Chapter 7
A Role for Neuronal Oscillations of Sleep in Memory and Cognition

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Sleep and Memory Across Species

This chapter deals with oscillations of neurons and networks that are relevant for different cognitive processes, in particular for memory retention in animals and humans during sleep. This first section gives a brief insight into sleep and memory in nonmammalian species.

The greatest amount of research on neuronal oscillations and plasticity has been conducted in vertebrates, more specifically on mammals. Studies on simpler invertebrate models—most notably the fruit fly and honey bee—have the advantage that the process of memory formation can more easily be dissected, from systems down to the molecular level, than for higher-order animals [1, 2]. Despite well-established proof of memory and plasticity in these species, behavioral rather than electrophysiological definitions of sleep are up to now mostly employed [3, 4]. Only very recently were 7–10 Hz oscillations discovered in the spontaneously sleeping fly [5]. In the olfactory nervous system of the Drosophila, several memory traces associated with short-term, intermediate, and long-term memory after conditioning with odors have meanwhile been reported [6]. For odor as well as for visual memories, a dynamic interaction between different brain regions across time reminiscent of memory in higher-order animals occurs [7, 8]. Neuronal oscillations in the honey bee brain have not been published. Yet, not only was sleep found relevant for consolidating navigation memory [9], but presentation of a contextual odor during sleep enhanced subsequent retention performance [10]. Although the dependence on neuronal activity during sleep has, to the authors' knowledge, not yet been investigated, separate studies have revealed in crayfish both brain electric activity characteristic of sleep [11], as well as evidence of spatial and motor learning [12, 13].

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Avian non-rapid eye movement (NREM) sleep is dominated by slow-wave activity, with slow waves found to propagate within the hyperpallium, yet sleep spindles and hippocampal sharp-wave ripples (SPWRs) have not been detected [14–16]. Studies relating neuronal oscillatory activity to memory consolidation are not as fine-grained as in mammals, yet sleep-dependent memory consolidation together with increased slow EEG activity occurred in visual imprinting [17], and a spatial discrimination task [18]. In seeming accordance with the absence of hippocampal SPWRs in birds, which in mammals are closely coupled to neocortical activity [19, 20], conclusive evidence for a hippocampal to extra-hippocampal transfer of information for long-term storage in birds is lacking [14].

Neuronal Oscillations in Sleep

From the above, it is evident that neuronal oscillations of sleep and their putative function cannot a priori be addressed universally across species. Even within mammals, distinctions between different preparations of the same tissue are necessary, as evidenced, e.g., by different cortical layers from which the cortical slow oscillation has been found to initiate in the brain slice of ferrets vs. human patients [21, 22]. Nevertheless, deductions on the mechanisms and function of human sleep spindles are necessarily often made on the basis of activity within brains or brain tissue of laboratory mammals.

Sleep Spindles

In essence, sleep spindles are generated by rhythmic spike-bursts in GABAergic cells of the thalamic reticular nucleus, which induce inhibitory postsynaptic potentials (IPSPs) in target thalamocortical cells, e.g., via corticothalamic input. The hyperpolarization with deeper NREM sleep of the membrane potential in these thalamocortical cells de-inactivates the Ca^{2+}-dependent current, I_t, activates the intrinsic I_h current, and enables generation of a low threshold calcium spike crowned by high-frequency bursts of fast Na^+-mediated action potentials [23–25]. The bursts of thalamocortical neurons induce in cortical neurons rhythmic excitatory postsynaptic potentials (EPSPs) and occasional action potentials. Synaptic interactions between reticular and thalamocortical neurons represent the spindle pacemaker, in particular during the mid-portion of a spindle. On the other hand, the cortex appears to be involved in spindle synchronization during spindle initiation as well as in the desynchronization of thalamic activity during spindle termination [25, 26]. In contrast to the abovementioned tonic shift toward hyperpolarization with deeper NREM sleep, recent simultaneous intracranial thalamic and cortical recordings in humans suggest that cortical slow oscillation down states and subsequent thalamic down states lead to a phasic hyperpolarization which presents the prerequisite for spindle generation [27]. Gardner and colleagues [28] recently differentiated between cortical subnetworks

activated in the medial prefrontal cortex (mPFC) in rats during spindle initiation and termination. During spindle initiation firing of "early" cells was strongly entrained and in-phase with spikes from cells of the thalamic reticular nucleus, whereby firing was antiphase during spindle termination. Interestingly, spindle length correlated most robustly with the ongoing activity of inhibitory reticular thalamic cells [29]. Neuronal firing patterns, cellular location, and spectral-temporal evolution of individual spindles were taken to suggest that across spindle epochs, distinct cortical subnetworks are differentially engaged.

Changes in intraspindle frequencies were found by several studies recording local field potentials (LFPs) in the mPFC [28, 30, 31]. The reports on the direction of frequency change from spindle onset to offset were, however, inconsistent. Interestingly, the two studies in humans show decreases in intraspindle frequency for fast and slow spindles [30, 31], whereas in rodents, increases were observed [19, 28]. Frequency changes are suggested to depend on thalamocortical (hyper)polarization level [19, 28, 30–33].

The existence of multiple spindle generators in humans has been concluded using various techniques: combined EEG and magnetoencephalogram (MEG) measurements, high-density EEG with source imaging [31, 34, 35], and intracranial recordings [30, 33]. Aside from existing in the neocortex and thalamus reliable spindles, detected within the range of 9–16 Hz, also appear to occur in the parahippocampus and hippocampus [30, 36]. As reflected in the EEG, slower spindles detected intracranially in humans occur predominantly in anterior regions, or have a greater percentage of anteriorly localized sources, and faster spindles are more pronounced in parietal regions [30, 33, 35, 37]. Regarding the timing of slow vs. fast spindles EEG, foramen ovale and intracranial depth recordings have indicated that fast posterior spindles precede slow frontal spindles by about 500 ms [30, 38, 39]. In a study recording simultaneously EEG and MEG, it was proposed that the ~150 ms earlier occurrence of MEG spindles, in the vast majority of cases, may reflect an initial local spindle source which then recruits active networks and shifts frontally, enabling subsequent detection in EEG derivations [31]. Using intracranial depth electrodes, Andrillon and colleagues distinguished a greater number of locally—as compared to globally—occurring sleep spindles, in particular in the beginning of nocturnal sleep. Notably, larger amplitude spindles were, more frequently, global than local in nature, i.e., occurring in concordance in different cortical and brain regions. Differences in timing of spindles between different cortical regions has been suggested to reflect propagation along the thalamic reticular nucleus rather than through intracortical pathways [30]. Interestingly, although cells of different thalamic nuclei revealed different preferred firing phases relative to the slow oscillation, timing was still dependent upon the ongoing cortical network pattern and also the exact activity of thalamocortical cells [40]. The distribution of current source density sinks and sources across cortical layers in humans gives strong support to the concept that thalamocortical core and matrix projections are reflected in different spindle features, at least when measured intracortically [41].

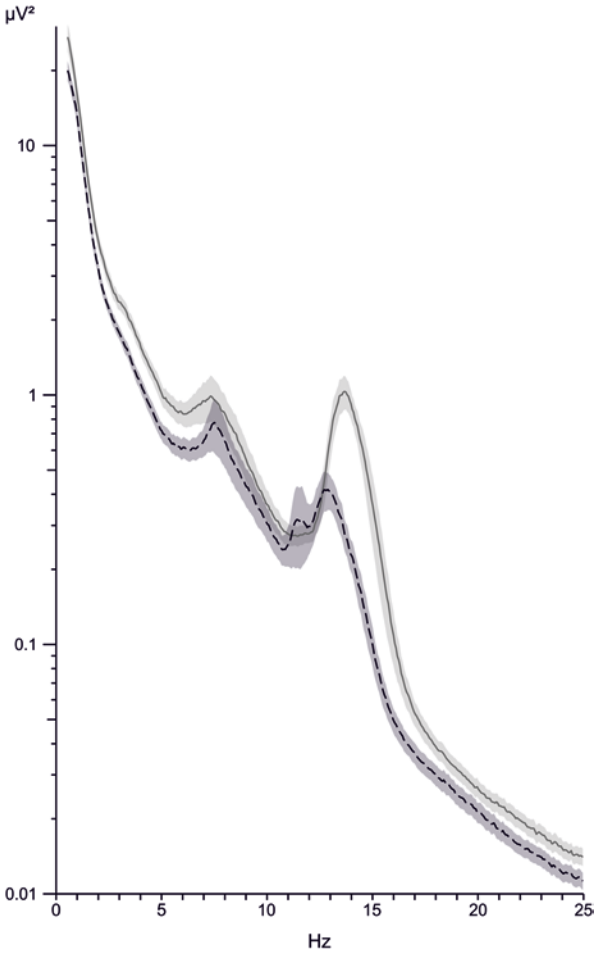

Fig. 7.1 Gender differences in sleep spindles: Mean (±SEM) spectral power for all epochs of stage 2 sleep across nocturnal sleep at Pz. Continuous gray lines, female; dashed black lines, male. Mean fast spindle power (11.5–15 Hz) was significantly higher in females than males (13.8 ± 0.1 Hz vs. 13.1 ± 0.2 Hz, $p < 0.01$, $N = 34$, 17 females; Aumann & Marshall, unpublished results)

A characteristic, frequently measured, feature of discrete spindles is their density. Comparisons in this measure between groups are hampered by the use of different recording derivations and detection algorithms, as well as by the use of different sleep spindle frequency bands. Further factors contributing to variance include the sleep stage and/or time intervals within which spindle power or discrete spindles are analyzed, and subject age and gender, aside from nontrivial interindividual differences [42, 43]. Especially fast spindles reveal pronounced gender differences in frequency and amplitude (Fig. 7.1).

The putative effects of these variables should be sufficiently reported and/or controlled when investigating the interaction with cognitive tasks. Within- and

between-subject comparisons can be differentially biased by these parameters. Some examples of variations are given below.

Spindle densities of 4–6/min are frequently reported in young, healthy (<30 years) subjects when spindle density was computed on the bases of calculating the root mean square of the spindle band signal or detected visually [44–48]. Studies reporting densities of only 2–3/min [49, 50] had investigated relatively older subject populations (mean age of 36 years), which may explain the relatively low spindle density [50], since density declines with age [48, 51]. The effect of analyzing spindle density within epochs of different sleep stages was documented in a study employing young (mean 25 years), healthy male subjects. Fast spindles (12–15 Hz) measured over averaged centro-parietal sites during stage 2 sleep revealed here a density of 5.8/min, whereas slow spindles (9–12 Hz) over fronto-central locations during slow-wave sleep (SWS) averaged only 3.4/min. Slow spindle density during stage 2 sleep and fast spindle density during SWS were intermediate [47].

Spindle density and spindle frequency measured intracellularly from 12 different neocortical regions along the caudo-rostral direction in humans correlated positively [33]. In line with this, both spindle frequency and spindle density can reveal a strong negative correlation with slow-wave activity during NREM sleep ($r = -0.81$, $p < =0.005$, and $r = -0.73$, $p = 0.02$, respectively) [30]. Slow and fast spindles also differ in the variability of their peak frequency between SWS and stage 2 sleep, with fast spindle frequency being more consistent. Slow spindle peak frequency in the above study was about 1 Hz slower in SWS (with a mean of 10.2 Hz) compared to stage 2 sleep (Fig. 7.2) [30, 47].

Slow-Wave Activity and Slow Oscillations

SWS is characterized by cortical slow wave activity (SWA, <4 Hz) and the sleep slow oscillations, which in human EEG[1] and rat LFP are ~0.8 Hz and ~1.4 Hz, respectively [52].

Delta activity (typically 1–4 Hz) is a historically older term, which distinguishes between two types of oscillations generated as the result of either (synaptic) cortical or (intrinsic) thalamic activity [53]. The sleep slow oscillation is well defined down to the cellular level, where it was initially described [54, 55]. It is generally acknowledged that during the sleep slow oscillation neurons (excitatory and inhibitory) undergo a bistable state lasting each hundreds of milliseconds during which either membrane depolarization and vigorous firing (up state), or hyperpolarization and neuronal silence (down state) dominate [56–59]. Initial EEG and LFP measurements suggested widespread cortical activity, yet high-density EEG demonstrate that slow oscillations and slow wave activity can also be locally regulated [56, 60, 61]. In fact,

[1] Note that slow oscillation will be used here as defined electrophysiologically, i.e. human EEG large amplitude oscillations during NREM sleep, >−80 μV negative peak, >140 μV peak-to peak, in a 3.5 Hz low-pass filtered signal, with lengths between positive-to-negative zero crossings from 0.9 to 2 s [39].

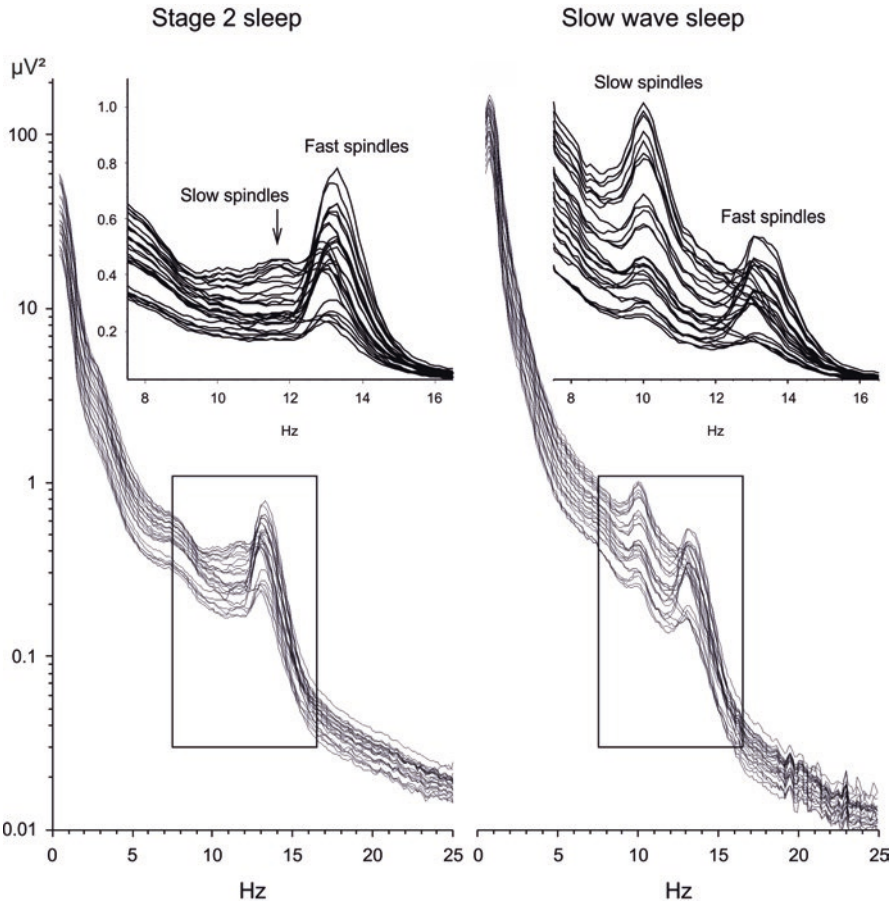

Fig. 7.2 EEG power during NREM sleep across the whole night. EEG power during stage 2 sleep and SWS reveal pronounced differences within the spindle frequency bands. Insets show enhanced views of spindle activity. Although there are clear peaks for slow and fast spindle activity during SWS, only fast spindle activity shows a clear peak during stage 2 sleep. Lines represent the 27 EEG channels. (Republished with permission of American Academy of Sleep Medicine. Mölle M, Bergmann TO, Marshall L, Born J. Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep. 2011;34(10):1411–21; permission conveyed through Copyright Clearance Center, Inc.)

the molecular and cellular mechanisms for the contribution of local brain activity to the regulation of sleep per se [62], and to the initiation and maintenance of the slow oscillation state [63, 64], are becoming increasingly evident. Further features of the slow oscillation (or SWA) per se, such as anterior to posterior propagation [61], dynamical changes across the night [56, 65, 66], or basic cellular/network generators and the specific contribution of cortical inhibitory interneurons, are not to be presented here, but have been reported elsewhere [57, 67–70]. Although the concept has for long prevailed that slow oscillations were generated exclusively by intrinsic and

synaptic mechanisms within the neocortex, recent data argue toward the relevance of the thalamocortical network for understanding slow oscillation generation in natural sleep and anesthesia [71].

Sleep spindles occur consistently during the up state of the slow oscillation. Less known is that slow and fast spindles occur at different phases of the slow oscillation. Indeed, slow frontal and fast centro-parietal spindles in humans differ in other features aside from frequency and topography. Phase-amplitude cross-frequency coupling between the slow oscillation and each of the two spindle bands with center frequencies fc = 10.5 Hz and fc = 13.5 Hz within SWS of each subject revealed that the amplitude of the slow spindle did not couple as consistently to the phase of the slow oscillation as that of the fast spindle. Significant coherence for fast spindles at Pz (Fz) was measured for 49 (42) out of 54 subjects, whereas for slow spindles at Fz (Pz) within the same SWS epochs significant phase-amplitude coupling [72] was only calculated for 20 (6) of the 54 subjects (D. Aumann and L. Marshall, preliminary results). A comprehensive investigation into differential coupling characteristics was recently conducted by cox and colleagues [73].

Induced Oscillations in Sleep

The relevance of induced oscillations and phase relationships can be well investigated by applying low-intensity sensory stimulation during sleep. Tones, acoustic bursts, or verbal stimuli can induce spindle or K-complex-/slow oscillation like cortical responses in EEG [74–79]. The relevance for memory consolidation was initially investigated by Ngo and colleagues [75], and subsequently by others as reviewed in Wilckens and colleagues [80]. Ngo and colleagues showed that the delivery of an auditory tone which induced a potential in-phase with the ongoing rhythmic occurrence of a slow oscillation led not only to an enhanced slow oscillation rhythm, but also to increased fast and slow spindle power. Above all, stimulation led to increased retention of words in a paired-associate learning task. Phase-independent auditory stimulation, however, did not improve declarative memory performance [81]. Therein slow oscillations and slow-wave activity were enhanced, but both fast and slow spindle power were decreased. These and other data argue that a specific constellation of neuronal oscillations, such as slow oscillations together with sleep spindles, are of functional relevance for memory consolidation [69, 82, 83]. Transcranial magnetic stimulation (TMS) has also frequently been employed to modulate neuronal oscillations [84–87], and to induce local processes of plasticity in subsequent sleep [88, 89], but to the author's knowledge no study incorporates the modulation of higher cognitive processes by TMS during sleep while recording any kind of brain electric activity in humans.

Another method of probing the interaction between oscillatory activity and memory processes during sleep is by transcranial application of weak electric stimulation. In particular, oscillatory stimulation has been impressively shown in vitro to entrain local field potentials after several stimulation cycles [90]. In principle,

due to its low current strength (typically between 0.25 and 2 mA) weak electric stimulation only modulates neuronal networks at the subthreshold level. Thus, effects of oscillatory weak electric stimulation are more moderate and act via different mechanisms than those produced by auditory stimulation [90, 91]. This putative subthreshold action means also that responses to weak electric currents are strongly dependent on the ongoing brain electric activity. Furthermore, as shown by experimental data and on theoretical grounds, oscillatory weak electric currents or fields are most effective at the resonance frequency of the network [92, 93]. Indeed, slow oscillating stimulation applied during NREM sleep has been shown to enhance power in the slow oscillation, spindle frequency bands, and/or retention of declarative but not non-declarative memories [94–97]; yet a lack of modulation has also been reported [80]. Along the same vein, retention of a declarative memory was impaired by ~5 Hz weak electric stimulation, i.e., at a nonresonant frequency, which also suppressed EEG slow oscillation and slow spindle power [97]. Interestingly, when applied during REM sleep ~5 Hz oscillatory tDCS had no effect on memory consolidation, but enhanced gamma band activity (25–45 Hz) in the poststimulation interval. It might therefore be hypothesized that lucid dreaming, which is associated with enhanced gamma band activity over the frontal cortex [98], may be susceptible to this stimulation. In fact, recently, 40 Hz oscillatory stimulation applied during REM sleep was effective in enhancing both endogenous gamma band activity and self-reflective awareness in dreams [99].

The feature that weak electric stimulation is strongly dependent on brain state is not only a virtue of the method in that the system is minimally disturbed by manipulation, but also a caveat. The efficacy of weak electric stimulation is dependent on covert properties, i.e., properties of the brain neuronal activity escaping measurement. During application of slow oscillatory weak electric stimulation phase ampli-

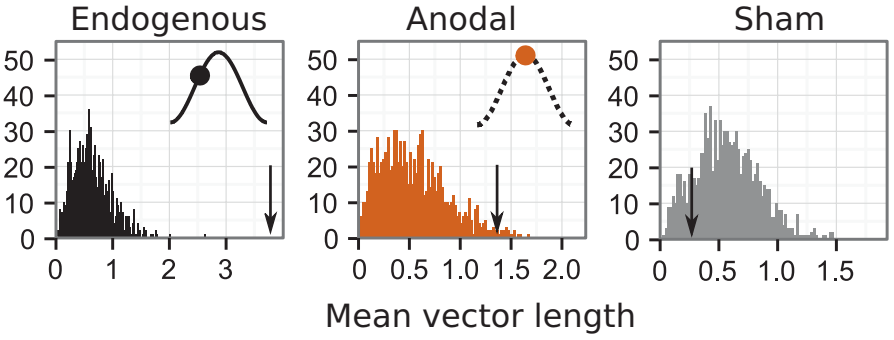

Fig. 7.3 Mean vector length reflecting coupling strength of fast spindles at Pz to the endogenous slow oscillation (left), anodal transcranial slow oscillatory stimulation (middle), and a virtually generated sham signal. Whereas coupling to the endogenous oscillations is highly significant ($p < 0.001$), coupling to the weak electric stimulation is weaker ($p < 0.05$). (Adapted by permission from Springer Nature. Campos-Beltrán D, Marshall L. Electric stimulation to improve memory consolidation during sleep. In: Axmacher N, Rasch B, editors. Cognitive neuroscience of memory consolidation. New York: Springer; 2017. p. 301–12)

tude coupling to spindles reached significance, but coupling strength was much weaker than between endogenous oscillations (Fig. 7.3). As will be described in the following, neuronal activity reflected in oscillatory potential fluctuations does not only effect cognitive processing during sleep, but presleep experience in turn also modifies neuronal oscillations of sleep. Thus, the efficiency of weak electric stimulation may well be significantly influenced by the extent of presleep learning, or existing interindividual trait-like electrophysiological features [100, 101].

Optogenetic activation of channelrhodopsin2-expressing thalamocortical neurons enabled the systematic modulation of cortical slow oscillation frequency in anesthetized rats [102]. The highest amplification of endogenous slow oscillation EEG power occurred when optogenetic activation was applied at the prevailing slow oscillation frequency.

Sleep's Influence on Memory

Although the impact of sleep deprivation on numerous cognitive functions has been reported [103, 104], the effect of specific neuronal oscillations in sleep on cognitive aspects has been most intensely investigated for memory consolidation. Within the process of memory formation, the consolidation of a memory occurs following learning, i.e., uptake and encoding of the contents to be remembered. The retention of a memory reflects the consolidation and is typically measured as the difference in performance between retrieval of the stored memory (recall performance) and encoding/learning performance.

Historically, the first experimental evidence for a positive influence of sleep on retention of memory came about 90 years ago from Jenkins and Dallenbach [105]. This finding was, however, explained within the framework of the passive interference reduction hypothesis, which posits that sleep is beneficial for memory due to less interference from external stimuli.

Results of some studies [106, 107] argued that it was not just sleep per se that was relevant for memory, but the temporal proximity of sleep to the learning. A recent study employing both 12- and 24-h retention intervals with sleep and wakefulness in different orders underlined the relevance of the proximity of sleep to learning for the consolidation of spatial associative memory [108]. But training-induced changes in SWA despite a delay before sleep were also recently reported [109]. The consolidation theory (first put forth by Müller and Pilzecker in 1900) expressed that memories initially exist in a labile state before they go into a longer term storage form [110]. More direct evidence in favor of the consolidation function of sleep did not arise until more detailed features of sleep and sleep types—such as REM sleep and the cyclic organization of sleep [111, 112]—were described.

Already in the 1970s interactions between type of material learned and different benefits of sleep dependent upon sleep stage were reported [113–115]. (For a review, see Cipolli [116].) A further conceptual advancement was the dual process

hypothesis, which explicitly stated that SWS, which is dominant in humans during the first half of the night, is beneficial for the consolidation of declarative memory. Sleep during the second half of the night (REM sleep predominant), on the other hand, is proposed by the concept to be most beneficial for procedural memories. The sequential hypothesis in contrast underscores the relevance of the cyclic succession of NREM and REM sleep (for in-depth recent reviews on studies supporting these theories, see Rasch and Born [70], Giuditta, et al. [117], and Rauchs, et al. [118]). Both hypotheses posit an active role of sleep and ongoing neuronal activity to memory consolidation (as opposed to the passive interference reduction hypothesis). A third concept contrasting to the active consolidation theory is the opportunistic consolidation hypothesis. Here it is put forth that any brain state (not, e.g., SWS per se) occurring in close temporal proximity to learning is beneficial to memory consolidation, such as quiet wakefulness or also certain drugs, as long as the hippocampus is not occupied in encoding new memories [119].

Sleep has often been shown to be more beneficial for the consolidation of emotional vs. neutral memories. REM sleep, REM-rich sleep periods, in particular phasic REM epochs, have been found beneficial in regard to the consolidation of memories with high emotional valence, for preserving emotional reactivity, fear conditioning, and extinction, in both humans [120–124] and rodents [125, 126]. During REM sleep pontine-geniculate waves arising from the brainstem and theta oscillations in the amygdala, hippocampus, and medial prefrontal cortex, and most importantly their coherent occurrence, appear to be the most relevant underlying neuronal rhythms of the forebrain [126–128]. Significant differences between humans and rodents have, however, been measured regarding consistency and topography of hippocampal and cortical theta waves [129]. Successful fear extinction memory was dependent upon phasic pontine wave activity during post-training REM sleep arising from glutamatergic cells with high-frequency (>500 Hz) spike bursts (3–5 spikes/burst) on the background of tonically increased firing rates (30–40 Hz) [125]. It is beyond the scope of this chapter to report in depth on putative mechanisms of neuronal oscillations and their generators affecting memory; for this recent comprehensive reviews are referred to [42, 130–132].

Aside from specific neuronal oscillations, sleep and distinct sleep stages are associated with other physiological parameters, most apparently changes in neuromodulatory tone and neurotransmitter activity, but also autonomic events, which may contribute essentially to sleep-dependent plasticity [70, 133–135]. These physiological effects of sleep also need to be considered when drawing conclusions from the impact of specific sleep stage suppression on the relevance of that particular sleep stage for a specific cognitive function [136, 137].

In addition to the consolidation of memories learned before sleep, sleep-dependent generalization, or the incorporation of recent into existing memories, as well as sleep's role in selective forgetting are processes receiving increasing attention. Whether reactivation occurs during REM sleep, SWS, or both is an ongoing question [138–141].

Post-learning Neuronal Oscillations

Since neuronal activity during sleep is linked to prior neuronal activity [142, 143], it is not surprising that presleep learning and cognitive activity overtly modify the macroscopic neuronal oscillations and activity during sleep, specifically sleep spindles and slow wave features [39, 46, 52, 62, 144–147]. Several developments emerging in the second half of the twentieth century were essential in forwarding research on postexperience neuronal oscillations and/or brain electric activity in association with memory. One was the emergence of concepts for neurophysiological memory trace formation, according to which information is transferred to the neocortical long-term memory store via hippocampo-cortical connections during hippocampal SPWR events of slow-wave sleep (SWS) [148–151]. Later developments incorporated mechanisms of long-term potentiation (LTP), the relevance of behavior, and state-dependent changes for defining neuronal oscillatory patterns into the two-stage model [148, 149, 152]. There was also an upsurge in the interest of linking patterns of brain electric activity to biochemical states of neurons during sleep subserving neuroplasticity, in particular the putative role of spindle oscillations in provoking a massive Ca^{2+} entry into neurons and long-term changes in cortical networks [153–156]. In most recent years, Ca^{2+} imaging has much contributed to elucidating the participation of different cell types to neuronal oscillations in sleep [68, 69]. A third development was the renewed interest in hippocampal place cells [157] in association with theta oscillations during exploratory behavior in rats. Mostly during SWS, postexperience spatially selective firing of hippocampal place cells and hippocampal spatiotemporal activity patterns were investigated [142, 143, 158–162]. Results emerging from this time, on the temporal relations between hippocampal SPWRs and thalamocortical sleep spindles, have since obtained extensive support, and finely tuned interactions between neocortical, hippocampal, and thalamic firing and local field potentials (LFPs) have been demonstrated [19, 20, 73, 131, 163–165]. Experience-dependent reactivations during sleep have been mostly investigated in the hippocampus and neocortex, but particularly in relation to the motor system reactivations in other brain regions, e.g., the striatum are shown [70, 166–173]. A further boost in knowledge and in the search for answers to newly arising questions on spatial and temporal relations between brain regions involved in postexperience sleep came with the increased use of fMRI during human sleep (see Chap. 6 of this volume: Functional Neuroimaging of Brain Oscillations during Human Sleep).

Investigations into post-learning neuronal oscillations in human EEG during sleep also gained momentum toward the end of the twentieth century due to technical advancements in long-term data recording and analyses, which enabled digital time-saving detection of electrical events throughout a period of nocturnal sleep to become a standard procedure.

In this chapter the distinction between neuronal oscillations being induced by prior-learning and contributing to cognitive processing in sleep is artificial and drawn mostly from different experimental approaches. The following studies describe neuronal oscillations induced by presleep learning as compared to those of a non-learning control, preferably of comparable sensory input and/or cognitive load.

In the same laboratory in which studies in humans first indicated that SWS-rich sleep in the first part of the night was beneficial for declarative memory formation, and REM-rich sleep in the second half of the night was relevant for procedural memory [174], the impact of learning on spindle activity was intensively investigated. Gais and colleagues [46] found significantly higher spindle density in stage 2 sleep within the first half of the night after learning on a declarative task paired-associate lists of unrelated words, as compared to a within-subject non-learning control task matched for visual input and difficulty. The difference in spindle density was most pronounced at Fz within the first 90 min of sleep. Neither spindle density in SWS nor any measure of EEG power or time spent in any sleep stage differed between the two experimental conditions. Similarly, Schabus and colleagues [175] found higher spindle activity of detected spindle events during stage 2 sleep following an association task of randomly related word pairs as compared to a matched control condition. The spindle activity measure also correlated strongly with the overnight change in memory performance. Subsequent to exploring a maze as compared to no exploration, spindle activity as well as time spent in sleep stage 2 were reported enhanced (Fig. 7.4) [176].

Memory content can also be relevant for subsequent neuronal oscillations in sleep: for instance, both SWA and sleep spindles were found to increase after learning words of sparse (or low) as compared to high semantic neighborhood density [177].

Conditions at learning furthermore impact post-learning neuronal oscillations: post-learning EEG power in the slow oscillation frequency, time spent in stage 4 sleep, and spindle count in SWS were enhanced when subjects expected to be retested on the learned material as compared to subjects without this expectation [178]. In a similar vein, parietal fast spindles over the left hemisphere reflected best the

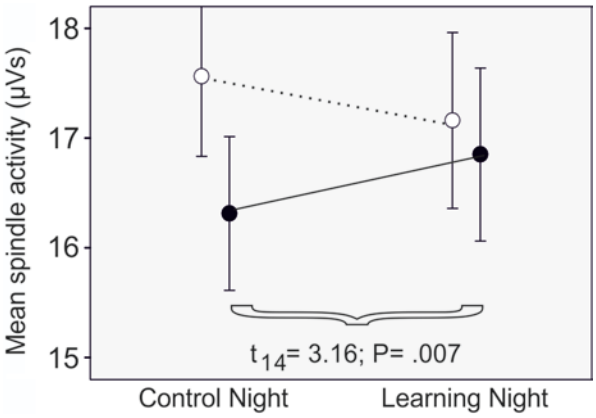

Fig. 7.4 Post-learning modification in fast spindle activity. Mean (±SEM) spindle activity revealed a relative increase in subjects improving on the memory task, but a relative decrease in subjects who did not improve. (Modified with permission from Schabus M, et al. Individual sleep spindle differences and their relation to learning-related enhancements. Brain Res. Vol. 1191. P. 127–35. © 2008. With permission from Elsevier)

effect of instruction at learning, to either remember or forget presented words. As compared to wake, sleep selectively facilitated the class of cued items to be remembered, but not the words to be forgotten. Investigation of other electrophysiological events was not reported. Figure 7.4 shows an increase by learning of spindle activity, but only for those subjects which revealed good memory performance [179].

sLORETA (standardized low-resolution brain electromagnetic tomography), an EEG-based neuroimaging technique, identified for the spindle time course a repeating loop of activity throughout a network in the superior parietal, temporal, and inferior frontal cortex [180]. These regions reveal not only fMRI correlates of fast spindles but were previously found to promote successful instructed-remembering over forgetting [179, 180]. Another study showed that odor cues associated with words presented in left or right hemifields could locally induce fast spindles during NREM sleep [168].

The integration of words in the "mental lexicon" rather than consolidation per se also correlated with spindle count: a larger increase in lexical competition, i.e., the slower response time (an indication of successful addition to the mental lexicon) of test familiar base-words to familiar control base-words, was associated with a greater spindle count. In contrast, the overnight increase in consolidation of novel words per se, tested as recall or recognition of the novel words, did not correlate with spindle count [141].

Post-learning effects of the procedural tasks, particularly in regard to changes in sleep spindles and rapid eye movements, were investigated intensely by Smith and Fogel. It was hypothesized and verified vastly in experiments, that simple motor procedural learning tasks are associated with stage 2 sleep modifications, in particular spindle density, while implicitly learning procedural rules and new cognitive strategies ("cognitive procedural") were associated with increases in density of rapid eye movements [44, 181, 182].

Four simple motor tasks requiring the refinement of motor skills, and not requiring the learning of rules or the development of a strategy—pursuit rotor, a simple version of the mirror tracing task, ball-and-cup game, operation—increased sleep spindle density as well as duration of stage 2 sleep across the night compared to a non-learning control group of six female subjects. In group comparisons of slightly larger sample size, mirror tracing led to an enhancement in REM density [181]. Subjects conducting both the mirror tracing and tower of Hanoi tasks before sleep, i.e., tasks with a large procedural component, revealed significant enhancements in the number of rapid eye movements in later sleep cycles as compared to a control group. No changes in sleep architecture of any type were found, neither spindle density nor EEG power of any frequency band were measured [183]. The relevance of REM density for consolidation is presumably linked to increased P-wave or ponto-geniculo-occipital (PGO) wave occurrence [184, 185]. As far as known to the author, no direct modulation of PGO waves has occurred parallel to any measurement of cognitive or mnemonic parameter.

Interestingly, long-range coupling within MEG delta activity during NREM sleep was recently reported subsequent to conducting a mirror tracing task. The coupled brain regions had been previously identified based on their enhanced involvement during the visuomotor mirror tracing task as compared to a control task in which slow (0.1 Hz) fluctuations in beta band power became synchronized [186].

Motor sequence learning tasks are widely used in sleep research, most frequently reported to increase number and/or duration of spindles, or spindle power, with striatal involvement developing over time [70, 169, 187, 188]. The combination with imaging methods is also particularly advanced for motor-related paradigms [189]. Correlative analyses have shown for discrete spindles that their amplitude can predict overnight gains in performance on an explicitly learned motor sequence task. Correlations were additionally found between BOLD activity in motor-related brain regions and spindle amplitude [190]. A MEG study revealed enhancement of both fast spindles and delta MEG activity during SWS of the first sleep cycle as compared to pre-training sleep. The most prominent region of interest displaying modifications in sigma and delta MEG power was the supplementary motor area (SMA), as detected via source localization [191]. The serial reaction time task can be employed to contrast implicit and explicit learning and the effect of sleep on gaining explicit sequence knowledge [124]. Subjects who had or had not acquired explicit sequence knowledge prior to sleep differed in their level of EEG slow spindle power during SWS [192]. Resting state fMRI during wakefulness, immediately after acquisition of an explicitly or implicitly learned serial reaction time task, revealed a differential involvement of brain regions including the frontal cortex [193].

In a motor adaptation task, a local increment in slow-wave activity over parietal regions and a less robust increase in spindle power as compared to a non-learning control were reported, with a positive correlation between SWA increase and performance improvement [61, 109]. Increased SWA over the frontal cortex, up to 60 min post-training without any change in spindle frequency band, was observed in rats following a task known to elicit long-term potentiation [194].

Conclusion

Taken together, the picture that the sleep-dependent consolidation of declarative vs. non-declarative memory contents represents a dichotomy and is simply attributed to disparate brain structures and mechanisms has greatly diminished. At the same time, the picture is quickly developing that fine-tuning among neuronal oscillations within and between different structures represents the essence of communication within the brain. The latter has been longer discussed regarding working memory function [195], but less in respect to cognitive processing during sleep [196–198]. Oscillatory field potential activity incorporates both general global and network-specific local components. Local aspects are defined not only topographically, but also by coherence strength among networks, by the sleep stages and times of the sleep period at which these oscillatory events mainly arise, as well as through slight variations in oscillatory frequency [196, 199]. In the conceptual Fig. 7.5 neuronal oscillations of memory and cognition are imbedded in the biological system. It reflects the basic principles of experience impacting postexperience neuronal activity. The latter is strongly dependent upon salience and emotional valence of the presleep experience, affecting strength of encoding or innervation of the relevant

brain regions and networks. During sleep basic state-dependent neuronal oscillations and experience-dependent neuronal reactivation (super firing or subthreshold modulation) interact. Tonic and phasic neuromodulatory activity as well as other non-neuronal central-nervous or peripheral inputs signaling immunologic, metabolic, and epigenetic events or processes [62, 200, 201] can further modify the fine-tuning of inter- and intraregional neuro-oscillatory interactions of the brain. On the other hand, neuro(glial)-oscillatory networks can feedback on other systems ranging from the molecular level, e.g., through fluctuations in intracellular ionic concentrations, to global system-wide effects, e.g., via interactions with circadian clock mechanisms.

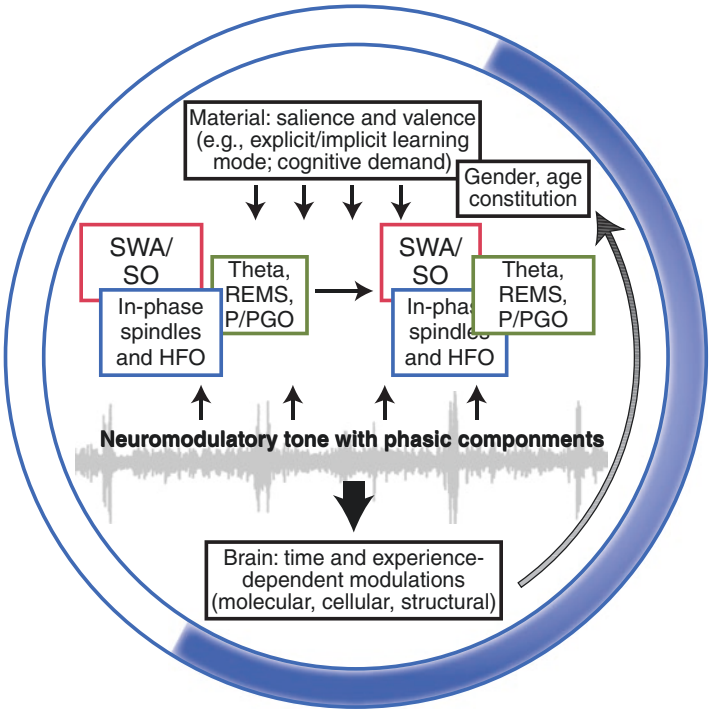

Fig. 7.5 Speculative conceptual framework for neuronal oscillations of memory and cognition within the biological system. The dynamically changing neuronal oscillations and electrophysiological events occurring across the sleep period (SO/SWA, spindles, HFO, theta, REMS, P/PGOs) result mainly from state-dependent neuronal oscillations and experience-dependent neuronal reactivation. Features affecting postexperience modifications are indicated at the top. Neuronal oscillatory activity affects not only ongoing membrane polarization levels, but can induce structural changes (e.g., at dendritic spines and interregional connectivity) in the brain, as indicated at the bottom. The long thin gray arrow on the right indicates that the latter serve to update the biological system for newly incoming information. The expression of neuronal oscillations is also dependent upon trait-like, persistent state and developmental features indicated by gender, age and constitution (see text for more details). *SO/SWA* sleep slow oscillation/slow wave activity, *REMS* rapid eye movements of REM sleep, *P/PGO* P-waves/ponto-geniculate-occipital waves, *HFO* high-frequency oscillations (>30 Hz)

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References

1. Abel T, Kandel E. Positive and negative regulatory mechanisms that mediate long-term memory storage. Brain Res Brain Res Rev. 1998;26(2–3):360–78.
2. Bushey D, Cirelli C. From genetics to structure to function: exploring sleep in Drosophila. Int Rev Neurobiol. 2011;99:213–44.
3. Kamyshev NG, Iliadi KG, Bragina JV. Drosophila conditioned courtship: two ways of testing memory. Learn Mem. 1999;6(1):1–20.
4. Zimmerman JE, Naidoo N, Raizen DM, Pack AI. Conservation of sleep: insights from non-mammalian model systems. Trends Neurosci. 2008;31(7):371–6.
5. Yap MHW, Grabowska MJ, Rohrscheib C, Jeans R, Troup M, Paulk AC, et al. Oscillatory brain activity in spontaneous and induced sleep stages in flies. Nat Commun. 2017;8(1):1815.
6. Davis RL. Traces of Drosophila memory. Neuron. 2011;70(1):8–19.
7. Pan Y, Zhou Y, Guo C, Gong H, Gong Z, Liu L. Differential roles of the fan-shaped body and the ellipsoid body in Drosophila visual pattern memory. Learn Mem. 2009;16(5):289–95.
8. Van Swinderen B. Fly memory: a mushroom body story in parts. Curr Biol. 2009;19(18):R855–7.
9. Beyaert L, Greggers U, Menzel R. Honeybees consolidate navigation memory during sleep. J Exp Biol. 2012;215(Pt 22):3981–8.
10. Zwaka H, Bartels R, Gora J, Franck V, Culo A, Gotsch M, et al. Context odor presentation during sleep enhances memory in honeybees. Curr Biol. 2015;25(21):2869–74.
11. Ramon F, Mendoza-Angeles K, Hernandez-Falcon J. Sleep in invertebrates: crayfish. Front Biosci (Schol Ed). 2012;4:1190–200.
12. Bierbower SM, Shuranova ZP, Viele K, Cooper RL. Comparative study of environmental factors influencing motor task learning and memory retention in sighted and blind crayfish. Brain Behav. 2013;3(1):4–13.
13. Tierney AJ, Lee J. Spatial learning in a T-maze by the crayfish Orconectes rusticus. J Comp Psychol. 2011;125(1):31–9.
14. Rattenborg NC, Martinez-Gonzalez D, Roth TC, Pravosudov VV. Hippocampal memory consolidation during sleep: a comparison of mammals and birds. Biol Rev Camb Philos Soc. 2011;86(3):658–91.
15. Tobler I, Borbély A. Sleep and EEG spectra in the pigeon (Columba livia) under baseline condtions and after sleep deprivation. J Comp Physiol A. 1988;163:729–38.
16. van der Meij J, Martinez-Gonzalez D, Beckers GJL, Rattenborg NC. Intra-“cortical” activity during avian non-REM and REM sleep: variant and invariant traits between birds and mammals. Sleep. 2019;42(2).
17. Jackson C, McCabe BJ, Nicol AU, Grout AS, Brown MW, Horn G. Dynamics of a memory trace: effects of sleep on consolidation. Curr Biol. 2008;18(6):393–400.
18. Nelini C, Bobbo D, Mascetti GG. Local sleep: a spatial learning task enhances sleep in the right hemisphere of domestic chicks (Gallus gallus). Exp Brain Res. 2010;205(2):195–204.
19. Peyrache A, Battaglia FP, Destexhe A. Inhibition recruitment in prefrontal cortex during sleep spindles and gating of hippocampal inputs. Proc Natl Acad Sci U S A. 2011;108(41):17207–12.
20. Wierzynski CM, Lubenov EV, Gu M, Siapas AG. State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. Neuron. 2009;61(4):587–96.

21. Csercsa R, Dombovari B, Fabo D, Wittner L, Eross L, Entz L, et al. Laminar analysis of slow wave activity in humans. Brain. 2010;133(9):2814–29.
22. Sanchez-Vives MV, Mattia M, Compte A, Perez-Zabalza M, Winograd M, Descalzo VF, et al. Inhibitory modulation of cortical up states. J Neurophysiol. 2010;104(3):1314–24.
23. Destexhe A, Sejnowski TJ. Thalamocortical assemblies. Oxford, UK: Oxford University Press; 2001.
24. Steriade M, Deschenes M. The thalamus as a neuronal oscillator. Brain Res. 1984;320(1):1–63.
25. Steriade M, McCarley RW. Synchronized brain oscillations leading to neuronal plasticity during waking and sleep states. In: Brain control of wakefulness and sleep. 2nd ed. New York: Springer; 2005. p. 255–344.
26. Contreras D, Destexhe A, Sejnowski TJ, Steriade M. Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science. 1996;274(5288):771–4.
27. Mak-McCully RA, Rolland M, Sargsyan A, Gonzalez C, Magnin M, Chauvel P, et al. Coordination of cortical and thalamic activity during non-REM sleep in humans. Nat Commun. 2017;8:15499.
28. Gardner RJ, Hughes SW, Jones MW. Differential spike timing and phase dynamics of reticular thalamic and prefrontal cortical neuronal populations during sleep spindles. J Neurosci. 2013;33(47):18469–80.
29. Bartho P, Slezia A, Matyas F, Faradzs-Zade L, Ulbert I, Harris KD, et al. Ongoing network state controls the length of sleep spindles via inhibitory activity. Neuron. 2014;82(6):1367–79.
30. Andrillon T, Ni Y, Staba RJ, Ferrarelli F, Cirelli C, Tononi G, et al. Sleep spindles in humans: insights from intracranial EEG and unit recordings. J Neurosci. 2011;31(49):17821–34.
31. Dehghani N, Cash SS, Halgren E. Emergence of synchronous EEG spindles from asynchronous MEG spindles. Hum Brain Mapp. 2011;32(12):2217–27.
32. Nakamura M, Uchida S, Maehara T, Kawai K, Hirai N, Nakabayashi T, et al. Sleep spindles in human prefrontal cortex: an electrocorticographic study. Neurosci Res. 2003;45(4):419–27.
33. Peter-Derex L, Comte JC, Mauguiere F, Salin PA. Density and frequency caudo-rostral gradients of sleep spindles recorded in the human cortex. Sleep. 2012;35(1):69–79.
34. Dehghani N, Cash SS, Chen CC, Hagler DJ Jr, Huang M, Dale AM, et al. Divergent cortical generators of MEG and EEG during human sleep spindles suggested by distributed source modeling. PLoS One. 2010;5(7):e11454.
35. Del Felice A, Arcaro C, Storti SF, Fiaschi A, Manganotti P. Electrical source imaging of sleep spindles. Clin EEG Neurosci. 2013;45(3):184–92.
36. Clemens Z, Mölle M, Eross L, Barsi P, Halasz P, Born J. Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. Brain. 2007;130(Pt 11):2868–78.
37. Anderer P, Klosch G, Gruber G, Trenker E, Pascual-Marqui RD, Zeitlhofer J, et al. Low-resolution brain electromagnetic tomography revealed simultaneously active frontal and parietal sleep spindle sources in the human cortex. Neuroscience. 2001;103(3):581–92.
38. Clemens Z, Mölle M, Eross L, Jakus R, Rasonyi G, Halasz P, et al. Fine-tuned coupling between human parahippocampal ripples and sleep spindles. Eur J Neurosci. 2011;33(3):511–20.
39. Mölle M, Bergmann TO, Marshall L, Born J. Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep. 2011;34(10):1411–21.
40. Slezia A, Hangya B, Ulbert I, Acsady L. Phase advancement and nucleus-specific timing of thalamocortical activity during slow cortical oscillation. J Neurosci. 2011;31(2):607–17.
41. Hagler DJ Jr, Ulbert I, Wittner L, Eross L, Madsen JR, Devinsky O, et al. Heterogeneous origins of human sleep spindles in different cortical layers. J Neurosci. 2018;38(12):3013–25.
42. Clawson BC, Durkin J, Aton SJ. Form and function of sleep spindles across the lifespan. Neural Plast. 2016;2016:6936381.
43. Cox R, Schapiro AC, Manoach DS, Stickgold R. Individual differences in frequency and topography of slow and fast sleep spindles. Front Hum Neurosci. 2017;11:433.
44. Fogel SM, Smith CT. Learning-dependent changes in sleep spindles and stage 2 sleep. J Sleep Res. 2006;15(3):250–5.

45. Gaillard JM, Blois R. Spindle density in sleep of normal subjects. Sleep. 1981;4(4):385–91.
46. Gais S, Molle M, Helms K, Born J. Learning-dependent increases in sleep spindle density. J Neurosci. 2002;22(15):6830–4.
47. Mölle M, Marshall L, Gais S, Born J. Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. Proc Natl Acad Sci U S A. 2004;101(38):13963–8.
48. Peters KR, Ray L, Smith V, Smith C. Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. J Sleep Res. 2008;17(1):23–33.
49. van Kesteren MT, Rijpkema M, Ruiter DJ, Fernandez G. Retrieval of associative information congruent with prior knowledge is related to increased medial prefrontal activity and connectivity. J Neurosci. 2010;30(47):15888–94.
50. Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV, et al. Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? Biol Psychiatry. 2012;71(2):154–61.
51. Martin N, Lafortune M, Godbout J, Barakat M, Robillard R, Poirier G, et al. Topography of age-related changes in sleep spindles. Neurobiol Aging. 2013;34(2):468–76.
52. Mölle M, Eschenko O, Gais S, Sara SJ, Born J. The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur J Neurosci. 2009;29(5):1071–81.
53. Steriade M. Cellular substrates of brain rhythms. In: Niedermeyer E, Lopes F, editors. Electroencephalography: basic principles, clinical applications, and related fields. Baltimore: William & Wilkins; 1993. p. 27–62.
54. Steriade M, Nunez A, Amzica F. Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. J Neurosci. 1993;13(8):3266–83.
55. Steriade M, Nunez A, Amzica F. A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J Neurosci. 1993;13(8):3252–65.
56. Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, et al. Regional slow waves and spindles in human sleep. Neuron. 2011;70(1):153–69.
57. Steriade M. Grouping of brain rhythms in corticothalamic systems. Neuroscience. 2006;137(4):1087–106.
58. Timofeev I, Grenier F, Steriade M. Disfacilitation and active inhibition in the neocortex during the natural sleep-wake cycle: an intracellular study. Proc Natl Acad Sci U S A. 2001;98(4):1924–9.
59. Volgushev M, Chauvette S, Mukovski M, Timofeev I. Precise long-range synchronization of activity and silence in neocortical neurons during slow-wave oscillations. J Neurosci. 2006;26(21):5665–72.
60. Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, et al. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. Nat Neurosci. 2006;9(9):1169–76.
61. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. Nature. 2004;430(6995):78–81.
62. Krueger JM, Nguyen JT, Dykstra-Aiello CJ, Taishi P. Local sleep. Sleep Med Rev. 2018;43:14–21.
63. Poskanzer KE, Yuste R. Astrocytes regulate cortical state switching in vivo. Proc Natl Acad Sci U S A. 2016;113(19):E2675–84.
64. Szabo Z, Heja L, Szalay G, Kekesi O, Furedi A, Szebenyi K, et al. Extensive astrocyte synchronization advances neuronal coupling in slow wave activity in vivo. Sci Rep. 2017;7(1):6018.
65. Menicucci D, Piarulli A, Debarnot U, d'Ascanio P, Landi A, Gemignani A. Functional structure of spontaneous sleep slow oscillation activity in humans. PLoS One. 2009;4(10):e7601.
66. Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, et al. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep. 2007;30(12):1643–57.

67. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11(2):114–26.
68. Funk CM, Peelman K, Bellesi M, Marshall W, Cirell C, Tononi G. Role of Somatostatin-positive cortical interneurons in the generation of sleep slow waves. J Neurosci. 2017;37(38):9132–48.
69. Niethard N, Ngo HV, Ehrlich I, Born J. Cortical circuit activity underlying sleep slow oscillations and spindles. Proc Natl Acad Sci U S A. 2018;115(39):E9220–9.
70. Rasch B, Born J. About sleep's role in memory. Physiol Rev. 2013;93(2):681–766.
71. Crunelli V, David F, Lorincz ML, Hughes SW. The thalamocortical network as a single slow wave-generating unit. Curr Opin Neurobiol. 2015;31:72–80.
72. Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, et al. High gamma power is phase-locked to theta oscillations in human neocortex. Science. 2006;313(5793):1626–8.
73. Cox R, Mylonas DS, Manoach DS, Stickgold R. Large-scale structure and individual fingerprints of locally coupled sleep oscillations. Sleep. 2018;41(12).
74. Dang-Vu TT, Bonjean M, Schabus M, Boly M, Darsaud A, Desseilles M, et al. Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A. 2011;108(37):15438–43.
75. Ngo HV, Martinetz T, Born J, Molle M. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron. 2013;78(3):545–53.
76. Riedner BA, Hulse BK, Murphy MJ, Ferrarelli F, Tononi G. Temporal dynamics of cortical sources underlying spontaneous and peripherally evoked slow waves. Prog Brain Res. 2011;193:201–18.
77. Ruch S, Koenig T, Mathis J, Roth C, Henke K. Word encoding during sleep is suggested by correlations between word-evoked up-states and post-sleep semantic priming. Front Psychol. 2014;5:1319.
78. Schabus M, Dang-Vu TT, Heib DP, Boly M, Desseilles M, Vandewalle G, et al. The fate of incoming stimuli during NREM sleep is determined by spindles and the phase of the slow oscillation. Front Neurol. 2012;3:40.
79. Vyazovskiy VV, Faraguna U, Cirelli C, Tononi G. Triggering slow waves during NREM sleep in the rat by intracortical electrical stimulation: effects of sleep/wake history and background activity. J Neurophysiol. 2009;101(4):1921–31.
80. Wilckens KA, Ferrarelli F, Walker MP, Buysse DJ. Slow-wave activity enhancement to improve cognition. Trends Neurosci. 2018;41(7):470–82.
81. Weigenand A, Molle M, Werner F, Martinetz T, Marshall L. Timing matters: open-loop stimulation does not improve overnight consolidation of word pairs in humans. Eur J Neurosci. 2016;44(6):2357–68.
82. Binder S, Baier PC, Molle M, Inostroza M, Born J, Marshall L. Sleep enhances memory consolidation in the hippocampus-dependent object-place recognition task in rats. Neurobiol Learn Mem. 2012;97(2):213–9.
83. Cox R, Hofman WF, Talamini LM. Involvement of spindles in memory consolidation is slow wave sleep-specific. Learn Mem. 2012;19(7):264–7.
84. Bergmann TO, Mölle M, Schmidt MA, Lindner C, Marshall L, Born J, et al. EEG-guided transcranial magnetic stimulation reveals rapid shifts in motor cortical excitability during the human sleep slow oscillation. J Neurosci. 2012;32(1):243–53.
85. Manganotti P, Formaggio E, Del FA, Storti SF, Zamboni A, Bertoldo A, et al. Time-frequency analysis of short-lasting modulation of EEG induced by TMS during wake, sleep deprivation and sleep. Front Hum Neurosci. 2013;7:767.
86. Marshall L, Born J. Brain stimulation during sleep. In: Stickgold R, editor. Sleep medicine clinics. Philadelphia: WB Saunders; 2011. p. 85–95.
87. Massimini M, Ferrarelli F, Esser SK, Riedner BA, Huber R, Murphy M, et al. Triggering sleep slow waves by transcranial magnetic stimulation. Proc Natl Acad Sci U S A. 2007;104(20):8496–501.
88. Bergmann TO, Mölle M, Marshall L, Kaya-Yildiz L, Born J, Roman SH. A local signature of LTP- and LTD-like plasticity in human NREM sleep. Eur J Neurosci. 2008;27(9):2241–9.

89. Huber R, Maatta S, Esser SK, Sarasso S, Ferrarelli F, Watson A, et al. Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. J Neurosci. 2008;28(31):7911–8.
90. Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67(1):129–43.
91. Liu A, Voroslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun. 2018;9:5092.
92. Ali MM, Sellers KK, Frohlich F. Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. J Neurosci. 2013;33(27):11262–75.
93. Vosskuhl J, Struber D, Herrmann CS. Non-invasive brain stimulation: a paradigm shift in understanding brain oscillations. Front Hum Neurosci. 2018;12:211.
94. Campos-Beltrán D, Marshall L. Electric stimulation to improve memory consolidation during sleep. In: Axmacher N, Rasch B, editors. Cognitive neuroscience of memory consolidation. New York: Springer; 2017. p. 301–12.
95. Ladenbauer J, Ladenbauer J, Kulzow N, de Boor R, Avramova E, Grittner U, et al. Promoting sleep oscillations and their functional coupling by transcranial stimulation enhances memory consolidation in mild cognitive impairment. J Neurosci. 2017;37(30):7111–24.
96. Marshall L, Binder S. Contribution of transcranial oscillatory stimulation to research on neural networks: an emphasis on hippocampo-neocortical rhythms. Front Hum Neurosci. 2013;7:614.
97. Marshall L, Helgadottir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature. 2006;444(7119):610–3.
98. Voss U, Holzmann R, Tuin I, Hobson JA. Lucid dreaming: a state of consciousness with features of both waking and non-lucid dreaming. Sleep. 2009;32(9):1191–200.
99. Voss U, Holzmann R, Hobson A, Paulus W, Koppehele-Gossel J, Klimke A, et al. Induction of self awareness in dreams through frontal low current stimulation of gamma activity. Nat Neurosci. 2014;17(6):810–2.
100. Berryhill ME, Peterson DJ, Jones KT, Stephens JA. Hits and misses: leveraging tDCS to advance cognitive research. Front Psychol. 2014;5:800.
101. Koo PC, Molle M, Marshall L. Efficacy of slow oscillatory-transcranial direct current stimulation on EEG and memory—contribution of an inter-individual factor. Eur J Neurosci. 2018;47(7):812–23.
102. David F, Schmiedt JT, Taylor HL, Orban G, Di GG, Uebele VN, et al. Essential thalamic contribution to slow waves of natural sleep. J Neurosci. 2013;33(50):19599–610.
103. Alhola P, Polo-Kantola P. Sleep deprivation: impact on cognitive performance. Neuropsychiatr Dis Treat. 2007;3(5):553–67.
104. Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Semin Neurol. 2009;29(4):320–39.
105. Jenkins JK, Dallenbach KM. Obliviscence during sleep and waking. Am J Phys. 1924;35:605–12.
106. Graves EA. The effect of sleep on retention. J Exp Psychol. 1937;19:316–22.
107. Newman EB. Forgetting of meaningful material during sleep and waking. Am J Psychol. 1939;52:65–71.
108. Talamini LM, Nieuwenhuis IL, Takashima A, Jensen O. Sleep directly following learning benefits consolidation of spatial associative memory. Learn Mem. 2008;15(4):233–7.
109. Maatta S, Landsness E, Sarasso S, Ferrarelli F, Ferreri F, Ghilardi MF, et al. The effects of morning training on night sleep: a behavioral and EEG study. Brain Res Bull. 2010;82(1–2):118–23.
110. McGaugh JL. Memory—a century of consolidation. Science. 2000;287(5451):248–51.
111. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. J Neuropsychiatry Clin Neurosci. 1953;15(4):454–5.

112. Dement WC, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr Clin Neurophysiol. 1957;9(4):673–90.
113. Empson JA, Clarke PR. Rapid eye movements and remembering. Nature. 1970;227(5255):287–8.
114. Fowler MJ, Sullivan MJ, Ekstrand BR. Sleep and memory. Science. 1973;179(4070):302–4.
115. Yaroush R, Sullivan MJ, Ekstrand BR. Effect of sleep on memory. II. Differential effect of the first and second half of the night. J Exp Psychol. 1971;88(3):361–6.
116. Cipolli C. Sleep and memory. In: Parmeggiani PL, Velluti RA, editors. The physiologic nature of sleep. London: Imperial College Press; 2005. p. 601–23.
117. Giuditta A, Ambrosini MV, Montagnese P, Mandile P, Cotugno M, Grassi ZG, et al. The sequential hypothesis of the function of sleep. Behav Brain Res. 1995;69(1–2):157–66.
118. Rauchs G, Desgranges B, Foret J, Eustache F. The relationships between memory systems and sleep stages. J Sleep Res. 2005;14(2):123–40.
119. Mednick SC, Ca DJ, Shuman T, Anagnostaras S, Wixted JT. An opportunistic theory of cellular and systems consolidation. Trends Neurosci. 2011;34(10):504–14.
120. Baran B, Pace-Schott EF, Ericson C, Spencer RM. Processing of emotional reactivity and emotional memory over sleep. J Neurosci. 2012;32(3):1035–42.
121. Groch S, Wilhelm I, Diekelmann S, Born J. The role of REM sleep in the processing of emotional memories: evidence from behavior and event-related potentials. Neurobiol Learn Mem. 2013;99:1–9.
122. Menz MM, Rihm JS, Salari N, Born J, Kalisch R, Pape HC, et al. The role of sleep and sleep deprivation in consolidating fear memories. NeuroImage. 2013;75:87–96.
123. Nishida M, Pearsall J, Buckner RL, Walker MP. REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex. 2009;19(5):1158–66.
124. Wagner U, Gais S, Born J. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem. 2001;8(2):112–9.
125. Datta S, O'Malley MW. Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. J Neurosci. 2013;33(10):4561–9.
126. Popa D, Duvarci S, Popescu AT, Lena C, Pare D. Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. Proc Natl Acad Sci U S A. 2010;107(14):6516–9.
127. Genzel L, Spoormaker VI, Konrad BN, Dresler M. The role of rapid eye movement sleep for amygdala-related memory processing. Neurobiol Learn Mem. 2015;122:110–21.
128. Totty MS, Chesney LA, Geist PA, Datta S. Sleep-dependent oscillatory synchronization: a role in fear memory consolidation. Front Neural Circuits. 2017;11:49.
129. Cantero JL, Atienza M, Stickgold R, Kahana MJ, Madsen JR, Kocsis B. Sleep-dependent theta oscillations in the human hippocampus and neocortex. J Neurosci. 2003;23(34):10897–903.
130. Navarro-Lobato I, Genzel L. The up and down of sleep: from molecules to electrophysiology. Neurobiol Learn Mem. 2019;160:3–10.
131. Skelin I, Kilianski S, McNaughton BL. Hippocampal coupling with cortical and subcortical structures in the context of memory consolidation. Neurobiol Learn Mem. 2019;160:21–31.
132. Ulrich D. Sleep spindles as facilitators of memory formation and learning. Neural Plast. 2016;2016:1796715.
133. Eschenko O, Magri C, Panzeri S, Sara SJ. Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. Cereb Cortex. 2012;22(2):426–35.
134. Lee MG, Hassani OK, Alonso A, Jones BE. Cholinergic basal forebrain neurons burst with theta during waking and paradoxical sleep. J Neurosci. 2005;25(17):4365–9.
135. Naji M, Krishnan GP, McDevitt EA, Bazhenov M, Mednick SC. Coupling of autonomic and central events during sleep benefits declarative memory consolidation. Neurobiol Learn Mem. 2018;157:139–50.
136. Genzel L, Dresler M, Wehrle R, Grozinger M, Steiger A. Slow wave sleep and REM sleep awakenings do not affect sleep dependent memory consolidation. Sleep. 2009;32(3):302–10.

137. Morgenthaler J, Wiesner CD, Hinze K, Abels LC, Prehn-Kristensen A, Goder R. Selective REM-sleep deprivation does not diminish emotional memory consolidation in young healthy subjects. PLoS One. 2014;9(2):e89849.
138. Feld GB, Born J. Sculpting memory during sleep: concurrent consolidation and forgetting. Curr Opin Neurobiol. 2017;44:20–7.
139. Gupta AS, van der Meer MA, Touretzky DS, Redish AD. Hippocampal replay is not a simple function of experience. Neuron. 2010;65(5):695–705.
140. Spencer RM. Neurophysiological basis of sleep's function on memory and cognition. ISRN Physiol. 2013;2013:619319.
141. Tamminen J, Payne JD, Stickgold R, Wamsley EJ, Gaskell MG. Sleep spindle activity is associated with the integration of new memories and existing knowledge. J Neurosci. 2010;30(43):14356–60.
142. Hirase H, Leinekugel X, Czurko A, Csicsvari J, Buzsaki G. Firing rates of hippocampal neurons are preserved during subsequent sleep episodes and modified by novel awake experience. Proc Nat. Acad Sci U S A. 2001;98(16):9386–90.
143. Wilson MA, McNaughton BL. Reactivation of hippocampal ensemble memories during sleep. Science. 1994;265(5172):676–9. [See comments].
144. Clemens Z, Fabo D, Halasz P. Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience. 2005;132(2):529–35.
145. Pugin F, Metz AJ, Wolf M, Achermann P, Jenni OG, Huber R. Local increase of sleep slow wave activity after three weeks of working memory training in children and adolescents. Sleep. 2015;38(4):607–14.
146. Ramadan W, Eschenko O, Sara SJ. Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. PLoS One. 2009;4(8):e6697.
147. Schmidt C, Peigneux P, Muto V, Schenkel M, Knoblauch V, Munch M, et al. Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. J Neurosci. 2006;26(35):8976–82.
148. Buzsaki G. Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience. 1989;31(3):551–70.
149. Buzsaki G, Haas HL, Anderson EG. Long-term potentiation induced by physiologically relevant stimulus patterns. Brain Res. 1987;435(1–2):331–3.
150. Marr D. A theory for cerebral neocortex. Proc R Soc Lond B Biol Sci. 1970;76(43):161–234.
151. Marr D. Simple memory: a theory for archicortex. Philos Trans R Soc Lond Ser B Biol Sci. 1971;262(841):23–81.
152. Chrobak JJ, Buzsaki G. High-frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat. J Neurosci. 1996;16(9):3056–66.
153. Contreras D, Destexhe A, Steriade M. Intracellular and computational characterization of the intracortical inhibitory control of synchronized thalamic inputs in vivo. J Neurophysiol. 1997;78(1):335–50.
154. Rosanova M, Ulrich D. Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci. 2005;25(41):9398–405.
155. Sejnowski TJ, Destexhe A. Why do we sleep? Brain Res. 2000;886(1–2):208–23.
156. Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. Science. 1993;262(5134):679–85.
157. O'Keefe J, Recce ML. Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus. 1993;3(3):317–30.
158. Lee AK, Wilson MA. Memory of sequential experience in the hippocampus during slow wave sleep. Neuron. 2002;36(6):1183–94.
159. Louie K, Wilson MA. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron. 2001;29(1):145–56.
160. Nadasdy Z, Hirase H, Czurko A, Csicsvari J, Buzsaki G. Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci. 1999;19(21):9497–507.

161. Pavlides C, Winson J. Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. J Neurosci. 1989;9(8):2907–18.
162. Skaggs WE, McNaughton BL. Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science. 1996;271(5257):1870–3.
163. Mölle M, Yeshenko O, Marshall L, Sara SJ, Born J. Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. J Neurophysiol. 2006;96(1):62–70.
164. Siapas AG, Wilson MA. Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron. 1998;21(5):1123–8.
165. Sirota A, Csicsvari J, Buhl D, Buzsaki G. Communication between neocortex and hippocampus during sleep in rodents. Proc Natl Acad Sci U S A. 2003;100(4):2065–9.
166. Brodt S, Pohlchen D, Flanagin VL, Glasaue S, Gais S, Schonauer M. Rapid and independent memory formation in the parietal cortex. Proc Natl Acad Sci U S A. 2016;113(46):13251–6.
167. Buhry L, Azizi AH, Cheng S. Reactivation, replay, and preplay: how it might all fit together. Neural Plast. 2011;2011:203462.
168. Cox R, Hofman WF, de Boer M, Talamini LM. Local sleep spindle modulations in relation to specific memory cues. NeuroImage. 2014;99:103–10.
169. Fogel S, Albouy G, King BR, Lungu O, Vien C, Bore A, et al. Reactivation or transformation? Motor memory consolidation associated with cerebral activation time-locked to sleep spindles. PLoS One. 2017;12(4):e0174755.
170. Oudiette D, Paller KA. Upgrading the sleeping brain with targeted memory reactivation. Trends Cogn Sci. 2013;17(3):142–9.
171. Pennartz CM, Lee E, Verheul J, Lipa P, Barnes CA, McNaughton BL. The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. J Neurosci. 2004;24(29):6446–56.
172. Rasch B, Born J. Maintaining memories by reactivation. Curr Opin Neurobiol. 2007;17(6):698–703.
173. Sadowski JH, Jones MW, Mellor JR. Ripples make waves: binding structured activity and plasticity in hippocampal networks. Neural Plast. 2011;2011:960389.
174. Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci. 1997;9(4):534–47.
175. Schabus M, Gruber G, Parapatics S, Sauter C, Klosch G, Anderer P, et al. Sleep spindles and their significance for declarative memory consolidation. Sleep. 2004;27(8):1479–85.
176. Meier-Koll A, Bussmann B, Schmidt C, Neuschwander D. Walking through a maze alters the architecture of sleep. Percept Mot Skills. 1999;88(3 Pt 2):1141–59.
177. Tamminen J, Lambon Ralph MA, Lewis PA. The role of sleep spindles and slow-wave activity in integrating new information in semantic memory. J Neurosci. 2013;33(39):15376–81.
178. Wilhelm I, Diekelmann S, Molzow I, Ayoub A, Molle M, Born J. Sleep selectively enhances memory expected to be of future relevance. J Neurosci. 2011;31(5):1563–9.
179. Schabus M, Hoedlmoser K, Pecherstorfer T, Anderer P, Gruber G, Parapatics S, et al. Interindividual sleep spindle differences and their relation to learning-related enhancements. Brain Res. 2008;1191:127–35.
180. Saletin JM, Goldstein AN, Walker MP. The role of sleep in directed forgetting and remembering of human memories. Cereb Cortex. 2011;21(11):2534–41.
181. Fogel SM, Smith CT, Cote KA. Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. Behav Brain Res. 2007;180(1):48–61.
182. Smith C. Sleep states and memory processes in humans: procedural versus declarative memory systems. Sleep Med Rev. 2001;5(6):491–506.
183. Smith CT, Nixon MR, Nader RS. Posttraining increases in REM sleep intensity implicate REM sleep in memory processing and provide a biological marker of learning potential. Learn Mem. 2004;11(6):714–9.
184. Miyauchi S, Misaki M, Kan S, Fukunaga T, Koike T. Human brain activity time-locked to rapid eye movements during REM sleep. Exp Brain Res. 2009;192(4):657–67.

185. Steriade M, Pare D, Bouhassira D, Deschenes M, Oakson G. Phasic activation of lateral geniculate and perigeniculate thalamic neurons during sleep with ponto-geniculo-occipital waves. J Neurosci. 1989;9(7):2215–29.
186. Piantoni G, Van Der Werf YD, Jensen O, Van Someren EJ. Memory traces of long-range coordinated oscillations in the sleeping human brain. Hum Brain Mapp. 2015;36(1):67–84.
187. Morin A, Doyon J, Dostie V, Barakat M, Hadj TA, Korman M, et al. Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. Sleep. 2008;31(8):1149–56.
188. Walker MP. The role of slow wave sleep in memory processing. J Clin Sleep Med. 2009;5(2 Suppl):S20–6.
189. Spoormaker VI, Czisch M, Maquet P, Jancke L. Large-scale functional brain networks in human non-rapid eye movement sleep: insights from combined electroencephalographic/functional magnetic resonance imaging studies. Philos Trans A Math Phys Eng Sci. 2011;369(1952):3708–29.
190. Barakat M, Carrier J, Debas K, Lungu O, Fogel S, Vandewalle G, et al. Sleep spindles predict neural and behavioral changes in motor sequence consolidation. Hum Brain Mapp. 2013;34(11):2918–28.
191. Tamaki M, Huang TR, Yotsumoto Y, Hamalainen M, Lin FH, Nanez JE Sr, et al. Enhanced spontaneous oscillations in the supplementary motor area are associated with sleep-dependent offline learning of finger-tapping motor-sequence task. J Neurosci. 2013;33(34):13894–902.
192. Verleger R, Ros M, Wagner U, Yordanova J, Kolev V. Insights into sleep's role for insight: studies with the number reduction task. Adv Cogn Psychol. 2013;9(4):160–72.
193. Sami S, Robertson EM, Miall RC. The time course of task-specific memory consolidation effects in resting state networks. J Neurosci. 2014;34(11):3982–92.
194. Hanlon EC, Faraguna U, Vyazovskiy VV, Tononi G, Cirelli C. Effects of skilled training on sleep slow wave activity and cortical gene expression in the rat. Sleep. 2009;32(6):719–29.
195. Fell J, Axmacher N. The role of phase synchronization in memory processes. Nat Rev Neurosci. 2011;12(2):105–18.
196. Benchenane K, Tiesinga PH, Battaglia FP. Oscillations in the prefrontal cortex: a gateway to memory and attention. Curr Opin Neurobiol. 2011;21(3):475–85.
197. Colgin LL. Oscillations and hippocampal-prefrontal synchrony. Curr Opin Neurobiol. 2011;21(3):467–74.
198. Girardeau G, Zugaro M. Hippocampal ripples and memory consolidation. Curr Opin Neurobiol. 2011;21(3):452–9.
199. Heib DP, Hoedlmoser K, Anderer P, Zeitlhofer J, Gruber G, Klimesch W, et al. Slow oscillation amplitudes and up-state lengths relate to memory improvement. PLoS One. 2013;8(12):e82049.
200. Ribeiro S. Sleep and plasticity. Pflugers Arch. 2012;463(1):111–20.
201. Zovkic IB, Guzman-Karlsson MC, Sweatt JD. Epigenetic regulation of memory formation and maintenance. Learn Mem. 2013;20(2):61–74.