

Sleep for Preserving and Transforming Episodic Memory

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Abstract

Sleep is known to support memory consolidation. Here we review evidence for an active system consolidation occurring during sleep. At the beginning of this process is sleep's ability to preserve episodic experiences preferentially encoded in hippocampal networks. Repeated neuronal reactivation of these representations during slow-wave sleep transforms episodic representations into long-term memories, redistributes them toward extrahippocampal networks, and qualitatively changes them to decontextualized schema-like representations. Electroencephalographic (EEG) oscillations regulate the underlying communication: Hippocampal sharp-wave ripples coalescing with thalamic spindles mediate the bottom-up transfer of reactivated memory information to extrahippocampal regions. Neocortical slow oscillations exert a supraordinate top-down control to synchronize hippocampal reactivations of specific memories to their excitable up-phase, thus allowing plastic changes in extrahippocampal regions. We propose that reactivations during sleep are a general mechanism underlying the abstraction of temporally stable invariants from a flow of input that is solely structured in time, thus representing a basic mechanism of memory formation.

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INTRODUCTION

In our mind, the continuous flow of incoming information is organized into representations covering the dimensions of time and space. Memory refers to the maintenance of these representations, or parts of them, over time. The consolidation of memory denotes a hypothetical process that transforms newly encoded representations from an initially labile into a more stable form that allows individuals to use the acquired information for future behavior and plans (Müller & Pilzecker 1900, Dudai 2012). A fundamental issue of consolidation theory refers to the stability–plasticity dilemma:

With the accumulation of incoming information in a network of limited storage capacity, the storage of new information tends to overwrite older memories (Marr 1971, McClelland et al. 1995). How can the network keep stable older representations and, simultaneously, provide sufficient plasticity to incorporate new representations? As a solution, the standard consolidation theory proposes a two-stage memory system by which the flow of incoming information is acutely fed into a temporary store. From these temporarily stored memories, some information is selected to be gradually integrated with preexisting knowledge into a long-term store, thereby leaving these older memories intact. Once a representation has been redistributed to the long-term store, it is resistant to immediate interference from information continuously fed into the temporary store.

In the past two decades, major breakthroughs in memory research indicate that sleep plays a pivotal role in this consolidation process (Stickgold 2005, Diekelmann & Born 2010). Here, we do not comprehensively review the vast amount of studies on the link between memory and sleep but, instead, focus on evidence for a specific involvement of sleep in system consolidation. We argue, basically, that episodic memory during waking hours is continuously encoded into temporary representations and is transformed by neuronal reactivations during succeeding slow-wave sleep (SWS) such that only the gist of this information becomes integrated with preexisting memories without erasing them.

A CONCEPT OF MEMORY FORMATION IN THE ADULT BRAIN

Episodic memory combines in a unique personal experience what happened, where, and when: Specific to episodic memory is that upon its one-time occurrence, the experienced event (item) becomes bound to the particular spatial and temporal context in which it took place (Tulving 2002). The episodic memory concept arose from human research with particular

Consolidation:

transforms a temporary memory representation into a more persistent long-term representation; unlike encoding and retrieval, it occurs offline

SWS: slow-wave sleep

reference to autozoetic consciousness during recollection. Therefore, in animal studies, the term episodic-like memory is preferably used. In contrast with episodic memory, semantic memory stores knowledge about the world in the broadest sense in the absence of contextual information (e.g., objects, concepts, facts). Semantic memories can arise from the repeated encoding or activation of overlapping episodic memories.

What kind of memory is processed during sleep? Standard consolidation theory was proposed with reference to declarative memories whose retrieval is explicit (i.e., “conscious”) and initially relies on the hippocampus as a temporary store with fast encoding capabilities. Over time, system consolidation is assumed to stimulate a gradual redistribution of the representation to extrahippocampal, preferentially neocortical and striatal structures that are slower to encode and serve as long-term stores so that these memories eventually become independent of hippocampal circuitry (McClelland et al. 1995, Frankland & Bontempi 2005). Importantly, this theory assumes that the mechanism underlying consolidation is equivalent for the two subtypes of declarative memory, i.e., episodic and semantic memory. Standard consolidation theory has been challenged by evidence that some memories, particularly those with a strong autobiographical component, never become completely independent from hippocampal function (Nadel & Moscovitch 1997).

Unlike standard consolidation theory, the trace transformation theory (TTT) and its harbinger, i.e., the multiple trace theory, provide an account for the specific nature of episodic memory (Nadel & Moscovitch 1997, Winocur et al. 2010). These theories posit that initially the hippocampus rapidly and sparsely encodes key features of an experienced episode, whereby hippocampal neurons serve as an index for extrahippocampal circuits that encode semantic features of the episode. When these traces are later reactivated in an altered context, further new hippocampal traces are encoded, which in turn bind new traces in ex-

trahippocampal circuits. Consequently, based on invariant overlapping activation and statistical regularity, the gist from multiple episodes is extracted to form a semantic representation that is independent of any specific context. The TTT emphasizes the transformation that an episodic representation undergoes with repeated reactivations, resulting in abstract semantic and schema-like representations, as well as the dynamic interplay between episodic and semantic memories during the reactivation process. Importantly, if a memory is retained as a context-dependent episode, it will still require the hippocampus, but the hippocampus is basically dispensable when retrieving semantic memories. Which specific events are encoded into the hippocampal episodic memory system, as well as retrieval within this system, is essentially controlled by prefrontal cortical attention systems (Battaglia et al. 2011).

Although research has experimentally described the abstraction of semantic knowledge from episodic memories, mainly with reference to perceived stimulus categories and schemata, some of the mechanisms underlying this extraction process may likewise contribute to procedural skill learning. An increasing number of studies shows that in the adult brain, at least at an initial stage of training, the acquisition of sequenced motor skills recruits hippocampal circuitry, interacting with striatal and motor cortical areas (Schendan et al. 2003, Albouy et al. 2008, Henke 2010). The conscious practice of a motor skill represents an episode featuring the repeated activation of overlapping motor-related representations, which eventually helps to shape a dominant skill representation that enables high performance on motor routines independent of contextual stimuli and effector conditions. Motor skills can also be acquired, however, independent of the hippocampal system, although at a slower pace.

PROCESSING OF HIPPOCAMPAL MEMORY DURING SLEEP

Sleep has been known for a long time to support memory retention (Jenkins & Dallenbach

System

consolidation: entails the redistribution of the (hippocampal) representation toward different (extrahippocampal) neuronal networks and qualitative changes in memory content and is sleep-dependent

SO: slow oscillation

SW-R: sharp-wave ripples

Synaptic

consolidation:

stabilization of a representation by synaptic mechanisms whereby the representation remains in the same neuronal networks; it occurs during sleep and wakefulness

REM sleep: rapid eye movement sleep

1924, Stickgold 2005). Initial studies ascribe the effect to sleep's passive protection of newly encoded memories from retroactive interference, i.e., from being overwritten by new information, because the encoding of new information is obviously hampered during sleep (Ellenbogen et al. 2006). Robust evidence from recent research, however, supports an active role of sleep in memory consolidation, in addition to the protection from interference, which led us and others to posit an active system consolidation view of memory formation during sleep (Born et al. 2006, Diekelmann & Born 2010, Payne & Kensinger 2010, Lewis & Durrant 2011). This concept of a sleep-dependent active system consolidation process, which gradually integrates new memories relevant for an individual into preexisting knowledge networks, is basically rooted in the standard consolidation theory. Recent developments connect the active system consolidation view with the transformation of memory representations as proposed by the TTT.

Key to the active system consolidation view on memory processing during sleep are findings in rats of neuronal replay of activity occurring in hippocampal place cell assemblies during sleep, specifically during SWS (see **Figure 1** for the basic phenomenology of sleep), in the same temporal order as during the encoding phase before the sleep period (Wilson & McNaughton 1994, Skaggs & McNaughton 1996, O'Neill et al. 2010). The active system consolidation account proposes a dialogue between the hippocampus and extrahippocampal, mainly neocortical and striatal, networks that regulates the formation of long-term memory during waking and sleep (Buzsáki 1996, Diekelmann & Born 2010). During the wake phase, episodic information to be stored is initially encoded in both extrahippocampal and hippocampal networks; the hippocampal network encodes the binding aspects of the episodes, thus placing the experienced events into a spatiotemporal context. During subsequent periods of SWS, the newly encoded hippocampal representations are repeatedly reactivated. These reactivations transiently

strengthen the hippocampal episodic aspects of the representation, but they also, via efferent CA1 entorhinal pathways, simultaneously feed reactivated memory information from the hippocampus into neocortical and striatal networks. In these structures, the reactivations spreading from the hippocampus initiate plastic changes that mediate the formation of a transformed representation that preferentially resides in extrahippocampal networks and preserves the decontextualized gist of the episode. The communication between hippocampal and extrahippocampal circuitry is regulated by electroencephalographic (EEG) oscillations, primarily by the neocortical slow oscillations (SOs) that hallmark SWS and drive memory reactivations occurring conjointly with sharp-wave ripples (SW-R) in the hippocampus. As the SOs concurrently drive spindles originating from thalamocortical circuits, they allow spindle-ripple events to form as a mechanism that transfers reactivated hippocampal memory information to respective neocortical and striatal sites. The information arrives at these sites during the highly excitable SO up-state and, by triggering intracellular Ca^{2+} influx, can tag respective networks for long-term synaptic changes (Sejnowski & Destexhe 2000) (**Figure 2**). Whereas reactivations during SWS aid episodic memory transformation, synaptic consolidation processes occurring during subsequent REM sleep may help stabilize the newly transformed representation (Diekelmann & Born 2010); this idea derived from the sequential hypothesis assuming that the succession of SWS and REM sleep epochs serves a complementary function in memory processing during sleep (Giuditta et al. 1995). Synaptic consolidation mechanisms thus represent locally acting subroutines that support the system consolidation process specifically during REM sleep (Dudai 2012), i.e., a period in which both external stimulus inputs as well as communication between brain regions are reduced to a minimum (Achermann & Borbely 1998, Axmacher et al. 2008, Montgomery et al. 2008). Below, we discuss important experimental data relevant to this concept.

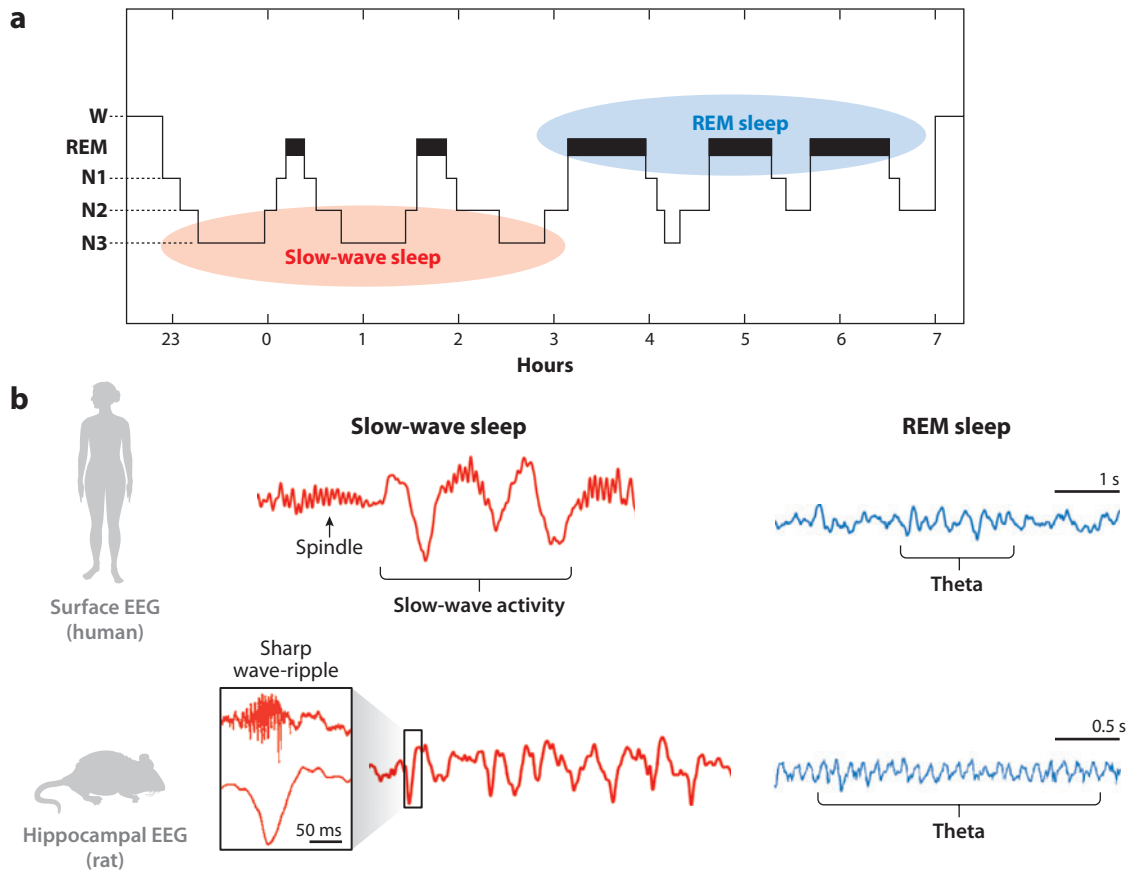


Figure 1

Physiological sleep. (a) Human nocturnal sleep profile. Sleep is determined mainly by continuous recordings of electroencephalogram (EEG) complemented by electrooculogram and electromyogram, subsequent 30-s epochs of which are classified into wakefulness (W), the non-rapid eye movement (non-REM) sleep stages N1, N2, N3, and REM sleep, according to standard criteria. The deepest non-REM sleep stage, N3, defines slow-wave sleep (SWS). In rodents, classification of sleep stages concentrates on SWS and REM sleep. An equivalent of N2 sleep is not discriminated. Non-REM and REM sleep periods alternate in cycles of ~90 min, which, during early nocturnal sleep, are dominated by SWS with little REM sleep and, during late sleep, by REM sleep with little SWS. (b) EEG characteristics of SWS and REM sleep. During SWS, the surface EEG (*upper trace*) is hallmarked by high-amplitude slow-wave activity in the frequency range between 0.5 and 4 Hz, whereby the <1 Hz range refers to the slow oscillation and the 1–4 Hz range to the delta waves. SWS, and even more so N2 sleep, is also characterized by spindle activity (12–15 Hz). The rat hippocampal EEG (*lower trace*) reveals sharp wave-ripples (SW-R); the sharp waves represent fast depolarizing events generated in CA3 that are superimposed on (100–250 Hz) ripple activity originating in CA1. The enlarged detail (*left*) shows the ripple (*upper trace*) and sharp wave (*lower trace*) components of a SW-R in separately filtered recordings at higher temporal resolution. During REM sleep, the surface EEG is characterized by a low-amplitude EEG of mixed fast frequencies. Especially the rodent hippocampal EEG shows high (4–8 Hz) theta activity.

DOES SLEEP PREFERENTIALLY CONSOLIDATE EPISODIC MEMORY?

Assuming that reactivations during SWS originate from hippocampal representations, the sleep-associated consolidation process

is expected to affect episodic features more strongly than aspects of memories represented in extrahippocampal networks. Nevertheless, the proposed transformation of the memory established during sleep implicates secondary effects on extrahippocampal representations,

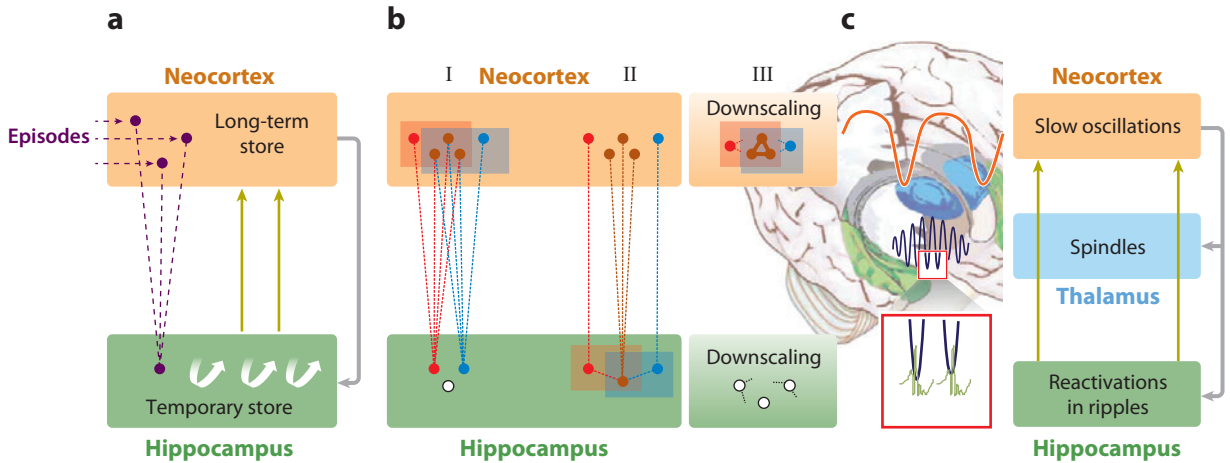


Figure 2

Active system consolidation during sleep. (a) System consolidation relies on a dialogue between the hippocampus serving, for part of the information, as temporary store, and extrahippocampal, mainly neocortical networks serving as long-term store. During the wake phase, an episode is encoded in both hippocampal and extrahippocampal networks (*dashed purple arrows*), whereby the hippocampus encodes aspects of the representation binding an experienced event into its unique spatiotemporal context. During subsequent slow-wave sleep (SWS), repeated reactivations of the hippocampal representation (*circular white arrows*) support its redistribution such that parts of it become preponderantly represented in extrahippocampal regions (*dark yellow arrows*). The redistribution of episodic memory representations is accompanied by a transformation toward more decontextualized schema-like representations. (b) The abstraction of a schema-like representation resulting from reactivations of episodic representations that overlap, i.e., share neuron assemblies either (I) in the neocortex or (II) in the hippocampus. Reactivations originate in the hippocampus and spread to neocortical networks. (III) Shared assemblies undergo stronger reactivation that, based on Hebbian learning, potentiates and strengthens (*thick gray lines*) the connections between neurons contributing to the overlap. Concurrent global processes of synaptic downscaling generally weaken and eventually erase connections (*truncated dashed red, blue, and black lines*) of the nonoverlapping portion of the representations as these undergo less reactivation. Downscaling may be more effective in hippocampal networks, where it also counteracts the persistence of potentiation in overlapping portions of a representation. Nonoverlapping areas preferentially represent idiosyncratic details and specific context of an episode (modified from Lewis & Durrant 2011). (c) The communication between the hippocampus and extrahippocampal circuitry during consolidation is regulated by EEG oscillations. During SWS, the depolarizing up-phases of slow oscillations (SO, *orange*) originating preferentially from the prefrontal cortex act top-down repeatedly to drive neuronal reactivations of representations in the hippocampus, where these reactivations occur simultaneously with sharp wave-ripples (SW-R, *green*). The concurrent drive of the SO up-phase on thalamocortical spindles (*blue*) allows spindle-ripple events to form; ripples and entrapped reactivated memory information become nested into the excitatory phases, i.e., troughs, of the spindle oscillation (*shown enlarged in insert*). Spindle-ripple events represent a mechanism mediating the bottom-up transfer of reactivated hippocampal memory information to extrahippocampal (mainly neocortical) regions. Reactivated memory information nested in spindle troughs arrives at these regions still during the excitable SO up-phase, which initiates Ca^{2+} -dependent intracellular processes of synaptic plasticity that mediate the long-term storage of the information in these extrahippocampal regions.

i.e., semantic and procedural aspects of a memory, which might appear only with longer periods of intervening sleep. Overall there is a paucity of studies directly dissociating effects of sleep on hippocampal and extrahippocampal representations.

Human Studies

Numerous studies have demonstrated that sleep after learning of declarative tasks im-

proves the retention of these memories, which rely on hippocampal function (reviewed in Marshall & Born 2007). In fact, the first experimental work in this field relied exclusively on the use of declarative tasks such as the learning of nonsense syllables, words, and paired associate words, among others (e.g., Jenkins & Dallenbach 1924), and the beneficial effects of postlearning sleep on memory retention seen in these early studies were confirmed in more recent studies (e.g., Yaroush et al. 1971, Fowler

et al. 1973). Compared with a postlearning wake interval, sleep not only distinctly slowed the trajectory of forgetting over time, but also made the memory more resistant to interference (Ellenbogen et al. 2006). Comparisons of sleep periods rich in SWS, as they occur during the early night, with those rich in REM sleep, as occurring during the late night, indicated that SWS is much more relevant for strengthening declarative memory than is REM sleep (Plihal & Born 1997). REM-rich sleep appeared to strengthen preferentially procedural memories considered less dependent on hippocampal function, although these findings were questioned by later studies using pharmacological REM-sleep suppression (Rasch et al. 2009). However, although they differentiated declarative from procedural memories, few of these studies provided clues about which type of declarative information is influenced by sleep, i.e., semantic or episodic memory or item versus spatiotemporal context aspects of episodic memory.

Emerging evidence from recent studies supports preferential strengthening of context over item (what) memory during sleep, if context is considered to refer more generally to relational features of an episode, comprising where (spatial) and when (temporal) an event happened, as well as to background features and details of the event that are deemed more or less irrelevant in the context of learning (Aly & Moscovitch 2010). Indeed, "context" often lacks a clear conceptual definition in relevant studies. Neuroimaging and lesion studies indicate that contextual features of episodic memory critically depend on hippocampal function, whereas item memory is supported by extrahippocampal structures, mainly the perirhinal cortex (Davachi 2006, Eichenbaum et al. 2007). Napping (maximally 120 min) was indeed revealed to selectively enhance signs of context memory, leaving item memory unaffected (van der Helm et al. 2011). In this study, participants learned two lists of words (defining item memory) while facing two different posters (contexts). At a delayed retrieval test, the nap group, compared with a no-nap

control, showed significantly better memory for the poster associated with a word, whereas recognition of the words per se did not differ. The enhanced context memory was correlated with the amount of non-REM sleep stage 2 and EEG spindles during the nap. However, while learning, subjects were instructed to form associations between the words and the poster images, which may question whether the posters represented context in the strict sense. Sleep-dependent enhancements in context memory in the absence of changes in item memory were likewise revealed with the what-where-when task, during which participants learned two lists of nouns (items) one after the other (when), with the words written either on the top or on the bottom of a page (where) (Rauchs et al. 2004). The forgetting rate for temporal context was lowest across SWS-rich sleep, whereas memory for spatial context appeared to be relatively enhanced following late REM-rich sleep. Fittingly, sleep also enhanced temporal order, as a principle underlying episodic memory, when memory for temporal sequences of word-triplets was studied in isolation by comparing retrieval of forward and backward associations in these triplets (Drosopoulos et al. 2007b). Sleep selectively strengthened the forward associations of the learned word triplets, matching the observation that memory replay in hippocampal neuron assemblies during SWS exclusively occurs in a forward direction (Foster & Wilson 2006). Sleep also strengthened memory for temporal order in picture sequences (Griessenberger et al. 2012), and such effects were blocked by administration of the stress hormone cortisol, which affects limbic-hippocampal circuitry in particular (Wilhelm et al. 2011b). Benefits of sleep on context memory were enhanced by varying the emotionality of the context (Lewis et al. 2011).

Interestingly, contextual associations also strengthened sleep-dependent benefits for procedural tasks that may not require hippocampal involvement per se. Comparing the effects of sleep on implicitly trained noncontextual and contextual versions of a serial reaction time task (SRTT), Spencer et al. (2006)

revealed a sleep-dependent gain in response time only for the contextual but not for the noncontextual SRTT version. Rather than responding directly to spatial cues, participants in the contextual version responded to the color of the cues (again following a sequence of spatial targets). Because the formation of such contextual associations depends on the hippocampus, these observations strongly support the view that gains in procedural skill from sleep also represent a hippocampus-mediated process. Presumably via amygdalar-hippocampal interactions, this process is subject to emotional influences because sleep-dependent gains in mirror tracing, a task in which hippocampal involvement is also not mandatory, were greater when the skill had been practiced with aversive than with neutral stimulus materials before sleep (Javadi et al. 2011).

Clues about sleep's specific influence on the episodic features of a memory can be also obtained from the remember/know paradigm (Yonelinas 2001, Rugg & Yonelinas 2003). Remembering is associated with the conscious recollection of the encoded event and thus reflects episodic memory features, whereas knowing to have seen something but being unable to recollect the specific features of the encoded event merely invokes a sense of familiarity that is not considered episodic in nature. Explicit recollection critically relies on hippocampal function, whereas familiarity-based implicit processes of recognition can be achieved by extrahippocampal regions alone. In direct comparisons of explicit recollection and familiarity-based judgments on memory for words and pictures, postlearning sleep consistently enhanced explicit recollection of memories, whereas familiarity-based judgments remained unaffected (Rauchs et al. 2004, Drosopoulos et al. 2005, Daurat et al. 2007, Atienza & Cantero 2008). Two of these studies (Rauchs et al. 2004, Daurat et al. 2007) also revealed a significant link between enhanced recollection and the occurrence of SWS during postlearning sleep.

Overall the picture emerging from these human studies suggests that sleep, in particular SWS, exerts an immediate strengthening effect

on episodic memory. The effect is preponderantly seen on contextual aspects of episodic memory, where most consistent benefits of sleep were revealed for temporal contexts.

Animal Studies

Tasks examining the binding of item memory to a spatiotemporal context also demonstrated the presence of episodic-like memory and its genuine dependence on the hippocampus in animals (Kart-Teke et al. 2006, Devito & Eichenbaum 2010). Rats with lesions to dorsal CA3 and rats that, after kainate-induced epilepsy, showed some minor cell loss restricted to CA3, CA1, and ventral dentate gyrus performed well on tasks separately testing what, where, and when aspects but failed on a task requiring the binding of these three aspects into an episodic-like representation, a result that may be related to a disturbance in the coherent processing between these hippocampal areas of item and contextual information conveyed from lateral and medial entorhinal inputs, respectively (Li & Chao 2008, Inostroza et al. 2010). Notably, this binding of an event into the spatiotemporal context required sleep if rats needed to retain the episodic memory for more than 80 min (Inostroza et al. 2013). This study compared memory retention across 80-min postencoding intervals during which the rats either had normal morning sleep or were sleep deprived. A third condition took place during the evening hours when the rats were spontaneously awake during the retention interval. At retrieval testing, only in the sleep condition the rats displayed significant memory for the episode, i.e., signs that the events experienced during encoding were remembered in correct temporal order and correct place. As an indicator of memory, the study used the rat's natural novelty preference, i.e., the tendency to explore more intensely (*a*) objects that were placed at a novel rather than at the same location as that used during the encoding phase and (*b*) objects that were encountered earlier than objects encountered later in the encoding phase (Mitchell & Laiacina 1998, Kart-Teke et al. 2006). The

study also separately assessed memory for the spatial and temporal contexts using an object-place recognition task and a temporal memory task, respectively. Retention of both spatial and temporal memory critically relied on the occurrence of sleep during the 80-min retention interval. By contrast, item memory tested in a novel-object recognition task did not require sleep but was retained in the wake and sleep-deprivation conditions to virtually the same extent as was found in the sleep condition. Overall, this pattern corroborates the view that sleep specifically supports the maintenance of hippocampus-dependent memories because novel-object recognition was the only task employed in the study which does not require the integrity of this structure (Bussey et al. 2000, Mumby et al. 2002). Of note, the tasks of temporal and object-place memory used in this study to dissect the effects of sleep on memory for respective spatiotemporal context aspects, per se, also comprise clear episodic features; i.e., context-item binding, inasmuch as recall of the contexts (i.e., the location and temporal order of the objects) implies that the rat also correctly remembers the objects encountered during learning. Because as in a figure-ground relationship context is, by definition, uniquely bound to an event, an isolated assessment of context memory, in the absence of any item memory formation, is basically impossible.

That the retention of spatial context over a short period of 2 h requires sleep has been confirmed in a further study using the object-place recognition task (Binder et al. 2012). The effect was associated with high amounts of both SWS and spindles. However, in mice, different from rats, sleep also enhanced item memory tested in a novel-object recognition task (Palchykova et al. 2006, Rolls et al. 2011). The reason for this divergence is not clear. Periods of sleep deprivation (>4 h) and retention intervals (24 h) in these studies were longer than those used in the rat studies, which may increase the likelihood for secondary memory effects on extrahippocampal representations. The relational features of the tasks may also have been more complex and demanding, forcing the mice

into hippocampus-based strategies. In another study, mice trained on a spatial maze shifted from a hippocampus-dependent spatial strategy to a striatum-dependent response strategy when deprived from sleep (for 5 h) after each daily training (Hagewoud et al. 2010).

Fear conditioning, although stressful, bears features of episodic memory because learning is achieved typically in a single trial, thus avoiding confounding effects resulting from repetitive stimulus presentations (Maren 2001). Contextual fear conditioning, a task that depends on hippocampal function, was revealed to be sensitive to sleep deprivation, whereas cued fear conditioning, which does not require hippocampal involvement, did not profit from sleep (Graves et al. 2003). Only sleep in the 5-h interval immediately following conditioning was effective; sleep occurring 5–10 h after conditioning was not effective. Later studies confirmed the sensitivity of context fear memory to sleep (Cai et al. 2009b) and identified cyclic adenosine 3',5'-monophosphate (cAMP)-protein kinase A (PKA)-dependent synaptic plasticity as a mechanism mediating this effect in hippocampal circuitry (Vecsey et al. 2009, Hagewoud et al. 2011), but studies were not clear about the contributions of specific sleep stages. In addition to SWS, contributions of REM sleep are likely due to the stressful nature of the task. This notion is suggested by studies using the Morris water maze, in which sleep (particularly REM sleep) benefited spatial memory only in the hidden-platform version of the task, which requires hippocampal functioning, but not in the visible-platform version, which does not require hippocampal functioning (Smith & Rose 1996, 1997).

Altogether the reviewed studies in rodents rather consistently point to a preferential consolidation of episodic memory during sleep, although mostly they compared hippocampus-dependent tasks with tasks that do not essentially rely on hippocampal function. By contrast, memories thought to be represented primarily in extrahippocampal circuitry do not require sleep to be maintained in the short term, i.e., within the first couple

IS THERE SYSTEM CONSOLIDATION DURING WAKING SIMILAR TO THAT DURING SWS?

Assembly reactivations together with hippocampal sharp wave-ripples (SW-R) occur during quiet wakefulness as well, which has stimulated the view that system consolidation would take place during waking in much the same way as it does during slow-wave sleep (SWS) (Mednick et al. 2011). However, this view neglects that reactivations during SWS and waking occur in entirely different neurochemical milieus. Acetylcholinergic activity is minimal during SWS but maximal in the wake state in which it mediates a tonic suppression of hippocampal CA1 outputs (Hasselmo & McGaughy 2004). Owing to minimal cholinergic activity, this inhibition is released during SWS, thus permitting reactivated memory information to spread to extrahippocampal areas in this state. Other signals, e.g., low corticosteroid levels during SWS, add to this effect. In humans, consonant with reconsolidation theory, wake reactivations transiently destabilized representations, whereas reactivations during SWS immediately strengthened them (Diekelmann et al. 2011). These findings suggest distinct functions of reactivations depending on the brain state: Wake reactivations and subsequent memory destabilization may provide an acute opportunity to update a representation with new information, whereas reactivations in SWS may essentially serve to incorporate hippocampal memory information within preexisting extrahippocampal representations.

of hours after learning, which does not exclude secondary effects on such representations occurring more gradually over time. Benefits for hippocampal representations appear to be linked to SWS, but REM sleep may also contribute in certain conditions, in particular when memories are emotional. Note, despite the evidence for preferential consolidation of hippocampus-dependent memory during sleep, sleep, perhaps through different mechanisms, can also enhance memories that do not involve the hippocampus (e.g., Frank 2011).

NEURONAL REACTIVATION OF REPRESENTATIONS DURING SLEEP

The active system consolidation view assumes as a key mechanism the neuronal reactivation of

memory representations encoded during waking during subsequent periods of sleep (Pavlidis & Winson 1989; for reviews, see Sutherland & McNaughton 2000, O'Neill et al. 2010). Recordings of spike activity in hippocampal CA1 place cells revealed patterns of correlated activity in these cell assemblies while the rat was running along a track for food reward, and these correlation patterns were reactivated during subsequent SWS (Wilson & McNaughton 1994). Importantly, assembly reactivation during SWS occurs, although at a faster speed, in the same temporal order of place cell spiking and in the same forward direction as that observed during wake encoding of the spatial task (Skaggs & McNaughton 1996, Nadasdy et al. 1999, Ji & Wilson 2007). Initially, investigators questioned the link between assembly reactivations during SWS and a one-time episodic experience because in the first studies the rats were highly overtrained on the tasks; thus, the tasks lacked any new learning. However, in later studies, reactivations during SWS were similarly revealed after rats had engaged in exploring new environments (Ribeiro et al. 2004, O'Neill et al. 2008). In these studies, neuron assemblies linked to place fields that were longer or more frequently explored showed stronger reactivation during succeeding sleep.

Assembly reactivations have been observed almost exclusively during SWS and rarely during REM sleep. In rats highly familiar with a track, REM sleep-associated reactivations in the hippocampus were shifted in phases toward the troughs of the EEG theta rhythm, suggesting that such reactivations help erase superfluous episodic memory information from hippocampal circuitry once a task becomes familiar (Poe et al. 2000, Booth & Poe 2006). However, others failed to identify patterned reactivations during REM sleep, questioning their existence (e.g., Kudrimoti et al. 1999). During SWS, reactivations in the hippocampus typically co-occur with SW-R events (O'Neill et al. 2010) that also occur during quiet wakefulness but rarely occur during REM sleep (see sidebar, *Is There System Consolidation During Waking Similar to that During SWS?*).

Neuronal reactivation:

temporally sequenced replay of neuronal firing patterns that accompany episodic memory encoded during subsequent offline periods of sleep or wakefulness

Neuronal reactivations during SWS are also observed in extrahippocampal regions, including frontal, parietal, and visual cortical areas as well as the ventral striatum (Pennartz et al. 2004, Euston et al. 2007, Ji & Wilson 2007, Lansink et al. 2009, Peyrache et al. 2009). Assembly reactivations in these extrahippocampal areas slightly followed (by less than 50 ms) signs of reactivation in hippocampal circuitry, which is consistent with the notion that hippocampal reactivations play a leading role for reactivations occurring in distributed representational networks outside the hippocampus. Reactivations originating from newly encoded hippocampal memories and spreading to neocortical and striatal sites may help strengthen these extrahippocampal parts of the representation, thereby also fitting them into preexisting knowledge networks. Brain-imaging studies in humans confirmed that reactivations occur during non-REM sleep and SWS in hippocampal as well as extrahippocampal, i.e., neocortical, regions after learning of hippocampus-dependent declarative (spatial navigation, face-scene associations; Peigneux et al. 2004, Bergmann et al. 2012) and procedural tasks (visual texture discrimination; Yotsumoto et al. 2009).

The causal role reactivations play for memory consolidation has been demonstrated in both humans and rats. In humans, olfactory and auditory cuing was used to experimentally induce reactivations of newly encoded memories during sleep (Rasch et al. 2007, Rudoy et al. 2009). An odor presented while subjects learned place-object associations enhanced memories for the learned associations if it was presented again during subsequent SWS but not when re-exposed during REM sleep. Reexposure of the odor during SWS reactivated the hippocampus; this reactivation was distinctly stronger than that observed during wakefulness, suggesting that the hippocampus during SWS is particularly sensitive to stimuli capable of reactivating memories. In rats, conditions of diminished pattern reactivation and accompanying SW-R were consistently associated with impaired retention of hippocampus-dependent memories

(Girardeau et al. 2009, Bendor & Wilson 2012). Diminished formation of spatial memory in old compared with young rats was associated primarily with a disturbed temporal sequence in the reactivation patterns during sleep, while patterns of mere coactivation persisted (Gerrard et al. 2008). Indeed, considering the importance of temporal sequence in neuronal replay activity during SWS and its origin from hippocampal circuitry, it is tempting to conclude that these reactivations reflect primarily reprocessing of episodic memory aspects, although reactivations during sleep after strictly episodic tasks have not been assessed so far.

TRANSFORMATION OF MEMORY REPRESENTATIONS DURING SLEEP

The active system consolidation theory assumes that, in addition to immediately enhancing the memory representation per se, reactivations during sleep induce the transformation of memory representations. Specifically, reactivations originating from the hippocampal circuitry during SWS are expected to decontextualize episodic memory information, whereby semantic and skill representations are generated that can be applied independently from their specific spatiotemporal context during acquisition. Such transformation implies that memories change in quality during sleep, an aspect that has so far been less intensely studied, probably because persistence, rather than its dynamic nature, is traditionally considered the hallmark of memory (Dudai 2012).

Human functional magnetic imaging studies have consistently indicated that post-encoding sleep, aside from increased hippocampal activation, favors the redistribution of declarative memory representations (for word pairs, pictures, etc.) toward enhanced neocortical, mainly medial prefrontal cortical involvement as well as increased functional connectivity between medial frontal cortical and hippocampal areas at delayed retrieval (e.g., Gais et al. 2007, Sterpenich et al. 2007, Takashima et al. 2009, Payne &

Assimilation: process in which newly encoded memory information is integrated into preexisting knowledge and schema-like representations

Abstraction: process in which invariant patterns are distilled from multiple overlapping episodic memory representations to eventually form a more generalized schema-like representation

Kensinger 2011). For tasks with a strong procedural motor component, postencoding sleep appears to enhance the involvement of striatal regions and their functional connectivity with the hippocampus (Fischer et al. 2005, Orban et al. 2006). Yet, despite the obvious system-level reorganization that memory representations undergo during sleep, the qualitative changes in memory associated with such reorganization are presently not well characterized.

Available evidence points to two major processes that might be supported by system consolidation during sleep: assimilation and abstraction (Lewis & Durrant 2011). Assimilation refers to the integration of newly encoded memory information into preexisting knowledge networks and schemas. In rats, once an associative spatial schema representation (of a large event arena) is established in neocortical long-term memory networks, newly learned additional locations in this arena can be incorporated into this schema within 48 h (Tse et al. 2007). As expected, memory for the new locations was impaired by lesions to the hippocampus made 3 h after learning. However, it remained intact with lesions made 48 h after learning. Although not systematically explored in these experiments, sleep may have been critical for this relatively fast assimilation to extrahippocampal schemas, since only the 48-h but not the 3-h interval contained sleep. In humans, sleep promoted the assimilation into existing knowledge networks of learned spoken novel words that phonologically overlapped with familiar words, as measured by a lexical competition task (Dumay & Gaskell 2007), and this integration was associated with increased spindle activity during postlearning sleep (Tamminen et al. 2010).

Abstraction refers to a process in which rules and regularities are distilled from multiple episodic memory representations to eventually form a more generalized schema in long-term memory. Thus, in different tasks, such as the number reduction task, the SRTT, and statistical learning tasks, sleep consistently promoted the abstraction of explicit knowledge from hidden structures embedded in the

implicitly learned materials (Wagner et al. 2004, Fischer et al. 2006, Drosopoulos et al. 2011, Durrant et al. 2011). When asked to generate deliberately the sequence underlying an SRTT trained under implicit conditions before a retention interval of sleep or wakefulness, only after sleep had subjects developed a significant amount of explicit sequence knowledge (Fischer et al. 2006, Drosopoulos et al. 2011). Postencoding sleep also improved performance on transitive inference tasks (Ellenbogen et al. 2007) and enhanced production of false memories in the Deese-Roediger-McDermott (DRM) paradigm (Payne et al. 2009, Diekelmann et al. 2010). In infants, sleep promoted grammar-related abstraction processes in a language-learning task (Gomez et al. 2006, Hupbach et al. 2009). In the infants who had napped, memory for the words per se was worse than in the wake control infants, suggesting that sleep acts primarily to transform rather than to enhance representations directly.

Hints at abstraction processes supported by sleep were likewise obtained in studies of procedural memory. On a finger-sequence tapping task, posttraining sleep favored the development of an effector-independent representation, i.e., sleep benefited tapping the sequence of target keys independent of whether tapping was performed with the same hand as during training or with the other hand (Cohen et al. 2005, Witt et al. 2010). Sleep enhanced sequence finger-tapping performance when learning occurred by observation (van der Werf et al. 2009b). Thus, sleep appears to transform skill representations such that they become less dependent on a specific stimulus context or effector system. Beyond this decontextualization of memory by sleep, the studies showed for the discussed declarative and procedural tasks that the transformation of representations is linked to non-REM sleep and SWS and associated EEG oscillations (e.g., Yordanova et al. 2008, Tamminen et al. 2010, Durrant et al. 2011, Yordanova et al. 2012); there were no consistent clues for additional contributions of REM sleep, although the

possibility cannot be excluded (Cai et al. 2009a, Walker & Stickgold 2010).

Transformation Toward Increased Executive Control

Findings that postencoding sleep facilitates insight and awareness of rules hidden in implicitly learned materials suggest that the abstraction process during sleep goes along with an increased explicitness of memory in the sense that various effector systems (verbal, motor) can be flexibly used to express the memory in different stimulus conditions (Marshall & Born 2007). Sleep reorganizes representations such that they become not only decontextualized but also more accessible via the prefrontal-hippocampal system, i.e., the executive control system mediating explicit recollection. This view could also explain that enhancing effects of sleep on memory are typically more robust when delayed retrieval is tested by free recall rather than by a recognition procedure (see, for example, regarding the production of critical lures in the DRM paradigm; Diekelmann et al. 2008, 2010; Payne et al. 2009). Against this backdrop, it is tempting to speculate that the transformation of memory representations during SWS serves primarily to enhance their accessibility to executive behavioral control by prefrontal cortex structures rather than to enhance the content per se. Yet, such a distinction is difficult to make on the basis of behavioral retrieval measures alone.

MECHANISMS UNDERLYING MEMORY TRANSFORMATION

The transformation of episodic memory that leads to the formation of decontextualized schema-like representations is thought to be a gradual process originating from the repeated activation of multiple overlapping episodes that share common items, so that spatiotemporal context and idiosyncratic details of the episodic representation attenuate and eventually completely disappear (Nadel & Moscovitch 1997). Accordingly, overlap between episodic

representations determines how memories are transformed during sleep-associated reactivations. However, it is not clear how hippocampus and extrahippocampal areas in representing episodic memories contribute to such overlapping reactivation (**Figure 2b**). Overlap in spatial representations can already emerge during encoding in hippocampal CA3 and CA1 as a result of experience on two tasks performed in environments with graded dissimilarities (Guzowski et al. 2004, Lee et al. 2004, Leutgeb et al. 2004). Reactivation of such generalized mapping across episodes in CA1, as the major hippocampal output region, may then be considered a principal mechanism underlying the induction of abstract representations in extrahippocampal networks. However, the exact (spatial) conditions under which CA1, in the course of encoding different episodes, forms overlapping generalized or separated maps are not well understood. Alternatively, Buzsáki (2005) speculated that SW-R covering wider areas of hippocampal circuitry create opportunities to cross multiple separate episodes at the timescale of synaptic plasticity, the resulting concordant reactivation of these representations allowing abstract representations to form in neocortical areas. In this case, overlap would be acutely generated only in the course of redistributing representations to extrahippocampal networks in a process that may also integrate top-down inputs to the hippocampus originating from preexisting knowledge networks.

The “information overlap to abstract” concept proposed by Lewis & Durrant (2011) provides a more theoretical account of how neocortical overlap in representations could contribute to the formation of abstract schema memories. The concept assumes that repeated reactivations during SWS of newly encoded representations that show overlapping cortical areas, based on Hebbian learning rules, lead to the gradual strengthening, i.e., abstraction, of conceptual schemas representing those areas that, owing to the overlap, undergo the strongest reactivation. Concurrently, global synaptic downscaling processes gradually erode the more idiosyncratic aspects of each single

EEG coherence:

phase synchronization of field potential oscillations, coordinates the timing of neuronal spiking and resulting synaptic plasticity across distributed brain regions

representation. The model receives preliminary support from a study of interference learning (Drosopoulos et al. 2007a), which compared the effects of retention sleep and wakefulness after subjects learned two-word pair lists that, according to an A-B, A-C paradigm, overlapped and thus produced retroactive interference, or, according to an A-B, C-D paradigm, did not overlap and thus did not produce interference. Consistent with the information overlap to abstract concept, the sleep-dependent improvement in recall of A-B associations was greater when these overlapped during learning with A-C associations, compared with the learning of nonoverlapping word lists. Related findings were reported by others for declarative (Ekstrand 1967) and also for procedural types of memories (Fenn et al. 2003, Walker et al. 2003). However, the superior benefit of sleep for A-B associations when learned in the overlapping interference condition may be due to their generally weaker strength when entering sleep rather than resulting from reactivations of overlapping representations. In fact, some evidence indicates that profits from sleep are greatest for memories with an intermediate presleep encoding strength (e.g., Tucker & Fishbein 2008, Wilhelm et al. 2012a).

Control of Communication During Sleep-Dependent System Consolidation

The transformation of episodic representations during sleep implicates the redistribution of reactivated hippocampal memory toward preponderant representations of the memory information in extrahippocampal regions, a process that entails a fine-tuned communication between these regions. System communication between brain regions is considered to be basically controlled by electrical field potential rhythms (Buzsáki & Draguhn 2004). The EEG coherence, specifically the phase coherence in these rhythms, provides a mechanism whereby neuronal activity sent from one region can activate another network in a temporally coordinate manner, allowing also for the induction

of Hebbian and spike time-dependent synaptic plasticity underlying the formation of representations in the receiving network (Benchenane et al. 2011). The spread of reactivated hippocampal memory information during SWS is thought to be orchestrated by three different oscillatory rhythms: the ~ 0.75 Hz SO, the classical 12–15 Hz spindles, and the SW-R (the ripples oscillate between 100 and 300 Hz) (**Figures 1 and 2c**; Diekelmann & Born 2010).

SOs comprise highly synchronous alterations of virtually every cortical neuron between periods of membrane depolarization accompanied by sustained firing (up-state) and periods of hyperpolarization associated with neuronal silence (down-state). The SO thus provides a global time frame whereby the network is reset by the hyperpolarizing phase and processing is limited to the subsequent depolarizing up-phase (Steriade 2006, Mölle & Born 2011). The SO is generated primarily in neocortical networks; the depolarizing up-states are presumably triggered by summation of miniature excitatory postsynaptic potentials as a residual synaptic activity in local synaptic circuits, which is increased after potentiation of respective synapses, e.g., when information encodes in these circuits during prior waking (Bazhenov et al. 2002). Spindles originate from GABAergic thalamic networks; glutamatergic thalamocortical projections mediate their widespread propagation to cortical regions (Gennaro & Ferrara 2003). In the neocortex, spindles, independent of their synchronization with the central thalamic spindle generator, typically emerge as local phenomena that are restricted to specific circuitry (Nir et al. 2011, Ayoub et al. 2012). SW-R accompany memory reactivations in the hippocampus where they impact firing of discrete local circuits (Csicsvari et al. 1999). Evidence indicates that all three types of oscillations, SOs, spindles, and ripples, preferentially occur in previously potentiated synaptic networks (e.g., Behrens et al. 2005, Tononi & Cirelli 2006, Bergmann et al. 2008) and, conversely, can support plastic synaptic processes such as long-term potentiation (King 1999, Rosanova & Ulrich 2005). For SOs and

ripples, studies have demonstrated a causal involvement in consolidation of hippocampus-dependent memories during sleep by directly suppressing or enhancing them through electrical stimulation (Marshall et al. 2006, Girardeau et al. 2009, Marshall et al. 2011). For spindle activity, studies have shown robust increases during postlearning sleep that predicted the retention of the acquired memories, including specifically episodic aspects in these memories (e.g., Gais et al. 2002, Fogel & Smith 2011, van der Helm et al. 2011).

The dialogue between the hippocampus and extrahippocampal regions underlying memory transformation during SWS appears to be controlled mainly by the SOs that arise most powerfully from prefrontal circuitry engaged in information encoding during prior waking. SOs globally entrain neuronal activity not only in the neocortex but also in many other structures, including the thalamus and the hippocampus, where spindle activity and SW-R together with reactivated memory information likewise become synchronized with the SO up-state (Clemens et al. 2007, Csercsa et al. 2010). Prior learning strengthens the top-down control of SOs on spindles and ripples and also promotes the occurrence of trains of several succeeding SOs (Mölle & Born 2011, Ruch et al. 2012). In these SO trains, spindles appeared not only to be driven by the SO up-state but, conversely, to enforce also the succeeding SO, suggesting a key role for spindles in maintaining memory processing (Mölle et al. 2011).

The synchronous drive of the SO up-state on the thalamus and the hippocampus allows spindle-ripple events to form during this depolarizing period, when ripples and reactivated memory information enwrapped in these ripples are nested into the succeeding troughs of a spindle (Siapas & Wilson 1998, Clemens et al. 2011). Mutually stimulating influences between spindles and ripples may add to the formation of spindle-ripple events (Mölle et al. 2009, Wierzynski et al. 2009). [Note, these relationships do not apply to the slow 10–12 Hz frontal spindles, which represent a separate type of spindles that occur later

in the SO cycle (Mölle et al. 2011, Peyrache et al. 2011)]. Spindle-ripple events are a strong candidate mechanism for the bottom-up transfer of memory information to neocortical and striatal regions (Sirota & Buzsáki 2005, Mölle & Born 2011), where they might induce plastic processes to support specifically the storage of semantic and procedural features in episodic memories. Indeed, in humans signs of conjoint reactivations in relevant neocortical and hippocampal regions occurred in temporal synchrony with spindles after subjects learned face-scene associations (Bergmann et al. 2012). Also, spindles, in addition to ripples, phase-lock EEG gamma-band activity as an indicator of coherent information processing in local neocortical networks (Ayoub et al. 2012). In rats, spindle activity following exposure to a novel spatiotactile experience predicted immediate early gene (*arc*) expression in the somatosensory cortex during subsequent REM sleep, suggesting that, by facilitating Ca^{2+} influx into pyramidal cells, spindles help tag the newly formed neocortical representations for persistent synaptic strengthening during subsequent REM sleep (Ribeiro et al. 2007).

CONSOLIDATION OF HIPPOCAMPAL MEMORIES IS SELECTIVE

The brain's capacity to store memories is limited. Even if the enhancing effect of sleep on memory was restricted to the episodic memory system, overflow would inevitably occur. Such considerations have stimulated concepts that sleep entails processes counteracting any imminent overload resulting from encoding of information during wakefulness. In this vein, the synaptic homeostasis hypothesis proposed that SWS via slow-wave activity induces a global and proportional downscaling of synapses that were potentiated during wakeful information encoding (Tononi & Cirelli 2006). However, proportional synaptic downscaling alone can explain neither why memories are enhanced by sleep nor why this enhancing effect is selective. It is obvious that

some episodic memory content is strengthened by sleep, whereas some other content is not (Diekelmann & Born 2010).

Selectivity of memory enhancement can be adequately explained in the context of memory transformation occurring during sleep, specifically in the context of abstracting and assimilating episodic memory information into schemas. Notwithstanding this theoretical account, experimental work has revealed that sleep preferentially strengthens those memories that are relevant for the individual's future plans. Sleep strongly supported the maintenance and delayed execution of plans in prospective memory paradigms (Scullin & McDaniel 2010, Diekelmann et al. 2012). The enhancing effect of sleep on declarative word-pair memories was distinctly greater in subjects who were informed (or merely suspected) that recall would be tested later as compared with subjects who had no such expectations; only in the informed subjects did later recall performance correlate with slow-wave activity during postlearning sleep (Wilhelm et al. 2011a). Comparable results were revealed for procedural skill memories (Cohen et al. 2005, Fischer & Born 2009).

Processing of goal-directed anticipatory aspects of behavior and retrieval is strongly associated with prefrontal cortex executive functions (Miller & Cohen 2001, Polyn & Kahana 2008). In allocating relevance (for future actions), the prefrontal structures may tag hippocampal memories to facilitate their access to system consolidation during sleep. Indeed, growing experimental evidence supports the notion that offline system consolidation is not only achieved in a bottom-up process, in which reactivation of hippocampal representations promotes the incorporation of some of this information into preexisting neocortical knowledge networks, but also entails significant top-down processing (Morris 2006). Thus during spatial learning, medial and limbic prefrontal regions can quickly (in a single trial) encode associations that overlap with a preexisting spatial schema (Lesburgueres et al. 2011, Tse et al. 2011), and such rapid prefrontal

encoding may also enable a top-down tagging of hippocampal memories as a prerequisite for subsequent offline consolidation.

A candidate mechanism conveying prefrontal tagging of memories for consolidation during sleep is the EEG theta rhythm (Benchenane et al. 2011). In a Y-maze task theta coherence between the prefrontal cortex and the hippocampus was increased at the choice point of the maze as soon as the rats had learned to choose the correct arm (Benchenane et al. 2010). Notably, assembly pattern firing in the prefrontal cortex present during increased theta coherence was likely reactivated during subsequent SWS. In addition to prefrontal-hippocampal circuitry, the theta spanning network includes regions such as the ventral tegmental area and the amygdala (Fujisawa & Buzsáki 2011, Lesting et al. 2011), which may help integrate reward-related and emotional aspects into the tagging process. Together with studies of rhythmic electrical stimulation (Marshall et al. 2006, Kirov et al. 2009), these observations converge on the idea that the same prefrontal-hippocampal network producing theta during wake encoding to tag memories changes into the SO rhythm during subsequent SWS to consolidate the tagged memories.

PERSPECTIVE

A wealth of evidence now indicates that sleep contributes to the formation of long-term memories in an active system consolidation process. Although the main features of this concept appear to be firmly anchored in human and rodent research, a number of questions are left unanswered. What exactly is the role of prefrontal top-down control in this consolidation process? Do neocortical SOs transfer schema-related information that supports the selection of representations to be reactivated in the hippocampus? Do they moreover contribute to downscaling and erasing of superfluous memory information from hippocampal circuits (van der Werf et al. 2009a, Grosmark et al. 2012)? How exactly do hippocampal reactivations contribute in a bottom-up fashion to

transforming representations toward more abstract schema-like representations? What happens when schemas are not readily available in long-term memory, i.e., during early development? Sleep appears to play a pivotal role for memory formation during development (Frank 2011, Wilhelm et al. 2012b). Thus, sleep-dependent formation of song representations in young birds has been conceptualized as a bottom-up feedforward process in which sensory inputs that are too complex and dynamic to be integrated into song production online are reactivated during sleep to program motor

song areas in the absence of potentially disturbing acute feedback (Konishi 2004, Margoliash & Schmidt 2010). Indeed, offline neuronal reactivation during sleep may work as a principal mechanism to form any kind of memory, i.e., as a mechanism that serves to abstract temporally stable invariants from a complex stream of inputs that is dynamic and only structured in time. Regardless of what answers we find for these questions, the past research described here has firmly established a picture of sleep as a brain state most essential to the genuine understanding of memory.

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