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CHAPTER 7

Slow oscillations orchestrating fast oscillations and memory consolidation

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Abstract: Slow-wave sleep (SWS) facilitates the consolidation of hippocampus-dependent declarative memory. Based on the standard two-stage memory model, we propose that memory consolidation during SWS represents a process of system consolidation which is orchestrated by the neocortical <1 Hz electroencephalogram (EEG) slow oscillation and involves the reactivation of newly encoded representations and their subsequent redistribution from temporary hippocampal to neocortical long-term storage sites. Indeed, experimental induction of slow oscillations during non-rapid eye movement (non-REM) sleep by slowly alternating transcranial current stimulation distinctly improves consolidation of declarative memory. The slow oscillations temporally group neuronal activity into up-states of strongly enhanced neuronal activity and down-states of neuronal silence. In a feed-forward efferent action, this grouping is induced not only in the neocortex but also in other structures relevant to consolidation, namely the thalamus generating 10–15 Hz spindles, and the hippocampus generating sharp wave-ripples, with the latter well known to accompany a replay of newly encoded memories taking place in hippocampal circuitries. The feed-forward synchronizing effect of the slow oscillation enables the formation of spindle–ripple events where ripples and accompanying reactivated hippocampal memory information become nested into the single troughs of spindles. Spindle–ripple events thus enable reactivated memory-related hippocampal information to be fed back to neocortical networks in the excitable slow oscillation up-state where they can induce enduring plastic synaptic changes underlying the effective formation of long-term memories.

Keywords: slow wave sleep; memory consolidation; spindles; ripples; reactivation; human; hippocampus-dependent memory.

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Introduction

It is a long-standing idea dating back to Ebbinghaus (1985) and the beginnings of experimental memory research, that sleep supports the consolidation of memory. Initially, this memory function of sleep was attributed to a passive protective effect of sleep, as during this state, no new information could become encoded that would override and thereby erase any fresh memory traces encoded prior to sleep (Ellenbogen et al., 2007). However, more recently, convergent evidence has accumulated that sleep actively enhances memories in a so-called process of system consolidation in which selected fresh memories are reactivated and thus transferred from a temporary into a long-term store (Diekelmann and Born, 2010).

In fact, a basic issue of memory research—referred to as the stability–plasticity dilemma—is the question of how the brain can maintain previously learned memories while it continues to learn new things that tend to override the old memories but, rather become incorporated into the networks of preexisting long-term memories (Carpenter and Grossberg, 1988). Also, many aspects of episodes experienced during wakefulness are irrelevant and do not necessarily need to be stored for the long term. A widely held concept providing a solution to these issues is the standard two-stage model of memory (Marr, 1971; McClelland et al., 1995) which assumes the existence of two separate memory stores one that learns at a fast rate and serves as a temporary store holding information only initially, and the other that learns at a slow rate but shows also a slow rate of forgetting and serves as the long-term store. New information is initially encoded in parallel into both the temporary and the long-term store. In subsequent periods of consolidation, the newly encoded memory traces are repeatedly *reactivated* and thereby become reorganized such that the representations in the temporary store become more sparse whereas, those in the slow learning long-term store are gradually strengthened. The reactivation and redistribution of memories to the long-term store leads to an adaptation of the new to the preexisting old representations in the long-term store, and can also promote the extraction of relevant features from the new memories. Because both stores are used also for encoding of information, this encoding could interfere with proper consolidation. Therefore, to prevent such interference, the transfer of memory from the temporary to the long-term store takes place offline, that is, during sleep when there are no encoding demands.

A model of active system consolidation taking place during slow-wave sleep

Based on the standard two-stage memory model, we have recently proposed a concept of the consolidation of hippocampus-dependent declarative memories during sleep, aiming to integrate a large variety of experimental findings in humans and animals (Born et al., 2006; Diekelmann and Born, 2010). The declarative memory system is considered to be specialized in the storage of episodic and semantic knowledge (Eichenbaum, 2000; Zola-Morgan and Squire, 1990).While our model has been elaborated for hippocampus-dependent memories, with the hippocampus serving as the temporary store and mainly the neocortex serving as the long-term store, this concept, in principle, may also account for hippocampus-independent forms of system consolidation.

The concept (outlined in Fig. 1) assumes that sleep, and in particular, slow-wave sleep (SWS) is engaged in active system consolidation of hippocampal memories, involving the reactivation and subsequent redistribution of the freshly encoded memories to neocortical sites of long-term storage. According to this concept, events experienced during wakefulness are initially encoded in parallel in neocortical networks and in the hippocampus including adjacent medial temporal lobe structures. Direct encoding into the hippocampus proper is probably restricted to certain aspects, that is, the episodic features of an event binding different semantic elements into

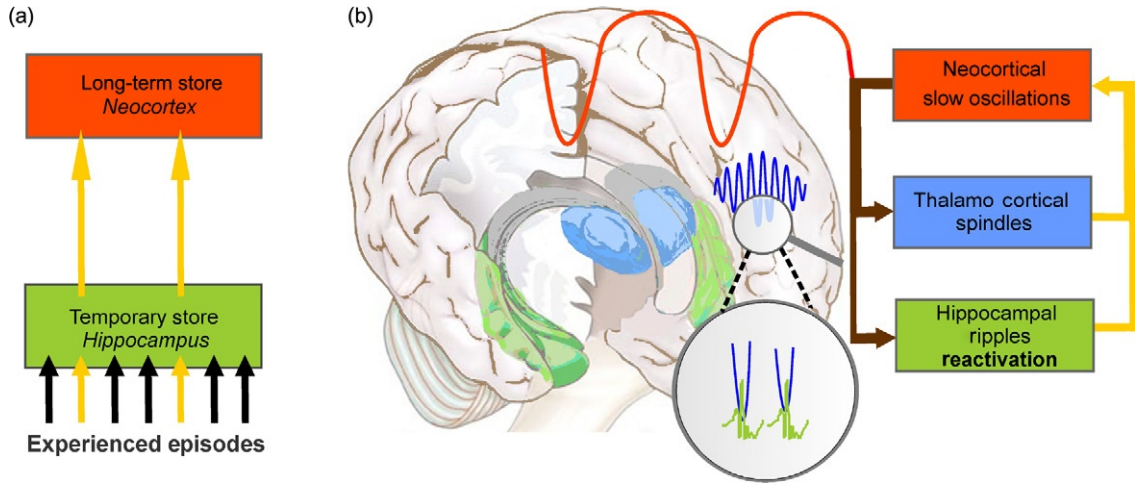

Fig. 1. Active system consolidation during sleep. (a) During slow-wave sleep (SWS) memories newly encoded into a temporary store (i.e., the hippocampus in the declarative memory system) are reactivated to be redistributed to the long-term store (i.e., the neocortex). (b) System consolidation during SWS relies on a dialog between neocortex and hippocampus under top-down control by the neocortical slow oscillations (red). The depolarizing up phases of the slow oscillations drive the repeated reactivation of hippocampal memory representations together with sharp-wave ripples (green) in the hippocampus and thalamocortical spindles (blue). This synchronous drive allows for the formation of spindle–ripple events where sharp-wave ripples and associated reactivated memory information becomes nested into single troughs of a spindle (shown at larger scale). Spindle–ripple events are considered an effective mechanism of information transfer by which reactivated hippocampal memory information nested into spindle troughs can trigger—via Ca^{2+} influx into neocortical pyramidal cells and subsequently enhanced synaptic expression of AMPA receptors—enduring plastic changes underlying the long-term storage of the information in specific neocortical circuitry. Adapted from Born and Wilhelm (2011).

space and time. During subsequent periods of sleep and, here during SWS, the newly acquired memory traces are repeatedly reactivated which stimulates the gradual redistribution of these memories such that synaptic connections within the neocortex are strengthened forming more persistent memory representations. The binding role for memory ascribed to the hippocampus in this way becomes partly transferred to the neocortex, preferentially to medial prefrontal cortical circuits (Frankland and Bontempi, 2005). Additionally, the semanticization that memories undergo in the course of hippocampo–neocortical redistribution, may lead to an increased involvement of the anterior temporal cortex (e.g., Patterson et al., 2007).

The reactivation and redistribution of memories during SWS is regulated in a dialog between neocortex and hippocampus that is essentially under feed-forward control of the slow oscillations which hallmark the EEG during SWS and occur in human sleep at a spectral frequency of ~0.75 Hz. The slow oscillations are generated primarily in neocortical networks, partly as a function of the prior use of the networks for encoding of information, that is, the more information is encoded during wakefulness the higher the amplitude of the slow oscillations is over respective cortical areas during succeeding SWS (Huber et al., 2004; Mölle et al., 2004). By temporally grouping neuronal activity into hyperpolarizing down- and depolarizing up-states with the latter revealing wake-like levels of neuronal firing (Steriade, 2006), the slow oscillations synchronize neuronal activity not only in the neocortex, but via efferent pathways also in numerous

other regions relevant to memory consolidation, including the thalamus where thalamocortical spindles are generated, and the hippocampus where reactivations of memory representations are generated. Spindles arise in thalamocortical networks conjointly with sharp wave-ripples in the hippocampal EEG. By synchronizing the occurrence of sharp wave-ripples with spindles, the depolarizing up-phase of the slow oscillations enables the formation of so-called spindle–ripple events where sharp wave-ripples and associated reactivated memory information become nested into the spindle troughs. Such spindle–ripple events are considered a mechanism underlying the effective transfer of reactivated memory information to neocortical circuitry, arriving at the networks still in the depolarizing up-phase of the slow oscillation (Siapas and Wilson, 1998; Sirota et al., 2003). Spindles, especially when occurring during the depolarization up-state of the slow oscillation, can prime long-lasting synaptic changes underlying the storage of reactivated memory information within respective neocortical networks by promoting Ca^{2+}-influx into neocortical pyramidal cells (Destexhe et al., 2007; Rosanova and Ulrich, 2005). In summary, our concept assumes that slow oscillations provide a global temporal frame whereby the depolarizing up-phase exerts a top-down control to synchronize hippocampal memory reactivations, with thalamocortical spindles allowing the bottom-up transfer of reactivated memory information embedded in spindle–ripple events. Whereas the redistribution of memories to the neocortical long-term store thus takes place during SWS, during succeeding periods of REM sleep, processes of synaptic consolidation may support the persistence of the redistributed representations (Diekelmann and Born, 2010).

While the psychological implications of this model cannot be discussed here in depth, in the following we will address in more detail the role that slow oscillations play for synchronizing spindles and ripples and the associated reactivations of hippocampal memories, as well as the role of spindle–ripple events as a possible mechanism of hippocampo-to-neocortical transfer of memory information.

Inducing slow oscillations by electrical stimulation

A most direct proof of the significance of the slow oscillations for memory consolidation can be obtained by inducing slowly oscillating potential fields through transcranial direct current stimulation (tDCS). In two initial studies, we stimulated young healthy students during sleep via electrodes attached bilaterally over the prefrontal cortex and referenced to electrodes at the mastoids, with tDCS oscillating between 0 and +260 μA at the 0.75 Hz slow oscillation frequency and at a very slow 30-s on/30-s off frequency (Marshall et al., 2004, 2006). The stimulation was applied during early SWS-rich nocturnal sleep for durations of 25 and 30 min, respectively. Compared with sham stimulation conditions, both types of stimulation produced an immediate increase in <4 Hz slow-wave activity. In fact, tDCS oscillating at the 0.75 Hz frequency enhanced power particularly in the <1 Hz slow oscillation frequency band, as measured during 1-min breaks that separated the five 5-min periods of stimulation in this study (Marshall et al., 2006; Fig. 2). Moreover, this induced slow oscillation activity was associated with a significantly enhanced frontal slow (10–12 Hz) spindle activity. Notably, both tDCS oscillating at 0.75 Hz and at the very slow 30-s on/30-s off rhythm significantly improved the retention of hippocampus-dependent memories for word-pairs the subjects had learned before stimulation sleep. Applying tDCS slowly oscillating at 0.75 Hz in the same way but toward the end of nocturnal sleep when REM sleep is dominant had no clear effect on SWS or associated endogenous slow oscillations, and was also ineffective in improving memory retention.

Further studies indicated the specificity of the tDCS effects with regard to the frequency of the oscillating stimulation and to the brain state

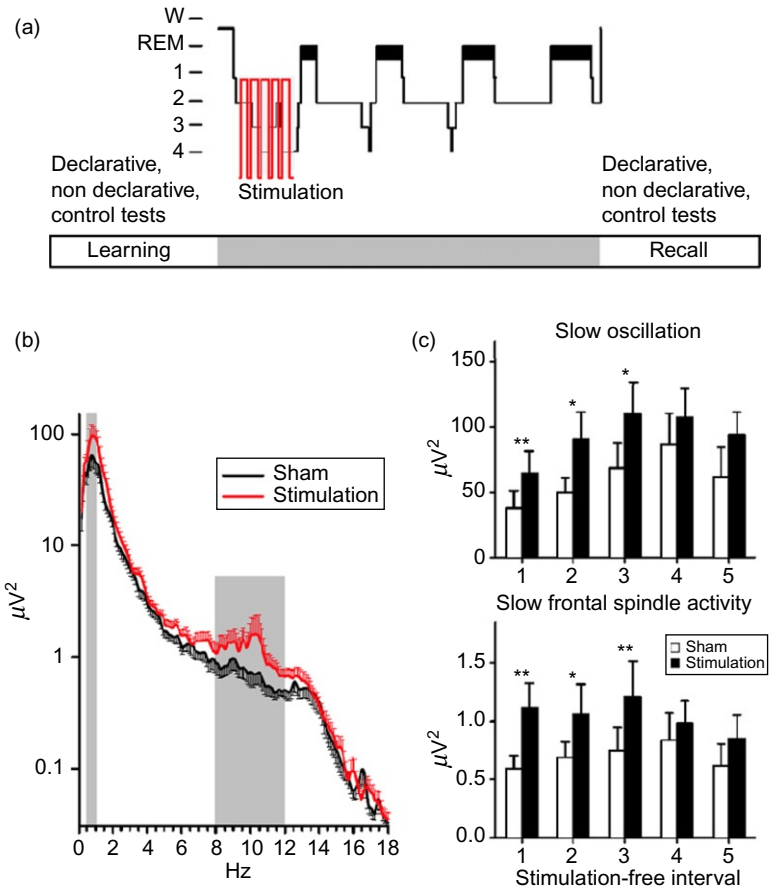

Fig. 2. Induction of slow oscillations by transcranial direct current stimulation (tDCS) oscillating at 0.75 Hz. (a) Experimental procedure: Human subjects learned declarative and nondeclarative tasks before nocturnal sleep (illustrated by an individual sleep profile). Recall was tested on the next day. tDCS was applied during early SWS-rich sleep for five 5-min intervals separated by 1-min stimulation-free intervals (red line). (b) Average EEG power spectrum at the midline frontal recording site averaged across the first three stimulation-free intervals of the stimulation condition (red) and corresponding time intervals in a sham control condition (black). During ongoing stimulation, the EEG signal cannot be recorded properly. Shaded areas indicate frequency bands for slow oscillations (0.5–1 Hz) and slow frontal spindle activity (8–12 Hz). (c) Time course of power in the five stimulation-free intervals for slow oscillations and slow frontal spindle activity at midline frontal recording site. Stimulation significantly enhanced slow oscillation and slow frontal spindle power ($^{**}p < 0.01$, $^{*}p < 0.05$) for pairwise comparison. Adapted from Marshall et al. (2006).

during which stimulation is applied. Thus, stimulating subjects during SWS-rich sleep with tDCS oscillating at the 5-Hz theta frequency rather than the 0.75 Hz slow oscillation frequency, did not increase but strongly suppressed endogenous slow oscillation activity, and also suppressed slow frontal spindle activity (Marshall et al., 2011). Simultaneously, theta stimulation significantly impaired the retention of word-pair memories. Applying the ~0.75-Hz slow

oscillation stimulation to subjects while they were awake, rather than during early nocturnal sleep when the brain itself is prone to generate slow oscillations, induced only a very limited increase in slow oscillation activity that was restricted to the electrode sites most closely located to the sites of stimulation (Kirov et al., 2009). Instead, stimulation at ~0.75 Hz during waking induced a widespread increase in EEG theta activity (4–8 Hz). This increase in theta activity, rather than enhancing the retention of word-pair memories, was associated with an increased encoding of such declarative memories, as reflected by an improved immediate recall of word lists during acute stimulation. In combination with the effects of ~0.75 Hz slow oscillation-tDCS during early SWS-rich sleep, these data suggest that the theta-producing networks which are used for encoding of information during waking are functionally coupled to the slow oscillation-producing networks that are used for consolidation of memories during SWS. In all of these studies, the estimated potential fields induced by tDCS in underlying neocortical tissue were about the same size as those naturally occurring during SWS and waking vigilant behavior. Therefore, the data indicate that potential fields characterizing slow oscillations, and also theta activity, are not mere epiphenomena of the EEG recording, but themselves contribute to the brain's processing of memories (Fröhlich and McCormick, 2010; Ozen et al., 2010). Altogether, these data speak strongly for a causal role of slowly oscillating potential fields in cortical tissues for the consolidation of hippocampus-dependent declarative memories.

Slow oscillations grouping spindles

The <1 Hz slow oscillation, as first described by Steriade's group in cats, is built up by the rhythmic sequence of up- and down-states reflecting alterations in the membrane potential of neocortical neurons between depolarized and hyperpolarized levels, whereby the depolarization phase is associated with depth-negative and surface-positive EEG field potentials, and conversely the hyperpolarizing phase with a depth-positive, surface-negative EEG potential (Contreras and Steriade, 1995; Steriade et al., 1993a,b, 1994). The same group demonstrated in cats a grouping influence of the slow oscillation on thalamocortical spindle and neocortical fast oscillatory activity (20–60 Hz) such that these rhythms appeared to be driven during the depolarizing phase of the slow oscillation, whereas the hyperpolarizing phase was associated with neuronal silence (Contreras and Steriade, 1995; Contreras et al., 1996b, 1997; Steriade, 1999; Steriade and Amzica, 1998).

In several studies, we have demonstrated that the slow oscillation exerts a likewise synchronizing effect on spindles in the human EEG (Mölle et al., 2002, 2004, 2009). In these studies, slow oscillations were identified during SWS and non-REM sleep stage 2 in the EEG after filtering the signal in the 0.16–4 Hz frequency band, using a standardized thresholding algorithm. The accurate detection of slow oscillations is of great importance, particularly in comparing results between different laboratories—that is, an issue that may also explain some variability among the findings of different studies. For this reason, a brief account on the newest version of this algorithm is given in Fig. 3. Spindle activity in these studies was determined as the root mean square (r.m.s.) amplitude signal within the 12–15 Hz frequency band of ongoing EEG activity. Additionally, discrete spindles were identified by a thresholding procedure as described similarly by Schimicek et al. (1994). Basically, this procedure identifies transient increases in the ongoing spindle r.m.s. signal with the waxing and waning flanks of the signal increment falling into a specified time interval (0.5–3 s).

Our studies consistently revealed slow oscillations during human SWS with a spectral frequency peak at ~0.8 Hz, which were associated with a distinct suppression of

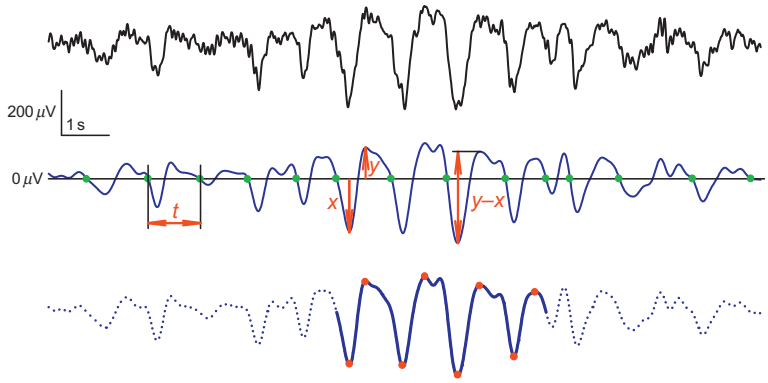

Fig. 3. Algorithm for detection of slow oscillations in human EEG: First, the original EEG (black trace) is filtered between 0.16 and 4 Hz. Secondly, in the filtered signal (blue trace) all time points of positive to negative zero crossings (green dots) are computed and the length of all intervals of positive to negative zero crossings (t) is measured. Third, for intervals with a length of $0.8 \leq t \leq 2$ s, the averages of the negative peak amplitudes (x), the positive peak amplitudes (y) and their difference ($y-x$) are calculated. Finally, intervals of positive to negative zero crossings in which the corresponding negative peak amplitude x is lower than a threshold ("thr") multiplied by the average of all x, and the corresponding amplitude difference (positive peak minus negative peak) is larger than thr times the average of all ($y-x$), are marked as slow oscillation epochs, with thr set to >0.75. (The higher the value for thr is, the larger are the amplitudes of the selected slow oscillations.) Lower blue trace (solid part) shows example of selected slow oscillation sequence, with negative and positive peaks (red dots) marked for further analyses. Importantly, based essentially on zero crossings of the filtered signal, this algorithm takes into account the fact that the depolarizing positive half-wave of the slow oscillations, although lower in amplitude, typically exhibits a distinctly longer duration than the relatively short-lived and sharper hyperpolarizing negative half-wave.

12–15 Hz spindle activity during the negative half-wave followed by a rebound in spindle activity coinciding with the positive going depolarizing half-wave of the slow oscillation (Clemens et al., 2007; Mölle et al., 2002, 2004, 2009). Also, discrete spindles identified during non-REM sleep stage 2 and SWS occur preferentially during the depolarizing up-phase of slow oscillations. For the beta-frequencies (15–25 Hz) adjacent to the spindle band, a similar though weaker modulation was observed. We did not examine gamma band activity in these studies, although a parallel modulation of gamma band activity during the slow oscillation is suggested by recent studies (Compte et al., 2008; Csercsa et al., 2010).

There is coherent evidence from human and animal studies that spindle activity is implicated in memory processing during sleep. In the human EEG, the term "spindle activity" generally refers to regular ~12–15 Hz oscillations, which are typically most prominent over central and parietal cortical areas. Spindle activity is expressed in non-REM sleep stage 2 as discrete waxing and waning spindles. It is likewise present at substantial levels in SWS, in particular during the initial periods of SWS although overall, compared with non-REM sleep, spindle activity during SWS is somewhat lower and forms less clearly discrete spindles (De Gennaro and Ferrara, 2003; Marshall et al., 2003). Spindle activity originates in the thalamus from an interaction between GABAergic neurons of the nucleus reticularis which functions as a pacemaker, and glutamatergic thalamocortical projections, which mediate the synchronized and widespread propagation of spindles to cortical regions (Contreras et al., 1996a; De Gennaro and Ferrara, 2003; Steriade, 2003). Within neocortical networks,

spindle activity is thought to be associated with a massive calcium influx into pyramidal cells, possibly facilitating synaptic plastic changes (Contreras et al., 1997; Sejnowski and Destexhe, 2000). Repeated spindle-associated spike discharges can efficiently trigger long-term potentiation in neocortical synapses (Rosanova and Ulrich, 2005; Timofeev et al., 2002) and synchronous spindle activity occurs preferentially at synapses that were previously potentiated during encoding of information (Werk et al., 2005).

Studies in rats and humans have consistently revealed increases in spindle density and activity during non-REM and SWS after learning (Eschenko et al., 2006; Fogel and Smith, 2006; Gais et al., 2002; Morin et al., 2008; Schabus et al., 2004; Tamaki et al., 2009). In humans, spindle increases are observed both after acquisition of hippocampus-dependent declarative tasks and procedural motor skills, and in some cases correlated with the overnight improvement in memory (Clemens et al., 2005, 2006; Nishida and Walker, 2007; Tamaki et al., 2008) and were localized to cortical areas most strongly involved during prior learning of the task (Clemens et al., 2005, 2006; Nishida and Walker, 2007; Schabus et al., 2004; Tamaki et al., 2008).

The strong grouping effect exerted on spindle activity by the slow oscillation makes the conjoint effect of prior learning on slow oscillations and spindle activity during subsequent sleep of utmost interest, and, specifically raises the question of whether learning-dependent enhancements in spindle activity might occur selectively during the slow oscillation up-state. Intense declarative learning of word-pairs over a period of about 1 h was, indeed, found to increase EEG coherence in the 0.5–1.5 Hz slow oscillation frequency band, and also in the 1–4 Hz delta frequency bands during subsequent periods of SWS, with these increases being essentially limited to the depolarizing up-states of the slow oscillation. In the corresponding control condition, SWS was assessed after subjects had performed a non-learning vigilance task where they merely had to count the number of certain letters occurring in the same word-pairs (Mölle et al., 2004). These observations are consistent with results by Huber et al. (2004) who observed a similar increase in power in the 0.5–4 Hz slow-wave activity frequency band (including both the <1 Hz slow oscillation range and the 1–4 Hz delta range) after subjects had performed on a visuomotor learning task. The increase was locally restricted to the neocortical motor area most strongly involved in task performance at learning and, interestingly, was significantly correlated with the performance improvement measured at a retest after the sleep period. There also appeared to be a slight local increase in fast spindle activity around 15 Hz after learning in this study.

In a more recent study (Mölle et al., 2009), we compared effects of prior learning on slow oscillations and associated spindle activity in humans and rats, using a word-pair learning task and an odor–reward association task, respectively. In humans, learning compared with non-learning shaped the slow oscillation waveform such that the depolarizing up-states exhibited increased amplitude after learning. Learning also sharpened the hyperpolarizing negative slow oscillation peaks which were followed by a steeper increase in subsequent positivity. Importantly, learning not only produced a general increase in 12–15 Hz spindle activity, but this increase clearly focused on slow oscillation up-state periods. There were no significant changes occurring during the hyperpolarizing down-state. In rats, the effects of prior learning on slow oscillation morphology as well as on the grouping of learning-dependent increases in spindle activity was generally less distinct, possibly indicating that the odor task employed in the rat studies may not particularly rely on functions of thalamocortical circuitry (Mölle et al., 2009). Notwithstanding the fact that the issue of a possible task specificity of the effects needs further clarification, overall the studies support the view that the encoding of information during learning increases subsequent sleep slow oscillations and spindles in a temporally coordinate manner. Specifically, the

neocortical slow oscillation appears to exert a top-down control whereby learning-dependent increases in spindles become focused on the depolarizing up-states of the slow oscillations.

Fast spindles versus slow spindles

There is considerable evidence, mentioned above, indicating that learning leads to enhanced spindle activity during subsequent sleep and that this spindle activity is synchronized by the depolarizing up-phase of the slow oscillation. However, these findings mainly refer to the classical fast spindles, which in the human EEG show peak frequencies from 12 to 15 Hz and have a rather widespread distribution with maximum amplitudes over central and parietal cortical areas. Against this background, a growing number of studies have provided support for the existence of a second distinct type of "slow" spindles with peak frequencies between 9 and 12 Hz and a more focused topography dominating over frontal cortical regions (Anderer et al., 2001; De Gennaro and Ferrara, 2003; Terrier and Gottesmann, 1978). Whereas fast spindle activity is equally present both during non-REM sleep stage 2 and SWS, slow spindle activity appears to be predominant in SWS. Functional magnetic resonance imaging indicates distinct patterns of brain activation associated with the two types of spindles (Schabus et al., 2007). Beyond common activity in the thalamus and superior temporal gyri, slow spindles were associated with increased activity in the superior frontal gyrus, whereas fast spindles recruited a set of cortical regions involved in sensory motor processing, as well as the medial frontal cortex and hippocampus.

In a recent study (Mölle et al., 2011), we aimed to characterize the temporal relationships between the slow oscillation and the two types of sleep spindles during human SWS under basal conditions as well as after learning (Fig. 4). In striking contrast to the fast centroparietal spindles which revealed the expected synchronization to the depolarizing slow oscillation up-state, the slow frontal spindles were associated with fading depolarization at the transition into the hyperpolarizing down-state of the slow oscillation. Correspondingly, within the depolarizing up-phase, fast spindles tended to precede the occurrence of slow frontal spindles by a variable time of about 500 ms. Further analyses on trains of several succeeding slow oscillations revealed a particular importance of the fast centroparietal spindles, as these were not only driven by the depolarizing slow oscillation up-state but appeared to feedback themselves to enforce the succeeding slow oscillation, as well as the likelihood of associated frontal spindles. This dynamics was clearly enhanced after the subjects had performed a lengthy declarative word-pair learning task. Thus, prior learning not only increased the occurrence of slow oscillations in trains of several succeeding waves, but also distinctly enhanced fast spindle activity during the initial slow oscillation of such trains. In contrast, learning induced-increases in slow spindle activity were less pronounced and occurred mainly toward the end of the train of slow oscillations (Mölle et al., 2011).

Importantly, these findings show that the widely held concept of the emergent depolarizing slow oscillation up-state driving thalamic spindle generation accounts only for the classical fast spindles, but not for slow frontal spindles occurring during the waning depolarization phase at the transition into cortical hyperpolarization (Contreras and Steriade, 1995; Destexhe et al., 1999; Steriade, 2006; Timofeev and Bazhenov, 2005). Although a contribution of thalamic activity to the generation of slow spindles cannot be excluded (Schabus et al., 2007), slow spindles could alternatively be primarily of cortical origin, developing in the aftermath of peak network depolarization. This view would correspond to the idea that slow frontal spindles are functionally associated with corticocortical coupling, whereas centroparietal spindles are linked to activity in thalamocortical loops (Doran, 2003).

The finding that prior learning increased the occurrence of slow oscillation trains together with a quite robust increase in fast spindle activity during the initial slow oscillation in the train

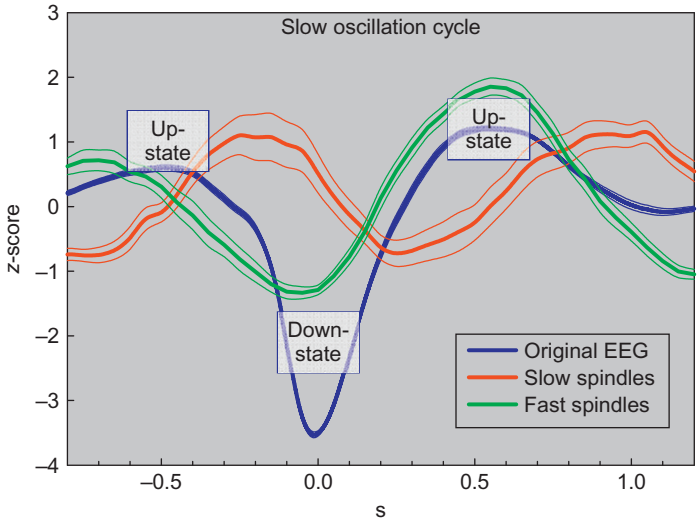

Fig. 4. Temporal distribution of fast and slow spindle activity during slow oscillations recorded in slow-wave sleep. Time courses of original EEG during slow oscillation (blue line), slow (red) and fast (green) spindle activity are given as means (thick lines) ± s.e.m. (thin lines) across 11 human subjects (after z-transformation of individual averages). Spindle activity was calculated on the basis of the number of peaks and troughs in detected spindles. Averaging was performed with reference to the negative peak ($t=0$) of the slow oscillations. Note, fast spindle activity increases in synchrony with the depolarizing up-phase of the slow oscillation whereas increases of slow spindle activity occur toward the end of the up-states when depolarization is fading. Data are from Mölle et al. (2011).

points to a key role that fast spindles may play for launching and maintaining sleep-dependent memory processing. A loop-like scenario is suggested where the fast spindles, possibly by promoting Ca^{2+} influx into cortical pyramidal cells (Destexhe et al., 2007; Sejnowski and Destexhe, 2000), enhance the likelihood and amplitude of succeeding slow oscillations together with slow frontal spindles developing during waning depolarization of these subsequent slow oscillations. Emergent depolarization in this slow oscillation cycle, conversely, drives the generation of the next fast spindle, although due to refractoriness fast spindle amplitude gradually decreases across the train of slow oscillations (Luthi and McCormick, 1998). Prior learning enforces the driving impact of fast spindles on the generation of such slow oscillation–spindle cycles. The view of a priming role of fast spindles for sleep-dependent memory processing is also consistent with findings that learning also induces robust increases in fast spindle activity during non-REM sleep stage 2 which is less dominated by slow oscillations but, inevitably occurs before SWS is entered (Fogel and Smith, 2006; Gais et al., 2002; Schabus et al., 2004). Generally enhanced levels of fast spindle activity during stage 2 non-REM sleep, on a larger time scale, could serve to support the generation of slow oscillation activity during subsequent SWS. Indeed, learning-dependent increases have been most consistently observed for non-REM sleep stage 2-associated fast spindles, and there are presently only a few studies reporting such increases for SWS-associated fast or slow spindle activity (Clemens et al., 2005, 2006; Nishida and Walker, 2007; Rasch et al., 2009; Tamaki et al., 2008, 2009).

Slow oscillations grouping hippocampal ripples and memory reactivations

The reactivation during sleep of neuronal firing patterns associated with the encoding of memories during prior wakefulness is considered a basic mechanism underlying the consolidation of these memories. First evidence for the occurrence of neuronal reactivations was provided by studies in rats showing that spatiotemporal patterns of neuronal firing present during exploration of a novel environment and simple spatial tasks were reactivated in the same sequential order in the hippocampus during subsequent SWS (O'Neill et al., 2010; Pavlides and Winson, 1989; Rasch and Born, 2007; Wilson and McNaughton, 1994). Neuronal network reactivations of waking experience were observed almost exclusively during SWS, and rarely during REM sleep (Louie and Wilson, 2001). Compared with activity at encoding, reactivations during SWS occur at a distinctly faster rate. Reactivations have been observed also in other regions including striatal and neocortical networks (Euston et al., 2007; Ji and Wilson, 2007; Pennartz et al., 2002; Ribeiro et al., 2004). First evidence for a causal role of reactivations for memory consolidation during sleep has been provided by a study in humans, showing that the experimental reactivation of newly encoded hippocampal memories induced by (memory-associated) odor cues presented during SWS, distinctly strengthened the postsleep recall of these memories (Rasch et al., 2007). Reactivation of memories by odor cuing during REM sleep was ineffective.

Importantly, the reactivation of neuronal firing patterns appears to occur in timeframes corresponding to the up-phase of the slow oscillation in neocortex and hippocampus, whereby hippocampal reactivations tended to lead reactivations in neocortex and striatal regions (Ji and Wilson, 2007; Lansink et al., 2009). This temporal synchrony with the slow oscillation up-phase has been likewise revealed for sharp wave-ripples which normally accompany reactivations in hippocampal networks (Buzsáki, 1998; Diba and Buzsaki, 2007; Wilson and McNaughton, 1994). Several studies in rats demonstrated that sharp wave-ripples preferentially occur during or at the transition into the depolarizing up-phase of the slow oscillation (Battaglia et al., 2004; Isomura et al., 2006; Mölle et al., 2006; Sirota et al., 2003). However, possibly depending on the specific hippocampal region examined, they can be observed also during down-states (O'Neill et al., 2010; Sirota and Buzsaki, 2005). In epileptic humans, recordings from parahippocampal electrodes revealed a clear increase in sharp wave-ripple activity time-locked to the depolarizing phase of the neocortical slow oscillation (Clemens et al., 2007). Interestingly, increases in parahippocampal ripple activity also preceded neocortical spindles in these patients suggesting a downstream influence of hippocampal sharp wave-ripples on thalamic generation of spindle activity.

Sharp wave-ripples sensitively reflect memory processing during SWS. In rats, training on an odor–reward association task was followed by a robust increase in ripple number during the first hour of subsequent SWS, and an increase in ripple magnitude for up to 2 h during posttraining SWS (Eschenko et al., 2008). In humans (epileptic patients), consolidation of picture memories acquired before a nap correlated with the number of rhinal ripples (Axmacher et al., 2008). Two recent studies in rats pointed toward a causal role of hippocampal ripples in sleep-associated memory consolidation. In these studies, the selective disruption of local ripples by electrical stimulation during the postlearning rest period hampered the formation of long-term memories in spatial tasks (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009). Whether and to what extent postlearning increases in hippocampal ripple activity are synchronized to the occurrence of neocortical slow oscillations is presently obscure. In one study, postlearning increases of ripples did not reveal a clear association with the slow oscillation

up-phase (Mölle et al., 2009). However, as mentioned, this lack of an association might have been due to the odor–reward association task used in these experiments as it does not essentially involve neocortical circuitry. Of note, despite the missing synchronization with the neocortical slow oscillation, the learning induced increase in ripple activity in these experiments showed a clear temporal association to increases in spindle activity.

Spindle–ripple events

By jointly synchronizing hippocampal sharp wave-ripples and the thalamic generation of spindles, slow oscillations allow for the formation of so-called spindle–ripple events which have been proposed as a mechanism to mediate the transfer of hippocampal memory information to the neocortex in a temporally fine-tuned manner. Siapas and Wilson (1998) were the first to demonstrate in rats the existence of a weak but highly significant temporal association between hippocampal ripples and cortical spindles that was also reflected in the correlated activity of single neurons within these brain structures. A robust temporal correlation between spindles recorded from somatosensory cortex and hippocampal ripples was likewise revealed in mice (Sirota et al., 2003). In these studies, the synchronous cortical unit discharge associated with spindles occasionally increased firing of hippocampal neurons within 30–50 ms. This increase in activity was often associated with the occurrence of a sharp wave-ripple which led the authors to assume that spindle-associated discharges can promote hippocampal ripples and associated reactivation of memories (Sirota and Buzsaki, 2005; Sirota et al., 2003).

However, there is also evidence for effects in the reverse direction that become manifest during spindle–ripple events. Ripple associated synchronous discharges of CA1 neurons and of downstream subicular and entorhinal neurons are well known to provide a most effective output to the neocortex (Chrobak and Buzsaki, 1994). A recent study in rats revealed a nonlinear relationship between the magnitude of hippocampal ripple bursts and cortical spindle-like responses, such that smaller ripple bursts led to a single-peaked, short-latency cortical response, whereas larger bursts were associated with an additional peak $\sim$100 ms later (Wierzynski et al., 2009). Such patterning of peaks might indeed reflect a promoting influence of ripple-associated discharge on spindle band activity arising within sufficiently excited corticothalamic circuits.

The temporal relationship between spindles and hippocampal ripples during SWS is also sensitive to prior learning. Examining in rats the co-occurrence of spindle and ripple activity by event-correlation histograms during time intervals of several seconds, we found that spindle activity distinctly increased in the presence of hippocampal ripples, with this increase starting about 200 ms before the onset of a ripple and persisting for up to 1 s, that is, long after the ripple had ceased. This enhancement of spindle activity was significantly prolonged for up to 2 s after the ripple when the rats had been trained on an odor–reward association task before sleep (Fig. 5). Altogether, this pattern speaks for a loop-like scenario in which emergent thalamocortical spindle activity and associated neocortical firing drives ripple activity and associated neuronal discharge from hippocampal CA1 output regions, which in turn feeds back to support the generation of continuing thalamic spindle activity (Mölle et al., 2009). This feedback action of ripples on spindles is enhanced after learning, possibly due to facilitated generation of ripples in select hippocampal circuitry that were potentiated during learning.

Such loop-like coordination between thalamocortical and hippocampal network activity could enable a temporally fine-tuned hippocampo-to-neocortical information transfer where ripples and associated memory reactivation feed exactly into the excitatory phases of the

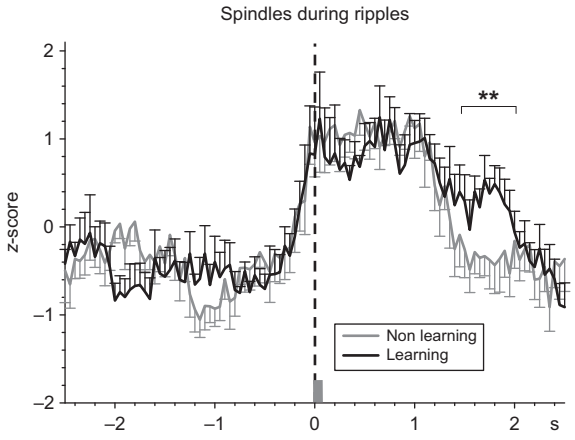

Fig. 5. Spindle activity during hippocampal ripples. The event-correlation histogram indicates prefrontal spindle activity in a 5-s interval around the onset of hippocampal ripples recorded during SWS in rats which had been (learning) or had not been trained (nonlearning) before sleep on an odor–reward association task. The *x*-axis zero represents ripple onset (as determined by first peak or trough above threshold). Spindle activity (*y*-axis) was calculated on the basis of the number of peaks and troughs in detected spindles. Indicated are mean (±s.e.m.) spindle activity across eight rats (after *z*-transformation of individual histograms). Horizontal bracket indicates period with significant ($p < 0.01$) differences between the learning and nonlearning condition. Note, spindle activity increases shortly before ripple onset with this increase outlasting the ripple (typical duration <75 ms, gray bar) by more than 1 s, in particular, after learning. Adapted from Mölle et al. (2009).

spindle cycle. This view has been also substantiated by studies in humans using intracranial recordings from parahippocampal cortex in epileptic patients (Clemens et al., 2011). Apart from frontal and parietal spindles, spindles were observed in these patients at parahippocampal electrode sites which appeared to be closely synchronized in phase with the parietal spindles. Averaging ripple activity time-locked to the peak of the single spindles revealed that in particular for the parahippocampal spindles and to a slightly lesser degree for the parietal spindles, ripple activity becomes nested into the single troughs of a spindle (Fig. 6). In both types of spindles, ripple activity peaked ~10 ms before spindle troughs, with this time lag being remarkably similar across patients and also similar to that observed in rodents (Sirota et al., 2003). No such phase coupling was revealed for the slower frontal spindles, consistent with the notion that slow frontal spindles serve functions distinct from those of the classical fast spindles.

In summary, the close temporal relationship specifically between the fast neocortical spindles and hippocampal ripple activity observed consistently in humans and rodents supports the idea that spindle–ripple events form a basic mechanism coordinating information transfer between hippocampal and neocortical circuitry (Marshall and Born, 2007; Siapas and Wilson, 1998). Inasmuch as hippocampal output during ripples originates from reactivations of newly encoded memories, its nesting into spindle troughs might support the enduring redistribution of these memories to neocortical networks. Consistent with this idea, it has been shown that patterns of single unit burst activity during spindles can effectively induce synaptic long-term potentiation in neocortical networks (Rosanova and Ulrich, 2005).

Conclusion

We have proposed a concept of the slow oscillation as a key player in orchestrating the system consolidation of hippocampus-dependent memories during sleep. The consolidation process comprises the reactivation of newly encoded hippocampal memories and their redistribution to neocortical long-term storage sites where the memory information is integrated with preexisting long-term memories. The slow oscillations—specifically the down-to-up-state transition of these oscillations—synchronize the reactivation of hippocampal memory representations and accompanying ripple activity with the simultaneous occurrence of fast spindles in thalamocortical loops. The synchrony allows for the formation of spindle–ripple events whereby reactivated hippocampal memory

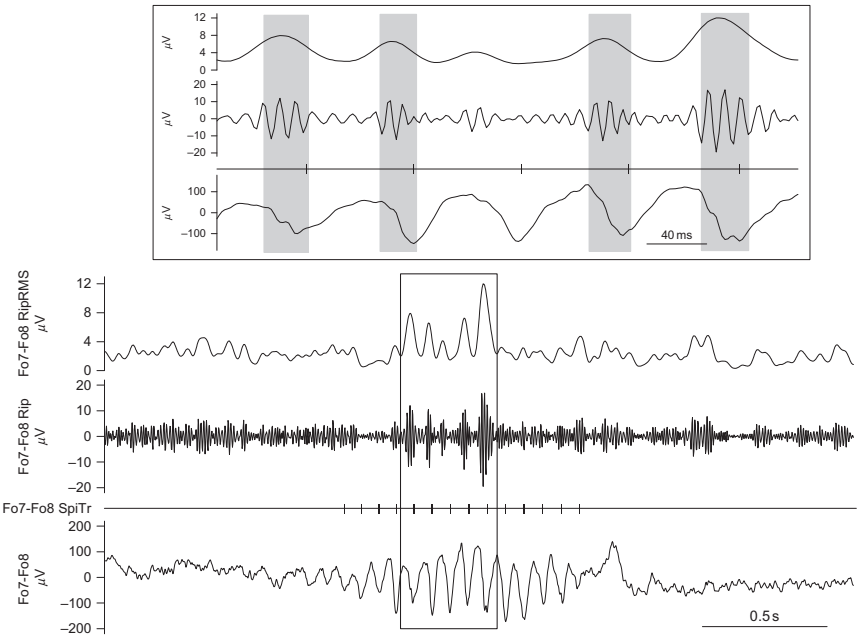

Fig. 6. Spindle–ripple events. Example of ripple activity nested within subsequent troughs of a spindle in original recordings obtained during non-REM sleep from intracranial parahippocampal electrode sites in an epileptic patient. Upper panel shows a 400-ms excerpt of recordings during an acute spindle seen in the lower panel. Traces indicate (from *bottom* to *top*) "Fo7-Fo8": original anterior parahippocampal EEG from foramen ovale electrodes, "Fo7-Fo8 SpiTr": event channel indicating identified spindle troughs, Fo7-Fo8 Rip: bandpass filtered (80–140) parahippocampal EEG indicating ripple activity, Fo7-Fo8 RipRMS: ripple root mean square signal. Shaded areas in the upper panel indicate distinct increases in ripple amplitude during and shortly before spindle troughs. Data are from Clemens et al. (2011).

information becomes nested into single troughs of a spindle. Spindle–ripple events that contain reactivated memory information and arrive at neocortical networks during the slow oscillation up-state represent a putative mechanism which serves the effective transfer and storage of hippocampal memory information within neocortical networks.

While recent studies in humans and rodents provide sizeable evidence in support of this concept, essential mechanisms remain to be clarified. Most imminent issues for future research concern: (i) the local generation of the slow oscillations within neocortical networks and whether in driving spindles and hippocampal memory replay, the down-to-up-state transitions of the slow oscillations additionally convey specific memory-related information from the neocortex to the hippocampus. If so, the type of information would be of interest, whether originating selectively from networks previously used for encoding or spreading to associated cortical networks and corresponding representations. (ii) It is presently unclear whether the slow oscillation-driven reactivation and transfer of hippocampal memory information is linked to a mechanism emptying hippocampal networks, thereby restoring capacities for encoding new information during subsequent wake phases. Slow oscillation activity has been demonstrated to ease the encoding of hippocampus-dependent memories during subsequent wakefulness (Van Der Werf et al.,

2009). Such facilitation of encoding could in principle result from an erasure of representations within hippocampal networks that had been acutely reactivated by the slow oscillations but, could also pertain to older memories unrelated to the reactivated representations. (iii) Finally, the detailed mechanisms underlying the long-term storage of hippocampal memory information within neocortical networks remain to be elucidated. Slow oscillations have been considered a process favoring downscaling and the depotentiation of cortical synapses (Tononi and Cirelli, 2003). On this background, further study is required into how memory information and associated synchronized neuronal discharge nesting in single troughs of spindles can induce long-lasting plastic synaptic changes in local neocortical circuits. Although there is preliminary evidence from *in vitro* studies that spindle-associated burst activity can induce long-term potentiation in neocortical networks (Rosanova and Ulrich, 2005), these findings need to be extended to *in vivo* conditions. The proposed concept assumes that spindle-associated discharges are particularly effective in inducing long-lasting synaptic changes when they arrive during the slow oscillation upstate. Future research tackling this issue will undoubtedly shed more light on the central role slow oscillations, play for memory function and, in so doing, might eventually reveal a twofold function for these oscillations in memory processing, namely, to promote the consolidation of certain memories (being of putative relevance for the organism) and simultaneously to help erase other irrelevant memories.

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