REVIEW

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Brain Rhythms During Sleep and Memory Consolidation: Neurobiological Insights

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Sleep can benefit memory consolidation. The characterization of brain regions underlying memory consolidation during sleep, as well as their temporal interplay, reflected by specific patterns of brain electric activity, is surfacing. Here, we provide an overview of recent concepts and results on the mechanisms of sleep-related memory consolidation. The latest studies strongly impacting future directions of research in this field are highlighted.

EEG; memory; oscillations; reactivation; sleep

Introduction

Memory formation encompasses both the learning (encoding) of information and the consolidation of learned content in long-term storage, with the contents assessed by subsequent recall. Examples of temporally graded retrograde amnesia spurned an entire field of research demonstrating how memories undergo gradual processes of reorganization at the system level, i.e., between brain regions. For example, freshly encoded episodic memories (as memories of events) stored in the hippocampus, become hippocampal-independent over a period of weeks to years, since they are represented in a more permanent form within the neocortex (21, 78). The notion that sleep and memory consolidation are associated has been around for a long time, and a large quantity of research has amassed compelling evidence that sleep particularly supports the consolidation of learned information into long-term memory (for reviews, see Refs. 36, 103).

The relationship between memory consolidation and sleep has been conceptualized under two basic overarching and non-exclusive concepts. One focuses on the homeostatic regulation of synaptic downscaling during sleep (128). This posits that sleep, specifically the slow oscillations of non-rapid-eye-movement (NREM) sleep, function toward global downscaling or synaptic renormalization. Synapses recently and strongly potentiated during prior waking, in contrast, are less prone to downscaling (reviewed in Ref. 129). This synaptic homeostasis hypothesis is supported by a wealth of molecular studies revealing the regulation of genes and the expression of proteins indicative of synaptic weakening after a period of sleep, including structural modifications to synapses as well as electrophysiological measures of synaptic potentiation (34, 129).

The other concept relies on an active role of sleep in the process of systems consolidation and will constitute the focus of this review. This concept originated following the observation that retention was dependent on different proportions of sleep stages (reviewed in Ref. 16). Experiments depriving sleep during the first vs. the second part of the night gave rise to the "dual-process hypothesis" in which NREM-rich sleep during the first part of the night was considered beneficial for declarative memories, and REM-rich sleep of the second half of the night was considered beneficial for non-declarative or implicit (e.g., procedural) memories (45, 73, 103, 106, 120). A further model, the "sequential hypothesis," underscored the relevance of the succession of processes occurring during NREM sleep and REM sleep for memory consolidation in both rodents (5) and humans (123).

To gain more elaborate insight regarding how memory consolidation transpires during sleep, researchers turned to studying electric activity of the brain, i.e., electrical signals of mixed frequency and amplitude resulting predominantly from neuronal activity. Rhythms or oscillations in these signals typically reflect the synchronized activity of large populations of neurons and are considered to reflect facilitated communication between neural populations (20, 86). Neural oscillations can be measured using non-invasive scalp sensors [e.g., electroencephalography (EEG) and magnetoencephalography (MEG)] or implanted intracranial electrodes. The latter can also detect activity of smaller neuronal populations and are used most widely when recording from laboratory animals and—to a lesser extent—in pre-surgical epileptic patients. The characteristic neural oscillations are used to define different stages in sleep (FIGURE 1). In humans, polysomnography (EEG, EOG, and EMG) is used to determine sleep stages. In laboratory

animals, EEG or local field potentials (LFPs) are measured. Although analysis of neural oscillations solely using EEG provides exceptional temporal resolution, a shortcoming of this approach is its poor spatial resolution. To unravel the neuronal processes that facilitate sleep-related memory consolidation, it is important to understand the brain structures involved in the processes of encoding during wakefulness and consolidation during sleep. In humans, where localized invasive electric recordings are limited, neuroimaging procedures [e.g., functional magnetic resonance imaging (fMRI)] have contributed greatly to determining the involvement of the brain regions involved in sleep-associated memory consolidation.

Mechanisms underlying sleep-related memory consolidation differ depending on the specific memory system. The two major long-term memory systems are most frequently discerned as being hippocampus-dependent (for humans, the term "declarative" is used) or non-hippocampus-dependent ("non-declarative" or "procedural"). Although not exclusively, we will focus this review on mechanisms of hippocampus-dependent memories, since a greater amount of studies on the neural underpinnings and associated brain rhythms of sleep-associated memory consolidation have investigated hippocampus-dependent memory consolidation.

There are different experimental approaches to investigate sleep-related memory consolidation. The first is based on measuring the impact on memory consolidation of partial sleep deprivation (i.e., on deprivation of specific sleep stages), which essentially gave rise to the dual and sequential hypotheses, as mentioned above. Another approach, aimed at more specifically disclosing the underlying neural mechanisms of sleep-associated memory, is to correlate brain electric activity during sleep with memory retention. Retention is typically measured as the difference in performance between recall and learning. A similar approach is to compare neural responses during sleep following a learning vs. non-learning baseline or control task.

In the 1990s, important studies on spatial learning and post-experience activity patterns of "place-cell" ensembles in sleep led to the concept that reactivation during sleep could represent a mechanism for sleep-associated memory consolidation. Reactivation describes the process by which the same neuronal networks that were active during learning are re-activated during sleep in a pattern that matches the relative sequence of original activation (reviewed in Refs. 19, 111). Experience-dependent reactivations were later observed in human studies as well (94, 104).

The study of brain rhythms during sleep provides the clearest available approach to understanding the physiological processes involved in sleep-related memory consolidation. This review presents an outline of the literature generated to date, including the emerging importance of temporal coordination between different sleep rhythms, as well as approaches to manipulate these rhythms toward uncovering causal evidence for sleep-related processes in memory consolidation. We will conclude this review with an outlook on future directions of research on sleep oscillations and memory consolidation, and a speculative opinion.

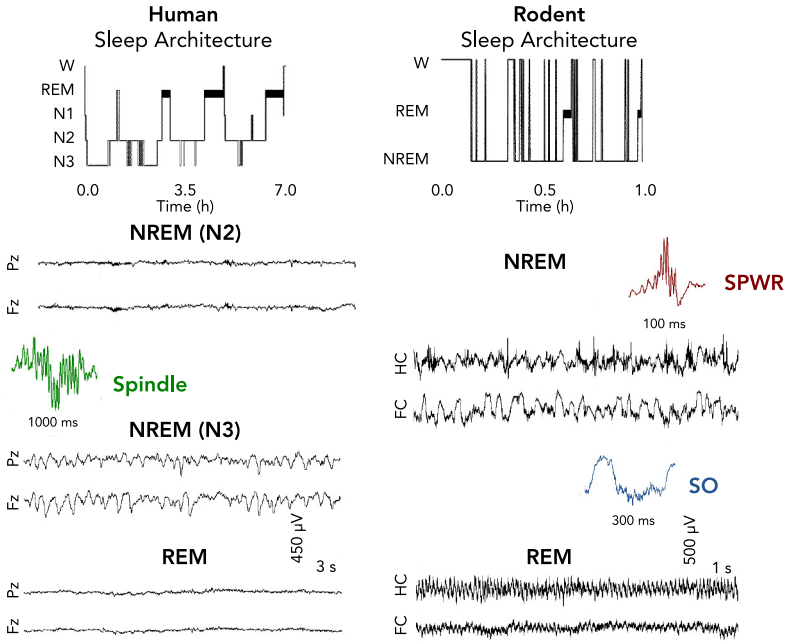

FIGURE 1. **Characteristic features of sleep architecture and predominant neural oscillations across the sleep period in humans and rodents**
Top: in both humans and rodents, a distinction is made between NREM and REM sleep stages. In humans, NREM sleep is further divided into stages N1–N3, depending on sleep depth. In rodents, a further subdivision of NREM sleep is uncommon due to the short duration of sleep episodes. *Bottom*: the traces show representative recordings from human EEG over frontal (Fz) and parietal (Pz) locations, and mouse intracranial local field potentials (LFP) in frontal cortex (FC) and dorsal hippocampus (HC). Discrete electrical events in NREM sleep are thalamo-cortical sleep spindles (green), cortical slow oscillations (SO; blue), and hippocampal sharp-wave ripples (SPWR; red). Sleep spindles (~10–16 Hz) are a hallmark of NREM stage N2 sleep. They are generated through inhibition of thalamo-cortical relay cells by the repetitive spike-bursting of GABAergic thalamic reticular neurons (121). As sleep deepens, neural activity slows and synchronizes. Both slow-wave activity (SWA; 0.5–4 Hz) and slow oscillations (~1 Hz) dominate. Slow oscillations are cortically generated biphasic rhythms consisting of the alternation between a hyperpolarizing state of neuronal silence (or "Down state") and a depolarizing state (or "Up state"), which reflects enhanced activity of both excitatory and inhibitory cortical neurons (88, 121). Note, the polarity of up and down states is reversed between humans and rodents due to the depth LFP recording in rodents. Sharp wave-ripples (SPWRs) are short-lasting (~50–100 ms), fast-oscillatory events of ~100–250 Hz observed in the hippocampal formation during NREM sleep (20), which are measured electrophysiologicaly by using invasive intracranial electrodes. During REM sleep, low-amplitude EEG frequencies appear. In rodents, continuous theta oscillations (~5–9 Hz) are clearly pronounced, with GABAergic neurons of the medial septum relevant for theta pacing of the hippocampus and other limbic cortical structures (20). In contrast to rodents, humans appear to have multiple theta generators producing only short theta sequences during REM sleep (24).

Evidence Linking Brain Oscillations During Sleep and Retention Performance

Of the predominant neural oscillations across the sleep period (FIGURE 1), sleep spindles (10–16 Hz) have arguably been the most widely investigated. The first line of evidence for a link between sleep spindles and memory consolidation came from studies correlating retention on a given memory task (e.g., a word-pair association task) with concomitant EEG-derived spindle activity during a period of sleep (either a full night or a daytime nap). An increased occurrence of spindles during sleep after learning in relation to increased retention performance has been found in multiple studies of human subjects (26, 27, 46, 116, 117). In particular, associations between spindle activity and verbal (26, 27, 46, 116, 117, 124) or visual declarative memory (30), as well as motor procedural memory (42, 43, 54, 68, 85, 89, 101), have been found. Interestingly, sleep spindles occurring during deep NREM sleep (stage N3 sleep) have appeared to be particularly responsible for potentiating declarative memories (30), whereas procedural motor learning could be specifically related to spindles occurring in light NREM (N2) sleep (42, 47).

Investigations have similarly found relationships between slow oscillations (~1 Hz)—as reflected by EEG spectral power in the slow-wave frequency band [slow-wave activity (SWA), 0.5–4 Hz]—and learning in human participants. For instance, learning on a visuo-motor task induced an increase in SWA over parietal brain areas during subsequent sleep, and this SWA change was positively correlated with the enhancement of task performance after sleep (55). Positive correlations between SWA and overnight retention were also reported for a procedural motor skill and a declarative task of learning a word list (54).

Post-learning increases in sharp-wave ripple (SPWR) density in rodents are likewise found and, moreover, were also associated with improved retention on a spatial memory and an odor-reward association task (38, 48, 102). In pre-surgical epileptic patients, numbers of ripples in rhinal cortex, but not in hippocampus, were correlated with recognition memory performance (8).

Taken together so far, correlational evidence detailed relationships between more efficient sleep-related memory consolidation and greater densities of sleep spindles, SPWRs, and/or slow oscillations, separately. Importantly, however, spindles and slow oscillations do not only occur independently but often synchronously, reflecting a unified thalamo-cortical generating system in which spindles tend to be nested within slow oscillations (28, 84). Indeed, in mice, concomitantly occurring slow oscillations and sleep spindles revealed increased calcium signaling (compared with the separate events), which is considered a potential prerequisite for processes of neuroplasticity, compared with isolated slow oscillations and sleep spindles (88). SPWRs are temporally associated with slow oscillations as well as spindles (72, 83, 119, 135) (but see Ref. 126 for extensive review). Methodologically, the application of cross-frequency coupling (CFC) analyses to neural oscillations (23) has greatly improved the ability to quantify interactions between sleep rhythms underlying sleep-related memory consolidation. For instance, phase-amplitude CFC determines the phase of a low-frequency component at which the amplitude of a high frequency is maximum. The phase at which spindles couple to the slow oscillation changes with age, and this phase has been associated with differences in memory consolidation (53, 80). In addition, the strength of coupling, i.e., its consistency across trials, can be quantified.

The actual interplay of neural oscillations is undoubtedly more complex. For instance, in humans, there are strongly pronounced differences between slow and fast sleep spindles; their occurrence within the slow oscillation differs, with fast spindles occurring during the slow oscillation Up state and slow spindles during the Up to Down slope, and coupling to the slow oscillation is stronger for the fast spindles (32, 82). It also has been observed that changes in fast sleep spindles after learning were correlated with the overnight consolidation of motor sequence learning, whereas slow spindles did not appear to be involved (9). It is thus possible that, in humans, the different types of spindles (slow or fast) contribute differentially to the consolidation of memory types. Moreover, there are indications that the function of sleep spindles during light (N2) and deep NREM sleep may differentially interact with processes of memory consolidation (35, 47). However, this field is relatively young, and more systematic evidence is required before a comprehensive model can be formulated.

Reactivation and Reorganization

Recordings from multiple brain regions, e.g., using simultaneous EEG and fMRI in humans, have revealed a topographic specificity of activity during memory consolidation, in particular in relation to spindle activity. Prior learning of face-scene associations has been shown to promote stronger coupling (covariance) between sleep spindle amplitude and neural activity in face scene-selective regions of the ventral visual cortex and hippocampus (13). An increased activation of the fusiform gyrus, critical for face recognition, was found temporally locked to fast

spindles during sleep following learning a face sequence declarative memory task compared with a control night (56). Importantly, in both studies, the coupling between spindle activity and fMRI responses was topographically restricted to regions that were activated during prior learning, and the extent of coupling was correlated either with learning performance before sleep (13) or with recall performance after sleep (56). Similar results have been shown for motor learning, and a reorganization of neural activity between brain structures often occurs during sleep-related procedural memory consolidation. Activity in the rostrodorsal striatum (an associative area) recruited during training on motor sequence tasks has been shown to subsequently transform to activity in the caudoventral subregion of the striatum (a sensorimotor area) post-learning (41, 69). This reorganization was also correlated with spindle-related reactivation of the putamen during sleep, the extent of which also related to overnight gains in performance (41). By using EEG source localization on the same data set, it was demonstrated that the coherence (functional binding) of cortical and subcortical brain activity during sleep spindles was related to post-learning gains in motor learning consolidation (17). Functional MRI studies in humans also showed that an interaction between striatal and hippocampal activity during training on a motor sequence predicted future gains in performance on a retest after sleep during retest (4). Further investigations should achieve a more consistent picture on the reorganization during sleep of memory representations post-learning (3).

A reorganization over time of post-experience neural activity may similarly be concluded from findings in rodents subsequent to a reward-searching task. The reactivation of ventral striatal firing was temporally associated with hippocampal ripple activity during NREM sleep, yet reactivation decayed slower in the ventral striatum than had been found for hippocampal reactivation (99). In general, sleep research is taking on the question of how and when memory systems centered on activity within different brain structures (e.g., relying on hipocampus, amygdala, and striatum) may interact during NREM sleep to consolidate memories (40, 134).

Investigations on electrophysiological brain activity emphasize the central role of hippocampal SPWRs in the coordination of network reactivations among distributed brain regions during NREM sleep after learning. Comparisons of neural activity during encoding and subsequent NREM sleep have revealed temporally coordinated activity between SPWRs and neural activity patterns that code for spatial or self-motion related information within the parietal (136) and entorhinal cortex (91). Reactivation associated with SPWRs was, however, also found in regions involved in encoding the location of material possessing a specific positive or negative valence, not only in brain regions involved in spatial processing. For instance, reactivation of both reward-related activity in the ventral striatum (99) and the basolateral amygdala encoding the location of an aversive airpuff on a running track (49) were modulated by hippocampal SPWRs during post-learning sleep. Typically, hippocampal reactivation is strongest for experiences or events of greatest salience (25), yet novelty of the fore-going experience may also contribute to greater reactivation or post-experience neuronal activity during sleep (38, 44, 66). The role of such factors as valence, salience, and emotional significance suggest that coordinated reactivations are particularly relevant for future adaptive behavior. SPWRs also serve a modifying function, as reflected in the above-mentioned study by Girardeau et al. (49) on coordinated reactivation of hippocampus and amygdala, in which stronger reactivations were measured for subgroups of amygdala cells representing the aversive stimulus. Also, in a study employing a sound-guided memory task in rats, reactivation of specific auditory cortex activity was shown to precede and follow SPWRs and even be capable of influencing SPWR content (109). Technological advancements, for instance, enabling paired recording and intervention at the level of neuronal populations in vivo (58, 125), bring novel possibilities to measure localized activity in parallel from multiple brain areas. If focused during distinct time periods, such as the occurrence of spindles or SPWRs, research is bound to reveal a clearer picture of interactions between different brain areas during sleep that are relevant for post-task memory consolidation.

Bidirectional and Intraregional Interactions

Many of the investigations described above were based on the physiological "two-stage" model of memory formation, which posits that new memories are initially encoded within the hippocampus and subsequently transferred to the neocortex for long-term storage (21, 78). The concept of a two-way interaction during sleep between hippocampus and cortex is, however, evolving. For instance, recent results of interactions at the cortical level have found neurons in the anterior cingulate (ACC) firing both before and after hippocampal SPWRs. All ACC neurons during sleep demonstrated increased activity ~200 ms before SPWR activity and correlated positively with SPWR amplitude. Preripple activation of the majority of ACC neurons were not present during the awake state, which supports a functional distinction between SPWRs occurring during sleep and waking (133). There is

further evidence suggesting the existence of a rapid cortico-hippocampal-cortical loop (109). Stimuli delivered during NREM sleep to rats following a sound-guided task elicited neuronal ensemble patterns within the auditory cortex that predicted the occurrence of hippocampal SPWRs. In turn, firing rates of cells in the auditory cortex were strongly modulated during hippocampal SPWRs.

Alongside communication between the hippocampus and (sub)cortical regions, intraregional interactions within the cortex have also proven relevant for sleep-associated memory consolidation. For example, non-hippocampus-dependent perceptual memory has been demonstrated to depend on top-down intracortical activity during NREM sleep. Here, opto-inhibition of the projection axons from the secondary motor cortex to primary somatosensory cortex within *post-task hour 1* (but not *post-task hours 6–7*) of NREM sleep reduced duration of retention for tactile memory. Retention appeared to rely on the synchronous activation of these cortical regions mediated by the secondary motor cortex projections. In fact, retention performance could be prolonged by photostimulation inducing synchronous activation in the two cortical regions (81). These latter findings on neuronal interactions may contribute to how neocortical schemas affect the rate or efficiency of consolidation, as previously described in models of memory consolidation (77, 90, 130).

Experimental Modulations of Brain Oscillations During Sleep and Related Impacts on Memory Consolidation

As indicated in FIGURE 2, various techniques have now been developed to modulate brain oscillations during sleep, with an attempt to influence memory recall post-sleep and highlight the causal importance of these rhythms in consolidation processes. One approach employed has been pharmacological modulation. Inducing an elevated spindle activity through selective serotonin or noradrenaline uptake blockers improves procedural memory performance on finger sequence tapping and mirror tracing tasks, despite supressing REM sleep, challenging originally held views on the beneficial effect of REM-rich sleep on procedural memory consolidation (105). Increasing spindle density with the gamma-amino-butyric acid (GABA)-A receptor agonist zolpidem increased recall performance on a declarative word-pair task but worsened performance to a perceptual discrimination task and had no effect on a motor sequence learning task (79). However, decreased spindle activity after administrating the anticonvulsant tiagabine (39) had no negative effect on declarative memory recall (39). Importantly, in all these studies, pharmacological reduction of spindle density also increased slow oscillations and

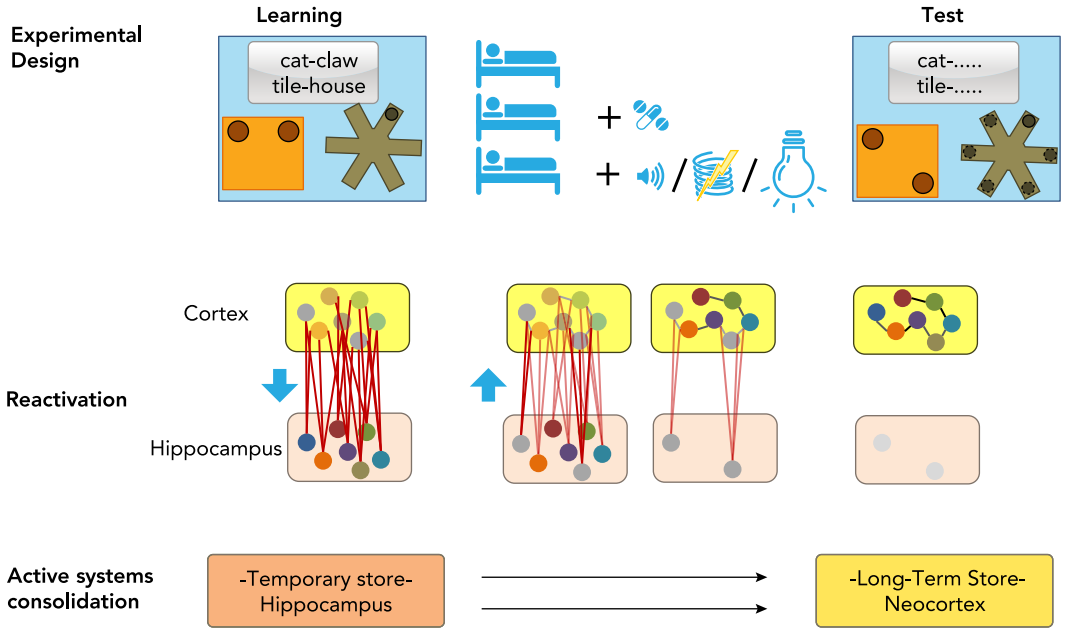

FIGURE 2. **Active systems consolidation and reactivation**
Top: different experimental designs have been created to assess the effect of sleep on systems consolidation of memory. These include providing a sleep opportunity between learning and recall testing, or a sleep opportunity paired with an intervention (pharmacological administration, acoustic stimulation, weak electrical currents, optogenetics, or targeted memory reactivation). *Middle*: information enters the hippocampus during learning, where it is temporarily stored. Reactivation of this information during sleep is presumed to transfer the memory representation, reorganizing the learned information. *Bottom*: the concept of active systems consolidation, the transfer of information during sleep from a temporary representation in the hippocampus to a permanent representation in the neocortex, is schematized.

SWA. Therefore, the reported effects on memory consolidation or lack thereof cannot be solely attributed to either a decrease in spindle activity or an increase in slow oscillations. Beyond the difficulties in modulating one type of brain oscillation specifically without inversely affecting the others, these pharmacological approaches are limited by both their spatial and temporal imprecision—that is, they cannot be targeted to specific brain regions or time points in the sleep period.

In an alternative approach, various types of sensory stimulation have been used to modify brain oscillations during sleep. For example, a recent study used a rocking bed to induce a continuous rhythmic sensory stimulation that increased slow oscillations and spindles during deep NREM sleep (100). Importantly, this stimulation also improved the overnight consolidation of a declarative memory task, which was positively correlated to the increase in spindle activity (100). More precise and targeted control over neural oscillations during sleep is possible by using stimuli—especially acoustic—that can be applied on an event-by-event basis. Acoustic stimulation was for instance timed to selectively suppress slow oscillations during NREM sleep, which prevented the improvement of procedural motor (65) and declarative (131) memories after sleep. More recently, closed-loop acoustic stimulation paradigms, in which stimulation occurred dependent on the ongoing activity of the signal to be targeted by the stimulation, have allowed automatically delivery of sounds in phase with the Up state of slow oscillations. These paradigms resulted in an enhancement of slow oscillations, an increase in spindle activity (113) and an improved retention of declarative memories during sleep compared with a control condition consisting of either sham (92, 97) or out-of-phase (87) stimulations. In addition, changes in memory performance were correlated with increases in slow oscillations (87, 93, 97) and/or spindle activity (87) associated with the in-phase stimulation. Together, these findings provide strong support for slow oscillations and sleep spindles in memory consolidation, and moreover for their concurrent enhancement to effectively improve cognitive perfomance (137, 138).

Over the past decade, a series of studies have been published using targeted memory reactivation (TMR) during sleep to enhance memory consolidation. In this paradigm, subtle cues (e.g., auditory or olfactory), which have previously been associated with specific learning during wakefulness, are presented during subsequent sleep. These studies have consistently reported an improved memory recall of the associated learned information, for both declarative and procedural motor memories, during the post-sleep assessment following TMR (22, 68, 95, 118). Interestingly, the timing of these cues in relation to neural oscillations of sleep appears to strongly influence the effects of TMR on memory recall. For instance, the beneficial effects of TMR for a declarative memory task appeared to be predicted by the phase of the cortical slow oscillation at the time of stimulus presentation, specifically the cortical Up state (11). Furthermore, TMR can yield significant increases in sleep spindle amplitude and frequency, the extent of which has been shown to mediate memory retention of a motor sequence task (68). In reporting a refractory period for spindles (i.e., spindles are more likely to occur 3–6 s after a previous spindle), one study found that TMR cues presented outside compared with inside this spindle refractory period were associated with a greater memory recall following sleep (6). This was suggested to reflect a potentiality for memory reactivation that is dependent on the temporal occurrence of spindles. These findings detailing the particular traits of TMR have painted an overall picture of complex interactions between sleep-state neural oscillations and memory consolidation, furthering the understanding of how memory consolidation may be processed during sleep.

Sensory (e.g., acoustic, olfactory) stimulation can be given with high temporal precision, yet these stimuli affect both subcortical and cortical structures. The application of weak electric currents to the scalp or cortex aims in contrast to primarily affect ongoing neocortical activity. Constant and oscillating weak electric currents applied via electrodes are capable of modulating ongoing brain electric activity and affecting memory consolidation. Frontal-to-mastoid weak electric stimulation during the transition to deep NREM sleep distinctly increased the retention of word pairs compared with sham stimulation, and enhanced temporal coupling between slow oscillations and spindles (64, 74, 76). In rats, a similar electrode configuration likewise improved post-sleep performance (14, 15). A reduced performance in a declarative but not procedural memory task could be observed after decreasing both frontal EEG spindle power and slow oscillations during NREM sleep by theta-frequency transcranial direct current stimulation (tDCS) in a later study (75). Although studies with contrasting results have since been reported (e.g., Ref. 98; reviewed in Refs. 137, 138), recent studies indicate that, due to the subthreshold character of the stimulation, covert interactions between the applied stimulation, inter-individual confounds and content can play a decisive role in the efficiency of oscillatory weak electric stimulation (57, 62).

In rodents, reinforcing the temporal coordination of cortical delta waves and spindles using SPWR-triggered electrical stimulation resulted in a reorganization of spatio-temporal spiking patterns of prefrontal pyramidal neurons, along with subsequent increased recall performance relative to controls (72). However, during sleep, studies have shown that endogenous neuromodulators interact with neural oscillations (7, 52, 114). For instance, optogenetically driven activation of cholinergic neurons influences the theta-to-slow oscillation ratio (132), and noradrenergic neurons fire phasically time-locked to the slow oscillation (37). These interdependencies may help explain why imposing a stereotyped external rhythm may not always be functionally efficient (61).

Targeted manipulation of oscillatory activity has also been conducted using optogenetic methods in rodents. For example, Latchoumane and colleagues induced a spindle-like rhythm in the thalamus of mice, either during the Up or Down state of ongoing cortical slow oscillations, and could thereby improve SPWR-slow oscillation coupling and memory consolidation (67).

Overall, the specific modulation of brain oscillations of sleep to impact memory consolidation is a relatively new area but provides substantial potential in unravelling the role of neural oscillations in the process of memory consolidation at both systems and cellular levels.

The Role of Brain Oscillations for Sleep-Related Memory Consolidation: Interactions Between Models and Future Directions

In this review, we emphasize that the major concept through which active systems memory consolidation takes place during sleep is by a fine temporal relationship between neural oscillations associated with sleep and reactivation, namely the Up and Down states of the slow oscillation, thalamo-cortical sleep spindles, hippocampal sharp wave-ripples, and coordinated activity of other brain regions (FIGURE 3). There are indeed indications that systems consolidation requires the coordination of multiple brain structures. The essential component of active systems consolidation theory posits that, over time, (episodic) memory representations lose their dependence on the hippocampus. For memories to become hippocampus-independent, the hippocampus must "train" the cortical associations during an offline period when no external influence can disturb memory representations to strengthen and stabilize these into "self-sustaining" representations. Sleep spindles originating from the thalamus may specifically serve to ensure this offline environment. In humans, brain responses to acoustic stimulation were profoundly dampened when presented in concurrence with an ongoing sleep spindle (29, 33). Thalamic gating of external sensory stimuli

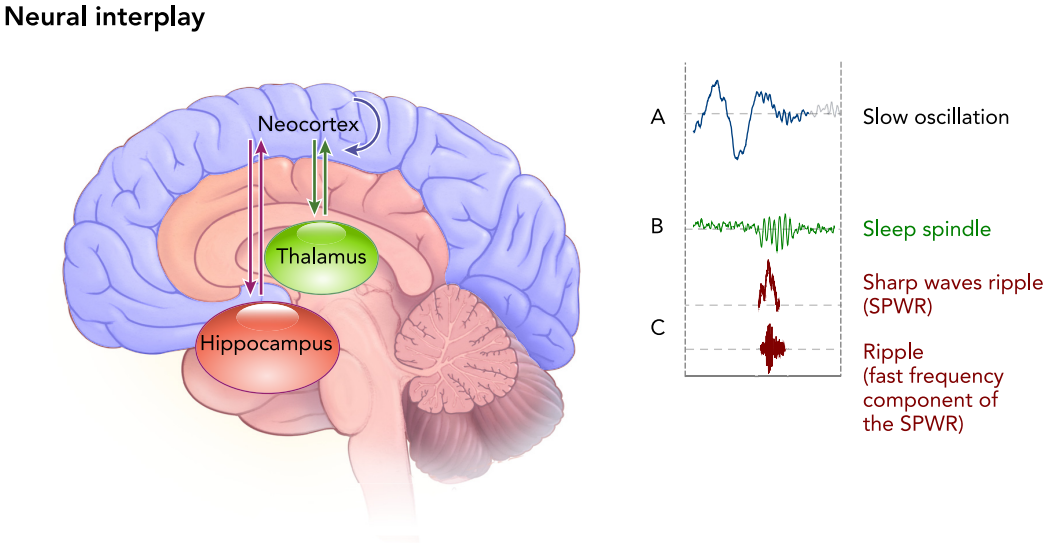

FIGURE 3. **Neural oscillations of memory consolidation in sleep**
Figurative model of the interplay of neural oscillations/brain rhythms during NREM sleep. Slow oscillations (*A*) in the neocortex temporally group neural activity in other brain structures such as thalamocortical spindles (*B*) and hippocampal sharp wave ripples (*C*). The timing of spindles relative to the phase of the slow oscillation and the coordinated reactivation of hippocampal SWPRs underlie the transfer of previously learned information on the memory representation to the neocortex, reorganizing, consolidating, and possibly generalizing the memory content as it becomes hippocampus independent (cp. FIGURE 2). During ongoing spindles, the thalamus performs sensory gating, thereby reducing external sensory input to the neocortex. Note, oscillations (*A–C*) are not scaled.

during spindles might contribute to protect the sleeping brain from external disuption, thereby faciliating internal reprocessing and integration, such as during memory consolidation.

Several lines of study, however, underscore the need for a more complex view. First, although the concept of active systems consolidation was developed for hippocampus-dependent (declarative) memories, the hippocampus may also be critical for forming "non-hippocampal" long-term memories, e.g., hippocampal inactivation impaired sleep-related consolidation on a non-hippocampus-dependent novel object recognition memory task (115). In addition, only few studies have investigated the specific role of REM sleep for retention of hippocampus-dependent memories (2). Indeed, most studies indicating an involvement of neural activity during REM sleep for memory consolidation have used behavioral paradigms of contextual fear or other emotional material or contexts (12, 60, 107). However, structures found to be activated during REM sleep (limbic structures, including the retrosplenial cortex) have all been implicated in hippocampus-dependent spatial memory (70). In fact, the relevance for memory consolidation of theta rhythm during REM sleep was demonstrated by using optogenetic techniques. Optogenetic silencing of medial septum GABAergic neurons in mice both selectively attenuated theta activity during REM sleep and impaired consolidation on two hippocampus-dependent tasks (18).

Second, there has been an emerging discussion on how the type of sleep-related memory representations may shift over time (108, 122). For instance, the memory for differently shaped single items was enhanced 10 h after learning, with a post-learning sleep period. Yet, testing the same subjects 1 year later showed that subjects who had slept after an initial encoding revealed improvement on more generalized knowledge, i.e., on a prototype memory of shapes (71). The specific mechanisms of sleep for such extraction of gist from specific information to form generalized schemas are an ongoing research focus. Discerning these mechanisms may also contribute to understanding how semantic memories are forged from episodic experiences.

Third, results from weak electric stimulation interventions show the greater need to focus on inter-individual response variability (61, 62). Advances in analysis procedures have facilitated the application of tools to measure features of neural oscillations, such as the phase coupling between slow oscillations and sleep spindles, at the individual subject level. Cox and colleagues revealed consistent inter-individual "fingerprints" of coupling phases between slow oscillations and both fast and slow sleep spindles (31). A future direction is the use of such analytic tools together with customized intervention procedures for investigating the causality of neural oscillations and sleep-related memory consolidation, with a stronger focus on inter-individual differences in responsiveness.

Fourth, although the two concepts of sleep-related memory consolidation—namely the synaptic homeostasis hypothesis and the concept of active systems consolidation—seem in opposition, several recent findings suggest a convergence in the cellular mechanisms associated with both theories. Optogenetic studies investigating the specific function of slow oscillation Up vs. Down states suggest that Up states may contribute to a selective downscaling of subthreshold inputs (10, 50). Indeed, when active Up-state firing in the primary motor cortex was optogenetically suppressed, the rescaling (downscaling of "indirect" neurons non-causally related to a task) was prevented, and post-sleep task behavior, namely for rats to control the angular velocity of a feeding tube, was impaired (51). These findings support a rescaling of task-related activity, as proposed by the synaptic homeostasis hypothesis, yet not as a passive but as an active (i.e., activity-dependent) process. These findings furthermore suggest that downscaling may operate locally and not globally, as initially hypothesized by the synaptic homeostasis hypothesis. Local modulations in neuroplasticity during sleep and activity-dependent local sleep-regulation are also indicated by local sleep-related synthesis of plasticity-related proteins (1). The concept of local sleep regulation emerged from findings that local use-dependent increases in cytokines and other sleep regulatory molecular components can affect local neuronal/glial network activity, and the theory posits that cellular events can induce effects at higher levels of tissue organization (63).

Finally, although our review has focused on neuronal interactions on memory, the process of sleep also involves systematic changes in non-neuronal cellular activity (e.g., astrocytes) and chemical neuromodulatory sytems that have been shown to affect cellular neuroplasticity and memory (63, 96, 112). New technologies enabling improved parallel monitoring of cellular and systems level activity patterns will definitely shed new light on the contributions of these elements to sleep-related memory consolidation. In fact, the identification of post-experience neuronal cell ensemble activity during systems consolidation has become possible by the recent combination of transgenic, optogenetic, pharmacogenetics, and optical imaging approaches. Findings indicate that such "engram cells" in both medial prefrontal cortex and hippocampus are formed rapidly on learning of context-fear conditioning but that medial prefrontal

cortex engrams have to undergo maturation over time with aid of hippocampal engram cells before they can be used for recall (59, 110) (for a review, see Ref. 127). However, until now, the fate of engram cells in different brain regions and their interaction has only been demonstrated for context-fear conditioning in laboratory rodents and has not been explicitly investigated in relation to sleep. For future research, it would be desirable to combine the above-mentioned methodological approaches with electrophysiology, and possibly the manipulation of sleep oscillations, to gain more insight into sleep-related memory consolidation at the engram cell level.

Taken together, it is essential for research on sleep and memory consolidation to uphold an integrative view ranging from systems to cellular levels, and from local to global levels. We believe neural oscillations during sleep reflect, on the one hand, previous "learning-related activity." On the other hand, results from studies on weak electric current stimulation indicate that neural oscillations per se can affect neuroplasticity. Learning-related activity is expressed at a multitude of levels (e.g., neuronal engram cells, with their activity-dependent intracellular molecular machinery; resulting dendritic spine dynamics; activity-dependent cellular release of cytokines; changes in neuromodulatory activity, possibly reflecting the learning materials' reward value for the individual subject; etc.), and each level is characterized by specific temporal dynamics. Which rules may govern communication within the brain? It is conceivable that these large-scale neural oscillations during sleep emerge from local use-dependent activity and in turn affect all ongoing local learning-related activity in a temporally coherent manner. The achieved effect is dependent on the specific learning-related history of the local network.

Science is accelerating the development of tools that can potentially narrow the gap between systems, network, cellular, and molecular level functions, and link online and offline neuronal activity to sleep-associated behavior. Future research should utilize these tools to scrutinize present and newly evolving concepts of memory consolidation. ■

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