents focused on the hippocampus, in which place cells coding for specific locations in an environment replay in the same sequential order during sleep as during prior awake spatial navigation.[78,79] Neuronal replay typically occurs in a temporally compressed fashion and can recapitulate the original event sequence in forward or reverse order.[80,81] Hippocampal replay occurs temporally coupled to hippocampal SPW-Rs, a characteristic pattern in the hippocampal LFP consisting of a large amplitude negative deflection originating from CA3, followed by a short fast oscillation in the range of 110–200 Hz, which appears predominantly during non-REM sleep, but also more generally during periods of immobility.[82]

Beyond positive correlations between sleep-dependent hippocampal reactivation and subsequent memory performance (e.g., Dupret et al.[83]), several studies identified a causal relationship between reactivation and memory consolidation. Disrupting postexposure hippocampal activity during SPW-Rs via electrical stimulation or optogenetic silencing diminished reinstatement of ensemble firing patterns and, subsequently, impaired memory recall during re-exposure to the learning task.[84,85] Notably, refining this approach by disrupting only specific reactivation events of a prior learning experience (through online decoding of the content of ensemble firing patterns) revealed a selective recall deficit that was restricted to the spatial environment whose reactivation was disturbed.[86]

While the vast majority of studies focused on the hippocampal, memory reactivation is a far more ubiquitous phenomenon, as it is observed in many brain regions, ranging from early sensory[87–89] and motor cortices,[65,90] over medial entorhinal cortex[91–93] and higher-order association areas like the parietal[94–96] and prefrontal cortices[97–99] to different subcortical areas.[100–103] Furthermore, these studies revealed sleep-associated reactivations across a variety of memory domains, including hippocampus-dependent spatial tasks with reward and emotional components as well as fear conditioning and motor skill learning.[65,97,100,102]

Reactivations in extrahippocampal/cortical areas tend to coincide with oscillatory hallmarks of memory consolidation during sleep, such as SOs and spindles,[65,88,90,96] but also with hippocampal SPW-Rs,[96,99,101,103] suggesting a temporal association of reactivation and replay across intra- and extrahippocampal sites. Indeed, parallel recordings from both hippocampus and cortical or subcortical regions revealed a close temporal coordination of reactivation across sites[92,100,102] consistent with the idea that reactivations conjointly occurring with hippocampal replay support the gradual emergence of stable representation in extrahippocampal circuits. Indeed, information flow during such coordinated reactivation events appears be organized in a loop-like manner, with activity in cortical regions predicting the content of hippocampal reactivations during SPW-Rs,[89] and hippocampal reactivations, in turn, leading reactivations in extrahippocampal regions.[89,92,102] There is, however, also evidence for hippocampus-independent replay in extrahippocampal sites, e.g., in superficial layers of medial entorhinal cortex and in prefrontal cortex.[91,93,98]

Similar to hippocampal replay, extrahippocampal reactivations have also been shown to positively correlate[65] and causally contribute to sleep-dependent memory consolidation. Clawson et al.[87] used a targeted recombination in active populations (TRAPs)-based approach to identify so-called engram neurons, i.e., neuron ensembles in visual cortex (V1) that were co-activated during learning a visually cued conditioned fear response, in combination with optogenetic stimulation or inhibition of these engram cells during subsequent consolidation periods. Inducing reactivations of the V1 engram cells during sleep after conditioning enhanced the formation of a cue-specific fear memory. Interestingly, inhibiting V1 engram cells during sleep induced a more generalized fear response irrespective of the visual cue presented. With a similar approach, Aly et al.[97] showed that the conjoint offline reactivation of engram cells in anterior cingulate cortex (ACC) coding for distinct experiences is necessary for forming generalized representations of spatial context during sleep. The experimenters exposed mice to several spatial environments differing more or less in their geometrical layout. Contextual fear conditioning in one of the spatial contexts produced freezing also in similar environments when tested 1 day later. This effect was abolished when the reactivation of anterior cingulate engram cells for the similar context was optogenetically disrupted during sleep after conditioning. Importantly, a coordinated reactivation of both engram cell populations was only observed during offline periods spent asleep, and the extent of co-reactivation correlated with freezing behavior in the similar context.

Collectively, these findings support the notion that neuronal reactivations of newly encoded experiences during sleep specifically contribute to the reorganization of respective representations in hippocampal-cortical systems.

Reactivations in humans

In spite of the methodological constraints regarding invasive recordings, offline memory reactivations and recently also signs of sequential replay[104,105] have been observed with noninvasive neuroimaging in humans. However, the vast majority of studies in humans focus on offline memory reactivations. Early attempts using magnetic resonance imaging (MRI) and positron emission tomography (PET) showed that brain regions that were activated during learning a task (e.g., motor cortex during finger tapping and hippocampus during route learning) displayed higher activation during subsequent sleep and that the extent of this regional activation was positively correlated with subsequent recall performance.[106,107] The reactivation of task-relevant regions was found to be particular prominent during sleep oscillatory events linked to memory consolidation, such as spindles and SOs.[108,109]

With the advancement of new techniques, studies have adopted mainly two approaches to enable a more specific content-related analysis of memory reactivations during human sleep: i.e., (1) the detection of spontaneous reactivations of specific patterns of encoding activity using multivariate data analyses and (2) the use of targeted memory reactivation (TMR) during sleep. With the first approach, several studies succeeded in

identifying signs of spontaneous memory reprocessing during post-learning sleep (e.g., Rubin et al.,[110] Sterpenich et al.,[111] and Zhang et al.[112]). Using machine learning classifiers, categories of previously encoded stimuli (e.g., faces vs. houses; objects vs. scenes) could be decoded solely from sleep EEG, revealing that category-specific information is reactivated during sleep.[113,114] In both of these studies, the accuracy of the classifier to correctly identify the previously encoded stimulus category was positively correlated to later memory recall, indicating that the classification relied on behaviorally relevant features. Besides EEG, intracranial recordings have provided corroborative evidence for stimulus-specific and sequential reactivations during human sleep.[110,112] Reactivations were found to occur coupled to the oscillatory hallmarks of non-REM sleep, specifically to hippocampal ripples[112] and to spindles coupled to SOs, but not to solitary SOs or spindles[114] and TMR has been used in many studies to induce reactivations during sleep by external stimulation. In TMR, cues, classically sounds, or odors that had been presented together, and were thus associated with the to be encoded stimuli during prior awake learning, are presented to the participant during post-encoding sleep at a sub-awakening threshold. Typically, the cues are presented repeatedly during a specific sleep stage, and non-specific effects are controlled for by presenting stimuli (of the same modality) that were not associated with the to be encoded stimuli. The beneficial effect of TMR during non-REM sleep on memory performance is well established across a variety of memory domains,[115] including visuospatial[116–119] and verbal[120,121] declarative memory as well as motor learning.[122–125] In fMRI recordings during sleep, the delivery of odor or auditory TMR cues during post-encoding SWS was found to enhance activation of and connectivity between brain regions relevant to the associated object-location association task, such as the hippocampus, parahippocampus, and posterior cortical areas, and these increases in activation were positively correlated with subsequent memory performance.[118,126] Multivariate pattern analyses have provided robust evidence that TMR actually induces a behaviorally relevant reactivation of cue-associated target information.[117,119,127] For example, using representational similarity analysis, Cairney et al.[117] reliably identified the image category (object vs. scene) associated with the verbal cue (adjectives) in the raw EEG traces during a time window of increased fast spindle power ~1.7–2.3 s after cue onset. Evidence for category-specific reactivations was strongest when cue delivery was accompanied by increased spindle activity and, moreover, predicted the TMR-induced gain in memory.

Cue delivery during TMR also affects memory-relevant oscillations. It is associated with increased SO power, amplitude and density,[120,125,128] increased spindle power and density,[116,117,120,128] as well as improved SO-spindle coupling,[120] and these characteristics are often associated with the TMR-induced memory advantage.[116,122,125] In turn, timing of cue delivery in relation to SOs,[129] spindles, or spindle refractory periods, respectively,[116,117,127] or the phase-coupling of spindles to the SO peak or trough[125] may substantially affect the effect of TMR on memory performance.

TMR has also been used in rodent studies, confirming that auditory cues, which had been paired to specific trajectories during a spatial learning task, enhance hippocampal reactivation of the associated trajectory when delivered during subsequent sleep.[89,130] Importantly, these studies revealed that, while biasing the content of memory reactivations toward the targeted memory information, TMR does not appear to increase the overall number of reactivation events. Such a shift in reactivation probabilities in favor of the cued stimuli is likewise suggested by studies in humans, which show a negative effect of TMR for the consolidation of uncued memories.[122,124]

Dynamics of sleep-dependent reactivation

Signs of reactivations appear to follow a specific temporal dynamic. In hippocampal networks, rates of replay and reactivation are highest within the first 10–30 min of post-encoding sleep and appear to rapidly fade later.[79,88,100,131] Assuming that the underlying neuron ensembles are synaptically connected, this dynamic basically argues against an immediate effect of replay "strengthening" synaptic connectivity in these ensembles.[132] The predominance of replay in the beginning of post-encoding sleep might rather reflect the importance of this period for initializing systems consolidation processes during sleep, although this temporal dynamic likely represents a general feature of reactivations showing maximum rates within ~30 min after encoding also during wakefulness.[81] The time course of reactivations might also depend on the familiarity of the encoded environments. Mostly, rodents were examined in highly familiar environments, whereas the experience of an entirely novel environment inducing the emergence of a new hippocampal map produced sustained reactivations during sleep for up to 7 h with a peak after 3–5 h.[133] This time course fits with findings in humans of preferential time windows for memory reactivations 3 and 6 h into sleep after encountering a novel visuospatial memory paradigm.[113]

Memory reactivations occur preferentially in non-REM sleep. Studies directly comparing non-REM and REM sleep found no evidence for hippocampal place cell reactivations[131] or coordinated hippocampal-subcortical reactivations in a spatial task with an aversive emotional component[100] during REM sleep. However, neural activity during REM sleep can be modulated by prior wake experience[106,134] and there have been occasional reports of reactivation-like phenomena in REM sleep.[68,113,135,136] However, REM reactivation differs from that during SWS, as it occurs independently of SPW-Rs, shows no temporal compression and mainly occurs during pre-task sleep.[68,135] In humans, REM-related reactivations did not show a relation to memory performance,[113,115] altogether suggesting that REM sleep related reprocessing of experience serves functions different from reactivations during non-REM sleep.

A specific role of sleep-dependent reactivation for memory consolidation?

Reactivation of ensemble firing patterns was first identified during sleep,[79,136] but the phenomenon occurs likewise during quiet rest as well as during active behavior, in rodents[80,81,137,138] as well as in humans.[104,105,112] The possibility to relate awake replay events to immediately preceding or upcoming behavior has sparked the concept that the content of reactivations expresses a flexible and adaptive model of the world.[139] In general,

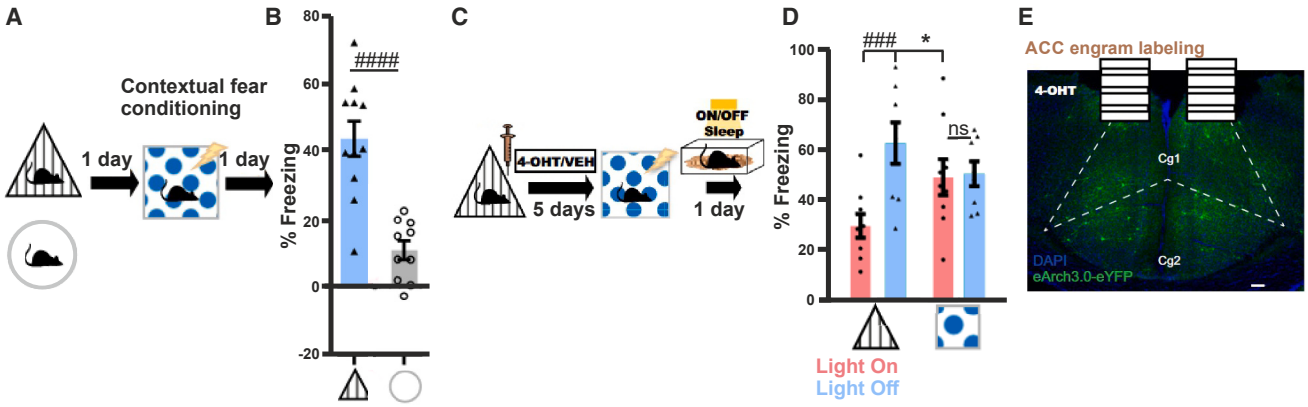


Figure 1. Memory reactivation during sleep promotes context generalization of a conditioned fear response

(A) Mice were pre-exposed to different contexts with different geometries (circle, triangle). 1 day later, they were fear conditioned in a novel context (square) with repeated foot shocks.

(B) After another day, the mice displayed higher freezing rates in the pre-exposed context that was more similar in geometry to the conditioned context, i.e., the triangle context, but not in the circular context.

(C) Engram ensembles coding for the similar (triangle) context were labeled in the anterior cingulate cortex (ACC) and optogenetically inhibited during sleep (non-REM and REM) for 3–4 h after contextual fear conditioning, preventing reactivation of the similar context (red).

(D) While at testing after 1 day, freezing rates to the conditioned context were not affected, the mice displayed reduced freezing rates in the similar context. In the absence of optogenetic inhibition (blue), freezing rates in the similar context were even slightly enhanced in comparison with freezing rates in the conditioned context.

(E) Coronal section of the ACC showing enhanced yellow fluorescent protein (eYFP) expression when injected with 4-hydroxytamoxifen (4-OHT). Dashed lines show the boundary of the ACC. Scale bars, 100 μm. Bar graphs show means ± SEM. *p < 0.05, ##p < 0.01, ###p < 0.001 (adapted from Aly et al.[97]).

reactivation and replay in both wake and sleep states display largely similar features.[140] They also share the factors that select which content is preferably reactivated, due to saliency or relevance, including novelty and reward.[80,81,141] For example, representations of rewarded spatial locations are preferentially reactivated in both wake and sleep states,[80,81,142–144] although there are also findings of a bias of reactivations in the opposite direction.[145,146] Signs of reward-related biasing of reactivations during sleep and wake have been likewise observed in humans using fMRI.[111,147] Beyond their dependence on novelty, salience, and reward, both sleep and wake replay can represent knowledge about an environment and also share anticipatory features, such that they can e.g., include offline "pre-activations" of trajectories entailing visible but yet unexplored paths and locations.[144,148–150] Finally, similar to sleep reactivations, awake memory reactivations have been shown to enhance subsequent recall performance.[83,151–153] Altogether, these similarities between reactivations occurring during sleep and wakefulness exclude that reactivation, and replay in the narrow sense, itself is the critical factor that explains superior consolidation effects during sleep.

Nevertheless, direct comparisons point to different functions of reactivations occurring in the wake and sleep states. Generally, sleep replay appears to feature a less faithful recapitulation of previous experience compared with wake replay.[137,154–156] In mice, optogenetically reactivating retrosplenial engram ensembles representing a recently acquired contextual fear memory produced a memory trace displaying all features of a remote, systems consolidated memory including higher engagement of neocortical areas during retrieval, contextual generalization, and decreased hippocampal dependence.[157] Intriguingly, this effect only appeared when stimulation was performed during sleep or light anesthesia, but not during wakefulness. Moreover, generalization of a specific contextual fear memory to a similar context, but not consolidation of individual contexts, critically depended on the co-reactivation of engram ensembles for both context experiences during sleep[97] (Figure 1). Likewise, similarity analyses on human intracranial EEG gamma band activity revealed robust evidence for wake and sleep memory reactivations of previously learned pictures of houses and landscapes,[112] but only reactivations triggered by hippocampal ripples in non-REM sleep were predictive of memory performance.

Collectively, these findings support the view that sleep replay serves a special function in memory consolidation, although sleep and wake replay both display largely similar features. While replay in both states may support stabilization of memories, sleep replay may be more effective in systems consolidation processes, i.e., when it comes to a reorganization of representations across hippocampal-neocortical networks.[158] This contribution might not be conveyed by the replay phenomenon itself but owed to the unique milieu during sleep. Specifically, the embedding of replay within SPWs, spindles, and SOs may enable the large-scale interaction between replay across hippocampal and thalamocortical networks supporting systems consolidation during sleep.

COUPLING OF SOs, SPINDLES, AND RIPPLES

Neuronal replay of ensemble firing patterns is a well described phenomenon supporting memory consolidation during sleep. However, in order to consolidate memory representations that are widely distributed across different brain regions, neuronal reactivations need to be temporally precisely synchronized between these distributed areas. This is generally achieved by

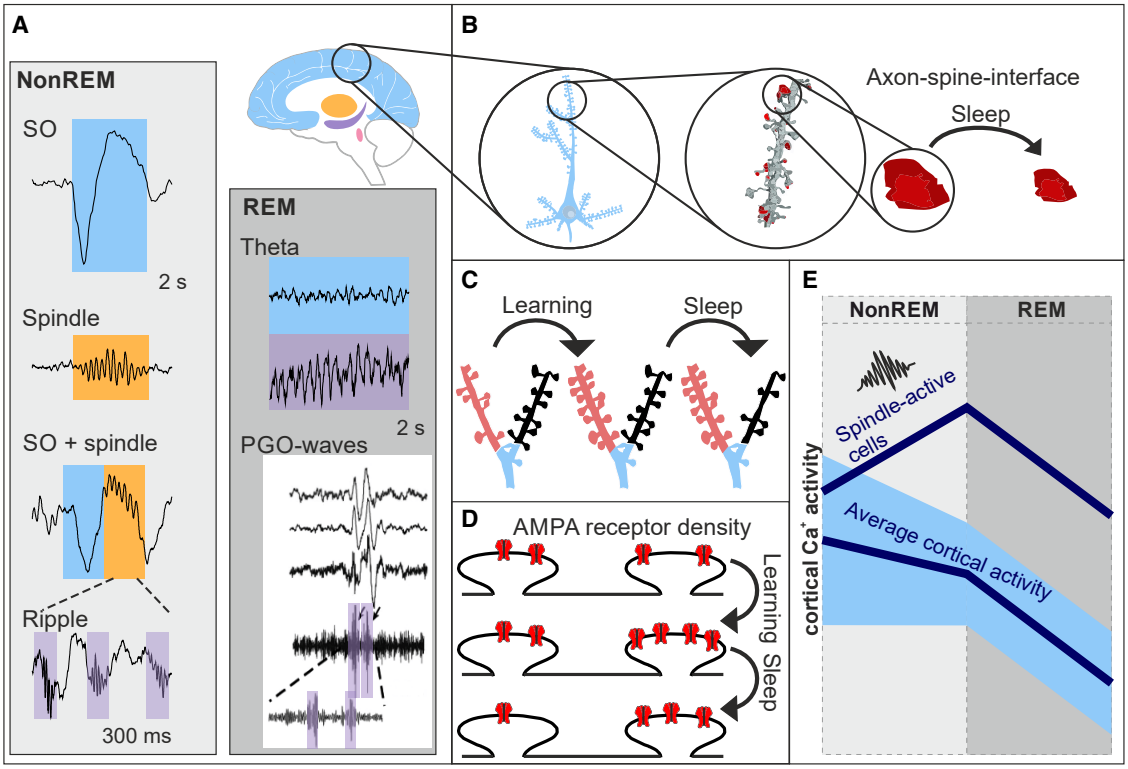


Figure 2. Sleep oscillations and synaptic plasticity

(A) Example traces of sleep oscillations involved in memory consolidation. SOs (<0.1 Hz) derive from alternations between synchronized membrane hyperpolarization (downstate) and depolarization (upstate) and are generated in cortex layer 2/3 and 5. Sleep spindles (11–16 Hz) are generated in the thalamus, reach cortical networks via thalamocortical projections, and tend to nest in the depolarizing SO upstate (SO + spindle). SOs nesting spindles appear to particularly fosters synaptic plasticity through releasing inhibition at pyramidal dendrites.[161] Ripples (80–140 Hz) in the hippocampus coordinate the temporally precise replay of cellular ensembles during sleep and tend to nest in the excitable trough of spindles. They are also associated with downscaling of hippocampal synapses.[132] REM sleep in humans is characterized by mixed frequency low-amplitude EEG signals and, in rodents, by theta activity (4–8 Hz) arising from hippocampal networks but capturing also cortical areas. During REM sleep, ponto-geniculo-occipital waves (PGO waves) occur that can phase-lock theta activity and, possibly, also ripples. How PGO waves contribute to memory consolidation is not clear (adapted from Ramirez-Villegas et al.[162]).

(B) Sleep globally induces a net decrease in synaptic connectivity (downscaling) which entails a reduction in the average size of axon-spine interfaces of cortical dendrites (assessed by structural 3D electron microscopy; partly adapted from de Vivo et al.,[163] right).

(C) Sleep downscaling also entails a reduction of dendritic synaptic spines, with branches involved in prior learning (red) being spared (assessed by two-photon imaging,[164] left).

(D) Synaptic AMPA receptor density increases during learning and is globally reduced during subsequent sleep. Downscaling includes the synapses that were upscaled during learning, although to a lesser extent.[165] It is not clear whether non-REM and REM sleep differentially affect AMPA receptor regulation.

(E) Sleep, particularly REM sleep, globally downregulates calcium activity in cortical pyramidal cells. Cells that are particularly active during sleep spindles are spared from this downregulation during non-REM sleep where these cells even increase their activity.[166,167]

brain oscillations that, with a shared frequency, synchronize membrane potential depolarization and hyperpolarization across extended neuronal networks.[159,160] In this way, oscillations prime synaptic plasticity by timing the firing properties of activated neurons to the excitable depolarizing phase of network oscillations. Oscillations of slower frequency typically synchronize neuronal excitability at a more global level than fast frequency oscillations that regulate excitability at a more local level, with the nesting of fast frequency into slow frequency oscillations reflecting the global-to-local network interaction and fine-tuning in this regulation. During SWS, three cardinal rhythms have been identified that eventually determine the efficacy of firing pattern reactivations occurring in local neuron ensembles, i.e., SOs, sleep spindles, and ripples (Figure 2A). During REM sleep, information flow appears to be mainly determined by theta oscillations, aside from PGO waves.

SWS

SWS is dominated by slow EEG activity in the 0.1–4 Hz range, with this SWA comprising the SOs (<1 Hz) and delta frequencies (1–4 Hz, frequency bands refer to human EEG). Slow waves reflect alternations between synchronized membrane hyperpolarization (downstate) and depolarization (upstate) in neocortical networks, often travel from anterior to posterior cortical regions, and also reach the hippocampus and brainstem, including the locus coeruleus (LC).[168–170] The mechanisms initializing cortical slow waves are not entirely resolved.[171] Apart from thalamic afferents and cortical astrocytes, somatostatin positive interneurons inhibiting pyramidal dendrites appear to be specifically implicated in the induction of downstates.[161,172,173] Stimulating somatostatin positive interneurons increased slow-wave amplitudes and their slopes.[174] The causal role for memory consolidation during sleep is supported by a body of findings showing

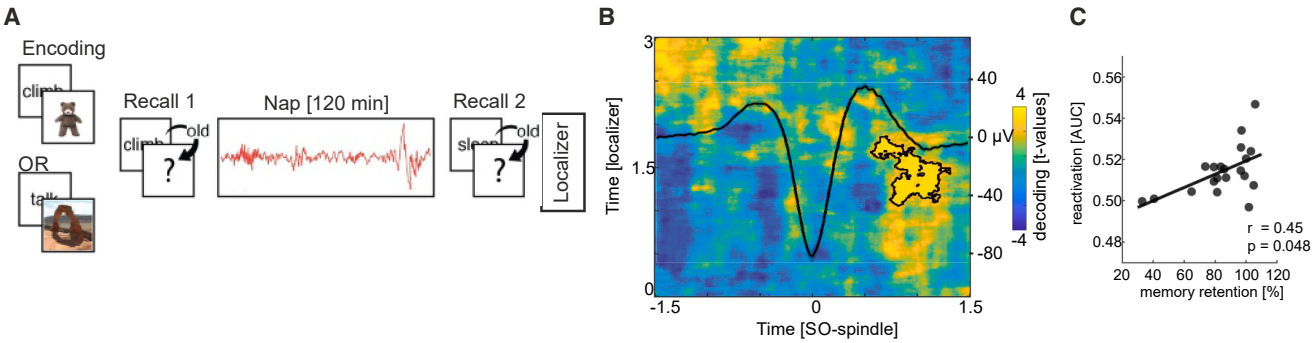


Figure 3. Memory reactivation in human sleep occurs time-locked to SO-spindle complexes

(A) In two sessions, participants encoded and recalled word-object and word-scene pairs, respectively, before taking a 2-h nap followed by a second recall. EEG signals were continuously recorded. A linear discriminant analysis classifier was trained to differentiate between objects and scenes on localizer data recorded with novel pictures at the end of the sessions (localizer).

(B) The trained classifier reliably decoded the category of the previously encoded pictures from the EEG signal (at Cz) during non-REM sleep (stage 2, SWS) when applied during the occurrence of SO-spindle complexes. Contour lines indicate the extent of the significant cluster representing the reactivated EEG signal, p = 0.016 corrected; color range (blue to yellow) represents t values against control, i.e., surrogate decoding performance. Overlaid solid black line indicates average EEG trace and illustrates the relationship of the observed reactivation signal with ongoing SO activity.

(C) Reactivation strength as defined by the integrated classifier performance (area under the curve [AUC]) correlated positively with memory retention (Spearman's r = 0.45, p = 0.048; adapted from Schreiner et al.[114]).

enhanced memory retention after applying noninvasive brain stimulation during sleep to induce slow waves.[50–52,63,175]

Although a dissociation between <1 Hz SOs and 1–4 Hz delta activity has been already proposed by Steriade[176] when describing the SO the first time in detail, it is still not clear how these slow-wave rhythms functionally differ, in particular, in their effects on memory processing.[12,177] Work by Kim and colleagues[178] points to opposing roles with only the SOs enhancing consolidation. In these experiments, rats were trained to control the activity of individual motor neurons which produced an enhanced reactivation of these neurons during subsequent SWS. In order to prevent reactivations of the trained motor neuron activations during sleep, the experimenters optogenetically inhibited motor cortex neuronal activity during post-training SWS, either during online identified SO upstates or during delta wave upstates. Suppressing motor cortex activity during the SO upstate, as expected, impaired memory for the trained motor neuron response. By contrast, suppression during delta wave upstates improved memory. Thus, unlike SOs enhancing cortical representations, delta waves may primarily serve their downscaling and forgetting.

Spindles originating from thalamic networks represents a second prominent EEG oscillation during SWS. Spindles are waxing and waning 11–16 Hz oscillatory events of 0.5–3 s duration that are generated in GABAergic feedback-loops including the nucleus reticularis of the thalamus and via afferent fibers widely spread to the cortex, reaching predominantly central and parietal areas.[59] They also reach the hippocampus possibly via the nucleus reuniens.[179] Spindle activity is increased over cortical regions involved in prior learning and, moreover, positively correlates with post sleep retrieval performance[180,181] and appears to accompany memory reactivations during sleep.[108,114] Thus, using a temporospatial association task, Petzka et al.[182] observed in human EEG recordings that spindle amplitudes during post-learning sleep specifically over those areas that had engaged in prior encoding of the task were most distinctly correlated with later retrieval performance. Encoding of the task, in this study, was indicated by a decrease in 6–20 Hz alpha/beta EEG activity, and the topographical overlap between this decrease and spindle power during post-learning sleep predicted later retrieval performance. Gamma band (>40 Hz) activity is an indicator of memory processing in local networks and occurs phase-locked to the spindle oscillation.[183] By phase-coupling local gamma band activities, spindles might serve to synchronize memory processing in distributed cortical networks.

Spindles co-occur with SOs, with the depolarizing SO upstate driving the thalamic generation of spindles.[4,114,176] Fine-grained temporal analyses of event patterns revealed a second type of slow (7–12 Hz) spindle that accompanies the up-to-downstate transition of the SO, shows a more frontal cortical distribution, and is probably of different origin.[184,185] The function of slow spindles in memory processing is presently unclear. As to the classical fast spindle, accumulating evidence indicates the importance of precise phase-amplitude coupling between these spindles and SO upstates for effective consolidation.[61,186] Spontaneous memory reactivations can be decoded from the EEG signal during SO-spindle complexes after the participants had learned word-image pairs using multivariate classification[114] (Figure 3). However decoding classification accuracy strongly depended on the precision of SO-spindle coupling, which in turn strongly correlated with memory performance after sleep. *In vivo* calcium imaging in naturally sleeping mice revealed that spindles, which nest into a SO upstate are characterized by a unique constellation of activity in cortical microcircuits, where inhibition (by somatostatin positive cells) is released from the dendrites of pyramidal cells that themselves display strongly increased calcium activity, whereas an effective somatic inhibition of the pyramidal cells appears to prevail when spindles occur in the absence of a SO.[161,173,187] These findings point to an upregulation of plasticity in cortical microcircuits during SO-spindle complexes. Indeed, optogenetically inducing spindles in the thalamic reticular nucleus in the presence but not in

the absence of a SO upstate, significantly enhanced retention of contextual fear and object-location memories.[58]

While SO-spindle events are traditionally assumed to originate at the cortical level, i.e., from cortical SO driving thalamic spindles, intrathalamic recordings from epilepsy patients suggest additional thalamic contributions, specifically from anterior thalamic nuclei (ANT[188]). SO downstates and subsequent spindles recorded in ANT preceded respective downstates and spindles in frontal cortex recordings by ~50 and ~100 ms, respectively, suggesting a leading role of the ANT in the initiation of SO-spindles and in optimizing their phase-amplitude coupling. The anterior thalamus might be specifically involved in coordinating hippocampal memory replay with thalamocortical activity.[189]

Ripples represent oscillatory events hallmarking SWS at the hippocampal level. Ripples occur with an oscillatory frequency of ~80 Hz (in humans) in hippocampal networks in conjunction with a sharp wave arising from cornu ammonis 3 (CA3).[82] They also occur during quiet wakefulness, and outside the hippocampus, including entorhinal cortex and neocortex.[190–192] Hippocampal ripples accompany the replay of firing patterns of place cell ensembles that emerged during prior encoding.[80] Memory performance was impaired after blocking hippocampal ripples[84,132] and enhanced when spontaneously occurring ripples were prolonged by closed-loop optogenetic stimulation.[193] In a recent study, ripples induced optogenetically in CA2 neurons following encoding of a social memory task enhanced recall 24 h later.[194]

Ripples during SWS tend to nest into the excitable troughs of the spindle oscillation thereby forming spindle-ripple events.[195–197] Optogenetically induced spindles synchronized hippocampal ripples to the spindle troughs independently of whether spindles were induced during a SO upstate or downstate[58] indicating a direct effect of thalamic spindles on the timing of hippocampal ripples and associated memory replay. Hippocampal ripple activity is, in addition, suppressed during the SO downstate.[198,199] Indeed, intracranial recordings in human patients and rodents confirmed a triple coupling of oscillations with hippocampal ripples nesting in the troughs of the spindle oscillation, and spindles nesting in the upstates of SOs.[58,196,197] The exact fraction of such triple-coupled events strongly depends not only on the specific recording conditions but, in particular, on how strict the criteria (amplitude, duration, etc.) are that are used for identifying SOs, spindles, and ripples and their co-occurrence (e.g., Oyanedel et al.[199]).

In humans, this triple coupling is most consistent at central and parietal electrodes but appears to spare SO-spindle complexes identified over frontal cortical regions. So far, there is no evidence that, conversely, hippocampal ripples affect thalamic spindles. However, hippocampal ripples can facilitate cortical SOs. Hippocampal ripples often precede SO downstates by ~200–130 ms,[199] and electrical stimulation of cortical networks time-locked upon the occurrence of hippocampal ripples induced SO in prefrontal cortex with spindles nesting in their upstates.[200] Indeed, ripple-triggered stimulation in this study not only enhanced the rate of joint occurrence of SOs, spindles and ripples but also the consolidation of object-location memories encoded prior to sleep. Likewise, rats training a prehension skill task initially showed increased hippocampal ripples coupled to SOs in primary motor cortex during post-training SWS.[201] Interestingly, once motor performance stabilized, the rats consistently exhibited a sharp increase in SO coupling between prefrontal and primary motor cortical areas which was accompanied by a drop in the coupling of hippocampal ripples to SOs in primary motor cortex. The switch indicated by this pattern, from predominant hippocampal-neocortical processing during the early training phase to predominant intracortical processing at an advanced training phase, appeared to occur independently of changes in spindles which nonetheless showed consistent coupling with local SOs in prefrontal and motor cortex. Overall, the findings support a scenario where cortical SOs provide a globally acting top-down signal that sets the temporal frame for the parallel facilitation of thalamic spindles and, depending on task and training phase, also of hippocampal ripples during the subsequent depolarizing SO upstate.

The findings overall support a scenario where cortical SOs provide a globally acting top-down signal that sets the temporal frame for the parallel facilitation of thalamic spindles and hippocampal ripples during the subsequent depolarizing SO upstate. Thereby, spindles reaching hippocampal networks synchronize ripples and associated memory replay activity to the excitable troughs of the spindle, as a mechanism that, in turn, facilitates the direct transmission of the reactivated hippocampal memory information back to the neocortex.[195,198] Thalamic spindles, in this view, serve as the core of this loop in that they precisely time and synchronize hippocampal processes of memory replay with the regulation of plasticity in neocortical circuitry underlying the long-term integration of the memory information into respective cortical storage sites. Indeed, sleep spindles have been found to be associated with signs of increased synchronization between hippocampal and neocortical activity in both mice[189] and humans.[34] In humans, higher spindle density during sleep after learning of object-word pairs and scene-word pairs increased functional connectivity between hippocampus and neocortex during recall testing on the next day, with this effect pertaining to functional connectivity between anterior hippocampus and ventromedial prefrontal cortex (vmPFC) for object-word pairs, and between posterior hippocampus and posteromedial cortex for scene-word pairs. From a wider angle, spindles have been proposed as a mechanism that enables selective and reliable hippocampo- neocortical information exchange during sleep-dependent consolidation, while at the same time suppressing possible interference from relaying cortico-cortical and sensory information flow as it occurs in the wake state.[179,202]

Interestingly, the occurrence of spindles during non-REM sleep fluctuates with an infra slow rhythm of ~0.02 Hz[203] and recent research indicates that this rhythm possibly reflects a modulation via LC-NA activity.[204,205] We discuss the emerging role of the LC-NA system for sleep-dependent memory consolidation in Box 1.

REM sleep

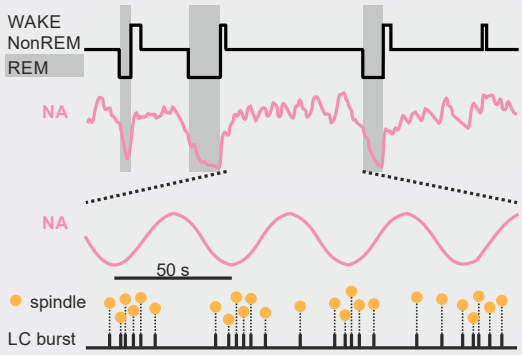
Whether and how oscillations characterizing REM sleep contribute to memory consolidation is presently not clear. Phasic REMs have been traditionally connected to visual dreaming and often considered a psychological form of memory reactivation.

Box 1. Noradrenergic modulation of memory consolidation during non-REM sleep

Noradrenaline (NA) is a ubiquitous neuromodulator in the brain that is essential for induction as well as maintenance of wakefulness. Its acute release mediates arousal and alertness levels,[206,207] and determines salience of incoming information (e.g., Rodenkirch et al.[208]). Importantly, the modulatory influence of NA is not limited to wake processes of memory encoding and retrieval but extends to the consolidation stage.[209] For example, associative memory performance was impaired by injection of NA antagonists 2 h after encoding, but not at shorter or longer delays.[210]

NA levels considerably vary between different brain states.[206] Tonic NA levels as well as LC firing rate decrease with increasing sleep depth with minimum levels reached during REM sleep.[206,204,211] In humans, pharmacologically increasing NA activity (by inhibiting synaptic reuptake) strongly suppresses REM sleep whereas changes in SWS are relatively small both after tonically increasing or decreasing NA activity (by administration of the α2-adrenoceptor agonist clonidine.[212,213] Beyond this tonic regulation, phasic changes in NA levels are linked to the sleep microstructure, as bursts of LC activity accompany the upstate of SOs in animals and humans.[170] Phasic activation of the LC-NA system is also involved in terminating spindles.[206,214] Measuring free NA in cortex and subcortical regions revealed strong infraslow fluctuations during SWS at a frequency of ~0.02 Hz similar to the infraslow fluctuations in spindle power but with a phase reversal such that minimum NA levels coincided maximum spindle activity.[205,204] It has been proposed that LC burst activity and phasic NA release during SO upstates and spindles might be particularly effective when they occur on a background of tonically downregulated NA activity.[170,215] Supporting this view, disturbing the infraslow NA rhythm by tonically upregulating NA activity during SWS impaired overnight memory consolidation.[204,213,214]

Whether and how the two infraslow rhythms in NA and spindle activity causally interact is not clear. Consonant with a suppressive action of NA activity on thalamic spindle generation, Kjaerby et al.[204] revealed increased spindle power following optogenetic inhibition of LC activity with longer 2-min periods of light stimulation which was followed by facilitated transitions into REM sleep, in conjunction with improved memory performance after sleep in a novel object recognition task. By contrast, in humans tonically inhibiting LC activity by clonidine impaired sleep-dependent memory consolidation whereas the administration of the NA reuptake inhibitor reboxetine increased memory consolidation together with spindle activity.[213,214] Related to this, an intriguing question is to what extent infraslow rhythms of NA activity directly affect the balance between so-called "sensory projecting" cell population that regulate sensory gating during the wake state and "limbic projecting cells" that regulate hippocampal-to-prefrontal neocortical information flow as required for sleep-dependent systems consolidation of memory.[4,216]



Modulation of brain NA levels during sleep

Example traces of NA levels during wakefulness (wake), non-REM (enlarged underneath), and REM sleep (recorded by Osorio-Forero et al.[205] in a mouse expressing the fluorescent NA sensor $GRAB_{NE1h}$). Note the oscillating NA levels during non-REM sleep that divide non-REM sleep into phases with high and low spindle density. Additionally, REM sleep is characterized by a strong decrease of NA levels (adapted from Osorio-Forero et al.[205]). Cortical spindles are accompanied by burst activity of NA cells in the LC that terminates spindles (bottom, Swift et al.[214]) and that may particularly enhance synaptic consolidation when occurring against a background of tonically lowered NA levels.

Field potentials and unit activity during phasic REMs resemble those observed during image presentation in the wake state.[217] Phasic REMs go along with a selective suppression of informative external inputs[218] and with a coordinate activation of thalamic head direction cells matching the direction of the phasic REMs.[219] Direction of phasic REMs can be likewise predicted by the pattern of PGO waves. PGO waves typically precede the onset of phasic REMs by ~25 ms[220] (but sometimes also occur during non-REM sleep especially during the transition into REM sleep). Thus, PGOs preceding phasic REMs might initiate memory reactivations accompanying these phasic REMs.[162] However, there is currently no evidence that PGO-REM complexes affect consolidation processes. Similarly, theta activity dominating tonic REM sleep has been proposed to support memory consolidation in some studies, particularly, of emotional memories. Selective optogenetic suppression of hippocampal theta activity during REM sleep impaired consolidation of object-location memory.[221] However, the overall picture is rather inconsistent, which might partly be explained by findings by Poe et al.[134] They found that place cells were reactivated during REM sleep in the peaks of the theta oscillation as long as the encoded environment was novel but shifted to the troughs of the

theta oscillation once the environment became familiar, with the reactivations during theta troughs assumed to weaken respective memory. This dual function of REM sleep theta may partly depend on input from melanin-concentrating hormone (MCH) producing hypothalamic neurons. REM sleep active hypothalamic MCH neurons produced forgetting of hippocampal memory possibly by increasing inhibition of hippocampal pyramidal cell firing,[222] whereas another study identified a subgroup of REM sleep active MCH neurons specifically projecting to the hippocampal CA2 region, which enhanced consolidation of social memories.[72]

MEMORY-SPECIFIC SYNAPTIC UPSCALING VS. GLOBAL SYNAPTIC NETWORK DOWNSCALING

At the level of global network regulation, sleep is considered to primarily serve the downregulation, i.e., in a strict sense a down-selection of synaptic connectivity.[223] This view has been comprehensively elaborated in the "synaptic homeostasis hypothesis" (SHY) by Tononi and Cirelli[223–225] (Figure 2B). The SHY assumes that during the wake phase, information is encoded into synaptic networks, which leads to the widespread potentiation of excitatory glutamatergic synapses. An ongoing uptake of information with extended periods of wakefulness would, thus, eventually produce saturation in the synaptic networks impairing further encoding of information. Moreover, the potentiation of synapses during wake encoding of information is expected to foster structural growth of synaptic spines and functional changes, i.e., increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors, and therefore to increase synaptic energy demands. Thus, in order to enable continuing effective encoding of information and to keep space and energy demands of the brain balanced, synaptic networks potentiated during the wake phase need to be re-normalized, and according to SHY, this is established during sleep. SHY is supported by a great body of research in animals and humans. In rodents, sleep has been shown to reduce the overall number of synapses,[163,226,227] synaptic AMPA receptor levels,[165,228] and cortical phosphorylation levels[229] in comparison with wakefulness. Using transcranial direct current stimulation and transcranial magnetic stimulation, studies in humans provided functional evidence for sleep decreasing cortical excitability.[230] Importantly, the concept of sleep generally downscaling and re-normalizing synaptic connectivity and network excitability conflicts with the idea that sleep enhances the consolidation of specific memories which, in theory, should manifest as a relatively enhanced synaptic connectivity and excitability of the memory representing neuron ensembles. Indeed, a central unresolved question in this field is how sleep can serve both the seemingly opposite functions of global synaptic downscaling and local memory-specific synaptic upscaling in parallel.

At the morphological level, there is evidence that synaptic downscaling during sleep is not ubiquitous but may spare some select synapses that are particularly large or were involved in prior encoding, resulting in increased connectivity at these synapses[163,164,228,231] (Figure 2C). In order to track synaptic spines before and after training a motor task (complex wheel running) and before and after subsequent sleep, Miyamoto et al.[165] used repeated *in vivo* two-photon microscopy in adult mice that expressed a red fluorescent protein in layer 2/3 pyramidal cells within motor cortex to label dendritic spines. Additionally, they tagged AMPA receptors with a green fluorescent marker allowing to quantify spine numbers and size as well as spine-surface expression of the AMPA receptor subunit GluA1. Spine-surface expression of GluA1 as well as average spine size, but not spine density, increased after training, and this increase was globally reduced during subsequent sleep, but not when the animals remained awake in the post-training interval. These results confirm that global sleep-dependent synaptic downscaling also captures networks after they were engaged in training a specific task. To dissect specific effects of sleep on memory, the study compared those spines that showed the largest increase in GluA1 expression during learning ("max spines") and therefore were considered to be most likely related to encoding the memory, with all other synapses. Importantly, this comparison revealed that the max spines—although also undergoing some downscaling—kept a relatively higher GLuA1 expression after sleep than after a post-training period of wakefulness. Thus, the data suggest the overall sleep-dependent synaptic downscaling effects to be relatively weaker for synapses putatively contributing to a specific task memory than for non-contributing synapses.

Whereas Miyamoto et al.[165] did not discriminate sleep stages, other studies suggest that synaptic scaling during sleep varies between SWS and REM sleep. On a morphological level, SWS following motor task training was found to support branch-specific spine formation in a subset of cells in motor cortex.[164] By contrast, REM sleep was found to be characterized by enhanced synaptic pruning that selectively omitted subsets of synapses formed during encoding of new motor memory prior to sleep.[231] Moreover, cortical and hippocampal neuronal activity showed more robust decreases across periods of REM sleep than SWS.[166,232]

E-I balance

Rather than focusing solely on excitatory synapses, it may be necessary to also consider dynamics of inhibitory synapses, i.e., the excitation-inhibition (E-I) balance, in order to more comprehensively address the question how local and global synaptic scaling processes interact to enable memory consolidation during sleep. The primary effect of sleep might well be to reduce overall network activity, and connectivity at excitatory synapses[233] by increasing inhibition, i.e., by pushing the cortical E-I balance toward increased synaptic inhibition. Indeed, inhibition globally increased within 4 h of sleep while synaptic excitation decreased.[167] Corresponding effects were found in humans.[234] Cortical inhibition is higher in REM sleep than SWS due to enhanced activity of parvalbumin-positive interneurons.[161,167,235] In an attempt to differentiate effects of sleep on cells contributing to sleep-dependent memory consolidation from global effects of sleep on the cortical E-I balance, Niethard et al.[166] (Figure 2D) used *in vivo* calcium imaging in mice to monitor the activity of excitatory and inhibitory cells in layer 2/3 over consecutive SWS and REM sleep epochs. Consistent with a global increase in inhibition, overall pyramidal cell activity decreased across both REM sleep and SWS epochs,

accompanied by a global increase in parvalbumin-positive interneurons during SWS epochs. Wide field imaging experiments using CaMKII as a marker for excitatory pyramidal cells confirmed this pattern across the dorsal cortex[167] although specific subgroups of excitatory cells (e.g., Thy-1 positive cells), contrary to the global decrease, have been found to increase activity during REM sleep particularly in retrosplenial and visual cortex.[236,237] Pyramidal cells most active during sleep spindles, which showed also enhanced activity during prior wake phases, were considered cells that more likely engaged in prior encoding activity. Interestingly, these spindle-active cells, against the trend toward downscaling in the overall population of pyramidal cells, upregulated their activity over the course of SWS, in line with the notion that sleep spindles selectively strengthen engram specific synaptic connections. During succeeding REM sleep epochs activity of these cells decreased, in parallel with the overall population. However, activity of these spindle-active cells remained at a relatively enhanced level at the end of REM sleep as well as during the subsequent wake periods, in line with the idea of concurrent global downscaling and select upscaling thereby preserving learning-related differences in scaling induced during prior wakefulness.

Although the studies have so far evidenced distinct synaptic scaling effects of sleep within circuits that do and do not contribute to the consolidation of memory during sleep, the mechanisms leading to this differential processing are not clear. One candidate here are ripples, which drive the replay of newly encoded representations in hippocampal circuits and its spreading to multiple extrahippocampal areas.[238] Interestingly, ripples appear to be also directly implicated in synaptic scaling, as closed-loop optogenetic suppression of hippocampal ripples in dorsal CA3 prevented spontaneous synaptic downscaling in these circuits.[132] A tentative scenario could be as follows: during SWS, hippocampal ripples drive the replay of ensemble firing patterns producing synaptic downscaling in hippocampal networks. At the same time, spindles coupling with hippocampal ripples time cortical reactivations thereby fostering memory-specific synaptic plasticity in cortical networks. Subsequent periods of REM sleep may primarily support the global downregulation of synaptic connectivity sparing those synapses that were strengthened during prior SWS.

Compartmentalized neuronal responses

Interestingly, beyond evidencing the co-occurrence of differential synaptic scaling during sleep at global and local levels, the findings overall point to a compartmentalized response in this regulation. This means, within the same cell both, synaptic strengthening and weakening can occur during SWS and REM sleep, possibly depending on synapse size,[163] AMPA receptor densities[165,228] as well as immediate early gene levels.[239] In the neocortex, the soma and widespread dendritic trees of pyramidal neurons might represent separate computational elements that are also subjected to a differential regulation of synaptic plasticity during sleep. Thus, similar to spine formation during learning, also spine formation during post-training SWS only pertained to select dendritic branches of motor cortex pyramidal cells.[164] Sleep spindles go along with reduced inhibition of the dendrites of cortical pyramidal cells thus enabling increased dendritic calcium influx while at the same time the soma of these cells is subjected to an increased inhibition by parvalbumin-positive interneurons.[161,240] A similar somato-dendritic decoupling of pyramidal cell regulation was revealed during REM sleep, where the optogenetic inhibition of dendritic activity (by stimulating vasoactive intestinal peptide positive interneurons) impaired formation of associative memory, whereas inhibition of the soma (by stimulating parvalbumin-positive interneurons) improved memory.[235] Assuming a dendritic-branch-specific representation of memory, local synaptic scaling processes during sleep may well contribute to the reorganization of these memories by changing the topographical distribution of synapses along the dendritic tree. For example, dendrites in layer 1 appear to mainly encode more abstract information compared with deeper layers where perceptual features are encoded.[241] A sleep-induced shift toward preferential strengthening of more distal synapses in layer 1 could thus explain the formation of more generalized memories and their integration into pre-existing schemas during sleep.[242] Yet, while highly intriguing, the question of how the compartmentalized regulation of synaptic plasticity contributes to the reorganization of memory during sleep clearly awaits further research.

MEMORY AND SLEEP DURING EARLY DEVELOPMENT

While sleep is well known to support long-term memory formation in adults, the memory function of sleep during early development is by far less well investigated. During infancy and childhood, humans, as well as rodents, spend much more time asleep than in adulthood. At the same time, there is a much greater need to form long-term memory and to accumulate knowledge over time. Assuming that the formation of long-term memory, and the putatively underlying machinery of an active systems consolidation process, represents a major function of sleep, one would expect that the early development of the brain state of sleep proceeds tightly interlinked with that of the relevant memory systems. Indeed, there is evidence that one major function of sleep during brain development is to promote experience-driven neural plasticity (e.g., Wilhelm et al.[243] and Blumberg et al.[244]), and it is likely that, conversely, such experience-driven memory formation contributes to gradually shaping the brain state of sleep during development.[245,246]

Development of sleep

The differentiation of sleep and wake states during the early stages of life goes along with the emergence of synchronized activity in cortical and hippocampal networks.[247] Human infants, during the first 3 months of life do not exhibit clearly separable periods of SWS and REM sleep, with the precursor states termed quiet and active sleep, respectively. Subsequent periods are then hallmarked by massive changes. Total sleep time decreases along with a change from a polyphasic to a monophasic distribution of sleep phases across the day.[246,248] Compared with adults, infants and children spent more time in SWS and REM sleep with the latter probably particularly contributing to the regulation of synaptic plasticity during development.[231,249] The EEG signatures implicated in memory consolidation likewise show distinct and partially protracted developmental trajectories, which are roughly comparable between humans and

rodents.[250] First, sleep spindles appear typically before the 3rd week after birth and may at this time also intrude into periods of active sleep.[244,251,252] At around the same time, brushes of delta activity are present, whereas mature forms of consolidated SWA and SOs as they hallmark adult SWS do not emerge until 4–5 months of age. Subsequently, slow oscillatory activity shows an inverted U-shaped trajectory peaking during early adolescence, which presumably reflects parallel changes in cortical synaptic connectivity and white matter microstructure.[253] Although present early in life, the first emergence of spindles and SOs does not necessarily constitute mature, adult-like types of these oscillatory events. For example, SO activity during the first 1.5 years of life dominates over occipital cortical regions, whereas in adults it dominates over frontal cortical regions.[254]

In the rodent hippocampus, at the end of the first postnatal week, "sharp wave bursts," as a first organized network event can be detected, while SPW-Rs in conjunction with neuronal reactivations only emerge at the end of the second postnatal week.[255,256] Offline place cell activity associated with SPW-Rs observed in rat pups before weaning (at postnatal day [PD] 21) reflected predominantly stationary locations in recently visited environments, whereas coordinate sequential replay of place cell ensemble firing patterns that encoded extended trajectories through space during exploration, emerged only gradually after weaning.[255] The rather delayed occurrence of both sequence replay during sleep in the presence of SPW-Rs, as well as the prior encoding of these sequences during ongoing wake theta activity, parallels the protracted trajectory for the formation of hippocampus-dependent episodic memory, and could partly reflect the late postnatal maturation in excitatory synaptic plasticity in hippocampal networks.[255] In fact, replay of sequential firing patterns during sleep appears to be the latest emerging signature of hippocampal activity during early development. Presently, little is known about whether and how these emerging signatures of neuronal processing during sleep causally contribute to long-term memory formation and its behavioral expression.

Behavioral assessment of sleep-dependent memory formation during development

Effects of sleep on memory as assessed by subsequent recall performance have been almost exclusively investigated in human infants and children. Overall, these studies indicate sleep-dependent benefits across a large variety of memory tasks, such as memory for objects and actions, declarative, emotional and language-related memories (e.g., Prehn-Kristensen et al.[257] and Seehagen et al.[258]), and impaired memory after sleep restriction (e.g., Lo et al.[259]). In line with the idea that in the mature brain, memory consolidating effects of sleep primarily relate to the hippocampus-dependent episodic memory system,[66,74] some studies in children suggest more robust benefits from sleep for episodic and declarative types of memory in comparison with task aspects less reliant on the hippocampus, similar to procedural motor skills or object recognition.[257,260] However, there are also findings indicating an only weak or even absent benefit from sleep for episodic or spatial aspects in memory,[261] suggesting that there are additional factors modulating sleep-dependent memory benefits. For example, testing 7- to 11-year-old children's spatial memories for card pairs showing the same object, Prehn-Kristensen et al.[262] found superior recall after post-encoding nocturnal sleep, in comparison with a daytime wake interval only when these memories were associated with a high reward. Furthermore, in light of the rather protracted maturation of not only the hippocampus but also medial prefrontal cortex, one might expect reduced benefits for hippocampus-dependent memories from sleep during early development. Contrasting with this hypothesis, children around 10 years of age showed greater sleep-dependent gains in explicit knowledge of a sequence than their adult controls.[46] The participants of this study were trained on a serial reaction time task (SRTT) under implicit conditions, i.e., not being aware of the underlying repeating SRTT sequence. Then, after periods of post-training sleep or wakefulness, they were asked to explicitly recall the sequence. The greater gain in explicit knowledge in the children was associated with higher amounts of slow oscillatory activity.[263] Children of similar age (7–12 years) showed likewise a greater sleep-dependent gain than adult controls for associative memories between artificial objects and their functions.[264] Magnetoencephalographic recordings indicated an involvement of hippocampal and parahippocampal regions at learning, whereas the sleep-dependent consolidation of the object-function associations in the children was associated with marked changes in prefrontal cortex activity at recall testing.[265] The findings led the authors to propose that sleep triggers a reorganization of memory-related brain activity toward prefrontal areas, which in the children occurs at a faster rate than in adults.

In humans, the ability to form episodic memories for events bound into a specific spatiotemporal context already emerges at an age between 3 and 4 years.[266] Given the lack of language skills at this age, the few studies addressing the role of sleep in the development of episodic memory function used non-verbal indicators of memory like "deferred imitation" (where memory is inferred from the child's imitation of a previously modeled behavior), exploratory eye movements, and event related brain potential (ERP) responses. Findings generally agree with the notion that sleep supports processing of episodic-like memories and its precursors also at this early developmental stage (e.g., Seehagen et al.[258] and Lokhandwala and Spencer[267]) with some findings suggesting that sleep in infancy particularly supports the formation of abstracted and generalized representations.[268] Thus, based on ERP indicators of memory for associations between spoken artificial words and visually presented artificial objects, Friedrich et al.[269] found in 9- to 16-month-old infants that the occurrence of sleep during a ~1.5-h napping period after encoding facilitated the generalization of the words to novel but similar objects, indicating a categorization process. This effect was accompanied by a strong N400 ERP component at test when a word was presented together with a novel but dissimilar object. Sleep, thus, helps the infants to acquire the semantic meaning of words. Using a similar ERP-based approach but word-object associations that were already known to 14–17-month-old infants, similar to the spoken word "ball" combined with a picture of a ball, the same group also demonstrated a facilitating effect of sleep on the formation of episodic-like memory, i.e., the memory for a unique word-object association.[270] Interestingly, the ERP pattern at test indicated

that after sleep-dependent consolidation, the newly stored word-object events are not processed semantically, although appropriate semantic memories were present and accessible by similar events that were not experienced right before the nap. It was speculated that such a temporarily restricted period of disabled semantic processing might protect newly formed precise episodic memory from interference with generalized semantic memories. In even younger 6- to 8-month-old infants, indicators of memory for sequential rules (nonadjacent dependencies in spoken artificial word strings) were found to be enhanced after sleep.[271] However, such rule memory was also found to be enhanced after a wake control period, although linked to a different pattern of ERP responses suggesting that rule memories formed during sleep and wake at this age differ in quality. Overall, these studies indicate that sleep in infants supports the consolidation of episodic memory as well as the formation of more abstracted generalized semantic-like memory and that both kinds of consolidation processes are established in parallel during sleep.

Neuronal mechanisms of sleep-dependent consolidation during early development

Available evidence provides only a fragmentary picture of how systems consolidation might be established in the developing brain. This is partly owed to the particular challenges linked to the assessment of brain structures such as the hippocampus and the prefrontal cortex during infancy and childhood. Using fMRI during sleep in 2-year-old toddlers, Ghetti and coworkers[272] observed signs of reactivations in the hippocampus to previously learned songs which were associated with an improved memory for the context in which the song had been encoded.[272,273] Specifically, toddlers who later remembered where, in which temporal order, and in the presence of which toy character they had heard the song exhibited stronger hippocampal activation when the song was played to them during sleep. The memory-related enhancement of hippocampal activation during sleep was still present when tested 1 week after the encoding session. However, whether the experimentally induced hippocampal reactivations indeed contributed to memory consolidation during sleep remained unclear because the fMRI sessions in these studies always took place in the end after retrieval testing.

There is consistent evidence of an association of sleep spindles with memory consolidation in infancy and childhood (e.g., Friedrich et al.[269] and Friedrich et al.[274]). Rat pups showed increases in spindle density in parallel with the emergence of hippocampal object-in-place memories during early development.[275] Trajectories of spindle density peaking during adolescence and spindle amplitude peaking during infancy likely reflect the maturation of thalamocortical brain regions.[252,276] Accordingly, sleep spindles in early development may not only serve the consolidation of specific memories but also to advance the development of the memory system in general. For example, 6-month-old infants following a nap showed signs of memory for semantic categories associated to artificial words, which were positively correlated with local spindle activity during the nap.[274] Strikingly, under natural learning conditions this process is only observed distinctly later during development.

Assuming that the hippocampal-neocortical dialog underlying sleep-dependent systems consolidation is mediated through a triple coupling between hippocampal ripples, spindles, and neocortical SO, more recent studies have focused on the phase-locking between these oscillatory events. In humans, the coupling strength of spindles to the SO upstate (i.e., how precisely an individual's spindles across events nest into a specific phase of the SO upstate), increased across childhood and adolescence, along with an increased capability to retain memory for word pairs across sleep,[60] and a similar parallel developmental course between the emergence of SO-spindle coupling and of object-in-place memory has been shown in rat pups.[275] Moreover, in school children aged 7–15 years the coupling strength of spindles to the SO upstate during post-encoding sleep predicted recall of word lists on the next day, with this relationship occurring independently of the children's age,[277] supporting the view that at this age the phase-locking of spindles to SO-up states is firmly established as a mechanism of memory consolidation. By contrast, the scarce available evidence suggests that such coupling might be weak or even entirely absent during infancy.[275] Even less is known about the coupling of hippocampal ripples with spindles during development. Preliminary findings suggest that ripple activity as well as ripples co-occurring with spindles decrease during early development.[275] Interestingly, in rat pups the sleep-dependent occurrence of adult-like persisting spatial object-in-place representations could be advanced to PD31 (corresponding to late childhood) by repeatedly exposing them to 5-min periods of discrete spatial experiences (configurational changes in two identical objects) on the days before[278] (Figure 4). In parallel, the pups displayed an increased percentage of hippocampal ripples coupled to parietal SO-spindle complexes, and a stronger ripple-spindle phase-locking during the post-encoding period of retention sleep. The findings are consistent with the idea that experience during development drives the maturation of the episodic memory system in general, by enhancing cortico-hippocampal information exchange, in parallel with the formation of individual integrated knowledge representations during sleep.

Overall, the available evidence suggests that the processing of episodic memory information profits from sleep during development. In specific task conditions, this benefit can be even greater than in the mature brain which has led some experimenters to propose that the sleep-dependent transformation of representations in the hippocampal-neocortical system during early development proceeds at a faster rate.[265] In stark contrast, the underlying hippocampal and neocortical networks, particularly in the medial prefrontal cortex as a hub in this system, are rather immature, as is also the coupling of SO, spindles and ripples assumed to mediate the dialog between hippocampus and neocortex during systems consolidation. This functional immaturity in conjunction with signs of a well-pronounced memory formation during sleep challenges the view of an active systems consolidation process that crucially relies on the precise transmission of hippocampally replayed information to neocortical long-term storage sites. Instead, memory processing and consolidation in the developing brain might be organized in a more parallel manner at the hippocampal and neocortical level which, in conjunction

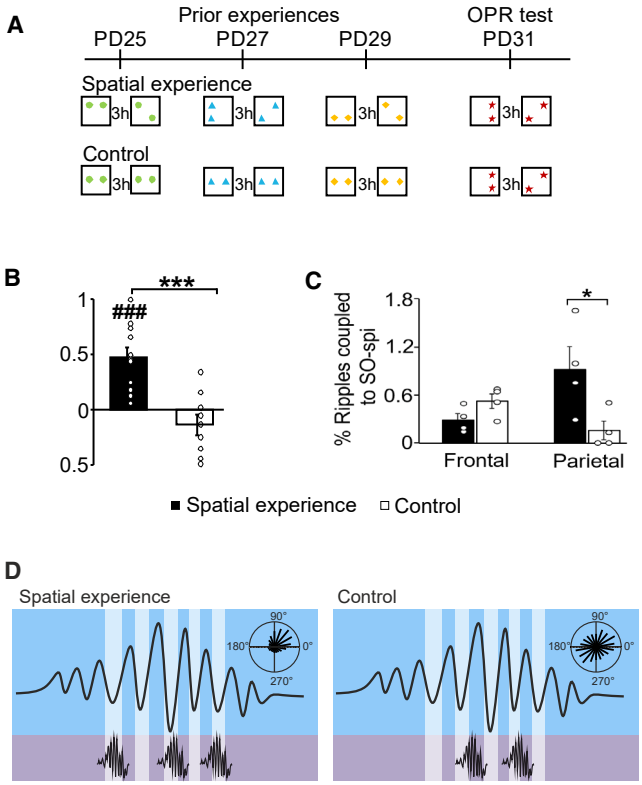


Figure 4. Experience-driven maturation of sleep-dependent memory consolidation

(A) Study design: two groups of rats were exposed to discrete experiences on PD25, PD27, and PD29, followed by testing spatial memory on an object-place recognition (OPR) task on PD31 (the total period roughly corresponding to the time from early to late childhood). For the rats of the spatial experience group (n = 11) prior experiences comprised a change in the spatial configuration of two identical objects with, each experience set up like an object-place recognition (OPR) task including a first (encoding) period during which the rat encountered the two identical object s in the arena and, delayed by 3 h, a second (retrieval) period in which one of the objects was displaced to a new location. For the control group (n = 9), the experiences were set up identically, except that in the second (retrieval) period both objects remained at the same place. OPR testing on PD31 was performed with novel objects.

(B) Mean ± SEM OPR memory performance (discrimination index) on PD31 for the spatial experience and control groups (dot plots overlaid). Only rats with spatial experience show above chance OPR performance which is also significantly higher than in the controls. #p < 0.05, ###p < 0.001, against chance level; ***p < 0.05 for comparisons between groups.

(C) Percentage of hippocampal ripples co-occurring with SO-spindle complexes during sleep in the 3-h retention interval between encoding and retrieval testing on the OPR task on PD31 is enhanced in parietal but not frontal recordings in the spatial experience group.

(D) Prior spatial experiences also enhance phase-locking of hippocampal ripples to the individual spindle oscillation (adapted from Contreras et al.[278])

with a generally increased plasticity especially during REM sleep[231,249] might produce stronger transformations at the neocortical level.

SLEEP VS. WAKE-DEPENDENT MEMORY CONSOLIDATION

Although the body of experimental evidence indicates a benefit of sleep in comparison with a post-encoding period of wakefulness, there is an increasing number of studies that failed to reveal such benefit, suggesting that the consolidation of long-term memory is not a unique function of sleep but also occurs in the wake state. The comparative study of sleep and wake consolidation processes, including their distinctness as well as their commonalities, is only in its beginnings.

Hippocampal dependency might be one feature dissociating consolidation in both brain states. Disrupting hippocampal activity during post-encoding sleep in rats impairs long-term memory not only on hippocampus-dependent spatial tasks but also on tasks like novel object recognition which can be encoded and retrieved in the absence of hippocampal function.[66] By contrast, consolidation during wakefulness for such tasks is not impaired but can be even enhanced when hippocampal activity is disrupted during the post-encoding wake interval.[6] In these experiments, adult rats were tested on a classical novel object recognition task with an encoding phase followed by a 3-h period during which the animals slept or remained awake. Inhibiting the hippocampus by muscimol injection during post-encoding sleep impaired object recognition tested 1 week later. By contrast, inhibiting the hippocampus during post-encoding wakefulness significantly improved object recognition memory at test, suggesting that hippocampal activity in the wake state interferes with ongoing consolidation. Interestingly, in the experiments natural awake consolidation turned out to be also superior to sleep consolidation when object recognition after 1 week was tested in an environmental context entirely different from that during encoding. These findings indicate that unlike sleep consolidating an event/object into memory as it is experienced in a specific spatiotemporal context, in the wake state the event/object is consolidated independently of its context.

Noteworthy, mediated via hippocampal receptors, glucocorticoids have also been found to exert opposing effects on consolidation depending on the brain state in humans and rats, increasing consolidation in wakefulness but impairing sleep consolidation.[279,280] In hippocampal slice preparations, low glucocorticoid concentrations increased rates of SPW-Rs typically accompanying memory replay whereas high glucocorticoid concentration suppressed SPW-Rs,[281] underlining the importance of naturally low glucocorticoid concentrations for consolidation during nocturnal sleep. In light of glucocorticoids enhancing wake consolidation, the idea is obvious that stress might represent a condition enhancing consolidation in the wake state. However, stressors applied after encoding produced rather mixed effects. In humans, enhancing effects of post-encoding stress on memory consolidation were only found when the stressor was administered in the same context as during encoding, and in rats detrimental effects of post-encoding stressors on memory prevailed,[282] arguing against the view that stress as an internal state and independent of its external origin modulates wake consolidation.

Against the backdrop that the mammalian hippocampus shows some homologies with the insect mushroom bodies in structure and function,[283] it is interesting that sleep and wake-associated consolidation has been also dissociated in *Drosophila*. Using Pavlovian conditioning, Chouhan et al.[7] trained starved flies to associate an odor with sucrose. For the 24-h period following conditioning, the flies either remained starved or were fed *ad libitum*. In addition, the flies were either

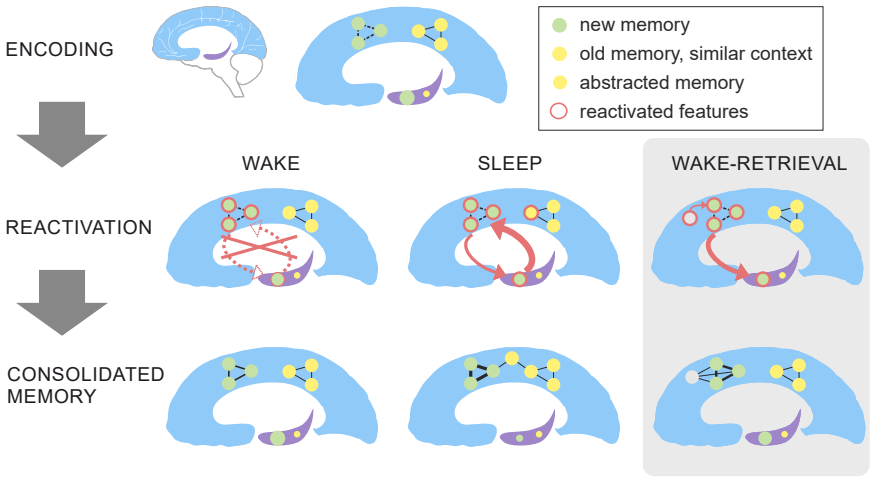


Figure 5. Consolidation of memory in the sleep vs. wake state

During encoding, a new memory trace (green circles) is formed in the neocortex (blue) and hippocampus (purple). In the (quiet) wake state, spontaneous reactivations (red outline) of the new memory occur separately and not in synchrony for neocortical and hippocampal ensembles, leading to moderate memory strengthening (black lines connecting dots) and a neocortical memory trace that is consolidated independently of contextual/episodic features as encoded in the hippocampus. In the sleep state, the unique milieu of triple-nested slow oscillations, spindles, and ripples occurring together with bursts of noradrenergic activity enables the synchronized reactivation of hippocampal and neocortical memory features. These synchronized reactivations promote the preferential transmission of contextual information from hippocampus to neocortex (thick red arrow) where this information is used to interlink the new memory with older memories (yellow circles) that were experienced in another but, to a certain extent similar context. Synchronized reactivations during sleep produce a stronger stabilization of the new memory (thick black lines) than desynchronized spontaneous reactivations during wakefulness, with the hippocampal-to-neocortical transmission of context information possibly guiding the evolution of abstracted memory (green-yellow circle) generalizing across experiences from different contexts. Right (gray shaded): active retrieval represents a specific case of wake reactivations where synchronized memory reactivations in neocortex and hippocampus are driven by a prefrontal cortical top-down process of mnemonic search initiated by a cue or prior knowledge (gray circle). Active retrieval also strengthens the respective neocortical memory traces but lacks the milieu-specific effects of hippocampal-to-neocortical context feedback during sleep.

deprived of sleep or were allowed to sleep during the first 6 h after conditioning. For later memory testing of the odor-sucrose pairing, a kind of T-maze was employed to assess the flies' tendency to approach the arm that was cued by the conditioned odor. Sleep was required for forming a long-term food-odor conditioning memory only in the fed animals, and these animals indeed also displayed increased sleep after conditioning. By contrast, when starved the flies formed such long-term memory also in sleep-deprived conditions. Sleep-independent memory formation in starved flies depended on the hunger signal neuropeptide F. Both hunger-dependent and sleep-dependent long-term memories involved distinct neuronal circuits in the mushroom bodies, i.e., the anterior-posterior α'/β' neurons in fed conditions, and the medial α'/β' neurons in starved conditions. Beyond pointing to distinct mechanisms mediating wake and sleep-dependent consolidation processes, the findings show that unlike sleep consolidation, wake consolidation strongly depends on internal organismic states such as hunger.

Systems consolidation in sleep vs. wakefulness

Consolidation during sleep is thought of as an active systems consolidation process in which SOs, spindles, and ripples repeatedly occurring in synchrony with memory replay transform memory representations such that they eventually reside primarily in neocortical long-term storage sites. Obviously, SOs and spindles do not contribute to consolidation during wakefulness, as these oscillatory events hallmark the state of sleep. However, the offline replay of ensemble firing patterns in conjunction with hippocampal ripples occurs also during quiet wakefulness.[138,150] Disturbing such wake replay activity has also been found to impair memory formation,[284,285] indicating that neuronal reactivations of newly formed representations represent a common core process for consolidation during sleep and wakefulness. It is, thus, the milieu in which the replay occurs that makes consolidation in the two brain states distinct, comprising not only brain oscillatory activity and events but also neurotransmitters and neuromodulators, such as acetylcholine, noradrenaline, and glucocorticoids, which are subject to a brain-state-specific regulation and, moreover, are implicated in consolidation and plasticity at the synaptic level (Figure 5).

Replay occurring during sleep has been proposed to specifically support systems consolidation in the hippocampus-dependent episodic memory system, based on evidence that, in particular, the milieu during SWS facilitates hippocampal-to-neocortical information transmission.[73] Indeed, conditions such as the globally low levels of acetylcholine and glucocorticoids together with the occurrence of SO, spindles and ripples that hallmark SWS, facilitate hippocampal replay, output, and the transmission of reactivated memory information toward neocortical long-term storage sites.[281,286–289] However, challenging the view of systems consolidation as a process exclusively linked to sleep, signs of systems consolidation can be also observed under certain conditions in the wake state.[290–293] Using fMRI and microstructural MRI in humans, these studies investigated changes in representations occurring with repeated retrievals on spatial (object-location and spatial navigation) and verbal (word lists) tasks and found that with increasing number of repetitions activation of task-relevant neocortical areas (such as the medial parietal cortex) increased, whereas activity in the hippocampus but also in medial prefrontal cortex was maximal on the first trial and decreased across trials. With intervening nocturnal sleep, the activity increase in neocortical areas remained stable for 24 h, was strongly related to memory retention, and was paralleled by microstructural changes indicating neocortical memory storage. Thus, representations with some stability can be formed during wakefulness in the neocortex within one session, suggesting a rapid type of systems consolidation.

Then, what is the difference between the systems consolidation process in the wake and in the sleep state? Does it differ

in the underlying mechanisms that, perhaps, capture different memory traces, as it is suggested by findings in *Drosphila*?[7] Given the similarity of replay during wake and sleep, sleep replay may basically be considered a further recapitulation of experience encoded and rehearsed during wakefulness, thus further stabilizing respective representations. Himmer et al.,[293] for example, observed a decrease in hippocampal fMRI activity with repeated retrieval of learned word lists during wakefulness, and this reduction in retrieval-related hippocampal activity remained stable only when the participants slept during the following night. The stabilizing effect of replay during sleep might be particularly strong as it occurs in the absence of interfering stimulation and is further increased as it occurs time-locked to SO-spindle events and bursts of activity in the LC-NA system, as well as by unknown factors that spare underlying synaptic consolidation processes from being down-scaled during SWS and REM sleep.

However, there are also reasons to assume that beyond stabilizing representations formed during the wake state, sleep consolidation impacts different engrams. Given that retrieval-related reactivations during wakefulness are driven by a conscious prefrontal cortical top-down process, the fast formation of neocortical representations in the wake state is presumably determined to a greater extent by direct inputs from cortical areas engaging in sensory-motor processing than by hippocampal inputs. In fact, suppressing hippocampal activity in rats during a post-encoding period of wakefulness improved rather than impaired memory consolidation,[6] indicating that spontaneous hippocampal offline inputs during the wake state interfere with, rather than support the formation of stable cortical representations. Along this line, wake replay is expected not to interfere with consolidation only when it is not "offline" but occurs briefly after encoding in the very same context as the encoded event.[284,285,293] Thus, spontaneous offline replay activity in hippocampal networks enhancing memory indeed appears to be a unique feature of sleep-dependent consolidation[66,74] (Figure 5). Such replay is distinct in that it involves, in hippocampal networks, a reinstatement of contextual features of various experienced episodes, tightly synchronized to memory processing in thalamocortical networks. Promoted through the depolarizing effects originating from cortical SO upstates, ripples emerging phase-locked to spindle oscillations may then provide a mechanism to immediately feedback the reinstated contextual information into thalamocortical networks for an integrative processing of newly encoded and pre-existing memory.[294] Importantly, rather than enhancing storage of the contextual information per se, this feedback might primarily serve to frame and gate processing within cortical long-term stores, for example, when it comes to merging experiences obtained across similar contexts and establishing generalized representations. However, despite some supporting evidence,[97] this hypothesis is clearly in need of further examination.

Conclusions

Our review describes the state of the art in research on the function and mechanisms of sleep in long-term memory formation. Although we identified a number of gaps in knowledge, the available evidence supports the notion that sleep promotes memory formation in an active systems consolidation process that is specifically established in the hippocampus-dependent episodic memory system. In this systems consolidation process, the synchronized occurrence of memory replay, hippocampal ripples, sleep spindles, and SOs during SWS provides a mechanism redistributing and transforming newly encoded experiences into longer-lasting representations residing preferentially in neocortical networks. Pressing open questions to be addressed in future research are (1) does sleep support the abstraction of gist memories and if so, what is the nature of these memories—is it memory for salient information or generalized information that are consolidated during sleep-dependent systems consolidation? (2) What are the synaptic mechanisms underlying the storage of such abstracted representations in cortical circuits. (3) Why are sleep-dependent memory benefits during early development preserved, or even stronger than in the mature brain, despite clear signs of a functional and structural immaturity of the hippocampal memory system, and finally (4) to what extent do the reactivation-related mechanisms and involved neuronal traces differ between wake and sleep-associated consolidation processes?

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AUTHOR CONTRIBUTIONS

All authors wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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