REVIEW

The Role of Sleep in Learning and Memory

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Sleep has been implicated in the plastic cerebral changes that underlie learning and memory. Indications that sleep participates in the consolidation of fresh memory traces come from a wide range of experimental observations. At the network level, reactivations during sleep of neuronal assemblies recently challenged by new environmental circumstances have been reported in different experimental designs. These neuronal assemblies are proposed to be involved in the processing of memory traces during sleep. However, despite this rapidly growing body of experimental data, evidence for the influence of sleep discharge patterns on memory traces remains fragmentary. The underlying role of sleep in learning and memory has yet to be precisely characterized.

There are two main types of sleep: rapid eye movement (REM) sleep, also known as paradoxical sleep (PS), and non-REM sleep, hereafter referred to as slow wave sleep (SWS). The latter is characterized by large-amplitude, low-frequency electroencephalographic (EEG) oscillations. The former is identified by low-amplitude, relatively fast rhythms on EEG recordings, by rapid eye movements, and by decreased muscular tone.

The function of sleep remains unknown despite our rapidly increasing understanding of the processes generating and maintaining sleep. A number of nonmutually exclusive hypotheses have been proposed: for example, energy conservation (*1*), brain thermoregulation (*2*), brain detoxification (*3*), and tissue "restoration" (*4*). Another hypothesis, on which we focus here, proposes that sleep periods are favorable for brain plasticity and, in the adult brain, for learning and memory. This hypothesis is experimentally testable. Three main steps may be operationally described: exposure to the new stimulus, processing of memory traces, and performance at retest. In this design, sleep is primarily involved in the processing of memory traces. The conventional view is that sleep processes participate in the consolidation of the memory traces. Consolidation refers to the processing of memory traces during which "the traces may be reactivated, analysed and gradually incorporated into long-term memory" (*5*). According to this hypothesis, the memory trace stays in a fragile state until the first postexposure sleep period has occurred (*6*). A large number of experimental findings are consistent with this notion, but at present there is no definitive evidence to prove the hypothesis (*7*, *8*). The fundamental debate is whether memory trace consolidation during sleep relies on specific patterns of neuronal activities and their effects at the subcellular level, or on other changes interacting with the sleeping brain (e.g., the effects of stress on hormone levels).

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Use-Dependent Versus Experience-Dependent Processes in Sleep

Brain activities during sleep that are dependent on the previous waking period have been interpreted in two different ways: as experience-dependent or use-dependent processes. Use-dependent sleep activity reflects the restoration of an optimal neuronal (essentially synaptic) function after the sustained waking neuronal activity. It does not assume any exposure to a new environment (stimulus, task), nor the expansion of the behavioral repertoire. For example, in humans, slow-wave activity has been shown to increase during SWS in the central area contralateral to a prolonged vibratory hand stimulation experienced during the previous waking period (*9*). However, the distinction between use- and experience-dependent sleep brain activity is not absolute, and it is not clear whether they reflect different processes. In some cases, it is difficult to decide whether the processes are use- or experience-dependent. The experimental treatment could often be interpreted as a new environmental condition (*10*). Moreover, because we do not know the basic mechanisms underlying these processes, we cannot rule out the possibility that similar cellular processes underlie both use- and experience-dependent activities. Use-dependent regulation of sleep is also believed to promote synaptic plasticity, through the local release of cytokines and growth factors (*11*). Use-dependent processes may reflect short-term adaptation to waking conditions, whereas experience-dependent mechanisms are mainly involved in long-term behavioral changes (*12*). In this respect, it is unfortunate that there are only a few studies showing that experience-dependent changes in sleep lead to long-lasting memory traces (*13*).

Testing the Hypothesis

The role of sleep periods in the processing of memory traces is a multidimensional problem. A large number of studies have been published that differ in important aspects (Table 1). It is not argued here that the same processes occur in each experimental condition. Rather, we emphasize that (i) there is a range of evidence relating sleep to memory processes; (ii) reactivation of neuronal populations are reported during posttraining sleep in various experimental conditions and might be involved in the processing of memory traces during sleep; and (iii) there are issues that have still to be addressed before the hypothesis can be accepted.

Behavioral level. First, posttraining sleep deprivation has been shown to impair subsequent performance on various tasks, both in animals (*14*, *15*) and in humans (*13*, *15*–*17*). However carefully these studies have been conducted, the sleep-deprivation paradigm in animals is inherently contaminated by nonspecific effects of the sleep deprivation (e.g., increased brain excitability, stress response) that might also lead to memory impairment (*18*). Although these indirect effects cannot be ruled out, the following arguments favor a genuine role for the lack of sleep in these results. Learning is impaired by sleep deprivation only if the task entails a new behavioral strategy (*19*, *20*). Impairment of performance is reported only if the sleep deprivation occurs during specific periods of time, the so-called paradoxical sleep (PS) windows (*21*). Similar deprivation outside these periods has no effect on subsequent performance (*22*).

Second, the general architecture of sleep is altered during the posttraining night. In humans, REM sleep increases following training in several experimental conditions (*23*–*28*). Likewise, in animals (mainly rodents), the training on various tasks is followed by an increase in REM sleep (*14*, *29*). REM sleep levels return to normal once the animals have mastered the task (*30*, *31*).

In animals, an unresolved issue is whether the stress response possibly accompanying the training sessions can explain these results. Indeed, stress can also lead to an increase in REM sleep (*32*). Moreover, depending on its timing and amplitude, an acute stress may favor memory formation (*33*). An important argument against a significant role of stress in sleep/memory studies is that the posttraining REM sleep rebound seems closely related to learning processes. No significant REM sleep increase occurs when there is no material to

learn (i.e., pseudo-conditioning) (*30*, *31*) or when the animals do not learn the task (*20*, *34*). In these two cases, control animals are subjected to the same stress as learning animals and still do not show any REM sleep increase. Future research should rule out the role of stress on subsequent REM sleep amount and examine the possibility that the stress-related response might modulate the experience-related sleep processes.

Reactivation of neuronal ensembles during posttraining sleep. In several experiments, the neural activity expressed during the waking behavior seems to be reinstated during sleep. These reactivations would allow for the adaptation of intercellular connection strengths between the elements of the network and the incorporation of the new experience into long-term memory. Accordingly, consolidating memory traces would involve not only the strengthening of certain synapses but also the pruning of other, inappropriate, connections that overload cerebral networks ["reverse learning" (*35*); see also (*36*)].

At the level of individual hippocampal cells, the firing pattern during sleep depends on previous waking experience. In an early report, the firing rates in CA1 place cells exposed to their place field during a previous waking period was increased during subsequent sleep, as compared with the firing rates in unexposed cells (*37*). The hippocampal place cells that show highly correlated firing during a food-seeking spatial task maintained high firing correlation during the posttraining sleep, especially during SWS (*38*). The temporal aspect of waking discharges seems to be maintained during postexposure sleep. The order in which pairs of place cells fire during posttraining sleep (mainly SWS) reflects, within a time window of 200 ms, the order of firing during the previous waking session (*39*). Sequences involving more than a pair of cells, within a similar time window, were replayed during SWS recorded after a wheel-running task (*40*). The replay of sequences is not specific to SWS. After repetitive exposure to a circular track, the patterns of discharges of multiple hippocampal units, reflecting up to several minutes of behavioral experience, are reproduced during REM sleep (*41*).

The time course of these reactivations, over several nights, has not yet been thoroughly investigated. However, during REM sleep, there is evidence that the novel representations are strengthened whereas the older ones are weakened (*36*). Hippocampal firing for novel experience during postexposure sleep occurs in phase with the theta rhythm, a condition known to induce long-term potentiation. In contrast, cells coding for familiar environments tend to fire out of phase with the theta rhythm, a situation that may lead to depotentiation.

At the network level in the rat, the activity of hippocampal cells is reflected in two types of macroscopic patterns (*42*, *43*). On the one hand, gamma oscillations (40 to 100 Hz) and theta rhythm (4 to 7 Hz) are recorded in the superficial layers of the entorhinal cortex, the gyrus dentatus, and the CA3 and CA1 fields of the hippocampus during exploratory activity and REM sleep. Awake immobility and SWS are characterized by sharp waves, crowned by high-frequency ripples (140 to 200 Hz). Ripples and sharp waves are initiated in CA3 and recorded in CA1 and the deep layers of the entorhinal cortex. It is believed that, during gamma and theta oscillations, neocortical inputs transmit information about the external world to the hippocampal structures through the entorhinal cortex. In contrast, during ripples and sharp waves, hippocampal information is thought to be played back to the entorhinal cortex (*42*, *43*) and through it, to neocortical areas (*44*). This two-stage operation could consolidate the memory trace, as has been suggested by computational simulations (*45*).

Despite their importance, these results do not provide definitive evidence for the involvement of sleep (i.e., discharges patterns in sleep) in memory processes. Although studies are presently under way to better characterize the neuronal discharges in the hippocampal formation during sleep in trained rats, there is no evidence that these neuronal activities eventually modify the behavioral adaptation to the new environment. There are also several methodological qualifications to be kept in mind. For example, in extracellular recordings, systematic changes in neuronal firing characteristics can lead to

Table 1. The role of sleep in brain plasticity: a multidimensional hypothesis.

Sleep stages
Given the substantial differences between SWS and REM sleep, it is likely that each sleep stage contributes in a different way to memory trace processing. Do they act in parallel (dual process) or serially (double-step process)?
- *Dual process*
  - SWS is particularly favorable to explicit memory traces
  - REM sleep is primarily involved in implicit memory consolidation
- *Double-step process*
  - Consolidation of memory traces requires SWS followed by REM sleep

Population
The role of sleep in brain plasticity is suspected in various homeotherm species. Sleep would be required both for brain maturation in early postnatal life and for learning and memory processes in the adult brain.
- *Class*
  - Birds
    - Zebra finch
  - Mammals
    - Rat
    - Cat
    - Human
- *Age*
  - Brain development
  - Adult brain

Description level
Evidence for the influence of sleep on memory trace processing emerged from observations at different levels of description:
- *Molecular level*
- *Neuronal assemblies*
- *Macroscopic brain system level*
- *Behavior*

Experimental design
Effect of the exposure to new environmental conditions on subsequent sleep
Exposure to a new environment modifies subsequent sleep, independently of the memory system involved or the time course of training sessions
- Memory systems
  - Hippocampal formation–dependent memory traces
  - Hippocampal formation–independent memory traces
- Exposure
  - Massed training
  - Distributed training

Sleep deprivation
The memory trace remains fragile as long as sleep does not intervene. Sleep deprivation alters the performance of a newly learned task both in animals and in humans.
- Total sleep deprivation
- Partial sleep deprivation
  - Selective REM sleep deprivation
  - Early-night versus late-night deprivation

apparent ordering effects, even in the absence of any discharge sequence (*46*). Also, it might be argued that these sequences only reflect the decay of activities that occurred during the previous waking period. However, the correlation structure of hippocampal ensembles attributable to one experience is still present during SWS even if another experience intervened before sleep onset (*47*).

Neuronal reactivations do not only occur in the hippocampal formation. Cortical neuronal activities during sleep can also be modified following training on a hippocampus-independent task. In the cat, fast (30 to 40 Hz) neocortical oscillations can be enhanced by instrumental conditioning during wakefulness, and a selective increase in these oscillations is observed during subsequent non-REM and REM sleep (*48*). More generally, SWS oscillations (slow rhythm, delta rhythm, spindles) are associated with rhythmic spike bursts in thalamic and cortical neurones, which lead to persistent excitability changes (*49*). These short-term plasticity processes could be used to consolidate memory traces acquired during wakefulness (*49*). It has been proposed that in the early stages of non-REM sleep, spindle activity would be related to massive Ca^{2+} entry into spindling cells (*50*). This would open the gate to subsequent long-term modifications in cortical networks. During SWS, large populations of thalamic and cortical neurons fire synchronously in a slow oscillation (<1 Hz), alternating phases of hyperpolarization and of depolarization (*51*). During the depolarized phase, the bursting neurons generate brief periods of fast oscillations that would iteratively recall and store information embodied in the assemblies primed during spindling (*50*). Alternatively, the neurons recruited by the slow oscillations would preferentially be those with the largest number of synapses recently potentiated during wakefulness (*52*).

Most importantly, postexposure brain reactivations during sleep seem to generalize across species. In order to learn their own song, young zebra finches have to establish the correspondence between their vocal production and the resulting auditory feedback. This cannot be done during wakefulness because the bird song arises from a tightly time-coded sequence of activity in the song area, whereas the auditory feedback, necessary to correct the vocal production, is inevitably delayed. During sleep, however, stored sensory feedback could easily be compared to the brain activities underlying the motor output. This seems to be the case, because spontaneous activity during sleep in a premotor area of the song system matches the activity recorded while the bird is singing during wakefulness (*53*).

Finally, preliminary results suggest that experience-dependent reactivations of neuronal populations also occur in humans during sleep. Using positron emission tomography, it was shown that during REM sleep, some brain areas were more active in human subjects previously trained on a serial reaction-time task than in naïve subjects (*54*). These results suggest that memory traces were reprocessed during REM sleep, for two reasons. First, the activated areas were among those previously engaged in the execution of the task. These cerebral regions were actually reactivated during posttraining REM sleep. Second, the subjects' performance on the task was improved in a postsleep retest session, suggesting that the influence of these reactivations, if any, was beneficial to memory traces. These data have yet to be confirmed but provide a perspective for future research.

Sleep creates functional contexts different from wakefulness and favorable to brain plasticity. Sleep could be a privileged period for memory consolidation because it allows reactivations of neuronal ensembles to occur in very distinctive contexts. It was earlier proposed that sleep oscillations themselves (theta and gamma oscillations, sharp waves and ripples, the various types of SWS oscillations) might favor brain plasticity by organizing cell firing patterns.

Likewise, in animals, ponto-geniculo-occipital (PGO) waves are prominent phasic potentials that occur during or immediately before REM sleep (*55*). Among various possible functions, PGO waves are hypothesized to promote brain development and to facilitate brain plasticity (*55*). Their density increases after aversive conditioning in rats (*56*). When induced by brainstem stimulation (*57*), they synchronize high-frequency activities (20 to 50 Hz), the expression of which can be experience-dependent during sleep (*48*). PGO activity during REM sleep could thus synchronize fast oscillations that convey recent information, over large-scale thalamocortical and intracortical circuits.

Another important context is imposed during sleep by particular patterns of neuromodulation. For example, REM sleep is characterized by a prominent cholinergic drive contrasting with a decreased adrenergic and serotonergic tone (*58*). Experimental data show that acetylcholine enhances cortical plasticity in adult mammals (*59–61*). In contrast, it has been shown that scopolamine, an acetylcholine antagonist, administered to rats during PS windows impairs subsequent performance on an avoidance task. Drug administration outside PS windows has no behavioral effect (*62*). The cellular consequences of the cholinergic modulation on memory trace processing during REM sleep are still to be characterized. It has been suggested that acetylcholine modulates molecular mechanisms of memory consolidation (*63*). For hippocampal-dependent memory traces, it has also been proposed that high levels of acetylcholine would favor the encoding of new information in the hippocampus during wakefulness, whereas during SWS, the lower acetylcholine levels would facilitate the spread of information from the hippocampus back to the cortex. During REM sleep, acetylcholine would allow the neocortex to undergo a process of reanalysis, thereby developing new feedforward representations for behavior (*64*).

Reactivations—down to the subcellular level? Consolidation of memory traces also involves a cascade of molecular events that lead to durable synaptic modifications. In this sense, memory consolidation entails gene transcription and local protein synthesis (*65*). The intervention of sleep in these processes is conceivable but has not been systematically investigated. The following results, although preliminary, set the stage for further research.

Brain protein synthesis persists and is even enhanced during sleep: There is a positive correlation between the duration of SWS and the level of cerebral protein synthesis in monkeys (*66*). On the other hand, in rats, learning is impaired when anisomycine, a protein synthesis inhibitor, is administered during REM sleep. This is a specific effect because it is exclusively observed when anisomycine is delivered during PS windows (*62*). Furthermore, evidence for gene transcription during postexposure sleep has recently emerged, with the documentation of an experience-dependent expression of zif-268, an immediate-early gene involved in neuronal plasticity (*67*). The expression of zif-268 in the brains of rats exposed to an enriched environment for 3 hours has been assessed during subsequent wakefulness, SWS, or REM sleep. Whereas nonexposed rats showed a generalized decrease in zif-268 expression during SWS and REM sleep as compared to wakefulness, zif-268 was up-regulated during (postexposure) REM sleep in the cortex and the hippocampus of exposed animals. These results only provide evidence compatible with an experience-dependent gene transcription. It remains to be shown which cascade of cellular events they trigger and whether these processes induce a subsequent modification of behavior.

Remaining Issues

In addition to the earlier-stated problems raised by specific experimental paradigms, three more issues can be identified.

Is sleep an absolute requirement for memory consolidation, or does sleep simply provide more favorable conditions for consolidating memory traces than other arousal states? Activity patterns involved in memory consolidation do not occur specifically in sleep. Sharp waves and ripples are observed both in SWS and quiet waking. The pattern of

activity, rather than SWS per se, would be a sufficient condition for memory processing (*47*). In contrast, recent human behavioral data suggest that sleeping during the night following a single training session is critical to visual perceptual learning (*13*). Subjects who were sleep-deprived during this posttraining night show virtually no performance improvement on the following days. Subjects allowed to sleep immediately after training showed a significant enhancement in their performance, as early as the first day after training and during the whole ensuing week. Finally, not all memories need sleep to consolidate. In contrast with perceptual learning discussed above, the ability of human subjects to make reaching movements in a force field is consolidated within the 5 hours of wakefulness that follow the training session (*68*). It is unclear why some memory traces require sleep to consolidate and others do not.

Second, as it appears from this review, most experiments on the role of sleep in memory have focused either on REM sleep or on SWS. At present, we lack a comprehensive understanding of the specific role of SWS and REM sleep in the processing of memory traces. Some experiments suggested a dual process in memory manipulation during sleep, whereby SWS and REM sleep act on different memory systems. Accordingly, SWS deprivation specifically impairs explicit memories (*17*, *69*–*71*), whereas REM sleep deprivation is more deleterious for implicit learning (*15*–*17*). However, other data suggest a double-step memory processing during sleep in which optimal learning would require the memory trace to be processed first in SWS, and then in REM sleep. Animal data point to the importance of the immediate succession of SWS and REM sleep periods (*72*). In humans, the role of these sequences has not yet been assessed. Preliminary evidence from a correlational study suggested that a sufficient amount of SWS in the first half of the night and of REM sleep in the second half is required to improve a visual perceptual skill (*73*). Accordingly, performance of the same task is improved if the subjects are allowed to sleep in the first part of the night and is even better if they are allowed to sleep the whole night. These results were interpreted as memory formation being prompted by early SWS-related processes with late REM sleep promoting memory formation at a second stage (*74*). However, late-night sleep includes large amounts of both REM sleep and stage 2 sleep. The specific influence of REM sleep remains uncertain.

Finally, future research will have to explain data that do not support the role of sleep in memory processes. For example, in contrast to the predictions, phasic motor events during REM sleep, like eye movements (*75*, *76*) or middle-ear muscle activity (*77*), are inversely correlated with the number of such events during the previous waking period. Likewise, it is intriguing that antidepressant drugs, which drastically reduce the amount of REM sleep, do not induce any deleterious effect on memory (*7*).

Conclusions and Perspectives

To confirm the role of sleep in memory trace processing, we need to realize four main goals. First, the characterization of task-dependent, regionally specific brain activities during posttraining sleep should be pursued, at different levels of cerebral organization. Second, it is necessary to demonstrate that these experience-dependent activities in sleep are ultimately related to long-lasting behavioral adaptation. Third, the specific role of sleep (i.e., sleep discharge patterns) in memory processing should be disentangled from other effects such as experimentally induced stress or circadian modifications. Fourth, the effects of SWS and REM sleep on the memory trace should be specified.

A more comprehensive understanding of the influence of sleep in memory processes could also reveal the commonalities with the role of sleep in other forms of brain plasticity, i.e., during neurodevelopment or during cerebral reorganization after brain damage.

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REVIEW

Sleep, Learning, and Dreams: Off-line Memory Reprocessing

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Converging evidence and new research methodologies from across the neurosciences permit the neuroscientific study of the role of sleep in off-line memory reprocessing, as well as the nature and function of dreaming. Evidence supports a role for sleep in the consolidation of an array of learning and memory tasks. In addition, new methodologies allow the experimental manipulation of dream content at sleep onset, permitting an objective and scientific study of this dream formation and a renewed search for the possible functions of dreaming and the biological processes subserving it.

It is 200 years since David Hartley (*1*) first suggested that dreaming might alter the strength of associative memories, but the basic proposition that either sleep or dreaming plays a role in the off-line reprocessing of memories remains hotly debated (*2*–*4*). Recent developments in molecular genetics, neurophysiology, and the cognitive neurosciences have produced a striking body of research that provides converging evidence for an important role of sleep in learning and the reprocessing of memories (*5*).

On the basis of patterns of brain electrical activity measured in the electroencephalogram (EEG), eye movements, and muscle tone (*6*), sleep can be broadly divided into rapid eye movement sleep (REM) and non–rapid eye movement sleep (NREM), with the human REM-NREM cycle typically having a 90-min period. Recent evidence strengthens the hypothesis that sleep plays a role in learning and memory processing at several levels, including the REM-dependent developmental wiring of binocular cells in visual cortex (*7*, *8*), procedural learning of a visual discrimination task (*9*–*12*), and the development of problem-solving skills (*13*).

In contrast, since Freud proposed his theory of dream interpretation (*14*), there has been a frustrating dearth of scientific evidence concerning the mechanism of dream construction and its possible functions. One such function might be as part of a multilevel system of sleep-dependent learning and memory reprocessing, wherein dreams would be the conscious manifestation of these processes. New approaches described below offer a methodology for experimentally approaching these questions.

Behavioral Studies of Learning and Memory in Sleep

Behavioral studies of sleep and learning in humans and animals, neurochemical and neurophysiological studies of the brain basis of possible sleep-dependent memory processing, and neurocognitive studies of information processing during sleep provide evidence for an interdependence between sleep, learning, and memory. Still, considerable controversy surrounds the question (*2*, *4*, *15*). For additional discussions of these questions, see the accompanying reviews by Maquet (*5*) and Siegel (*16*).

Research into sleep and memory began in earnest after the discovery of REM in 1953 (*17*). Since then, a wide range of animal studies have supported the hypothesis that REM plays a critical role in learning (*18*–*21*). A meta-analysis concluded that REM sleep plays a critical role in the consolidation of procedural learning but not of declarative memory (*22*). In a synthesis of the animal literature, Smith proposed the existence of "REM windows" (*18*), periods of time after procedural training when rats show increased amounts of REM and during which REM deprivation leads to diminished retention. For many of the early REM deprivation studies, the apparent decrease in recall after deprivation may be the consequence of deprivation-induced stress (*2*, *4*). But other studies (*23*) have demonstrated performance decrements 20 hours after REM deprivation, but not 8 to 16 hours after deprivation (*24*, *25*). This is the opposite of what a stress model would predict. Other studies have shown effects as long as a week after REM deprivation (*26*).

These findings in no way suggest that REM is critical for all memory consolidation. Substantial memory consolidation occurs during normal waking, and many memory tasks are unaffected by subsequent REM deprivation (*2*, *4*, *15*). Nor is there clear evidence that REM sleep enhances subsequent encoding (*27*). Furthermore, memory consolidation is most likely not the only function of REM sleep, not explaining, for example, the decrease in REM during the first year of life (*2*).

In humans, posttraining REM deprivation impairs retention of procedural learning (*20*, *28*). Declarative memory tasks in general have not shown any sleep dependence [e.g., (*29*)], although some studies have suggested that deep, slow-wave sleep (SWS) early in the night may aid in their consolidation (*30*, *31*).

REM may also enhance the processing of emotional memories. There is enhanced recall for emotionally salient memories after periods of sleep rich in REM (*32*), and several older studies similarly support a role for REM in processing emotional memories (*27*, *33*–*36*). In addition, shortenings of REM latencies and increases in REM densities have been reported in major depression (*37*, *38*), the state of bereavement (*37*, *39*), war-related anxiety (*40*), and, more generally, posttraumatic stress disorder (*41*).

Some of the strongest evidence for human learning being sleep dependent comes from a

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