# The Role of Sleep Spindles in Sleep-Dependent Memory Consolidation

**Elizabeth A. McDevitt, Giri P. Krishnan, Maxim Bazhenov and Sara C. Mednick**

**Abstract** A well-established literature supports a critical role of sleep for learning and memory (Abel et al. in Curr Biol 23(17);R774–R788, 2013; Diekelmann and Born in Nat Rev Neurosci 11(2):114–126, 2010; Rasch and Born in Physiol Rev 93 (2):681–766, 2013; Tononi and Cirelli in Sleep Med Rev 10(1):49–62, 2014). Studies have demonstrated memory improvements following a period of sleep compared to an equivalent time awake, and specific sleep features have been shown to correlate with improvements in discrete memory domains. For example, overnight procedural motor learning correlates with the amount of stage 2 sleep (Walker et al. in Neuron 35(1):205–211, 2002; Learn Mem 10(4):275–284, 2003), non-hippocampal dependent perceptual learning correlates with the product of the amount of slow wave sleep (SWS) and rapid eye movement (REM) sleep (Mednick et al. in Nat Neurosci 6(7):697–698, 2003; Stickgold et al. in J Cogn Neurosci 12 (2):246–254, 2000), and implicit priming also appears to depend on REM sleep (Cai et al. in Proc Natl Acad Sci U S A 106(25);10130–10134, 2009). One feature of sleep that is widely implicated in memory processing is the sleep spindle, short (0.5–3 s) bursts of oscillatory activity in the frequency range of approximately 12–15 Hz (Spindles have also been defined as slow as 8–12 Hz, with some

This work was supported by Bazhenov: Office of Naval Research/Multidisciplinary University Research Initiative Grant N000141310672 and National Institutes of Health Grants R01 EB009282, R01 MH099645; Mednick and Bazehnov: R01AG046646; Mednick: NSF BCS1439210; McDevitt: NSF fellowship.

E.A. McDevitt · S.C. Mednick (✉)
Department of Psychology, University of California, Riverside, USA
e-mail: smednick@ucr.edu

E.A. McDevitt
e-mail: mcdevitt@ucr.edu

G.P. Krishnan · M. Bazhenov
Department of Medicine, University of California, San Diego, USA
e-mail: gkrishnan@ucsd.edu

M. Bazhenov
e-mail: mbazhenov@ucsd.edu



N. Axmacher and B. Rasch (eds.), *Cognitive Neuroscience of Memory Consolidation*, Studies in Neuroscience, Psychology and Behavioral Economics, DOI 10.1007/978-3-319-45066-7_13

indication that these slow spindles may be physiologically distinct from alpha frequency, which oscillates in the same frequency range (8–12 Hz) but has a different spatial distribution (Manshanden et al. in Clin Neurophysiol 113 (12):1937–1947, 2002). However, more data is required to determine the distinctiveness of these two signals. For the purpose of this chapter, we will primarily discuss spindles defined as ~12–15 Hz.). This chapter aims to (1) summarize correlational and causal evidence supporting the role of sleep spindles in memory processing; and (2) describe spindle dynamics and how they may be related to proposed mechanisms of sleep-dependent consolidation.

**Keywords** Sleep spindles · Slow oscillations · Declarative memory · Procedural memory · Systems consolidation · Phase amplitude coupling

## An Introduction to Sleep Effects on Memory Consolidation

Sleep can be separated into four stages characterized by stereotypic electrical activity. The four stages progress in structured cycles from light Stages 1 and 2 through deep SWS (formerly Stages 3 and 4) and into REM sleep. Together, Stages 1, 2 and SWS are often referred to as non-REM (NREM) sleep. Stage 1 is briefly observed at sleep onset, and can be identified by the presence of slow rolling eye movements and a disappearance of alpha (8–12 Hz) activity over occipital regions. Stage 2 sleep is more synchronized than Stage 1 and is characterized by sigma activity (12–15 Hz, i.e., spindles) and occasional, high-amplitude K-complex signals. SWS is named for the high amplitude, slow wave activity [slow oscillations (0.5–1 Hz) and delta (1–4 Hz)] that predominates. REM sleep is characterized by fast, low-amplitude EEG similar to waking, as well as increased heart rate, increased cortical blood flow, muscle paralysis and its eponymous rapid eye movements.

Sleep spindles are an electrophysiological hallmark of NREM sleep (Fig. 1). In addition to duration and frequency criteria, spindles are defined as phasic events distinct from general background 12–15 Hz sigma activity with a distinct waxing and waning morphology (Astori et al. 2013; Gennaro and Ferrara 2003; Weiner and Dang-Vu 2016). Present in both Stage 2 and SWS, spindles occur along side several other features of NREM sleep such as vertex sharp waves, K-complexes, slow oscillations, or superimposed on delta oscillations during SWS. Additionally, two kinds of spindles can be differentiated by distinct spatio-temporal dynamics. "Slow" spindles (<12 Hz, with a spectral peak ~10.2 Hz) predominate over frontal sites and are more pronounced during SWS than Stage 2 sleep, whereas "fast" spindles (>12 Hz, with a peak spectral frequency ~13.4 Hz) are more densely distributed over parietal and central sites (Mölle et al. 2011). However the functional difference between these spindle types is unclear (Andrillon et al. 2011; Timofeev and Bazhenov 2005).

The need to understand the mechanisms and properties of sleep spindles is driven by their role in memory and learning. An open question in memory research

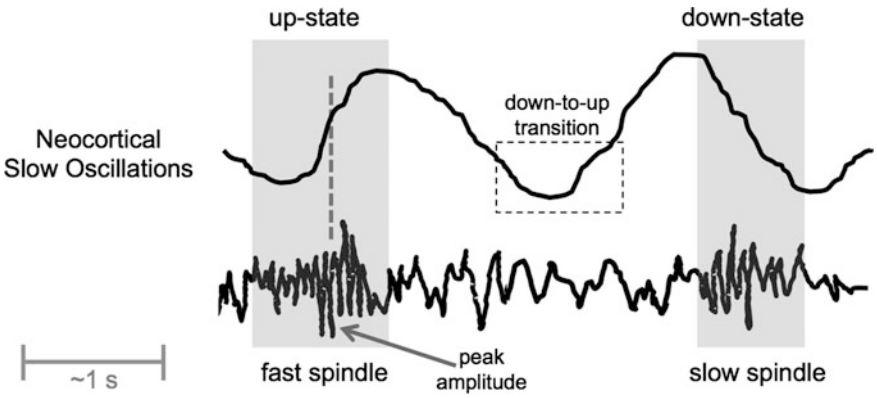


**Fig. 1** The coordination of sleep spindles and slow oscillations during sleep. Neocortical slow oscillations (<1 Hz) are characterized by up and down states that reflect periods of neuronal spiking and neuronal silence, respectively. Sleep spindles are phasic events with a distinct waxing and waning morphology. Spindles are sometimes classified as "slow" (<12 Hz) or "fast" (>12 Hz) depending on their peak frequency. During sleep, spindles often occur during the down-to-up transition of the slow oscillation, with the peak amplitude of the spindle aligned with the slow oscillation up-state (represented by the dashed vertical line). This pattern of coupling may be specific to fast spindles, with slow spindles more likely to follow fast spindles and occur during the slow oscillation down-state

asks how the human brain learns new information without overwriting previously stored memories, the so-called "stability-plasticity" problem. For declarative memory (i.e., conscious or explicit recall of episodic and semantic memories), theoretical models propose two separate memory stores that interact in a process of systems consolidation—a fast-learning, temporary store and a slow-learning, long-term store. The hippocampus and neocortex are the hypothesized neural structures associated with the temporary and long-term stores, respectively. New information is originally encoded concurrently in both stores. During subsequent periods of consolidation, successive reactivation, or "replay", of this network is presumed to allow new memories to become strengthened and integrated with pre-existing memories in the long-term store, as well as becoming less reliant on the fast-learning store. Off-line periods when no encoding is happening, such as sleep, are thought to be ideal times for replay to occur since no new, incoming information will interfere with consolidation (Mednick et al. 2011).

Neural replay has been observed in studies of rodent spatial memory,[1] where place cells that are activated in sequence together during spatial learning tend to fire

[1]Although best demonstrated in the hippocampus, it is possible that neural replay also occurs at the level of cortex, independent of the hippocampus (e.g., both temporary and long-term stores are within cortex). However, for the purpose of this review we will detail neuronal and behavioral evidence of replay involving the hippocampus, although it is likely that replay is a general mechanism of systems consolidation across memory systems and not specific to hippocampal-dependent memories.

in a similar sequence, and at a faster, time-compressed rate, during subsequent SWS (Lee and Wilson 2002; Wilson and McNaughton 1994). Replay-like activity has also been observed during periods of immobility, or quiet wakefulness (Foster and Wilson 2006), and REM sleep (Louie and Wilson 2001), but the replay dynamics are different than those observed during SWS. Specifically, studies have shown: (1) hippocampal replay during SWS in rats is coordinated with firing patterns in the visual cortex (Ji and Wilson 2007); (2) the hippocampus and cortex appear to communicate during sleep by means of hippocampal sharp waves and ripples (Buzsáki 1989), during which place cells are reactivated (Diba and Buzsáki 2007); and (3) these events are temporally correlated with spindles in the medial prefrontal cortex during SWS (Siapas and Wilson 1998).

The temporal coupling of thalamic sleep spindles and hippocampal ripples along with neocortical slow oscillations (<1 Hz) is proposed to be a key mechanism underlying the hippocampal-neocortical dialogue characteristic of systems consolidation. Generation of spindles in the thalamus and sharp wave-ripples in hippocampus is suppressed during the hyperpolarizing down-state of the slow oscillation, followed by a rebound in spindle and sharp wave-ripple activity during the succeeding depolarizing up-state. Thus, slow oscillations are thought to provide a top-down temporal frame for these oscillatory events, though it is not clear whether this thalamo-hippocampal-cortical circuit is driven by the thalamus, cortex, or a combination of both brain areas (Crunelli and Hughes 2010; Lemieux et al. 2014). Regarding the coupling of spindles and ripples, it has been demonstrated that individual ripple events are nested in the trough of succeeding spindles (Staresina et al. 2015; Timofeev and Bazhenov 2005) (see also chapters by Bergmann and Staresina and by Maier and Kempter). These "spindle-ripple" events might represent a bottom-up mechanism where reactivated hippocampal memory information (coded in ripples) is passed to spindles, which then reach neocortical networks via the slow oscillation. Thus, spindles appear to be one critical component of a complex interaction between several electrophysiological events that together provide a mechanistic explanation for memory reactivation during sleep. Given that spindles are easily detected and measured using scalp electroencephalogram (EEG), they provide a convenient and non-invasive method to examine one of the neural correlates of consolidation in humans.

## Sleep Spindles and Human Memory: Correlational Evidence

Although a plethora of studies in the past two decades have indicated that sleep spindles play a functional role in memory processing during sleep, it has also become apparent that the relationship between spindles and memory is quite complex and may be moderated by any number of factors including memory domain, task difficulty, initial skill level of the individual, sleep stage (Stage 2 vs. SWS), spindle frequency (fast vs. slow), scalp derivation (frontal vs.

centro-parietal), and other spindle characteristics (number, density, amplitude, duration, power). In the following section we discuss the neuronal correlates of sleep spindles and examine correlational evidence for the role of spindles in memory consolidation.

## *Neuronal Mechanisms of Sleep Spindles*

The presence of spindle oscillations after decortication provides strong evidence for the thalamic origin of this activity (Contreras et al. 1996; Morison and Bassett 1945; Timofeev and Steriade 1996). Studies suggest that the minimal substrate contributing to the generation of spindle oscillations is generated in the thalamus as a result of the interaction between thalamic reticular (RE) and relay (TC) cells (Steriade et al. 1985, 1990; Steriade and Deschenes 1984; Steriade and Llinas 1988; von Krosigk et al. 1993). According to this hypothesis, RE inhibitory neurons fire a spike burst that elicits an inhibitory post-synaptic potential (IPSP) in TC neurons. At the end of this IPSP, the TC neurons generate rebound spike-bursts that in turn excite RE neurons, which then generate spike-bursts, starting the next cycle of spindle oscillations. However, this minimal model may not describe all the mechanisms involved in spindle generation because (a) spindles can be generated in isolated RE nucleus (Steriade et al. 1987); and (b) during the early 3–4 IPSPs composing the spindle, many TC neurons do not display rebound spike-bursts (Bazhenov et al. 2000), suggesting that the reciprocal TC-RE connections are not contributing to the early phase of a spindle sequence. The simplest computational model sufficient to generate the spindle oscillations includes two reciprocally coupled RE neurons and two TC cells providing excitation to and receiving inhibition from RE neurons (Destexhe et al. 1996). Persistence of spindle-like activity in the isolated RE nuclei suggests a mechanism for spindle initiation, with activity of RE cells initiating a new sequence of spindle oscillations (Bazhenov et al. 2000).

Termination of spindles depends both on intrinsic and network mechanisms. The first includes $Ca^{2+}$ accumulation leading to cyclic adenosine monophosphate (cAMP) upregulation of hyperpolarization-activated non-specific cation current (Ih) and, following TC neurons depolarization, making rebound spike-bursts impossible (Bal and McCormick 1996; Budde et al. 1997; Luthi et al. 1998). The second includes the desynchronizing effect of cortico-thalamic projections (Andersen and Andersson 1968; Bonjean et al. 2011; Timofeev 2001), based on dissimilarity of intrinsic responses in different cortical and TC neurons. An extensive review of the intrinsic and synaptic mechanisms of spindle oscillations can be found in Timofeev and Bazhenov (2005). These thalamic mechanisms of spindle generation correspond to fast spindles, while the mechanisms of slow spindle generation remain to be investigated. Slow spindles could originate from the neocortex. At least, upon stimulation, isolated neocortical slabs are able to generate oscillations with frequencies around 10 Hz (Timofeev et al. 2002), i.e. the frequency range of slow spindles.

## *Learning Modulates Spindle Activity During Subsequent Sleep*

Early studies reporting an association between sleep spindles and memory in humans found that spindle activity during non-REM sleep is sensitive to previous learning experience (Gais et al. 2002; Meier-Koll et al. 1999). Gais et al. (2002) showed that compared with a non-learning task, memorizing unrelated word pairs (learning task) increased spindle density during Stage 2 and spindle density also correlated with recall performance, both before and after sleep, but the overnight effect was not assessed. A separate study found that encoding difficulty moderated the relationship between learning and spindles, such that difficult encoding (more abstract word pairs) resulted in a significant increase in the slow spindle frequency range (11.25–13.75 Hz) during Stage 2 sleep, whereas easy encoding (more concrete word pairs) did not alter sleep spindle activity compared to a control condition (Schmidt et al. 2006).

Similar learning-dependent increases in spindle activity have also been observed for motor memory. Fogel and Smith (2006) tested four procedural tasks before and after sleep and found that spindle densities were increased following learning and that the change in performance on the four learning tasks accounted for 98% of the variability in the change in spindle density. A second study expanded these results and showed that following learning a Pursuit Rotor task (but not a mirror tracing task), Stage 2 and SWS spindle densities as well as Stage 2 spindle duration were increased compared to a baseline night (Fogel et al. 2007). In both of these studies, the tasks were re-tested one week after learning and thus the immediate overnight gains in performance could not be examined. Additionally, studies have shown that the degree to which spindles correlate with motor learning may be moderated by task complexity (Fogel et al. 2007; Smith et al. 2004) and skill level of the experimental subject (Schmidt et al. 2006).

## *Correlations Between Sleep Spindles and Memory Improvement*

### Declarative Memory

A large number of studies have established that declarative memory shows less forgetting after a sleep period compared with wake, and that performance benefits are correlated with spindles (Clemens et al. 2005; Cox et al. 2012; Genzel et al. 2009; Schabus et al. 2004) (see also chapter by Schönauer and Gais). More recent studies have also found that spindles correlate with overnight integration of new memories with existing knowledge (Tamminen et al. 2010, 2013). Some variation has been reported in frequency of spindles that correlate with improvement. For example, Holz et al. (2012) reported that overnight retention of a word-list task was

correlated with sigma activity, a result exclusively driven by a correlation with slow sigma activity (12–14 Hz) whereas there was no significant correlation observed with fast sigma activity (14–16 Hz). However, many others have found the opposite, with memory performance correlating with fast spindle activity but not slow spindle activity (e.g., Saletin et al. 2011; van der Helm et al. 2011) or even no association in spite of large sample sizes (Ackermann et al. 2015, Sleep). More research is needed to understand the extent to which these divisions distinguish different types of spindles either functionally or topographically.

Additionally, although sleep is a global phenomenon in many respects, sleep spindles may exert their beneficial influence for declarative memory consolidation in a regionally specialized manner. Saletin et al. (2011) tested a directed forgetting task in a nap paradigm and found that subjects who napped recalled significantly more words that were cued to-be-remembered than subjects who spent an equivalent amount of time awake. There was no such sleep-related enhancement for words cued to-be-forgotten. This selective enhancement of to-be-remembered words was correlated with fast sleep spindle (13.5–15 Hz) density during NREM sleep. Specifically, spindles over the posterior parietal regions were positively correlated with the proportion of to-be-remembered words recalled, yet negatively correlated with words cued for forgetting at frontal locations. These results argue against models suggesting that sleep uniformly decreases forgetting or enhances learning (Tononi and Cirelli 2006), and suggest that spindles can benefit memory consolidation in a specific and selective manner (see also chapter by Rauss and Born).

### Procedural Skills

Several studies have demonstrated correlations between motor learning and sleep spindles. Nishida and Walker (Nishida and Walker 2007) capitalized on the known lateralized, offline plastic changes observed across a night of sleep using a motor-sequence task. They found that when subjects trained with their left hand and then took a nap, motor-skill memory improvements were correlated with the difference in spindle activity between the "learning" (contralateral, right hemisphere) and "nonlearning" hemisphere. This lateralization difference score was suggested to represent the homeostatic difference in spindle activity following learning, thereby providing evidence of regionally specific spindle associations with offline motor-skill learning in central locations. In another study, subjects were either trained on a motor-sequence task or a control task followed by a night of sleep (Morin et al. 2008). Subjects in the motor task condition showed increased number and duration of spindles during NREM sleep, and higher EEG power in the sigma (13 Hz) and beta (18–20 Hz) frequency bands, than the control task condition. However, none of these physiological changes during post-training sleep were correlated with overnight gains. A follow-up study found that specifically fast (13–15 Hz) but not slow (11–13 Hz) spindle densities were increased following motor learning compared to control (Barakat et al. 2011). Additionally, the difference in fast spindle density between the control and experimental nights was correlated with overnight

performance gain on the motor but not control task, suggesting that fast spindles, which are most prominent over central and parietal derivations, are implicated in motor sequence learning and consolidation.

## Experimentally Manipulating Spindles

It is possible that more spindles cause better memory consolidation, or that deeper encoding of information prior to sleep increases subsequent spindle activity (Fogel and Smith 2006; Gais et al. 2002), or even that individuals with better memory ability naturally have more spindles (Fogel and Smith 2011). For example, Tamaki et al. (2009) used a mirror-tracing task and found (1) mean amplitude and duration of fast spindles was greater on the learning night than nonlearning night; and (2) fast spindle density, amplitude, and duration were all positively correlated with overnight improvement on the learning night. However, upon closer inspection, fast spindle activity on the nonlearning night was also correlated with motor performance, indicating that individuals who had greater spindle activity always had better performance, and this effect was not specific to the learning night. Therefore, differences in fast spindle activity may be related to native motor learning ability. In the declarative domain, Lustenberger et al. (2015) highlighted how spindle activity is oftentimes positively associated with baseline encoding performance (indicating better learning abilities in individuals who have more spindle activity), and subjects with good encoding performance may have the least amount of overnight improvement, resulting in negative spindle associations with overnight performance. To better understand the role of spindles in memory consolidation, it is necessary to move beyond correlations between sleep features and memory improvement and discover critical mechanisms of memory consolidation by perturbing sleep and testing the effects on memory performance.

Important advances have been made by utilizing experimental methods that manipulate sleep features in order to test their effects on memory, such as transcranial stimulation to enhance (Marshall et al. 2006) or inhibit (Marshall et al. 2011) slow wave activity (see also chapter by Campos Beltran and Marshall), and pharmacology. Using pharmacological intervention, Mednick et al. (2013) increased sleep spindles with zolpidem (Ambien), and decreased sleep spindles with sodium oxybate (Xyrem) during a nap (Fig. 2). Declarative and motor memory performance was tested before and after the pharmacologically altered nap using a word paired-associates task and motor sequence task, respectively. They showed that pharmacologically enhancing sleep spindles with zolpidem in healthy adults produced exceptional declarative memory performance beyond that seen with sleep alone (placebo) or sleep with the comparison drug (SO), which showed decreased memory performance. Spindles were correlated with declarative memory improvement in all three conditions, suggesting that spindles are a neural correlate of verbal memory consolidation, and when enhanced produce a systematic increase in verbal memory retention.

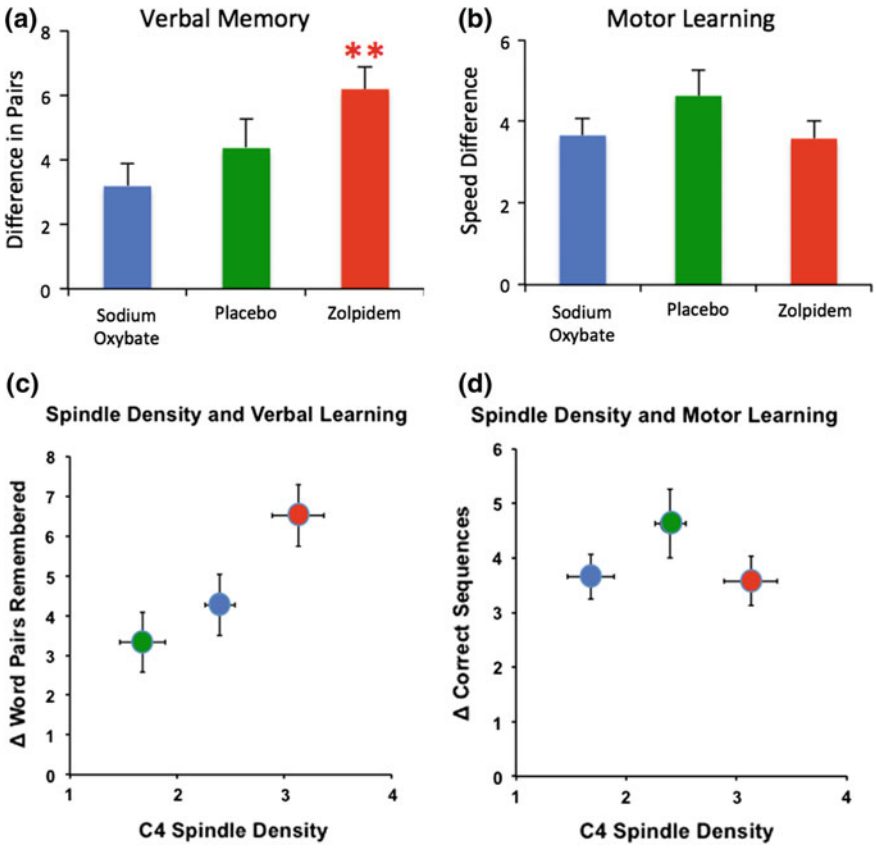


**Fig. 2** Pharmacologically enhanced spindles boost verbal learning but not motor learning. Verbal memory was increased with zolpidem (**a**), and there were no differences in motor learning across drug conditions (**b**). **c**, **d** Memory performance improvement plotted against spindle density for naps with different drug conditions—zolpidem (*red circle*), placebo (*green circle*), and sodium oxybate (*blue circle*). Zolpidem enhanced sleep spindle density, and spindle density was related to verbal memory performance (**c**), but not motor learning (**d**). Statistical comparisons were between drugs conditions and placebo. ** indicates $p$-value < .005. Data are from Mednick et al. (2013)

Contrary to predictions, motor learning was not altered by the drug intervention and motor performance was not correlated with spindles in the zolpidem condition. A similar null result in motor learning was found by enhancing slow wave activity and spindles via transcranial application of slow oscillations (0.75 Hz) (Marshall et al. 2006). These results indicate that spindles may not be directly related to motor learning and suggest that there might be a third variable related to sleep-dependent motor improvement heretofore unexamined. Alternatively, spindles may be more related to recovery from motor fatigue than learning per se, as suggested by results showing no sleep-dependent effects on motor learning when controlling for fatigue and time of day (Rickard et al. 2008). Taken together, these results point toward a

tighter coupling between sleep spindles and declarative verbal memory than motor learning. This difference may be attributable to the stronger dependence on hippocampal processing in the verbal task due to the associative nature of the task (Henke et al. 1999). In the case of hippocampal-dependent processing, spindles may be causally related to memory improvement by their direct role in hippocampal replay, whereas in non-hippocampal-dependent tasks, spindles may be a marker of a yet undefined process that correlates with consolidation.

In contrast with the Mednick et al. (2013) findings, Rasch et al. (2009) showed that administration of selective re-uptake inhibitors of serotonin (SSRI) and norepinephrine (SNRI) both decreased the amount of time spent in REM sleep, while the SNRI significantly increased amount of time spent in Stage 2 sleep, as well as the number and density of fast spindles (>13 Hz). Performance on a motor-sequence task was improved in both drug conditions compared to placebo, and overnight gains in performance were significantly correlated with the change in number and density of spindles between drug and placebo nights. Subjects were also tested on a declarative paired-associates task. Given the spindle enhancement with SNRI, one would predict improvement of declarative memory with SNRI. However, surprisingly they found no difference in number of words recalled in either SSRI or SNRI condition compared to placebo.

Using the same pharmacological intervention as Mednick et al. (2013), Kaestner et al. (2013) examined the role of sleep spindles in emotional memory consolidation (see also chapter by Cunningham and Payne). In this study, subjects encoded a full range of emotional pictures (negative, positive and neutral valence, as well as high and low arousal) before a nap with zolpidem or placebo. The authors reported that memory can be experimentally biased toward negative and highly arousing stimuli after a sleep period with pharmacologically elevated sleep spindles. Specifically, naps with zolpidem demonstrated increased sleep spindles and greater memory performance for negative and high-arousal stimuli compared with placebo or sodium oxybate. Both hypnotics elevated SWS, but only zolpidem increased spindle density, whereas sodium oxybate decreased spindle density. Thus, the increase in memory performance relative to placebo was more likely due to the increased spindle density rather than SWS. Importantly, total sleep time and all other measures of sleep were consistent across each drug manipulation suggesting that changes in memory performance were likely due to the drug manipulation of sleep spindle density.

## Interaction Between Spindle and Slow Oscillations

Although spindles are often treated as discrete events, they do not occur in isolation from other oscillatory events. Current advancements in the field have begun to tease apart the complex relationship between spindles and other brain activity patterns, namely neocortical slow oscillations. Slow oscillations (<1 Hz) are characterized by up and down states that reflect active and silent periods of spiking in individual

neurons (Steriade et al. 1993). During Stage 2 and SWS, spindles are often temporally coupled with slow oscillations. The spindle amplitude is observed to be highest during the up-state and lowest during the down-state of the slow oscillations (Contreras and Steriade 1995; Molle et al. 2002). Specifically, the peak of spindle amplitude often occurs during the beginning of the slow oscillation (i.e., the down-to-up-state transition) (see Fig. 1). These findings have been observed using scalp EEG (Molle et al. 2002) and intracellular recordings (Andrillon et al. 2011), and further supported by computational models (Bazhenov et al. 2002).

Co-occurring slow oscillations and spindles may be a key mechanism of memory consolidation during sleep (Mölle et al. 2011). In humans, spindle power during the up-state of the slow oscillations was increased following learning in a hippocampal-dependent task (Mölle et al. 2009). Ngo et al. (2013) used closed-loop stimulation to induce slow oscillations and observed an increase in spindles during the early phase of the slow oscillations, which was correlated with an increase in the memory retention task. Using the same pharmacological intervention as Mednick et al. (2013), who demonstrated increased spindle density using zolpidem, Niknazar et al. (2015) examined the relationship between the phase of the slow oscillation at which spindles occurred and memory performance (Fig. 3). In addition to boosting the rate of spindle events, zolpidem also increased the temporal consistency of when spindles occurred relative to the phase of slow oscillations, as measured by the modulation index between slow oscillation phase and spindle power (Fig. 3a, b). Phase-amplitude coupling between different neural oscillations has been observed in wake (Canolty et al. 2006; Lakatos et al. 2005), and this study provides evidence that such coupling is also observed with spontaneously occurring oscillations during sleep. Further, performance on the verbal memory task was significantly correlated with the phase of the slow oscillation at which the spindle peak was observed in the zolpidem and placebo conditions, but not in sodium oxybate (Fig. 3c–e). This suggests that memory improvement was increased when spindles occurred during the rising phase of the slow oscillation. Interestingly, when slow oscillation power, sigma power and phase/amplitude timing were allowed to compete for variance in performance change using a regression framework, phase/amplitude timing accounted for the most variance, followed by sigma, and slow oscillatory power was not a significant predictor. Overall, these studies strongly suggest that for hippocampal-dependent memory tasks, there is a preferred phase for spindle timing during the slow oscillation up-state to increase memory consolidation.

The exact neural mechanism underlying the coupling between spindles and slow oscillations (and hippocampal sharp-wave ripples), and how it enhances memory consolidation, is not known. Sleep spindles result in massive increases in intracellular $Ca^{2+}$ (Sejnowski and Destexhe 2000), which is required to induce long-term potentiation, and a coincidence of thalamic spindles with other sleep EEG events, such as hippocampal sharp waves (Battaglia et al. 2004), at the down-to-up transition phase of cortical slow oscillations may be necessary to form permanent memories. One hypothesis suggests that hippocampal ripples could initiate the thalamic inputs (Vertes et al. 2007), and hippocampus to cortical

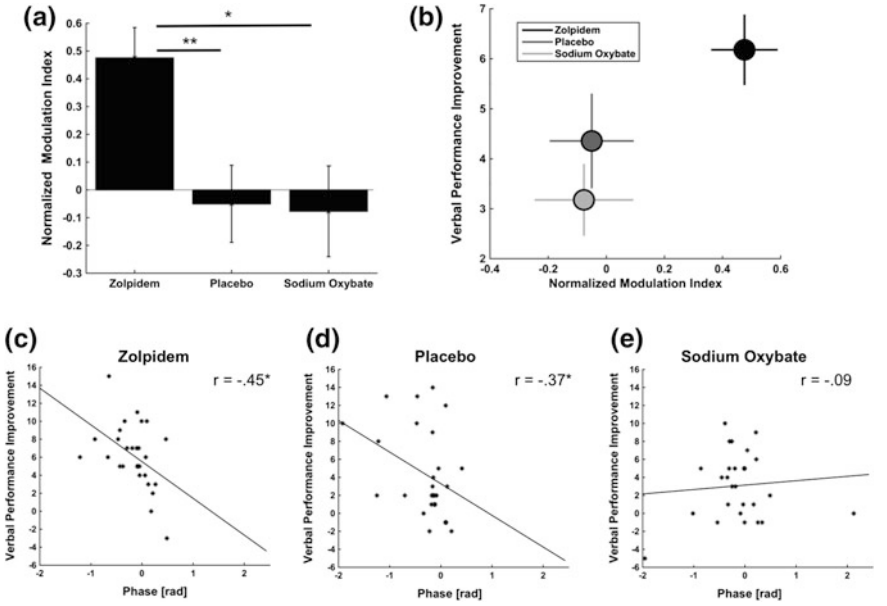


**Fig. 3** Phase amplitude coupling between slow oscillations and spindles influences memory improvement during sleep. **a** Normalized modulation index measured for SO phase and spindle power was significantly increased with zolpidem compared to placebo and sodium oxybate. **b** Memory performance improvement plotted against normalized modulation index for naps with different drug conditions—zolpidem (*black circle*), placebo (*dark grey circle*), and sodium oxybate (*light grey circle*). **c**–**e** The SO phase at spindle peak (i.e., phase/amplitude timing) was correlated with memory improvement in both zolpidem and placebo conditions, suggesting a general mechanism of memory formation. The negative correlation indicates better memory performance was associated with negative SO phase, i.e., spindle peak occurring during the SO up-state. * indicates $p$-value < .05; ** indicates $p$-value < .005. Data are from Niknazar et al. (2015)

projections (Jay and Witter 1991) could selectively modulate the spindle activity through spindle-ripple coupling during the initiation of up-state. Such events could lead to the replay and therefore enhancement of selective memory during the up-states. Indeed, recent intracranial recordings in humans have demonstrated a tight coupling between thalamic spindles, hippocampal sharp wave ripples and cortical slow oscillations (Staresina et al. 2015).

An up-state of the slow oscillation is also a time period of high synchrony within the cortical network, marked by the high amplitude activity observed in the EEG. This synchronization may facilitate synaptic weight changes due to spike-timing-dependent plasticity (STDP). Any input, such as hippocampal ripples, that occurs during the later phase of the down-state of the slow oscillation, would influence the timing of the cortical cell firing during the following up-state. Indeed, a recent computational study suggests that the spatiotemporal pattern of the slow oscillation determines synaptic changes during slow wave sleep (Wei et al. 2016). Furthermore, it found that spindles preceding the slow oscillation (as occurs during

the natural cycle of sleep state transitions) might influence the spatio-temporal pattern of slow oscillations and facilitate replay of selected memories.

**Acknowledgements** Research was supported by National Institutes of Health grants NSF Cognitive Neuroscience BCS1439210 (S.M.), R01 AG046646 (S.M. and M.B.), and R01 EB009282 (M.B.); Office of Naval Research/Multidisciplinary University Research Initiative Grant N000141310672; and National Science Foundation Graduate Research Fellowship Program (E.M.).

## Glossary

| | |
|---|---|
| **Declarative memory**: | Conscious memory of facts and events. This type of memory is dependent on the hippocampus and other areas of the medial temporal lobe. |
| **Non-declarative memory**: | Unconscious memories such as habits or skills. This type of memory is typically not dependent on the hippocampus. |
| **Rapid eye movement (REM) sleep**: | A sleep stage characterized by rapid eye movements, low muscle tone, and rapid, low-voltage electroencephalogram (EEG) waveforms. |
| **Slow wave sleep (SWS)**: | Also referred to as deep sleep; previously Stage 3 and Stage 4. Slow, high amplitude delta activity (1–4 Hz) predominates the EEG during SWS. |
| **Slow oscillations**: | Waveforms <1 Hz frequency with high voltage up and down states, which reflect periods of neuronal spiking and neuronal silence, respectively. |
| **Spindles**: | Bursts of oscillatory activity visible on an EEG that typically occur during NREM sleep. Spindles typically consist of 12–15 Hz waveforms that occur for at least 0.5 s. Spindle density refers to the number of spindles per minute of sleep. |
| **Sharp-wave ripple complexes**: | Composed of fast ($\sim$50–100 ms) bursts of spike activity (sharp waves) that are associated with high-frequency "ripples" ($\sim$150–200 Hz). These events are generated in the hippocampus. |
| **Systems consolidation**: | The process that refers to the time-limited role of the hippocampus in declarative memory storage. Information is originally encoded in both hippocampal and cortical regions. Successive reactivation of this hippocampal-cortical network is presumed to allow new memories to be gradually integrated with |

| | |
|---|---|
| | pre-existing memories and become independent of the hippocampus. |
| **Spike-timing-dependent plasticity**: | This refers to the process of change in synaptic weights, as a function of spike timing in pre- and post-synaptic neurons—there is an increase in synaptic weight when the pre-synaptic neuron fires prior to the post-synaptic neuron and a decrease in synaptic weight when the post-synaptic neuron fires prior to the pre-synaptic neuron. |
| **Phase amplitude coupling**: | This refers to modulation of the amplitude of one oscillation by the phase of another oscillation, and provides information about the temporal relationship between oscillations. For example, such coupling is observed between the peak amplitude of spindle frequency and slow oscillation phase. |
| **Modulation index**: | This index is one way to estimate the consistency of phase-amplitude coupling across various trials or events. |

## References

Abel T, Havekes R, Saletin JM, Walker MP (2013) Sleep, plasticity and memory from molecules to whole-brain networks. Curr Biol 23(17):R774–R788

Ackermann S, Hartmann F, Papassotiropoulos A, de Quervain DJ, Rasch B (2015) No associations between interindividual differences in sleep parameters and episodic memory consolidation. Sleep 38(6):951–959

Andersen P, Andersson S (1968) Physiological basis of the alpha rhythm, vol 1. Plenum Publishing Corporation

Andrillon T, Nir Y, Staba RJ, Ferrarelli F, Cirelli C, Tononi G, Fried I (2011) Sleep spindles in humans: insights from intracranial EEG and unit recordings. J Neurosci (The Official Journal of the Society for Neuroscience) 31(49):17821–17834

Astori S, Wimmer RD, Lüthi A (2013) Manipulating sleep spindles—expanding views on sleep, memory, and disease. Trends Neurosci 36(12):738–748

Bal T, McCormick DA (1996) What stops synchronized thalamocortical oscillations? Neuron 17 (2):297–308

Barakat M, Doyon J, Debas K, Vandewalle G, Morin A, Poirier G et al (2011) Fast and slow spindle involvement in the consolidation of a new motor sequence. Behav Brain Res 217 (1):117–121

Battaglia FP, Sutherland GR, McNaughton BL (2004) Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. Learn Mem (Cold Spring Harbor, NY), 11(6):697–704

Bazhenov M, Timofeev I, Steriade M, Sejnowski T (2000) Spiking-bursting activity in the thalamic reticular nucleus initiates sequences of spindle oscillations in thalamic networks. J Neurophysiol 84(2):1076–1087

Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ (2002) Model of thalamocortical slow-wave sleep oscillations and transitions to activated states. J Neurosci 22(19):8691–8704

Bonjean M, Baker T, Lemieux M, Timofeev I, Sejnowski T, Bazhenov M (2011) Corticothalamic feedback controls sleep spindle duration in vivo. J Neurosci (The Official Journal of the Society for Neuroscience) 31(25):9124–9134

Budde T, Biella G, Munsch T, Pape HC (1997) Lack of regulation by intracellular $Ca^{2+}$ of the hyperpolarization-activated cation current in rat thalamic neurones. J Physiol 503(1):79–85

Buzsáki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31(3):551–570

Cai DJ, Mednick SA, Harrison EM, Kanady JC, Mednick SC (2009) REM, not incubation, improves creativity by priming associative networks. Proc Natl Acad Sci U S A 106 (25):10130–10134

Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE et al (2006) High gamma power is phase-locked to theta oscillations in human neocortex. Science (New York, NY), 313 (5793):1626–1628

Clemens Z, Fabó D, Halász P (2005) Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience 132(2):529–535

Contreras D, Steriade M (1995) Cellular basis of EEG slow rhythms: a study of dynamic corticothalamic relationships. J Neurosci 15(1):604–622

Contreras D, Destexhe A, Sejnowski TJ, Steriade M (1996) Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science 274(5288):771–774

Cox R, Hofman WF, Talamini LM (2012) Involvement of spindles in memory consolidation is slow wave sleep-specific. Learn Mem (Cold Spring Harbor, NY), 19(7):264–267

Crunelli V, Hughes SW (2010) The slow (< 1 Hz) rhythm of non-REM sleep: a dialogue between three cardinal oscillators. Nat Neurosci 13(1):9–17

Destexhe A, Contreras D, Steriade M, Sejnowski T, Huguenard J (1996) In vivo, in vitro, and computational analysis of dendritic calcium currents in thalamic reticular neurons. J Neurosci 16(1):169–185

Diba K, Buzsáki G (2007) Forward and reverse hippocampal place-cell sequences during ripples. Nat Neurosci 10(10):1241–1242

Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11(2):114–126

Fogel SM, Smith CT (2006) Learning-dependent changes in sleep spindles and Stage 2 sleep. J Sleep Res 15:250–255

Fogel SM, Smith CT (2011) The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev 35(5):1154–1165

Fogel SM, Smith CT, Cote KA (2007) Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. Behav Brain Res 180(1):48–61

Foster DJ, Wilson MA (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature 440(7084):680–683

Gais S, Molle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22(15):6830–6834

Gennaro L De, Ferrara M (2003) Sleep spindles: an overview. Sleep Med Rev 7(5):423–440

Genzel L, Dresler M, Wehrle R, Grözinger M, Steiger A (2009) Slow wave sleep and REM sleep awakenings do not affect sleep dependent memory consolidation. Sleep 32(3):302–310

Henke K, Weber B, Kneifel S, Wieser HG, Buck A (1999) Human hippocampus associates information in memory. Proc Natl Acad Sci 96(10):5884–5889

Holz J, Piosczyk H, Feige B, Spiegelhalder K, Baglioni C, Riemann D, Nissen C (2012) EEG sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation. J Sleep Res 21(6):612–619

Jay TM, Witter MP (1991) Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. J Comp Neurol 313(4):574–586

Ji D, Wilson Ma (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10(1):100–107

Kaestner EJ, Wixted JT, Mednick SC (2013) Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. J Cogn Neurosci 25(10):1597–1610

Lakatos P, Shah AS, Knuth KH, Ulbert I, Karmos G, Schroeder CE (2005) An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. J Neurophysiol 94(3):1904–1911

Lee AK, Wilson MA (2002) Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36(6):1183–1194

Lemieux M, Chen J-Y, Lonjers P, Bazhenov M, Timofeev I (2014) The impact of cortical deafferentation on the neocortical slow oscillation. J Neurosci (The Official Journal of the Society for Neuroscience) 34(16):5689–5703

Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29(1):145–156

Lustenberger C, Wehrle F, Tüshaus L, Achermann P, Huber R (2015) The multidimensional aspects of sleep spindles and their relationship to word-pair memory consolidation. Sleep 38 (7):1093–1103

Luthi A, Bal T, McCormick DA (1998) Periodicity of thalamic spindle waves is abolished by ZD7288, a Blocker of $I_h$. J Neurophysiol 79(6):3284–3289

Manshanden I, De Munck JC, Simon NR, Lopes da Silva FH (2002) Source localization of MEG sleep spindles and the relation to sources of alpha band rhythms. Clin Neurophysiol (Official Journal of the International Federation of Clinical Neurophysiology) 113(12):1937–1947

Marshall L, Helgadóttir H, Mölle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444(7119):610–613

Marshall L, Kirov R, Brade J, Mölle M, Born J (2011) Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. PLoS ONE 6(2):e16905

Mednick SC, Nakayama K, Stickgold R (2003) Sleep-dependent learning: a nap is as good as a night. Nat Neurosci 6(7):697–698

Mednick SC, Cai DJ, Shuman T, Anagnostaras S, Wixted JT (2011) An opportunistic theory of cellular and systems consolidation. Trends Neurosci 34(10):504–514

Mednick SC, McDevitt EA, Walsh JK, Wamsley E, Paulus M, Kanady JC, Drummond SPa (2013) The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. J Neurosci (The Official Journal of the Society for Neuroscience) 33(10):4494–4504

Meier-Koll A, Bussmann B, Schmidt C, Neuschwander D (1999) Walking through a maze alters the architecture of sleep. Percept Mot Skills 88:1141–1159

Molle M, Marshall L, Gais S, Born J (2002) Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. J Neurosci 22(24):10941–10947

Mölle M, Eschenko O, Gais S, Sara SJ, Born J (2009) The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur J Neurosci 29(5):1071–1081

Mölle M, Bergmann TO, Marshall L, Born J (2011) Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep 34 (10):1411D–1421D

Morin A, Doyon J, Dostie V, Barakat M, Tahar AH, Korman M et al (2008) Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. Sleep 31(8):1149–1156

Morison RS, Bassett DL (1945) Electrical activity of the thalamus and basal ganglia in decorticate cats. J Neurophysiol 8(5):309–314

Ngo H-VV, Martinetz T, Born J, Mölle M (2013) Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 78(3):545–553

Niknazar M, Krishnan GP, Bazhenov M, Mednick SC (2015) Coupling of thalamocortical sleep oscillations are important for memory consolidation in humans. PLoS ONE 10(12):e0144720

Nishida M, Walker MP (2007) Daytime naps, motor memory consolidation and regionally specific sleep spindles. PLoS ONE 2(4):e341

Rasch B, Born J (2013) About sleep's role in memory. Physiol Rev 93(2):681–766
Rasch B, Pommer J, Diekelmann S, Born J (2009) Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat Neurosci 12(4):396–397
Rickard TC, Cai DJ, Rieth CA, Jones J, Ard MC (2008) Sleep does not enhance motor sequence learning. J Exp Psychol Learn Mem Cogn 34(4):834–842
Saletin JM, Goldstein AN, Walker MP (2011) The role of sleep in directed forgetting and remembering of human memories. Cerebral Cortex (New York, NY : 1991), 21(11):2534–25341
Schabus M, Gruber G, Parapatics S, Sauter C, Klösch G, Anderer P et al (2004) Sleep spindles and their significance for declarative memory consolidation. Sleep 27(8):1479–1485
Schmidt C, Peigneux P, Muto V, Schenkel M, Knoblauch V, Münch M et al (2006) Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. J Neurosci (The Official Journal of the Society for Neuroscience) 26(35):8976–8982
Sejnowski TJ, Destexhe A (2000) Why do we sleep? Brain Res 886(1–2):208–223
Siapas AG, Wilson MA (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Cell Press 21:1123–1128
Smith CT, Aubrey JB, Peters KR (2004) Different roles for REM and stage 2 sleep in motor learning: A proposed model. Psychol Belg 44(1–2):81–104
Staresina BP, Bergmann TO, Bonnefond M, van der Meij R, Jensen O, Deuker L et al (2015) Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat Neurosci 18(11):1679–1686
Steriade M, Deschenes M (1984) The thalamus as a neuronal oscillator. Brain Res Rev 8(1):1–63
Steriade M, Llinas RR (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68(3):649–742
Steriade M, Deschenes M, Domich L, Mulle C (1985) Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. J Neurophysiol 54(6):1473–1497
Steriade M, Domich L, Oakson G, Deschenes M (1987) The deafferented reticular thalamic nucleus generates spindle rhythmicity. J Neurophysiol 57(1):260–273
Steriade M, Jones EG, Llinás RR (1990) Thalamic oscillations and signaling. Wiley, Oxford
Steriade M, Nunez A, Amzica F (1993) A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J Neurosci 13(8):3252–3265
Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson Ja (2000) Visual discrimination task improvement: A multi-step process occurring during sleep. J Cogn Neurosci 12(2):246–254
Tamaki M, Matsuoka T, Nittono H, Hori T (2009) Activation of fast sleep spindles at the premotor cortex and parietal areas contributes to motor learning: a study using sLORETA. Clin Neurophysiol (Official Journal of the International Federation of Clinical Neurophysiology) 120(5):878–886
Tamminen J, Payne JD, Stickgold R, Wamsley EJ, Gaskell MG (2010) Sleep spindle activity is associated with the integration of new memories and existing knowledge. J Neurosci (The Official Journal of the Society for Neuroscience) 30(43):14356–14360
Tamminen J, Lambon Ralph Ma, Lewis Pa (2013) The role of sleep spindles and slow-wave activity in integrating new information in semantic memory. J Neurosci (The Official Journal of the Society for Neuroscience) 33(39):15376–15381
Timofeev I (2001) Contribution of intrinsic and synaptic factors in the desynchronization of thalamic oscillatory activity. Thalamus Relat Syst 1(1):53–69
Timofeev I, Bazhenov M (2005) Mechanisms and biological role of thalamocortical oscillations (Columbus F, ed). Trends Chronobiol Res
Timofeev I, Steriade M (1996) Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats. J Neurophysiol 76(6):4152–4168
Timofeev I, Grenier F, Bazhenov M, Houweling AR, Sejnowski TJ, Steriade M (2002) Short- and medium-term plasticity associated with augmenting responses in cortical slabs and spindles in intact cortex of cats in vivo. J Physiol 542(2):583–598
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10(1):49–62

Tononi G, Cirelli C (2014) Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81(1):12–34

van der Helm E, Gujar N, Nishida M, Walker MP (2011) Sleep-dependent facilitation of episodic memory details. PLoS ONE 6(11):e27421

Vertes RP, Hoover WB, Szigeti-Buck K, Leranth C (2007) Nucleus reuniens of the midline thalamus: link between the medial prefrontal cortex and the hippocampus. Brain Res Bull 71 (6):601–609

von Krosigk M, Bal T, McCormick D (1993) Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261(5119):361–364

Walker MP, Brakefield T, Morgan A, Hobson JAA, Stickgold R (2002) Practice with sleep makes perfect: Sleep-dependent motor skill learning. Neuron 35(1):205–211

Walker MP, Brakefield T, Seidman J, Morgan A, Hobson JA, Stickgold R (2003) Sleep and the time course of motor skill learning. Learn Mem (Cold Spring Harbor, NY), 10(4):275–284

Wei Y, Krishnan GP, Bazhenov M (2016) Synaptic mechanisms of memory consolidation during sleep slow oscillations. J Neurosci 36(15):4231–4247

Weiner OM, Dang-Vu TT (2016) Spindle oscillations in sleep disorders: a systematic review. Neural Plasticity 2016:1–30

Wilson M, McNaughton B (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265(July):5–8