

## Review article

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# Manipulating neural activity and sleep-dependent memory consolidation

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**Abstract:** Sleep contributes actively to the consolidation of many forms of memory. This review describes the neural oscillations of non-rapid eye movement (NREM) sleep, the structures underlying these oscillations and their relation to hippocampus-dependent memory consolidation. A main focus lies on the relation between inter- and intraregional interactions and their electrophysiological representation. Methods for modulating neural oscillations with the intent of affecting memory consolidation are presented.

**Keywords:** behavior; brain rhythms; human; rodent; stimulation

**Zusammenfassung:** Schlaf unterstützt aktiv die Konsolidierung vieler Arten von Gedächtnisprozessen. Dieser Übersichtsartikel beschreibt die neuronalen Oszillationen während des non-rapid eye movement (NREM) (Non-rapid eye movement)-Schlafs, die diesen Oszillationen zugrunde liegenden Hirnstrukturen und ihre Beziehungen zur hippocampusabhängigen Gedächtniskonsolidierung. Ein Schwerpunkt liegt hierbei in der Beziehung zwischen inter- und intraregionalen Interaktionen und deren elektrophysiologische Repräsentation. Es werden Methoden zur Modulation neuronaler Oszillationen mit der Absicht, die Gedächtniskonsolidierung zu beeinflussen, vorgestellt.

**Schlüsselwörter:** Verhalten; Hirnrhythmen; Stimulation; Human; Nager

## Introduction

During our active period, sensory systems take up information, which is typically processed and stored across varying time periods. Although sensory memory is stored up to hundreds of milliseconds, information in short-term working memory reflects activity sustained within neural circuits (e. g., within the prefrontal cortex) and lasting into the minute range; and long-term memory may last a lifetime. This latter form of memory is associated with persistent molecular and cellular changes in synaptic structure and neural circuits. Types of long-term memory are distinguished dependent upon the modified brain structures. A major distinction is made between hippocampus- and non-hippocampus-dependent memories. The formation of long-term memory consists of at least three processes: encoding (the uptake of information), consolidation (i. e., storage), and recall (i. e., retrieval of memory contents from storage). Processes involved in memory consolidation occur both at the cellular (and molecular) and systems levels. Systems consolidation refers to the transfer across time and among neuronal networks or brain regions of memory representations, their reorganization, and concurrent stabilization. According to the two-stage model of memory consolidation after encoding using a fast information storage system (as the hippocampus), a subsequent (offline) transfer to a long-term storage site (neocortex) occurs. This concept has been extended to non-hippocampus-dependent memory consolidation (Buzsáki, 2015; Diekelmann and Born, 2010). Studies across the last decades have shown that system consolidation benefits from sleep: a simple schematized experiment would reveal enhanced recall performance after a period of sleep as compared to wakefulness. Moreover, the discovery of neuronal ensemble reactivations, occurring most frequently during nonrapid eye movement (NREM) sleep, and the neuronal activity associated with the sleep slow oscillation (SO) indicated an active role of sleep in memory consolidation. (For comprehensive reviews on historical background, theories, and mechanisms of systems consolidation, the reader is referred to Diekelmann and Born, 2010; Klinzing et al., 2019; Marshall and Born, 2007; Rasch and Born, 2013.)

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This review focuses on the neural oscillations of the brain during NREM sleep and their relationship to sleep-associated hippocampus-dependent memory consolidation. Brain oscillations during NREM sleep are most closely linked to hippocampus-dependent memory consolidation. First, the neural oscillations characterizing NREM sleep and associated with memory consolidation are introduced: the cortical slow oscillation (SO), thalamocortical sleep spindles, and hippocampal sharp wave ripples (SPWRs). As these neural oscillations reflect activity within specific brain regions involved in the presumed transfer of memory representations, the endogenous temporal coordination of these rhythms is presented next. The field of sleep-associated memory consolidation is rapidly expanding. In the last part of this review, some directions of future research are presented from the perspective of our own findings.

## Neural oscillations of NREM sleep

### Neocortical SO

In the electroencephalogram (EEG) or cortical local field potential, NREM sleep is characterized by large-amplitude SOs of ~1 Hz. The sleep SO, first described by Steriade and colleagues in 1993, is a cortically generated biphasic rhythm consisting of widespread synchronized membrane potential fluctuations alternating between hyperpolarization, during the “down state,” and depolarization with firing of excitatory and inhibitory cells, during the “up state” (Steriade, 2006; Figure 1). The relatively clear association of neuronal activity patterns to local field potentials and to the superficial EEG raised great interest in this oscillation. Recently, distinct sequences of excitatory pyramidal, and inhibitory parvalbumin- and somatostatin-positive interneuron activity within a SO cycle were revealed. In fact, the activity of these different neuron populations differed dependent upon the occurrence of either an isolated SO, a SO conjointly with a sleep spindle during the SO up state, or an isolated spindle. The activity of a pyramidal cell and parvalbumin-positive interneurons (producing perisomatic inhibition of a pyramidal cell) were several-fold higher when a sleep spindle occurred conjointly with a SO, whereby the activity of somatostatin-positive interneurons (producing dendritic inhibition of a pyramidal cell) was decreased. This constellation of inhibitory inputs onto pyramidal neurons is believed to facilitate dendritic synaptic plasticity (Contreras et al., 1997; Niethard et al., 2018; Zucca et al., 2019).

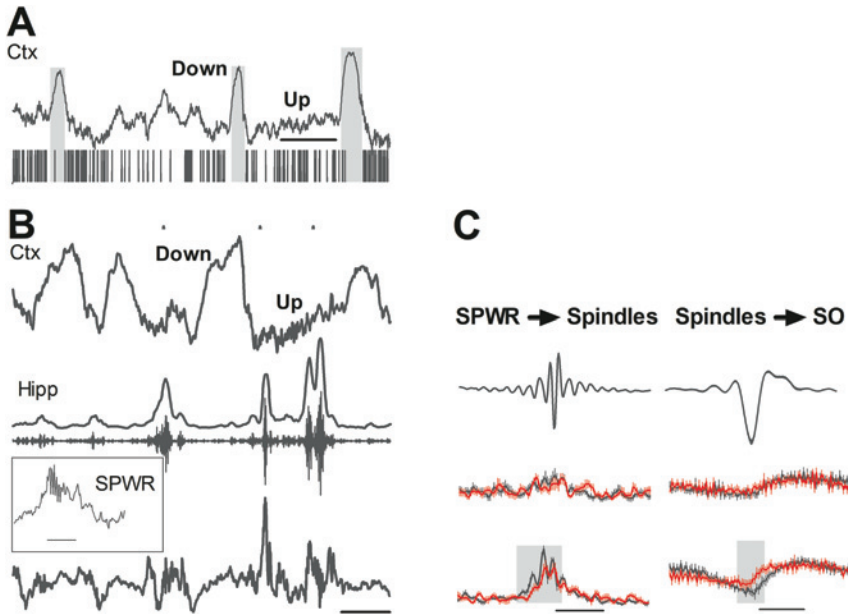
### Thalamocortical spindles and hippocampal SPWRs

Thalamocortical sleep spindles of NREM sleep commence at a lighter NREM sleep stage than SOs. Sleep spindles result from shifts in the membrane potential of thalamic reticular neurons as sleep deepens, enabling an emergent interaction between neurons in the GABAergic reticular thalamic nuclei and thalamocortical and cortical neurons (details of spindle generation can be found in Fernandez and Lüthi, 2019). Sleep spindle events in the EEG or cortical local field potential last 0.5–3 s and oscillate between about 9 and 15 Hz. Their amplitude, frequency, and spatial distribution across the cortex or scalp can vary. These variations are suggested to reflect divergent inputs and properties of network synchronization (Andrillon et al., 2011; Gretenkord et al., 2017; Kim et al., 2015; Klinzing et al., 2016). Most importantly, these properties are not static, but they change across the sleep period and with depth of NREM sleep, indicating dynamic changes in differential thalamocortical processing (Ayoub et al., 2013; Mölle et al., 2011; Nir et al., 2011).

A hippocampal SPWR is associated with a strong depolarization and is therefore a candidate event for information transfer from the hippocampus to the neocortex, as required for systems consolidation. A SPWR results from sequential activity in hippocampal subfields (termed “Cornu Ammonis” [CA]): pyramidal cell population bursting in CA3 (~100 ms) produce a strong depolarization in CA1 pyramidal cell apical dendrites in conjunction with high-frequency firing in these cells at a frequency of 150–200 Hz in rodents and at ~100 Hz in humans (Buzsáki, 2015).

### Coupling of rhythms in sleep and memory consolidation

Historically, the discovery of hippocampal place cell firing conjointly with hippocampal theta rhythms when performing a spatial task (i. e., encoding information) and the reactivation of this activity during subsequent sleep contributed strongly to the field of sleep-associated memory consolidation. Studies on postlearning modulations of sleep brain rhythms and their distinct events (e. g., density, amplitude, duration of SPWRs, spindles or SOs), as compared to activity after nonlearning conditions, revealed temporally coordinated network and cellular activity. Concepts on the relevance for memory consolidation of temporally fine-tuned communication between brain regions were boosted by findings on the time- and phase-dependent occurrence (phase-amplitude coupling) of SPWRs and



**Figure 1:** Neocortical and hippocampal recordings schematizing the prominent neural oscillations of NREM sleep and their coupling characteristics. (A) Depolarizing up state and hyperpolarizing down state of the cortical slow oscillation (SO) (depth local field potential, parietal cortex) and below cortical multiunit firing. The majority of units, but not all, fire during the up state (rat data from M. Mehta, UCLA). (B) Comparison of SOs in the cortex and sharp wave ripples (SPWRs) in the hippocampus reveals their temporal coupling. (Bottom) Local field potential from the dorsal region of the hippocampus (subfield Cornu Ammonis 1). (Row 3) Corresponding bandpass filtered signal (150–250 Hz) for ripple detection. (Row 2) Root mean square of the filtered signal. (Row 1) Cortical local field potential recording (medial prefrontal cortex). The dots indicate time points of detected hippocampal SPWRs. The inset indicates a SPWR with a scaling bar for 100 ms. All other scaling bars (A–C) represent 500 ms. (C) Coupling of the hippocampal SPWRs to spindles (left) and spindles (9–15 Hz) to SOs (SO, right) after learning on the Barnes maze. (Row 1) Averaged hippocampal SPWR activity time-locked to the deepest spindle trough (left), and averaged spindle activity time-locked to the negative peak (down state) of the SO. (Row 2) Event correlation histograms of hippocampal SPWR activity (number of peaks and troughs) with reference to the spindle trough at baseline (left) and of spindle activity with reference to the negative SO peak. (Row 3) Same as row 2 after learning on the Barnes maze for controls (black) and for mice after optoinhibition of monosynaptic hippocampal-prefrontal activity (red). Note: Significant decoupling (left) and decreased modulation (right) after optoinhibition (gray area; adapted from Binder et al., 2019). Amplitudes are z-scored. Ctx, cortical recording, Hipp, hippocampal recording.

spindle activity relative to slower neural events (for reviews, see Girardeau and Zugaro, 2011; Marshall et al., 2020).

Regarding phase of coupling, it is broadly consistent that (fast) spindles as well as SPWRs occur during or shortly preceding the SO up state (for reviews, see Skelin et al., 2019; Todorova and Zugaro, 2020; Figure 1). A major goal of research on neural oscillations in sleep is to identify which information is reflected in phase-dependent activity (or consistency of coupling). Timing during the SO phase may well reflect the nature of presumed information transfer. For example, SO-phase-dependent firing preferences differed for thalamocortical nuclei and for thalamic nuclei receiving major inputs from the cerebellum (ventrolateral nuclei) versus the basal ganglia (ventral anterior/ventromedial nuclei; Ushimaru et al., 2012). The locus ceruleus of the brainstem in rats also revealed transient SO-phase-dependent firing during the down- to up-state transition in post-learning NREM sleep (Eschenko et al., 2012). In relation to behavior, the locus ceruleus selectively increased firing

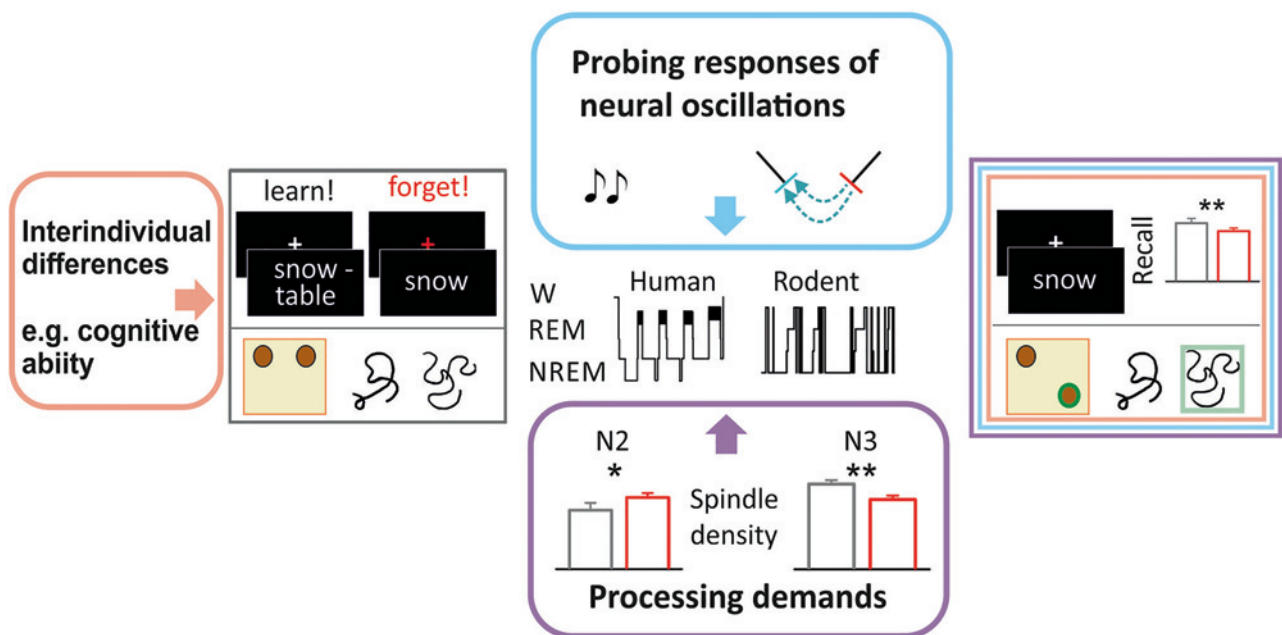
during postlearning sleep (Eschenko and Sara, 2008). Together, different brain structures become active at preferred phases of the SO, which may be indicative of specific processing steps during memory consolidation. The preferred phase of thalamocortical spindle activity with reference to the SO is most intensely studied and can differ strongly between subjects, but it is highly stable intra-individually. This spindle-to-SO coupling in humans also changes between light (stage N2) and deep (stage N3) NREM sleep, with (fast) spindles occurring at a slightly earlier phase in N3 than N2 (Cox et al., 2018).

### Memory consolidation – recent neuromodulatory approaches and research perspectives

Especially in humans, noninvasive brain stimulation, such as transcranial electric stimulation or sensory stimulation,

enable neural oscillations and their coupling to be targeted. Weak electric stimulation has the advantage of essentially targeting subthreshold activity. Sensory stimulation is typically suprathreshold and induces a temporally precise neural response. Thus, it has the advantage that delivery can target a specific phase of the ongoing oscillation. The phase-dependent occurrence of sleep events relative to the SO gave rise to the working hypothesis that facilitating SOs affects synaptic plasticity and the memory consolidation function of NREM sleep. Initial studies revealing that transcranial electric stimulation oscillating at the frequency of the SO or SO - auditory closed loop stimulation induce endogenous SO activity supported this postulate (Marshall et al., 2006; Ngo et al., 2013). However, the story is not so simple (for reviews of divergent findings, see

Campos-Beltrán and Marshall, 2017; Malkani and Zee, 2020). Recently, evidence that weak electric stimulation as typically applied in humans can indeed influence the timing of spiking activity in a frequency- and location-dependent manner was provided by an investigation in nonhuman primates (Krause et al., 2019; however, see also the review of Liu et al., 2018). Thus, what could underlie the frequent variability in results? We, as well as other investigators, suggest that deviant study outcomes should be taken as important indicators for interactions between undisclosed overt and covert confounding factors. Such confounding factors that can affect neural responses and memory consolidation are the precise phase of sensory stimulation relative to the endogenous coupling of rhythms (Wei et al., 2020; Weigenand et al., 2016), a different length in time



**Figure 2:** Potential levels of interaction during neural processing in sleep. The square boxes indicate learning and recall performance on three tasks: motivated forgetting (top), object-place recognition task (bottom left), and figural paired associate task (bottom right). In the motivated forgetting protocol, human subjects first learn word pairs (e. g., snow-table). In a subsequent phase, subjects are instructed to suppress memory for red-cued words (e. g., snow). In the recall box (tri-colored frame), in the condition of motivated forgetting, recall performance is suppressed (red) compared to a control condition (gray). In the figural paired-associate task, human subjects have to learn that the two figures belong together. At recall, the correct match (indicated by the small green square) is to be selected from a set of five other figures. In the object-place recognition task, rodents are placed in an open field with two objects for 10 min. After an interim period, subjects are introduced again to the open field wherein one object has been displaced. Due to novelty preference the displaced object, if its location is recognized as novel, is explored more intensely (indicated by the green circle). Thus, indicating the subject has remembered the objects' initial locations. Orange, blue and purple frames indicate endogenous and exogenous factors affecting neural processing in sleep and subsequent recall performance. The motivated forgetting task is associated with differential spindle density in light NREM sleep stage N2 and deep NREM sleep stage N3 as compared to sleep after a control condition. Thus, reflecting discrepant processing demands during both sleep states (control, gray; motivated forgetting, red; adapted from Dehnavi et al. 2019). Stimulation procedures reveal often weak effect sizes: In addition to stimulation efficacy depending on parameters of the stimulation and neuroanatomical features, induced neural responses depend on interactions between interindividual factors and processing demands. Tasks affected by stimulation are schematized for rodents by the object place recognition task and for humans by the figural paired-associate task (reviewed in Campos-Beltrán and Marshall, 2017; Koo et al., 2018). Hypnograms (human, 7 h; rodent, 1 h) schematize an interim period of sleep. W, Wake. The asterisks indicate significant differences: \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ .



between learning and stimulation (Lu et al., 2018; Miyamoto et al., 2016), subjects' cognitive ability (Koo et al., 2018), different processing demands of the learning material, and/or differences in NREM sleep stage composition at the time of stimulation (Dehnavi et al., 2019; Jiang et al., 2019; Lerner et al., 2019; Figure 2). For example, when, after learning a list of word pairs, subjects are instructed to forget correspondingly cued words (motivated forgetting), the relation of post-task spindle density during light versus deep NREM sleep differed as compared to a control condition (Figure 2). We found higher spindle density in N2 during sleep subsequent to motivated forgetting leading to the notion that spindles during N2 enhance the erasure of unwanted memories (Dehnavi et al., 2019; Figure 2). Regardless of the specific function, it is well conceivable that stimulation during post-task N2 versus N3 would differentially affect the ongoing consolidation process.

In rodents, optogenetic tools can be employed to interact with brain rhythms at high temporal precision. For instance, optogenetic stimulation with temporal resolution in the millisecond range was used to drive sleep spindles. Increased memory consolidation and increased coupling of SOs, sleep spindles, and ripples indicated the functional relevance of this manipulation (Latchoumane et al., 2017). In our study, we employed optogenetic inhibition of the monosynaptic connection from the hippocampus (ventral region) to the neocortex (medial prefrontal cortex) to investigate its role for both ongoing neural oscillations and behavior after systems consolidation (Figure 2). We showed that inhibition of this pathway during NREM sleep subsequent to consecutive days of learning on the Barnes maze reduced phase-specific coupling of SPWR-to-spindle and spindle-to-SO events as well as memory performance (Binder et al., 2019; Figure 1).

In summary, investigations into the underpinnings of sleep-associated memory consolidation have made major gains in the last few decades. It will be the task of future research to disentangle the relevance of activity at different hierarchical time and spatial scales and correlate it with behavioral output to discover functional relevance.

## Glossary

**NREM:** Nonrapid eye movement (sleep) is composed of different brain oscillations (or rhythms). In humans, light N1 to deep N3 stages differ. Sleep spindles commence in N2. Delta waves (1–4 Hz) and SOs (~1 Hz) are most pronounced in N3. In rodents, NREM sleep periods are shorter and the depth of sleep fluctuates more frequently; thus, a differentiation of sleep depths is not made.

**Phase-amplitude coupling:** This is a method to describe how oscillations in various frequency bands interact. It characterizes the modulation in the amplitude (or power) of one oscillation by the phase of a slower oscillation. A more general description is cross-frequency coupling, wherein the interaction of other signal parameters may interact (see also Jensen and Colgin, 2007).

**Reactivation:** This refers to the re-occurrence of neurons and/or neuronal networks that were active during encoding (learning) during postlearning sleep. Direct measurements assess cellular activity. Reactivation may be inferred indirectly from measurements assessing activity of larger networks (see also Klinzing et al., 2019).

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Maryam Ghorbani received her doctoral degree in biological physics at the Institute for Advanced Studies, Zanjan, Iran, in 2009. She started her research on sleep at the University of California, Los Angeles, CA, USA, as a postdoctoral scholar working under supervision of Prof. Robijn Bruinsma and Prof. Mayank Mehta. Since 2013, she has been an assistant professor at the Biomedical Engineering Department and the Rayan Center for Neuroscience at Ferdowsi University of Mashhad, Mashhad, Iran. Her present research focuses on neuronal modeling in addition to analysis of human EEG and rodent extracellular recordings to understand the mechanisms underlying the generation of sleep rhythms and their functional importance. She is also interested in understanding the effect of both external and endogenous electric fields on neuronal activity.



### Lisa Marshall

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Lisa Marshall studied biology and received her doctoral degree at the Institute of Physiology, Humboldt-University of Berlin, Charité (Peter Bartsch). At the Institute of Neuroendocrinology of the University of Lübeck (Jan Born), she began her research on sleep. During a habilitation scholarship in 2000, she was a research fellow at the Center for Molecular and Behavioral Neuroscience, Newark, NJ, USA (György Buzsáki). In 2009 she became Professor of Behavioral Neurobiology at the Department of Neuroendocrinology and in 2014 at the Institute of Experimental and Clinical Pharmacology and Toxicology, University of Lübeck (Markus Schwaninger). As the head of the Research Group Neuroplasticity and Rhythms, her present research on mice and humans focuses on the factors and mechanisms through which sleep-associated memory consolidation is modulated.