CHAPTER 9

Sleep EEG Rhythms and System Consolidation of Memory

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MEMORY AND SLEEP

The Two-Stage Model of Memory Formation

The adaptive capability of individuals is greatly enhanced by the brain's plasticity, i.e., the ability of the brain to acquire new information and new skills. However, for proper functioning the brain at the same time must preserve a certain degree of stability in memory, i.e., to keep a certain amount of stable knowledge about rules and regularities in the environment. This plasticity-stability dilemma asks how the brain achieves the task of providing stability, i.e., protecting already acquired traces from being continuously overwritten by new information, and, concurrently, plasticity that allows for the fast assimilation of adaptive information in the same storage system (Carpenter & Grossberg, 1988). The two-stage model of memory formation offers a solution to this problem as it enables the fast acquisition of new traces into memory and their subsequent integration within long-term memories without deleting them (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995). The model is a general basis of the standard theory of system memory consolidation (termed "standard consolidation theory") and more recent developments thereof (Nadel, Samsonovich, Ryan, & Moscovitch, 2000; Winocur & Moscovitch, 2011).

In this section we introduce the model and throughout the chapter we will add sleep's participation in this memory process. The model assumes that long-term memories are produced by the brain in a two-stage process. The first involves the storage of information into a readily established but transient memory representation, which constitutes a memory store able to learn at a fast rate, but which must only hold this information for a limited duration. However, this temporary store is expanded by a long-term store, which learns at a slower rate, which is, accordingly, also able to maintain the trace for a much longer time. At first, new information is encoded as

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a representation in the temporary memory system, which is associated to the specific information in the long-term store, thereby binding this pattern of information with similar old memories. The repeated reactivation of the trace stored in the temporary store in conjunction with older already established memories during subsequent periods of consolidation in a gradual process updates the long-term representation and thereby strengthens connections related to the new pattern of information and integrates it into the preexisting knowledge networks. This process also allows the extraction of relevant and invariant features of the new trace, as overlapping amounts of information are reactivated several times (Lewis & Durrant, 2011). Irrelevant features however may be erased due to only marginal reactivation.

The two-stage model has been applied to systems involving learning and subsequent consolidation. However, the declarative memory system has gained the most attention in this respect. Here, the role of the fast-learning, transient memory store is accredited to the hippocampus, whereas the slow learning long-term store resides in the neural network of the neocortex. Through repeated reactivation of the hippocampal representation the traces in the neocortex are strengthened and over a course of days to years may thereby lose their dependence on the hippocampal structure entirely (Frankland & Bontempi, 2005; McClelland et al., 1995; Zola-Morgan & Squire, 1990). The declarative memory system can be subdivided into two classes of memory (see Box 9.1 on declarative and procedural memory). Episodic memories include the representation of an event in a temporal and spatial context, thereby setting an episode. Semantic memories are independent of the hippocampus and can be viewed as memories that only contain the informational content of the event, while all context information is lost. Loss of the hippocampus leaves semantic memories more or less intact but heavily compromises associated episodic context (Nadel et al., 2000). In essence, semantic information is considered to be deduced from a series of episodes through consolidation, in the course of which most of the individual episodes are lost. Declarative memory is commonly distinguished from procedural memory for skills and habits that do not essentially rely on the hippocampus (see Box 9.1). However, both memories may not be as independent as originally conceptualized, as procedural skill representations, like semantic memory, may originate from a series of overlapping episodes of practicing a skill (e.g., Albouy et al., 2008; Packard & McGaugh, 1996; Schendan, Searl, Melrose, & Stern, 2003).

Memory formation according to the two-stage model represents a system consolidation process, in such a sense that the model assumes that

Box 9.1 Declarative and Procedural Memory

Memory can be subdivided into different systems, depending on the type of the stored information and the involved brain regions. One division is that into declarative and nondeclarative memory with the procedural memory representing the most important nondeclarative memory system (Squire, 1992; Winocur, Moscovitch, & Bontempi, 2010). Declarative memory is further divided into memory for facts (semantic) and memory for events (episodic), and is defined anatomically by its dependence on the hippocampus. Declarative memories are encoded fast, but thereafter also decay rapidly unless they are consolidated. Semantic memories can be considered to result from repeated episodes including overlapping items. For example, the knowledge that Paris is the capital of France results from repeated episodes including this association. In a process of semantization the episodic context (source), i.e., when and where this association was learned, is forgotten, whereas the fact (item) remains stored in memory.

Procedural memory is that of perceptual and motor skills and is learned through repeated practice and, henceforth, remains relatively stable. For this, motor skill memories rely on corticostriatal and corticocerebellar loops. Whereas declarative memories are encoded and retrieved explicitly, i.e., with the person's awareness of what information is learned and recollected, procedural memories can be acquired both explicitly and implicitly, i.e., without awareness. Normally, when a skill is learned, at first explicit attention and binding adherence to task rules is predominant; later as the task becomes automated attention and thus awareness towards the singular elements fades. It is important to note that, although traditionally procedural tasks are thought not to rely on the hippocampus, fMRI studies have shown hippocampal activation during explicit and implicit motor skill learning on a serial reaction time task (Schendan et al., 2003). This speaks at least initially for dependence on the hippocampus. Explicit acquisition of procedural skills involves in addition increased prefrontal cortex activation. Similar to semantic memory, procedural memory can be considered to originate from the repeated episodes of practicing a skill, including overlapping sequential elements. In an extraction process a procedural representation is formed whereby the representation loses its initially strong dependency on the context in which the skill was acquired (e.g., Packard & McGaugh, 1996).

different neuronal networks are used for storing the information temporarily and for the long term. System consolidation is commonly distinguished from synaptic consolidation, which implies the strengthening of memory representations at the synaptic level, i.e., within localized synaptic networks (Dudai, 2004). System consolidation is believed to take place

during offline periods of the brain, as the reactivation and redistribution of fresh memories heavily depends on the same neuronal resources as the processing of external stimuli, rendering these processes mutually exclusive. We will present here data indicating that system consolidation is mainly associated with slow wave sleep (SWS). Synaptic consolidation, on the other hand, may be more effective during REM sleep, to strengthen representations after redistribution during SWS, and during waking.

Sleep and Memory Consolidation—Preferential Consolidation of Explicit Memory

Sleep has been shown to benefit declarative and procedural memory (Diekelmann & Born, 2010). However, the specific impact of sleep on different aspects and forms of memory is dependent on multiple variables. We first review important psychological factors and modulators of sleep-dependent memory consolidation and then focus on the qualitative transformation of memory achieved during sleep.

Declarative memories are encoded and recollected explicitly, i.e., with conscious awareness, whereas procedural memories can be acquired also implicitly, i.e., without awareness of what is learned. There is evidence that sleep-dependent memory consolidation favors explicitly encoded information (see Box 9.1), as after sleep performance on a procedural serial reaction time task was more robust if sequences were trained explicitly than implicitly (Robertson, Pascual-Leone, & Press, 2004). In cases where all the information was encoded explicitly, memory consolidation favors strengthening of weak traces over strong traces (Drosopoulos, Schulze, Fischer, & Born, 2007). The degree to which a memory gains access to sleep's beneficial processes is also dependent on the task difficulty and the emotional tone of the event composing the task with the more demanding and more emotional tasks showing a greater benefit from sleep (Kuriyama, Stickgold, & Walker, 2004; Wagner, Hallschmid, Rasch, & Born, 2006).

The above-mentioned properties of explicit learning tasks are important modulators of sleep-dependent memory consolidation. Interestingly, in most of the studies participants are instructed to keep in memory the task items. However, a series of studies now shows that this instruction in itself is an important variable, gating if information is subject to sleep-dependent memory consolidation or not. These studies highlight the future-orientated and motivational character of sleep-dependent memory consolidation. The first study asked the participants to learn declarative (verbal and visual-spatial paired associates) tasks, and afterward participants

slept or stayed awake (Wilhelm et al., 2011). Following the learning of the tasks the participants were or were not informed they would have to retrieve the information the next day. Sleep benefited the performance at delayed retrieval to a distinctly greater extent for the participants who were informed about the recall. In the wake condition expectancy had no effect on performance. Hence, access of a memory to sleep-dependent consolidation is mediated by the expectancy that this memory will be used again. Interestingly, in these experiments EEG slow oscillation activity during post-learning non-rapid-eye-movement sleep (NREM) was increased in the expectancy group and, accordingly, this increase correlated with the performance at delayed retrieval.

The strengthening of a memory trace through sleep consolidation may likewise be manipulated by reward expectancy (Fischer & Born, 2009). In this study participants learned one sequence (A or B) of a procedural finger-sequence tapping task, and immediately afterwards they learned the other. After learning they were instructed that good performance only for one of the sequences would be rewarded with money during a later recall test, whereas performance for the other sequence would not be rewarded. However, before recall they were informed that actually good performance on both sequences would be rewarded equally, thereby mitigating the immediate effects of reward expectancy. Nonetheless, participants who slept in the retention interval between learning and recall performed better on the finger sequence they had been expecting to be rewarded for during the retention interval. If the retention interval consisted of only wakefulness, there was no difference in performance. Importantly, in both these studies participants were informed about reward or retention only after learning had occurred, thus expectancy could not afflict encoding of the material and subsequent sleep-dependent processing of memories, rather than the expectancy itself, influenced properties of the consolidation process.

Another study shows that sleep also improves memory for the implementation of future plans (Diekelmann, Wilhelm, Wagner, & Born, 2011 submitted). The comparison of early and late sleep, consisting mainly of SWS or REM sleep, respectively, revealed that the implementation of plans relies on SWS. If the participant had the opportunity to fulfill the plan before sleep, sleep did not influence the plan. Executing the plan corrupted the enhancing effects of sleep for prospective memories and even of retrospective memories constituting the plan.

This series of experiments indicates that the consolidation of memory during sleep, though it is a process of the unconscious state, is motivationally

driven and goal oriented, strengthening specifically those memories that are important for future actions and planned behavior. Importantly, this work underscores that the consolidation process is selective, not enhancing all memories, but preferentially those that are tagged during wakefulness as being relevant for the future. This tagging presumably occurs in the prefrontal cortex, which during anticipated retrieval of hippocampus-dependent declarative memories regulates the activation of memory traces (Cohen & O'Reilly, 1996; Hannula & Ranganath, 2009; Miller & Cohen, 2001; Polyn & Kahana, 2008). In fact, supporting this view, replay during subsequent SWS in neuron assemblies that were active during encoding is not only found in the hippocampus, but also in prefrontal areas (Euston, Tatsuno, & McNaughton, 2007; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009). Replay of neuron assemblies is considered a key process mediating system consolidation during SWS. Hence, for admittance to sleep-dependent memory consolidation it may be essential that the memory encoded under explicit control of prefrontal-hippocampal networks be tagged by afferents from the prefrontal cortex. Interestingly, the prefrontal cortex is the region most involved in the generation of slow oscillations during SWS (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004; Murphy et al., 2009) tempting one to speculate that these slow oscillations preferentially originate from prefrontal circuitry contributing to memory representations tagged as being relevant for the future, and thus for sleep-dependent consolidation.

Consolidation during Sleep Causing Qualitative Changes of the Representation

An interesting necessity of memory redistribution at the neuronal level is a change in its qualitative aspects at the behavioral level. The gradual transfer of information reduces the dependence, possibly to zero, of memory traces on hippocampal structures (Frankland & Bontempi, 2005). Recent fMRI studies show that this transfer of information from hippocampus to neocortical networks is promoted by sleep (Gais et al., 2007; Takashima et al., 2006). These qualitative changes in neuronal representation of a certain memory are paralleled by obvious qualitative changes at a behavioral level. Adopting the behavioral view, studies indicate that, via these structural changes, sleep extracts repetitive and invariant features of a memory trace and, thereby, for example, renders formerly implicit aspects of a memory accessible to consciousness, making them explicit. Also, through this process sleep can decrease dependence on contextual cues during recall, thus favoring a "semantization" of representations (Cairney, Durrant, Musgrove, & Lewis, 2011).

Using a number reduction task the influence of sleep on the extraction of explicit knowledge was tested (Wagner, Gais, Haider, Verleger, & Born, 2004). This task consists of multiple strings of numbers and participants are asked to process the numbers to finally reach a solution for each string. The result can be calculated using a prior defined set of rules, by processing each of the digits sequentially. However, unbeknown to the participants the strings are constructed in such a way that it is sufficient to only process the first two digits in order to reach the correct answer, once the subject gains insight into this hidden structure. First, the participants performed the task on 90 digit strings, which was not sufficient to induce insight. After a period of either sleep or wakefulness the participants performed on further strings. At this retest, twice as many subjects gained insight into the hidden rule if they were allowed to sleep as compared to subjects who remained awake. Importantly, this effect was not evident if subjects did not practice the task before sleep, thus ruling out an effect of sleep on the general faculty of problem solving, e.g., through facilitation of creative thinking. In fact, the data indicate this to be a phenomenon of memory, such that a representation of the task is formed and the redistribution of respective representations during sleep leads to the extraction of insight through the accumulating effect of overlapping information. Split-night experiments show this beneficial effect of sleep can be attributed to SWS rather than REM sleep (Yordanova et al., 2008), and closer examination of these data revealed that slow spindle activity during SWS is one marker that favors the transformation of implicitly encoded information to an explicit representation over the course of sleep (Yordanova, Kolev, Wagner, Born, & Verleger, 2011).

Relational memory tasks (Ellenbogen, Hu, Payne, Titone, & Walker, 2007) and serial reaction time tasks (SRTT) (Fischer, Drosopoulos, Tsen, & Born, 2006) are other approaches to investigate the influence of sleep on the transformation from implicit to explicit representations of memory traces. For the SRTT, participants are trained under implicit conditions to press a repeatedly presented sequence of cued buttons as fast as possible, without knowledge of the underlying sequence of cue positions (Fig. 9.1). Whether training induced explicit knowledge of the cued sequence is then tested in a generation task, where the participant is asked to deliberately generate the sequence of cue positions. Sleep after training produced a significant gain in explicit sequence knowledge, whereas subjects tested after a corresponding wake retention interval still performed at chance level on the generation task. This sleep-dependent gain does not

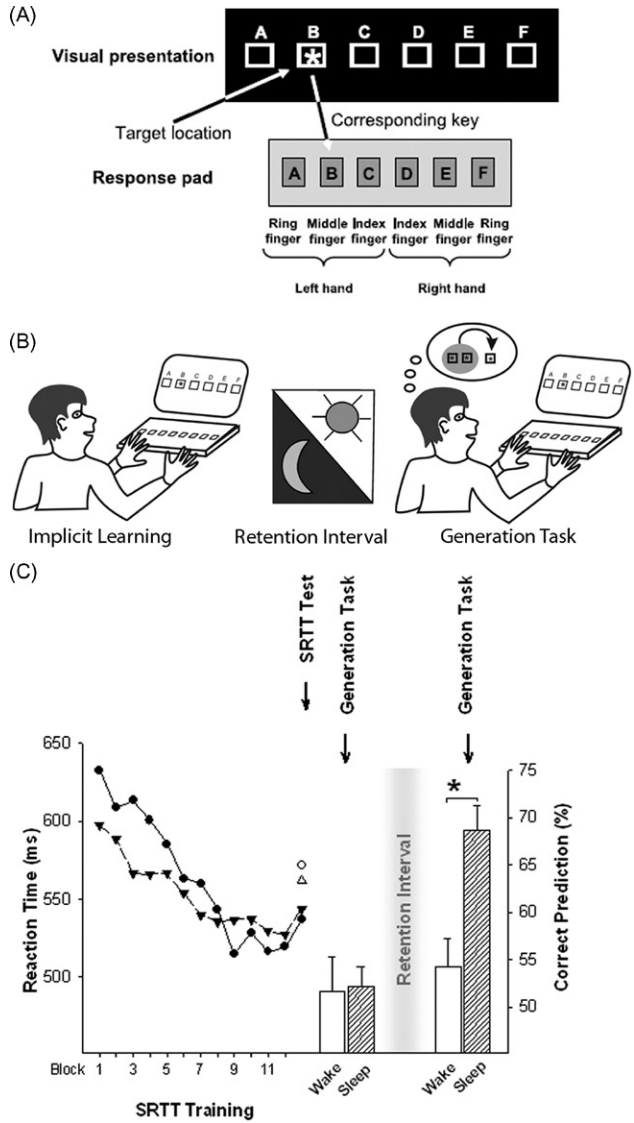


Figure 9.1 ***Effects of sleep on the generation of explicit sequence knowledge in a serial reaction time task (SRTT).*** (**A**) The SRTT: Subjects are presented six horizontally arranged target locations on a computer screen (white boxes). They are instructed to react as fast and as accurately as possible to the occurrence of a target stimulus (white star) at one of these locations by pressing a spatially corresponding key on a response pad. Upon responding, the target changes to another location. Unknown to the subject (i.e., implicit training conditions), the transitions of target locations follow a repeated sequence (grammar). (**B**) General experimental procedure: The participant is trained on the SRTT under implicit conditions (unaware of the regular repeating sequence underlying the target

depend on the participants knowing that there is an underlying grammar (Drosopoulos, Harrer, & Born, 2011). Preliminary findings point to an advantage in extraction of explicit sequence knowledge for children as compared to adults. This ability is connected to their ability to produce increased NREM slow wave activity (Wilhelm et al. 2012, submitted).

While these studies offer strong support for the extraction of explicit content from implicit training occurring during sleep and SWS, there may also be such reorganization of representations within a given memory system, i.e., for explicit memories that remain explicit and for implicit memories that remain implicit. Studies that use the false memories paradigm have provided such evidence, where sleep facilitates the extraction of explicit gist memory from a list of words, which was encoded explicitly before sleep (Diekelmann, Born, & Wagner, 2010; Payne et al., 2009). Applying procedural finger tapping tasks it is possible to show sleep benefits the transfer of skill from the hand used at training to the contralateral hand (D. A. Cohen, Pascual-Leone, Press, & Robertson, 2005; Witt, Margraf, Bieber, Born, & Deuschl, 2010). Sleep likewise benefited the implicit abstraction of statistical knowledge about tone strings and its generalization to novel strings, an effect associated with SWS (Durrant, Taylor, Cairney, & Lewis, 2011). Sleep even supports the tapping speed of a finger sequence if participants were only allowed to learn it by observation (van Der Werf, van Der Helm, Schoonheim, Ridderikhoff, & van Someren, 2009).

Figure 9.1 (*Continued*)
positions) before retention periods of daytime wakefulness or nocturnal sleep. At retrieval after the retention period, the participant performs on the "Generation task." For this task, the subject is informed that there was a repeating sequence in the SRTT he trained before the retention interval and, to test his explicit sequence knowledge, he is now asked to deliberately generate as accurately as possible this sequence. (**C**) Results from Fischer et al. (2006): Participants were trained (under implicit conditions) before the retention interval of either sleep (triangles) or wakefulness (circles) on 12 blocks of the SRTT (each block containing 196 target positions following a probabilistic 12-elements sequence). Mean (±SEM) reaction times (left ordinate) indicate a gradual decrease across blocks. Implicit sequence knowledge at the end of training is indicated by significantly faster reaction times to grammatically correct (filled symbols) as compared to random transitions of the target positions (empty symbols). Bar diagrams (left ordinate) indicate performance (number of correctly predicted target transitions) on the Generation task before and after retention intervals of sleep (hatched bar) and wakefulness (empty bar). Note, participants who slept showed a marked increase in explicit sequence knowledge, which was at chance level after the wake retention interval or before sleep. **$p < .005$. *Adapted from Fischer et al. (2006).*

Together these findings are indicative of a qualitative reorganization of implicitly encoded procedural and explicitly encoded declarative memories during sleep that also facilitates the extraction of explicit knowledge from implicit representations. The latter process of extracting explicit knowledge from implicit memories in the waking brain especially involves activity in the prefrontal cortical areas connected to the hippocampus and medial temporal lobe areas (Jung-Beeman et al., 2004; McIntosh, Rajah, & Lobaugh, 1999, 2003). An issue of future research is to what extent the reorganization and transformations of representations during slow wave sleep are subjected to a similar control by prefrontal-hippocampal circuitry.

MECHANISMS OF SLEEP-DEPENDENT MEMORY CONSOLIDATION

Active System Consolidation

As mentioned above, system consolidation in the two-stage model of memory formation heavily relies on the reactivation of memory traces in the temporary store to redistribute the representations to long-term storage sites. We here briefly review findings that speak for a causal role of reactivation for sleep-dependent memory consolidation.

Individual place cells in the rat brain fire at different locations during exploration of an arena and thereby may code spatial information. When investigating firing patterns of these individual neurons in the hippocampus, they show the same pattern of spatiotemporal firing during learning as during subsequent sleep (O'Neill, Pleydell-Bouverie, Dupret, & Csicsvari, 2010; Pavlides & Winson, 1989; Ribeiro et al., 2004; Sutherland & McNaughton, 2000; Wilson & McNaughton, 1994). This reactivation of neuron ensembles has been found robustly during SWS but only rarely during REM sleep. Additionally to the hippocampus, reactivation occurs in other regions, such as the striatum and neocortex (Euston et al., 2007; Lansink et al., 2008; 2009; Pennartz et al., 2004). Reactivations in these regions appear to be preceded by the reactivation in the hippocampus (Ji & Wilson, 2007; Lansink et al., 2009). By suppressing sharp-wave ripples that usually accompany neuronal reactivations in hippocampus during SWS, it is possible to impair the formation of hippocampus-dependent spatial memories in rats (Ego-Stengel & Wilson, 2010; Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009).

Hints towards the reactivation of memory representations during sleep have been also provided by human imaging studies (Maquet et al., 2000; Peigneux et al., 2004). In fact, a study in humans was also the first to

provide direct evidence for a causal role of reactivations to sleep-dependent memory consolidation as predicted by the two-stage model of memory formation (Rasch, Büchel, Gais, & Born, 2007). This study used odors that were associated to visuospatial memory (for card-pair locations) during a prior learning phase, allowing for cueing of these memories by presenting the odors during subsequent sleep (Fig. 9.2). Reexposure to the odor during post-learning SWS but not during periods of REM sleep significantly enhanced the memory for the card-pair locations learned prior to sleep. Odor stimuli have direct access to the hippocampus via the olfactory system. Consequently, in an imaging study the odor that was associated with the card-pair locations at learning led to an activation of the left hippocampus when reexposed during subsequent SWS. So the odor led to a reactivation of the card locations stored in the left hippocampus thereby strengthening their memory traces. The activations recorded during SWS were even larger than during a wake control condition, hinting at an enhanced responsiveness of the hippocampus to reactivating stimuli. While reactivation of memories through odor contexts is a most straightforward approach, as odor stimuli hardly influence sleep architecture (Badia, Wesensten, Lammers, Culpepper, & Harsh, 1990), this paradigm of cueing memories during sleep has also been shown to work with auditory stimuli (Rudoy, Voss, Westerberg, & Paller, 2009).

Reactivations also take place during wakefulness, when memories are retrieved or even when they are merely cued. However, during wakefulness, in contrast to sleep, the brain is constantly receiving interfering input from the sensory system. Importantly, it has been shown that after reactivation during wakefulness the memory trace is left in a destabilized state, which must be ameliorated by a subsequent phase of reconsolidation (Nader & Hardt, 2009; Sara, 2000). Adopting this reconsolidation framework to sleep-dependent memory consolidation, a study investigated if the reactivation of memories during SWS destabilizes these memories in the same way as during wakefulness (Diekelmann, Büchel, Born, & Rasch, 2010). The study used the same approach to reactivate visuospatial memories by odor cueing during sleep as in the above-mentioned study (Rasch et al., 2007; Fig. 9.2). As expected, in waking subjects reactivations induced by odor cueing destabilized the card-pair locations, because learning of an interference card-pair task immediately after the odor cueing distinctly impaired the memory for the originally learned card locations. Quite the opposite was true for the sleep condition. Here, the odor-induced reactivation, compared with a control without reactivation, produced immediate memory stabilization and, thus, enhanced recall

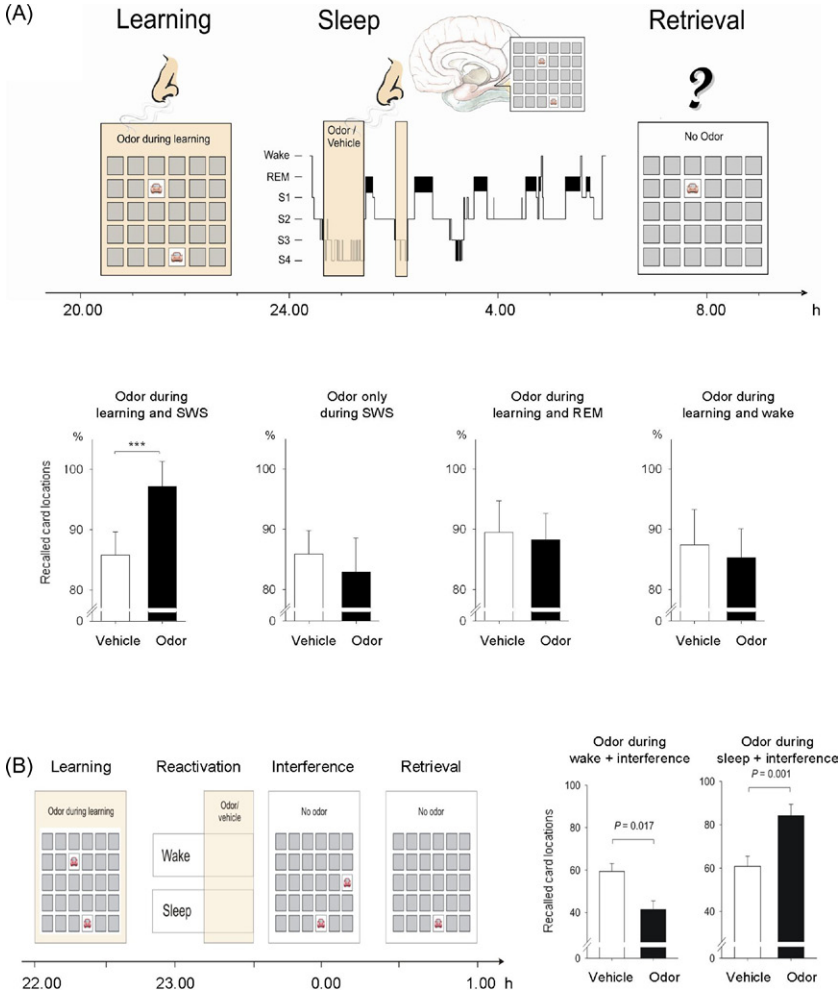


Figure 9.2 ***Reactivating memories by odor cues.*** (**A**) Procedure and task from Rasch et al. (2007): Participants learned a visuospatial 2D object-location task between 21.30 and 22.30 h while an odor was administered time-locked to the learning stimuli (Learning). During subsequent sleep (lights off at 23.00 h, awakening at 6.30 h), the same odor (versus vehicle) was delivered during the first two periods of slow wave sleep (SWS) in an alternating 30 s on/30 s off mode (to prevent habituation). Retrieval was tested between 7.00 and 7.30 h in the absence of odor. The 2D object-location task was similar to the game Concentration, consisting of 15 card pairs with each pair showing the same object (e.g., a red car) with all cards displayed upside down in the beginning. The participant is required to memorize the locations of the pairs of cards, i.e., at learning and for memory testing one card is displayed and he is asked to indicate the location of the corresponding second card of the pair. Underneath—Results: Participants performed significantly better on recall of the card-pair locations only if the odor was presented during learning and subsequent SWS, odor only during SWS,

for the originally learned card locations, despite the fact that the subjects had learned the interference card-pair task directly after odor cueing during SWS. Analyses of the fMRI data revealed that while reactivation during SWS took place mainly in the hippocampus and retrosplenial cortex, during wakefulness mainly right lateral prefrontal areas were involved. Hence, these findings indicate distinct functions of reactivation during wakefulness and sleep. It seems during wakefulness memories are destabilized after reactivation, possibly enabling an updating of the established memory network through lateral prefrontal networks, which introduces the need of subsequent reconsolidation, whereas reactivation during SWS leads to immediate stabilization of the memories, possibly through an enhanced hippocampus-mediated redistribution of the memory representations to neocortical networks. Through this redistribution memories become less dependent on traces deposited in the hippocampus, thereby becoming less vulnerable to retroactive interference, i.e., the overwriting of these still fresh memory traces through the encoding of new memory traces in the temporary hippocampal store (Kuhl, Shah, DuBrow, & Wagner, 2010).

Figure 9.2 (*Continued*)
during learning and REM sleep, or during learning and wakefulness had no effect. (**B**) Procedure from Diekelmann et al. (2011): Participants learned the object-location task in the evening in the presence of an odor. Half of the subjects stayed awake after learning; the other half slept for 40 min. To reactivate the newly encoded card-pair memories, the odor was again presented for about 20 min during SWS as well as during a corresponding time during wakefulness (reactivation). In a control session (no reactivation), odorless vehicle was presented. In order to probe the stability of the memory for the original object-location task, shortly after odor (or vehicle) reexposure—and after subjects in the sleep group were awakened—subjects learned an interference object-location task (without odor presentation) using the same card pairs as during learning, but with different locations (Interference). Retrieval of the original object-location task was tested 30 min after interference learning (without odor presentation). To the right—Results, left panel: Reactivating object-location memories by the reexposure of the odor during wakefulness, as expected, labilized these memories, as subsequent learning of the interference task significantly impaired recall of the originally learned task (black bar) as compared to recall performance without prior odor-cued reactivation (empty bar). Right panel: In contrast, odor induced reactivation during SWS significantly improved recall of the card-pair locations even if an interference task followed (right panel), indicating that reactivation of memory representations during SWS produces an immediate stabilization of the memory possibly because reactivations during SWS induce a redistribution of the memory representations to locations other than the hippocampus where they are at risk of becoming overwritten. *A Adapted from Rasch et al. (2007), B from Diekelmann et al. (2011).*

EEG Slow Oscillations for Memory Consolidation

Reactivation of memories during SWS has been proven to be a causal process implementing the redistribution of memories from temporary to long-term stores, i.e., in the declarative memory system from hippocampal to mainly neocortical storage sites. On the one hand, this information transfer requires a specific neurotransmitter milieu that appears to be established only during SWS. For example, only during SWS acetylcholinergic activity reaches an absolute minimum whereby the tonic presynaptic inhibition exerted via cholinergic afferents to the CA3 and CA1 regions is released (Hasselmo, 1999; Hasselmo & McGaughy, 2004). This disinhibition enables the occurrence of spontaneous neuronal (re-) activations in CA3 and greatly facilitates the outflow of reactivated memory information from hippocampus towards neocortical sites. In fact, experimentally increasing cholinergic activity during SWS-rich retention sleep completely blocked sleep-dependent consolidation of hippocampus-dependent word-pair memories (Gais & Born, 2004; Rasch, Born, & Gais, 2006).

On the other hand, the information transfer between hippocampus and neocortex is specifically regulated by EEG oscillatory events. There is increasing evidence that brain oscillations play a fundamental role in the coordination of information flow between distributed brain regions, and by synchronizing cycles of excitability in these regions determine spike-time dependent synaptic plasticity underlying the formation of distributed memory representations (Buzsaki, 2006; Varela, Lachaux, Rodriguez, & Martinerie, 2001). The EEG slow oscillations have been identified as a main rhythm supporting sleep-dependent memory consolidation in the declarative memory system. In the human EEG, the term slow oscillations refers to a rhythm <1 Hz with a spectral peak around ~0.75 Hz. The term "slow wave activity" instead refers to a wider frequency band (0.5–4 Hz) including besides the slow oscillations (0.5–1.0 Hz) also the delta frequencies (1.0–4.0 Hz). However, there is no clear evidence for functional differences between these rhythms. In fact, the slow oscillation rhythm, as measured in the scalp EEG, comprises also faster frequency components (especially in the falling and rising flanks of the oscillation) although its main constitutes are the lower frequencies.

Brain activity at the slow oscillation rhythm of <1 Hz was first described by Steriade's group in cats (Steriade et al., 1999a,b; Steriade, 2006) and is built up of rhythmically alternating up- and down-states that reflect the rhythmic changes in the membrane potential of neocortical neurons between depolarized and hyperpolarized levels. The slow oscillation rhythm synchronizes

widespread neocortical networks including virtually all excitatory and inhibitory neurons, and also thalamic networks, which themselves generate and contribute to the EEG slow oscillation rhythm (Crunelli & Hughes, 2010). The generation of the depolarizing up-state of the slow oscillation involves a persistent Na^+ current and activation of Na^+-dependent K^+ currents whereas generation of the hyperpolarizing down-state has been linked to Ca^{2+}-dependent K^+ currents as well as synaptic depression and inhibitory neuronal activity (Bazhenov, Timofeev, Steriade, & Sejnowski, 2002; Crunelli & Hughes, 2010; Le Bon-Jego & Yuste, 2007). Initiation of depolarizing up-states in thalamocortical cells is linked to activation of T-type Ca^{2+} channels and accompanying burst activity (Destexhe, Hughes, Rudolph, & Crunelli, 2007). Also, miniature excitatory postsynaptic potentials, occurring during SWS as residual synaptic activity in neocortical networks used for information encoding during prior waking, have been proposed as a mechanism launching a depolarizing up-phase out of the global deactivation present during the down-state (Bazhenov et al., 2002). Within the neocortex, slow oscillations appear to originate preferentially from layer 5 neurons. However, human data suggest any layer could initiate firing at up-state onset (Csercsa, et al., 2010). Mostly, slow oscillations arise from anterior prefrontal cortex where they also show maximum amplitudes (Massimini et al., 2004; Murphy et al., 2009). It has been shown that the slow oscillation amplitude during SWS is higher the stronger the underlying cortical network was engaged in encoding during prior waking, indicating a direct dependence on prior learning (Huber, Ghilardi, Massimini, & Tononi, 2004; Mölle, Marshall, Gais, & Born, 2004).

Oscillating transcranial direct current stimulation (tDCS) allows for studying of the impact of EEG oscillations on sleep-dependent memory processing by manipulating the EEG. The approach allows one to stimulate the brain with a desired frequency and even to entrain neuronal firing to a certain firing frequency (Frohlich & McCormick, 2010; Ozen et al., 2010). Oscillating tDCS has been employed in humans to directly prove that slow oscillations are causal to the enhancing effect of sleep on memory consolidation. Two studies applied tDCS to the prefrontal cortex during the first 25–30 minutes of nocturnal NREM sleep. One use stimulation oscillating at the 0.75 Hz slow oscillation frequency; the other study used very slowly alternating 30 s on/30 s off stimulation (Marshall, Helgadottir, Mölle, & Born, 2006; Marshall, Mölle, Hallschmid, & Born, 2004). In both cases, stimulation produced an immediate increase of slow wave activity when compared to sham. The 0.75 Hz stimulation especially

increased power in the <1 Hz slow oscillatory band, as measured during 1-minute breaks positioned between the 5-minute intervals of stimulation. tDCS-induced slow oscillation activity was associated with a significantly enhanced frontal slow spindle activity (10–12 Hz). Importantly, after sleep with tDCS, compared with sham stimulation, the participants showed an improved recall of declarative memories (lists of word pairs) they had learned before sleep. There was, however, no significant difference between tDCS and sham conditions in the sleep-associated improvement in procedural finger sequence tapping performance. If tDCS oscillating at 0.75 Hz was applied in the same way, but during the late half of nocturnal sleep, when REM sleep predominates, it did not produce any clear changes in slow wave activity and also did not improve memory performance.

It was further shown that the beneficial effect of tDCS during the SWS-rich beginning of nocturnal sleep critically depends on the stimulation frequency. tDCS oscillating at a faster rate of 5 Hz (in the theta range), instead of the 0.75 Hz rate, strongly suppressed endogenous slow oscillatory activity (Marshall, Kirov, Brade, Mölle, & Born, 2011). Slow frontal spindle activity was also suppressed, and the retention of learned word pairs was significantly impaired by this theta stimulation. Interestingly, applying tDCS oscillating at the 0.75-Hz slow oscillation frequency during wakefulness, when the brain is not prone to produce large amounts of endogenous slow wave activity, only induced very limited amounts of slow oscillations that were limited to areas close to the prefrontal sites of stimulation (Kirov, Weiss, Siebner, Born, & Marshall, 2009). Instead, that same stimulation that greatly increased slow oscillatory activity during NREM sleep boosted EEG theta activity (4–8 Hz) when applied during wakefulness. Consequently, the stimulation did not increase the consolidation of declarative memory (for word pairs), but actually improved encoding of such memories, as reflected by the improved immediate recall of word lists during acute stimulation. Overall these results suggest that the cortical networks that produce theta during explicit encoding of declarative memory in the wake period are functionally coupled to the slow oscillation producing networks that accomplish memory consolidation during subsequent sleep.

Overall, these data strongly suggest a causal role of the neocortical slow oscillation for the consolidation of hippocampus-dependent declarative memories. Of note, the estimated field potentials induced by the tDCS in these studies in the underlying cortical tissue are approximately the same size as those that occur naturally during SWS. Hence, these data suggest that the impact of slow oscillations on memory processing is not

only mediated via the underlying synchronization of neuronal firing activity. Rather the potential fields accompanying the synchronized changes in membrane potential during natural slow oscillations in themselves contribute to the effect on memory processing (Frohlich & McCormick, 2010; Ozen et al., 2010).

Slow Oscillations Setting a Time Frame for Hippocampal-Neocortical Communication

Although tDCS studies revealed a causative contribution of slow oscillations to the consolidation of hippocampus-dependent memories during sleep, these studies provided little insight into the mechanisms that could mediate this consolidation process. Apart from the neocortical slow oscillation rhythm, two other rhythms, i.e., spindles activity arising from thalamic networks as well as sharp-wave ripples arising from hippocampal rhythms, have been implicated in memory processing. In this section, we will first summarize evidence that slow oscillations provide a *top-down* signal synchronizing the occurrence of spindles and ripples to the depolarizing up-phase of the slow oscillation. We will then discuss data suggesting that so called spindle-ripple events, as a result of the synchronizing influence of the slow oscillation, might be a mechanism that serves the effective *bottom-up* transfer of memory information reactivated during hippocampal ripples, from hippocampal to neocortical sites.

Slow oscillation-spindle interactions. Spindle activity in the human EEG is referred to as ongoing oscillatory activity in the ~12–15 Hz frequency band with a maximum over central and parietal cortical areas. In NREM sleep stage 2 this activity is expressed in discrete spindles with waxing and waning oscillations. SWS also contains this activity especially in the beginning of the night, however, activity is lower and forms less clearly discrete spindles (De Gennaro & Ferrara, 2003; Marshall, Mölle, & Born, 2003). Spindle activity originates in the thalamus from an interaction of pacemaking GABAergic neurons of the nucleus reticularis with glutamatergic thalamocortical projections, which mediate the synchronized and widespread propagation of spindles to cortical regions (Contreras, Destexhe, Sejnowski, & Steriade, 1996; De Gennaro & Ferrara, 2003; Marshall et al., 2003). Spindle activity within the neocortical networks is probably associated with strong calcium influx into neocortical pyramidal cells, which may facilitate plasticity through calcium-dependent signaling cascades (Contreras, Destexhe, & Steriade, 1997; Sejnowski & Destexhe, 2000). Spindles occur preferentially at synapses that were potentiated during encoding of information (Werk,

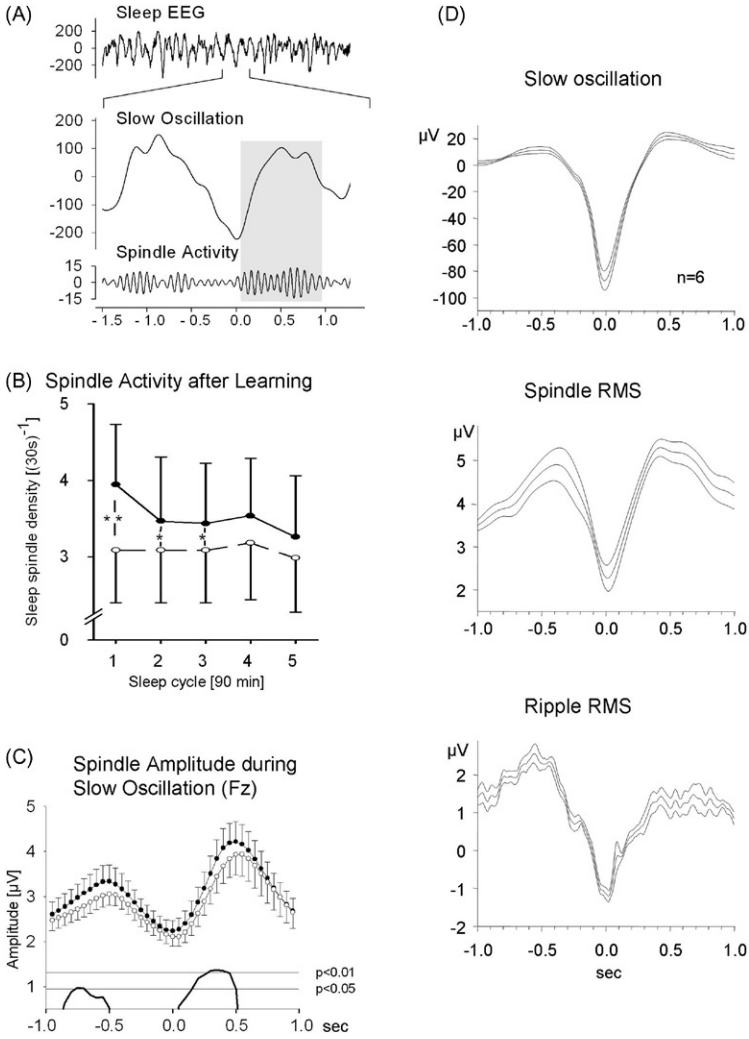


Figure 9.3 ***The slow oscillation up-phase driving spindle and ripple activity.*** (**A**) EEG recording during SWS (top panel), enlarged and filtered in the slow oscillation band (middle) and spindle band (bottom panel), respectively. Whereas spindle activity is suppressed during the hyperpolarizing slow oscillation down-phase, it is distinctly increased during the succeeding depolarizing up-state (gray box). (**B**) Spindle density during sleep after intense declarative learning (word pairs) and a nonlearning control condition. The mean (±SEM) number of sleep spindles (per 30-sec epoch of EEG-recording) during subsequent 90-min periods of a whole night of sleep is indicated. Note the distinct increase in spindle density during the first three 90-min periods in the learning condition. ** $p < .01$, * $p < .05$. (**C**) Amplitude of spindle activity during sleep slow oscillations after intense declarative learning (word pairs, filled circles) and a nonlearning control condition (empty circles). Averages (±SEM) time-locked to the negative half-wave of identified slow oscillations are indicated. Bottom lines indicate

Harbour, & Chapman, 2005). The participation of spindle activity in memory processing during sleep is indeed well established. Studies in both rats and humans have very consistently revealed increases in spindle density and activity during NREM sleep and SWS provoked by prior learning (e.g., Eschenko, Mölle, Born, & Sara, 2006; Fogel & Smith, 2006; Gais, Mölle, Helms, & Born, 2002; Morin et al., 2008; Schabus et al., 2004; Tamaki, Matsuoka, Nittono, & Hori, 2009). This increase, which in some cases is correlated to overnight gains in performance, is observed after both acquisition of declarative information and of procedural motor skills in humans (Clemens, Fabo, & Halasz, 2005, 2006; Nishida & Walker, 2007; Schabus et al., 2004; Tamaki et al., 2009). In some studies, the increase was found above cortical areas that were most strongly involved during encoding (Clemens et al., 2005, 2006; Nishida & Walker, 2007; Tamaki et al., 2009).

Steriade's group was not only the first to provide a thorough characterization of slow oscillations in cats but also the first to demonstrate that slow oscillations have a grouping influence on thalamocortical spindles as well as on neocortical fast oscillatory activity in the gamma frequency (20–60 Hz). During the depolarizing phase of the slow oscillations, the power of these rhythms is increased, whereas during the hyperpolarizing phase these rhythms are suppressed (Steriade, 1999, 2006; Steriade & Amzica, 1998). This synchronizing influence of slow oscillations on spindles was subsequently confirmed in the human EEG (Mölle, Bergmann, Marshall, & Born, 2011; Mölle, Eschenko, Gais, Sara, & Born, 2009; Mölle, Marshall, Gais, & Born, 2002; Mölle et al., 2004). The negative directed hyperpolarizing half-wave of the slow oscillations is associated with a distinct suppression of 12–15 Hz spindle activity, which is followed by rebound activity during the positive depolarizing half-wave (Fig. 9.3). This temporal relationship is also true for discrete spindles identified during NREM sleep stage 2 and SWS, as they

Figure 9.3 (*Continued*)
significance for pairwise comparisons of the learning and nonlearning conditions. Note the significant increase in spindle amplitude after learning that is restricted to the depolarizing up-phase of the slow oscillation. (**D**) EEG slow oscillation (upper panel) and associated spindle root mean square (RMS) and ripple RMS activity (middle and bottom panel, respectively). Averages (±SEM) are indicated, time-locked to the negative half-wave of the slow oscillation (0 sec). Slow oscillations and spindles were recorded from frontal electrode sites, ripples from intracranial parahippocampal sites. Recordings are from epileptic patients. Note that ripple RMS activity in parallel with spindle activity is decreased during the hyperpolarizing down-state of the slow oscillation and rebounds during the successive depolarizing up-state. *Data for A–C are from Gais et al. (2002). Data for D are from Clemens et al. (2007).*

preferentially occur during the depolarizing up-phase of the slow oscillations. A parallel but weaker modulation can be observed in the faster beta band and gamma rhythms (Compte et al., 2008; Csercsa et al., 2010).

In light of the strong grouping effect slow oscillations exert on spindle activity, the question arises whether increase in spindle activity that is induced by prior learning can be found, especially in the up-phase of slow oscillations. Indeed, not only is the learning-related increase in spindle activity concentrated on the depolarizing up-phase, but also learning induces an increase in the slow oscillation amplitude itself. In a comparative study in humans and rats Mölle et al. (2009) investigated the effects of learning of hippocampus-dependent materials (word pairs, odor-reward associations) on subsequent sleep slow oscillations and associated spindle activity. Compared with a nonlearning control condition, learning induced a distinct increase in 12–15 Hz spindle activity, and, as predicted, this increase in activity was clearly focused on the depolarizing up-phase of the slow oscillation. No significant changes occurred during the hyperpolarizing down-state. The effect did not occur after learning of odor-reward associations in rats, which probably reflects that this task does not essentially rely on the recruitment of thalamocortical circuitry. Prior learning also altered the slow oscillation in humans such that the up-state was more pronounced and the negative half-wave was sharpened. Consistent with these findings, another study revealed that intense prior learning of word pairs produced a distinct increase in EEG coherence between different cortical regions during the slow oscillation up-states of subsequent SWS in both the slow spindle frequency and the slow oscillation bands (Mölle et al., 2004). A joint increase in slow oscillation amplitude and local fast spindle activity was similarly observed during sleep after subjects had trained on a visuomotor rotation adaptation task (Huber et al., 2004). The increase in slow oscillation activity was most pronounced for the neocortical area, which was most strongly involved in training the task and was correlated with the skill performance after sleep. Overall, these findings support the notion that encoding of information during learning has an increasing effect on sleep spindles and slow oscillations and that this happens in a temporally coordinated fashion, such that the slow oscillation exerts a top-down control bundling learning-dependent increases of spindle activity into their depolarizing up-states.

Importantly, evidence is growing for the existence of two kinds of spindles that may differ in function with regard to memory processing, i.e., the classical fast spindles that show a peak frequency of 12–15 Hz and are

more widely distributed with maximum amplitudes over central and parietal cortical areas, and the slow spindles that are focused topographically over the frontal cortex areas and peak at about 8–12 Hz (Anderer et al., 2001; De Gennaro & Ferrara, 2003; Terrier & Gottesmann, 1978). Slow spindles are predominantly found during SWS, setting them apart from fast spindles that are usually present during NREM sleep stage 2, on average even more prominently so than during SWS. Fine-grained analyses of temporal relationships revealed a strikingly different occurrence of fast and slow spindles during the slow oscillation cycle: whereas fast spindles are closely associated with the depolarizing down-to-up transition, slow spindles occur mainly in association to the fading depolarization, i.e., at the transition to the down-state (Mölle et al., 2011).

This differential coupling to slow oscillations indicates that the widely held view of emergent slow oscillation depolarization driving the thalamic generation of spindles (Contreras & Steriade, 1995; Destexhe, 1999; Steriade, 2006; Timofeev & Bazhenov, 2005) holds true for the classical fast spindles only, but not for slow frontal spindles occurring when depolarization is already waning. Although thalamic contributions cannot be excluded (Schabus et al., 2007), slow spindles, unlike fast spindles, may be of mainly cortical origin, as a product of preceding peak network depolarization that was reached during the slow oscillation up-state. Fitting this view, blocking of Na^+ channels by administration of carbamazepine enhanced slow frontal spindle activity conjointly with slow oscillation power (Ayoub, Hörschelmann, Born, & Marshall, 2012 submitted). Contrary to slow spindles, fast centroparietal spindles were decreased by carbamazepine. It has been proposed in this context that slow frontal spindles might functionally be associated with corticocortical coupling whereas fast centroparietal spindles reflect activity in thalamocortical loops (Doran, 2003).

A look at trains of several succeeding slow oscillations admitted deeper insights into the finely tuned relationships between slow oscillations and spindles (Mölle et al., 2011). Indeed, slow spindles tend to follow fast spindles with a delay of approximately 500 ms in the depolarizing up-phase. Moreover, these analyses suggested that the fast centroparietal spindles are not only driven by the depolarizing slow oscillation up-phase but in fact exert themselves an increasing influence on succeeding slow oscillations and thus the likelihood of frontal spindles. Importantly, this dynamic was markedly increased if the participants had learned before sleep a lengthy list of word pairs. In detail, prior learning in this study not only increased fast spindles together with the occurrence of trains of slow oscillations, but

in particular increased the fast spindle activity during the initial slow oscillation of such a train. Slow spindle activity on the other hand was increased less clearly and such increases were found mainly at the end of the trains.

Thus the fast spindle seems to receive a pivotal role in launching and maintaining sleep-dependent memory processing, as prior learning increased slow oscillation train length in combination with a spindle increase during the first up-phase of this train. There may be a loop-like process at work, where the fast spindle, e.g., by way of promoting Ca^{2+}-influx into cortical pyramidal cells (Sejnowski & Destexhe, 2000), enhances the likelihood and amplitude of the next slow oscillation and in turn the development of slow frontal spindles during the waning depolarizing phase of these slow oscillations. The next emergent slow oscillation up-state exerts an even stronger drive on fast spindle generation. However, refractoriness induces a gradual decrease of fast spindle amplitude along the train of slow oscillations (Luthi & McCormick, 1998). The driving force of fast spindles on the generation of the slow oscillation-spindle cycles is increased by prior learning. This view that fast spindles serve a priming role in the process of sleep-dependent memory processing remains in line with the numerous findings that learning induces a robust increase of fast spindles also during NREM sleep stage 2 (e.g., Clemens et al., 2005; Gais et al., 2002; B. Rasch, Pommer, Diekelmann, & Born, 2009; Schabus et al., 2004), in which by definition slow wave activity is distinctly diminished, if one assumes that, on a larger time scale, the generally high amounts of spindles during NREM support the generation of slow oscillations during subsequent periods of SWS.

Slow oscillation-ripple interaction. As detailed above, memory processing during sleep is believed to rely on the basic mechanism of reactivation of neuronal firing patterns, which are associated with encoding during prior wakefulness. Reactivations occur mostly in association with sharp wave-ripples in hippocampal networks (Diba & Buzsaki, 2007; O'Neill et al., 2010; Wilson & McNaughton, 1994). Ripples are bursts of high frequency oscillations around 180 Hz that originate in the CA1 region of the hippocampus (Csicsvari, Hirase, Czurko, Mamiya, & Buzsaki, 1999) and occur in association with sharp waves emerging from the CA3 region (Buzsaki, 1986; Buzsaki, Horvath, Urioste, Hetke, & Wise, 1992). Compared with rats, human hippocampal ripples are of somewhat lower frequency (80–140 Hz). Importantly, there is evidence that both reactivated neuronal firing patterns in the hippocampal CA1 region as well as ripples are entrained to the slow oscillation up-states (Battaglia, Sutherland, & McNaughton, 2004; Ji & Wilson, 2007; Mölle, Yeshenko, Marshall, Sara, & Born, 2006; Peyrache, et al.

2009; Sirota, Csicsvari, Buhl, & Buzsaki, 2003), although the exact timing of ripples during the slow oscillation cycle depends also on the hippocampal region examined as well as on the method of recording (O'Neill et al., 2010; Sirota & Buzsaki, 2005). The hippocampus itself does not generate slow oscillations but is reached by neocortical slow oscillations with a slight delay of about 50 ms (Isomura et al., 2006; Sirota et al., 2003; Wolansky, Clement, Peters, Palczak, & Dickson, 2006). Peyrache et al. (2009) reported an entrainment to the slow oscillation up-state of hippocampal sharp wave-ripples that occurred in conjunction with assembly reactivations in medial prefrontal cortex during SWS after learning a rule shifting task. Importantly, the synchronizing influence of the slow oscillation on hippocampal ripple activity was confirmed also in human studies with epileptic patients, where in intracranial recordings from parahippocampal electrodes, sharp wave-ripple activity was clearly time locked to the depolarizing up-phase of the neocortical slow oscillation (Clemens et al., 2007; Fig. 9.3D).

Recent studies have compellingly demonstrated the involvement of hippocampal ripples in memory processing. In rats, training of an odor-reward association task was followed by a robust increase of ripple number during the first hour of subsiding SWS, and during the first 2 hours of SWS after learning ripple magnitude remained increased (Eschenko, Ramadan, Mölle, Born, & Sara, 2008). Similarly, in epileptic patients the number of ripples detected in the rhinal cortex was correlated with the consolidation of picture stimuli acquired before a nap (Axmacher, Elger, & Fell, 2008). Two studies in rats pointed towards a causal role of hippocampal ripples for sleep-dependent memory consolidation (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). They showed that selective electrical disruption of local hippocampal ripples during the rest periods after learning corrupted the later performance on the spatial learning task. Whether such increases in the expression of ripples during SWS after learning per se concentrate on the intervals of the slow oscillation up-state periods has not been thoroughly studied so far. Such modulation of ripples might occur only in tasks heavily involving prefrontal-hippocampal circuitry during encoding (Benchenane et al., 2010; Mölle et al., 2009; Peyrache et al., 2009).

Spindle-Ripple Events Supporting Bottom-up Transfer of Memory Information

The joint synchronization of hippocampal sharp wave-ripple generation and the generation of spindles in the thalamus by slow oscillations has been proposed to support the formation of so called spindle-ripple events

where ripples and associated reactivated hippocampal memory information becomes fed into the excitatory cycles of the spindle oscillation (Clemens et al., 2011; Mölle & Born, 2009; Siapas & Wilson, 1998; Sirota et al., 2003). Spindle-ripple events may thus represent a mechanism that effectively mediates the transfer of memory information from the hippocampus to the neocortex in a temporally fine-tuned manner, and may also prime the integration of this information within neocortical networks. In fact, there is an early demonstration of a weak albeit highly significant temporal association between hippocampal ripples and thalamocortical spindles in rats that was also reflected in the correlated activity of single neurons in these networks (Siapas & Wilson, 1998). In mice a robust temporal correlation between spindles recorded at somatosensory cortical sites and hippocampal ripples is evident (Sirota et al., 2003). These studies showed that the synchronous cortical unit discharge associated with spindles can increase firing in hippocampal neurons within ~50 ms. Because this increase in hippocampal activity was often related to the occurrence of a sharp wave-ripple, the authors concluded that spindle-associated discharges can promote hippocampal ripples and thus reactivation of memories (Sirota & Buzsaki, 2005; Sirota et al., 2003).

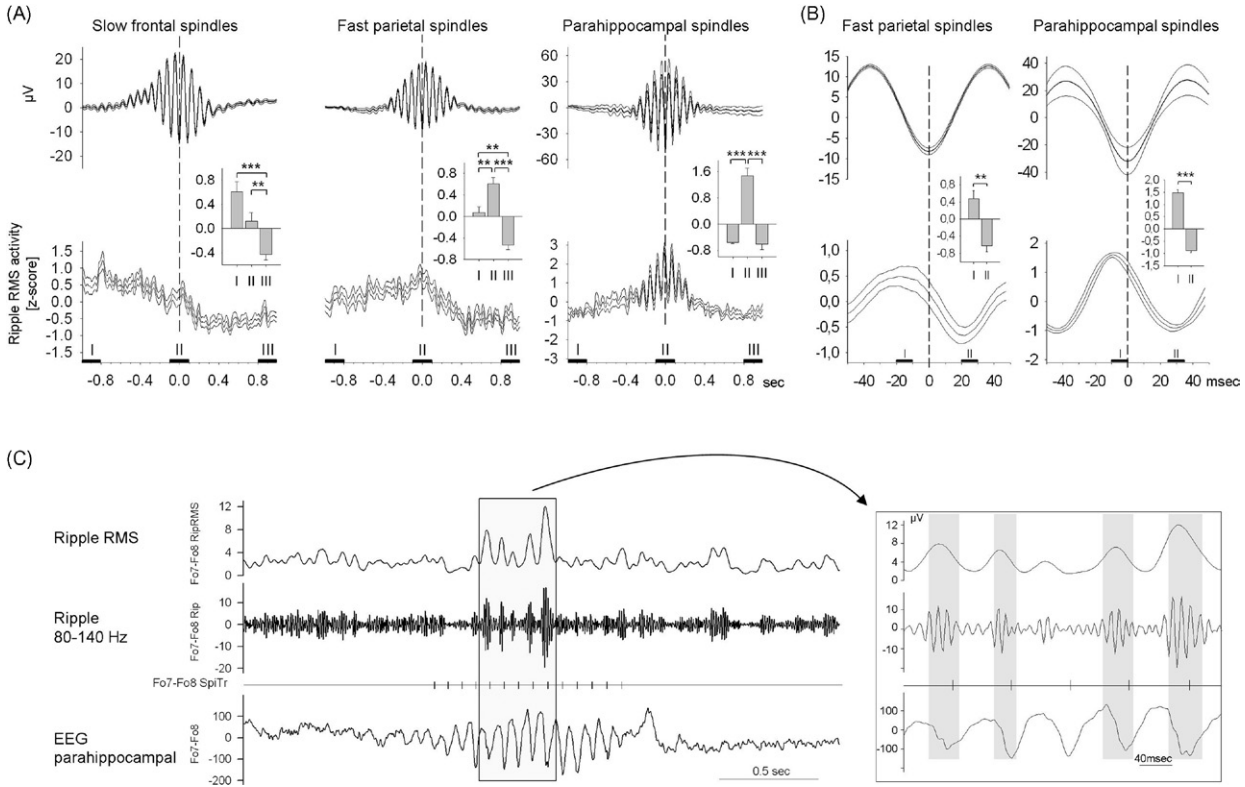
There is, however, also the possibility of a reverse effect in spindle-ripple events. In CA1 neurons and downstream in subicular and entorhinal neurons ripple-associated synchronous discharges provide a most effective output to the neocortex (Chrobak & Buzsaki, 1994). There exists a nonlinear relationship between the magnitude of hippocampal ripple bursts and spindle-like prefrontal cortical neuronal responses (Wierzynski, Lubenov, Gu, & Siapas, 2009). Smaller ripple bursts only lead to a single peaked, short latency cortical firing response, but larger bursts could issue an additional peak occurring 100 ms later, thus mimicking a spindle cycle. This observation suggests a promoting influence of ripple discharge on activity in the spindle range, if corticothalamic networks are sufficiently excited. A bottom-up influence of sharp wave-ripples on thalamic generation of spindle activity was likewise revealed by event-correlation histograms of data from intracranial recordings in epileptic patients, indicating that neocortical spindles are preceded by an increase in ripple activity recorded from parahippocampal sites (Clemens et al., 2007).

Again learning prior to sleep seems to be a relevant factor in the temporal relationship between spindles and hippocampal ripples during SWS. Like in epileptic patients, studies in rats on the cooccurrence of spindle and ripple activity during time intervals of several seconds revealed that spindle activity was distinctly increased in the presence of hippocampal ripples, with these

increases starting on average about 200 ms before the onset of a ripple (Mölle et al., 2009). Of note, such increases in spindle activity persisted for up to 1 second, i.e., long after the end of the ripple, and this enhancement was further prolonged to up to 2 seconds, if the rats had learned an odor-reward association task before sleep. Taken together, these data suggest a loop-like scenario, where emergent thalamocortical spindle activity and associated neocortical firing drives ripple activity and subsequent neuronal discharge in the CA1 output region of the hippocampus, which themselves feedback positively onto the generating mechanism of spindle activity. This feedback mechanism of spindles is possibly facilitated through generation of ripples in select hippocampal circuitry that was potentiated during prior learning.

Ripples in this model provide the memory reactivations and feed exactly into the excitatory phases of the spindle cycle to be transferred to neocortical sites. This view is substantially backed by two recent studies in humans (Bergmann, Mölle, Diedrichs, Born, & Siebner, 2011 in revision; Clemens et al., 2011). Using functional magnetic resonance imaging, Bergmann et al. provided evidence that spindles cooccur with reactivation of memory representations in hippocampal networks and, conjointly, also in cortical networks. Clemens, Mölle, et al. (2011) recorded spindles from neocortical sites (frontal and parietal) together with activity from intracranial parahippocampal sites in epileptic patients. In fact, spindles observed at parahippocampal sites were closely synchronized with parietal spindles. Averaging of ripple activity time locked to the maximum (trough) of a spindle indeed revealed that this activity becomes nested into the single spindle troughs. This holds for the hippocampal spindles and to a lesser degree for the parietal spindles (Fig. 9.4A). In both spindle types the peak of ripple activity was reached ~10 ms before the troughs (Fig. 9.4B) and was very consistent within the patient population and further is remarkably similar to the lag found in rodents (Sirota et al., 2003). There was no such effect for the slower frontal spindles, which underlines their distinct functionality.

A recent magnetencephalographic study showed that there is a phase-amplitude coupling not only between spindles and ripples, but also between (fast) spindles and neocortical gamma band activity between 30–80 Hz (Ayoub, Mölle, Preissl, & Born, 2011). The phase-locked generation of local gamma oscillations is presumably mediated by spindle associated thalamocortical inputs to inhibitory fast spiking neurons known to exert a common regulatory influence on both rhythms (Bartos, Vida, & Jonas, 2007; Gibson, Beierlein, & Connors, 1999; Peyrache, Battaglia, & Destexhe, 2011; Puig, Ushimaru, & Kawaguchi, 2008). Gamma band activity is a marker of ongoing


(A)
Slow frontal spindles
Fast parietal spindles
Parahippocampal spindles
μV
Ripple RMS activity [z-score]
sec
(B)
Fast parietal spindles
Parahippocampal spindles
msec
(C)
Ripple RMS
Ripple 80-140 Hz
EEG parahippocampal
Fo7-Fo8 RipRMS
Fo7-Fo8 Rip
Fo7-Fo8 SpiTr
Fo7-Fo8
0.5 sec
40msec

coherent information processing in local neocortical networks, and is associated also with network synaptic potentiation (Bikbaev & Manahan-Vaughan, 2008; Fries, Nikolic, & Singer, 2007). Thus, gamma power fluctuating in the rhythm of spindles nicely fits the view that spindles provide a fine-tuned time frame for the integration of hippocampal memory information within neocortical networks. Spindles arriving at neocortical sites may act by priming the respective networks, for example by inducing Ca^{2+}-influx, which is an important agent for subsequent plastic processes. This in turn would render ripples in hippocampal networks and gamma activity in local neocortical networks carrying the incoming information in the troughs of spindles to be most efficient in producing adaptive plastic changes of memories in the long-term store of the neocortical network. Consistent with this concept, spindle-associated spike discharge has been demonstrated to efficiently trigger long-term potentiation in neocortical networks (Rosanova & Ulrich, 2005; Timofeev et al., 2002). Inasmuch as spindles are able to synchronize gamma band activity between distant cortical locations, they may also contribute to linking quite distributed cortical aspects of the cortical representation.

To sum up, the close temporal relationship between spindles and ripples that provoke the term spindle-ripple event could well account for a basic mechanism of bottom-up information transfer between the hippocampus

◀ **Figure 9.4** ***Relationship between spindles and ripples in recordings from epileptic patients.*** (**A**) Upper panels show spindle recorded over frontal (left) and parietal (middle) cortical sites, and from intracranial parahippocampal sites (right), averaged time-locked to the maximum trough of a spindle. Lower panels show the associated root mean square (RMS) ripple activity recorded from parahippocampal sites. Means (±SEM) are indicated. Inserted bar plots indicate means of ripple RMS activity during the three marked 200 ms epochs at the beginning, the middle, and the end of the ±1 sec interval surrounding the spindle maximum, which were used for inference statistics of ripple RMS activity. ** $p < .01$, *** $p < .001$. Note the increase in ripple activity around the maximum of parietal and parahippocampal spindles, but not around the maximum of frontal spindles. (**B**) Finer grained analysis of temporal relationship between parahippocampal ripple RMS activity (lower panel) and parietal (left) and parahippocampal (right) spindle oscillations, both averaged time-locked to the troughs of a spindle (0 sec). Means (±SEM) for z-transformed values are indicated. Bar plots provide means of 10 ms intervals used for inference statistics. ** $p < .01$, *** $p < .001$. Note the strongly increased ripple activity shortly before the peak of a spindle trough indicating that ripples become nested into spindle troughs thus forming spindle-ripple events. (**C**) Example of recording (from parahippocampal sites) used for analysis of spindle-ripple events (box—enlarged to the right), ripples are nested in the troughs of the parahippocampal spindles. Upper trace—ripple RMS recording site, middle—EEG filtered between 80–140 Hz, bottom—original EEG recording. *Adapted from Clemens et al. (2010).*

and the neocortex (Marshall & Born, 2007; Fig. 9.5). So, to the degree that the hippocampal output during ripples originates in reactivation of memory, the nesting of hippocampal ripples in succeeding troughs of a spindle, together with a similar phase-amplitude coupling of neocortical

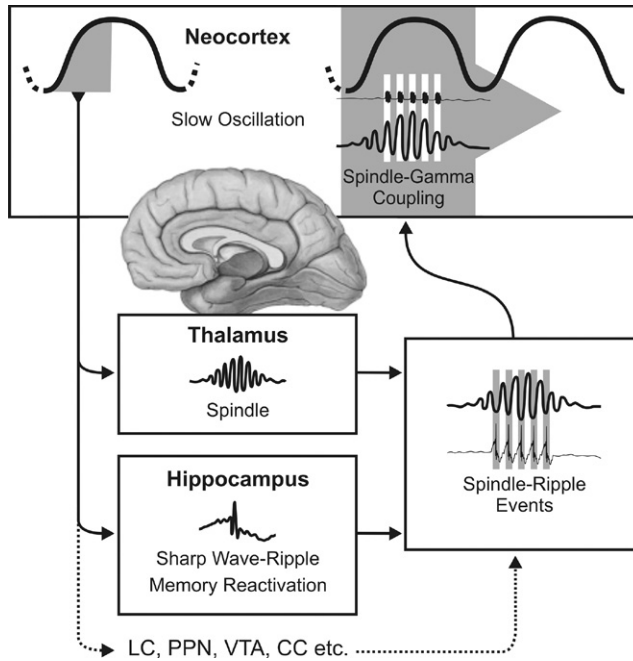


Figure 9.5 ***EEG rhythms involved in system consolidation during slow wave sleep (SWS).*** Slow oscillations (<1 Hz) mainly originating in the prefrontal cortex and spreading through the whole neocortex and brain issue a top-down control with the depolarizing up-phases of these oscillations driving fast (12–15 Hz) spindles originating in the thalamus and sharp wave-ripples that carry reactivated memory information from the hippocampus, as well as activity of other subcortical regions possibly involved in this process, e.g., locus coeruleus (LC), pedunculopontine nucleus (PPN), ventral tegmental area (VTA), and cerebellar cortex (CC). The concurrent drive enables the formation of spindle-ripple events where ripples and associated memory information are nested in the succeeding troughs of a spindle. Spindle-ripple events serve the bottom-up transport and integration of reactivated memory information into neocortical networks. They reach the cortex in a time-locked manner still during the depolarizing up-state of the slow oscillation when neocortical excitability is enhanced and induction of plastic synaptic processes may be facilitated. In fact, not only hippocampal ripple activity but also neocortical gamma band power shows a phase-coupling to spindle oscillations, suggesting that spindles exert a coherent regulatory influence on the processing of memory information allowing—during the phase of enhanced excitability of the spindle cycle—for the binding of information between distributed neocortical networks. In addition, spindle activity in a feed forward manner favors the occurrence of another slow oscillation cycle and thereby contributes to the perpetuation of memory processing.

gamma band activity to spindles, may also serve the integration of the reactivated memory information in distributed neocortical representations. Importantly, such spindle-ripple events are formed under top-down control of the neocortical slow oscillation. Thus, the driving force of the depolarizing up-state of these slow oscillations enables that the reactivated memory representation, enwrapped in these spindle-ripple events, arrives at the neocortical networks still during the slow oscillation up-state, i.e., a period of facilitated neocortical excitability.

Synaptic Homeostasis

A different theory does not consider memory consolidation during sleep an active process, but focuses on the homeostatic regulation of synaptic strength (Tononi & Cirelli, 2003, 2006). According to this theory the uptake of information and potentiation of involved synapses during the daytime wake period leads to an increase of net strength of synaptic connections in neocortical networks. Processes during sleep allow for global downscaling of synaptic strength to a sustainable level, in terms of energy consumption, tissue volume demands, and future capacity of potentiation for encoding (Cirelli & Tononi, 2000; Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008). It is assumed that slow oscillations play a critical role in downscaling. They show their maximum amplitudes at the beginning of the night, when synapses are most potentiated, due to encoding of information during prior wakefulness, and reduce their amplitude as a function of synaptic downscaling in subsequent sleep cycles. Memories are thought to be strengthened because they benefit from an improved signal-to-noise-ratio, as downscaling is thought to be linear and affect weak synapses to the same degree as strong synapses, thereby eliminating the weak ones and associated noise, and ameliorating information processing in networks with strong synapses (Tononi & Cirelli, 2006).

Although there is compelling evidence for synaptic downscaling to occur during sleep at a global scale, a mechanism of how slow oscillations induce synaptic downscaling remains elusive. The sequence of depolarization and hyperpolarization of slow oscillations may promote synaptic depression (N. Kemp & Bashir, 2001). While long-term depression is in fact favored over long-term potentiation by slow oscillations and associated activity of T-type Ca^{2+}-channels (Czarnecki, Birtoli, & Ulrich, 2007), thalamocortical spindles and hippocampal ripples that are time-locked to slow oscillations are associated to long-term potentiation (Buzsaki, Haas, & Anderson, 1987; King, Henze, Leinekugel, & Buzsaki, 1999; Rosanova & Ulrich, 2005). Moreover, synaptic long-term depression, though mediating

a depotentiation, may be more linked to specific learning rather than to unspecific desaturating processes globally affecting the entire neocortical network (Kemp & Manahan-Vaughan, 2007; Tsanov & Manahan-Vaughan, 2008). Also, the assumption that memory enhancement during sleep occurs on the basis of a linear influence of downscaling is difficult to reconcile with findings indicating that the slow oscillations mediating downscaling are not only highest in amplitude over the regions most closely involved in learning of a skill but also that this amplitude increase is correlated with the memory enhancement across sleep (Huber et al., 2004). Also, against the conclusion that synaptic downscaling benefits strong memory representations over weak ones, empirically, sleep benefits either both weak and strong traces to the same degree or even, under certain conditions, favors weak memory traces (Drosopoulos et al., 2007; Kuriyama et al., 2004).

Nevertheless, a desaturating of the effect of sleep slow oscillations, freeing the capacity of synaptic networks for encoding of new information, has also been demonstrated in human subjects. Inducing slow oscillations during a nap by transcranial direct current stimulating (oscillating at 0.75 Hz) in healthy young volunteers significantly improved subsequent encoding of a large amount of word pairs and picture stimuli (landscapes and houses) in these subjects, in comparison with a sham control condition, and this effect was not due to unspecific improvements in vigilance at post-sleep encoding (Antonenko, Diekelmann, Olsen, Born, & Mölle, 2011 submitted). Results of this study complement those of a previous study indicating that the explicit (i.e., hippocampus-dependent) encoding of similar materials was deteriorated after slow wave activity had been suppressed by auditory stimulation during a prior nap (Van Der Werf et al., 2009). Interestingly, in this study impaired encoding after suppression of slow wave activity was associated with reduced activation specifically in the hippocampus, i.e., a region that is not capable for generating slow oscillations itself (Isomura et al., 2006), rather than in the neocortex.

Given the positive evidence for synaptic downscaling the theory might be simply combined with that of active system consolidation, with the former acting nonspecifically at the global level to desaturate networks but sparing local networks in which select memories are actively consolidated. Accordingly, although markers for synaptic potentiation are globally reduced after a period of sleep, they are increased locally, especially if sleep was preceded by learning (Ribeiro et al., 2004; Ribeiro, Goyal, Mello, & Pavlides, 1999; Ribeiro et al., 2007), which indicates synaptic potentiation is possible during sleep. Further evidence for the cooperation of both processes during

sleep is provided by neuroimaging studies that show reduced task-related activity in cortical regions after sleep is accompanied by increased activity in other regions (Fischer, Nitschke, Melchert, Erdmann, & Born, 2005; Gais et al., 2007; Orban et al., 2006; Takashima et al., 2006). Such findings argue in favor of complimentary roles of downscaling for synaptic homeostasis in the memory system and active system consolidation for integration of freshly encoded traces into the memory system. To what extent these processes rely on directly interdependent mechanisms during sleep, particularly during the slow oscillations of SWS, is an issue of future research.

CONCLUDING REMARKS

Intense research in the last 20 years has confirmed that sleep plays a pivotal role for memory consolidation. However, we are only starting to understand the processes that are involved. Behavioral data indicate there are multiple variables that determine if a given memory gains access to sleep's strengthening power. Electrophysiological research both in humans and in animals points towards SWS as the key player in this process, which has been identified as a system consolidation process. Slow oscillations, spindles, and sharp wave-ripples coordinate reactivation and transfer of memory information from temporary to long-term stores that is thought to underlie the redistribution and qualitative reorganization of representations during SWS. Although this concept provides a promising approach to enlighten sleep's contribution to memory consolidation, a number of issues at the core of this concept remain to be solved. Thus, it will be interesting to understand how the brain translates information about relevance into an electrical code and how it is able to integrate old and new information into a unified representation and eventually into adaptive behavior.

Throughout this endeavor a role for REM sleep needs to be specified. Early research in this field indeed focused on REM sleep as the driving force in memory consolidation. However, recent studies indicated that sleep can stabilize and enhance memory regardless of whether REM sleep occurs or not (Diekelmann, Büchel, Born, & Rasch, 2011; Rasch et al., 2009). A "dual process" account on memory consolidation during sleep exists, which assumes that REM sleep profits procedural and emotional aspects of memory not essentially depending on hippocampal function whereas SWS enhances hippocampus-dependent declarative memories (Born, Rasch, & Gais, 2006; Plihal & Born, 1997). However, although this view may hold for emotional memory (Walker & van der Helm, 2009), its validity with

regard to procedural memories must be questioned in light of accumulating evidence also indicating the superior importance of NREM sleep for skill memories (e.g., Aeschbach, Cutler, & Ronda, 2008; Huber et al., 2004; B. Rasch et al., 2009). Considering these shortcomings of the dual process view, we have recently proposed a sequential hypothesis, following an idea by Antonio Giuditta (Diekelmann & Born, 2010; Giuditta, 1985). Based on the fact that in normal sleep REM sleep always follows SWS, the sequential model basically assumes that memory processing during sleep likewise follows a sequence in which REM sleep serves functions complementing those of SWS. Specifically, we proposed that during SWS memories are redistributed within the memory network through system consolidation and during REM sleep synaptic consolidation of the achieved new connections is accomplished (Diekelmann & Born, 2010; Giuditta, 1985). However, research elaborating on this hypothesis is still in its infancy (e.g., Ribeiro et al., 2007).

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