

The relationships between memory systems and sleep stages

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SUMMARY Sleep function remains elusive despite our rapidly increasing comprehension of the processes generating and maintaining the different sleep stages. Several lines of evidence support the hypothesis that sleep is involved in the off-line reprocessing of recently-acquired memories. In this review, we summarize the main results obtained in the field of sleep and memory consolidation in both animals and humans, and try to connect sleep stages with the different memory systems. To this end, we have collated data obtained using several methodological approaches, including electrophysiological recordings of neuronal ensembles, post-training modifications of sleep architecture, sleep deprivation and functional neuroimaging studies. Broadly speaking, all the various studies emphasize the fact that the four long-term memory systems (procedural memory, perceptual representation system, semantic and episodic memory, according to Tulving's SPI model; Tulving, 1995) benefit either from non-rapid eye movement (NREM) (not just SWS) or rapid eye movement (REM) sleep, or from both sleep stages. Tulving's classification of memory systems appears more pertinent than the declarative/non-declarative dichotomy when it comes to understanding the role of sleep in memory. Indeed, this model allows us to resolve several contradictions, notably the fact that episodic and semantic memory (the two memory systems encompassed in declarative memory) appear to rely on different sleep stages. Likewise, this model provides an explanation for why the acquisition of various types of skills (perceptual-motor, sensory-perceptual and cognitive skills) and priming effects, subserved by different brain structures but all designated by the generic term of implicit or non-declarative memory, may not benefit from the same sleep stages.

KEYWORDS episodic memory, perceptual representation system, procedural memory, semantic memory, sleep stages

INTRODUCTION

Memory consolidation refers to a slow process that converts a still labile memory trace into a more permanent or enhanced form, notably by establishing connections between the medial temporal lobes and neocortical areas (McGaugh, 2000). The idea that memory consolidation is supported by sleep is almost as old as the concept of memory consolidation itself, first proposed by Müller and Pilzecker (1900; see Wixted, 2004, for review), and some of the earliest experimental evidence for it came from the pioneering study of Jenkins and Dallenbach

(1924). Since this initial work, numerous studies relating sleep to memory have provided arguments in favour of two, non-antinomic, explanatory theories. According to the first ('dual-process theory'; see for example, Plihal and Born, 1997,1999a; Smith, 1995), sleep stages, essentially slow wave sleep (SWS) and rapid eye movement (REM) sleep (which prevail during early and late sleep, respectively), act differentially on memory traces, depending on the memory system these traces belong to. As we will see further on, SWS appears to be required for the consolidation of information in declarative memory (consciously accessible memories for facts and events), whereas the consolidation of non-declarative information relies, for some authors, on REM sleep but is actually more consistently related to non-rapid eye movement (NREM) sleep (not just SWS) and features of NREM sleep. However, we cannot

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exclude the possibility that residual amounts of REM sleep and SWS during early and late sleep contribute to the observed consolidation effects. Thus, several studies have provided evidence in favour of a second theory, the 'sequential' or 'double-step' hypothesis (Giuditta *et al.*, 1995), which stresses the importance of the orderly succession of NREM and REM sleep in memory consolidation. Thus, both sleep stages appear mandatory for consolidating memories, regardless of the memory system the trace belongs to. In this way, NREM and REM sleep would complement each other; the succession of sleep stages during the night would reflect the different neural processes operating on the labile trace to transform it into a more stable and permanent form. These two explanatory theories are not mutually exclusive. Indeed, even if both NREM and REM sleep are involved in memory consolidation, one of these sleep stages may be more important than the other for a particular kind of memory. Thus, declarative memory might benefit more from SWS, while non-declarative memory might derive greater benefit from NREM sleep.

We will focus first on the animal literature and then look at the studies carried out in humans. Animal studies will be grouped according to their methodological approach, whereas human studies will be organized according to long-term memory systems, as defined in Tulving's SPI (Serial, Parallel, and Independent; Tulving, 1995) model. The aim of the present review is to present the recent research, highlighting the methodological or theoretical issues that will need to be considered in future studies. Although this review remains on a largely psychological level, it nonetheless takes the neurophysiological mechanisms into account, albeit to a lesser degree.

ANIMAL STUDIES

In animals, memory can be divided into two systems, one dependent upon the hippocampus and medial temporal lobe structures, which can be compared with human declarative memory, the other functioning independently of the hippocampus and broadly corresponding to procedural memory. Most studies have concerned the hippocampal-dependent memory system.

Post-training sleep deprivation studies

Several lines of evidence indicate that REM sleep deprivation impairs memory consolidation when applied during specific periods, called paradoxical sleep windows (PSW) (Peigneux *et al.*, 2001; Smith, 1995, 1996, for review). These PSW correspond to periods following training when there is an increase in the normal amount of REM sleep. The latency of onset of these PSW ranges from several hours to several days after the end of the training (Smith, 1985, 1995). REM sleep deprivation applied after training disturbs the retention of this learning. However, the degree of deterioration is determined by the complexity of the task. Indeed, simple tasks (e.g. passive avoidance, one-way active avoidance, simple maze), which are quickly learned and do not require significant modifications of

the animal's behavioural repertoire, are largely, if not totally, unaffected by REM sleep deprivation. Conversely, complex tasks (e.g. discriminative and probabilistic learning, complex maze learning, instrumental conditioning, etc.), which require the assimilation of unusual information and the development of adaptive behaviours, take longer to acquire and are particularly sensitive to REM sleep deprivation (Hennevin and Leconte, 1977; Peigneux *et al.*, 2001, for reviews). Furthermore, REM sleep deprivation is effective only if the animal has reached a certain level of learning (Dujardin *et al.*, 1990; Hennevin and Leconte, 1977, for review).

In a recent study, Datta *et al.* (2004) examined whether the activation of the P-wave (PGO waves generated in the pons) generator could reverse the learning impairment observed after selective post-training REM sleep deprivation. Rats were trained on a two-way avoidance-learning task. They were then divided into three groups receiving either a saline or a carbachol injection in the P-wave generator and were selectively REM deprived or allowed to sleep normally. The rats that received both the saline injection and REM sleep deprivation showed learning deficits when compared with the control-saline injected rats that slept normally. By contrast, a carbachol-induced activation of the P-wave generator prevented this learning impairment associated with post-training REM sleep deprivation. Moreover, the level of P-wave generator activation after training was correlated positively with performance improvement during the retest session. These results suggest that the activation of the P-wave generator is one of the mechanisms subserving memory consolidation during REM sleep.

To sum up, these studies indicate that selective post-training REM sleep deprivation impairs consolidation of hippocampal-dependent memory. Nevertheless, this effect appears to depend on the moment at which REM sleep deprivation is applied, the complexity of the task and the level of training achieved. This memory impairment can nonetheless be prevented by activating the P-wave generator, which may therefore be one of the mechanisms leading to memory consolidation.

The potential role of SWS on memory consolidation cannot be explored using this deprivation approach since in animals, unlike humans, SWS cannot be distinguished from lighter sleep stages 1 and 2.

Post-training sleep modifications

In line with the results discussed above, studies assessing learning-dependent modifications of sleep have shown an increase in the amount of REM sleep after training on complex tasks, although not simple ones. This lengthening of REM sleep duration is due, in rodents, to an increase in the number, although not the length, of individual REM sleep episodes. Moreover, while animals with good performance present significant increases in REM sleep, more poorly performing animals do not show any modification of the amount of this sleep stage (Hennevin and Leconte, 1977, for review). Hence, an increase in the amount of REM sleep appears once a certain

level of learning has been reached and this increase is predictive of learning achievement (Hennevin *et al.*, 1995). In rats trained on an avoidance task, Datta (2000) observed an increase of P waves during the first four post-training REM sleep episodes. In addition, the changes in density between the first and the third episodes of REM sleep were proportional to the improvement in performance. These data suggest that the activation of the cells generating the P waves during REM sleep activate forebrain and cortical structures involved in memory consolidation, thus allowing recently-acquired information to be reprocessed.

Studies assessing the role of NREM sleep are scarce. However, it has been shown that the amount of NREM sleep increases, in parallel with that of REM sleep, after conditioning with positive reinforcement (Hennevin *et al.*, 1974). Moreover, in rats that fail to learn an active avoidance task the first day, the improvement in performance the following day was correlated with an increase in NREM sleep (Ambrosini *et al.*, 1988). This possible involvement of NREM sleep, which has not been thoroughly investigated using this methodology, suggests that these results could also be interpreted in the light of the sequential hypothesis of sleep function in memory consolidation (Giuditta *et al.*, 1995).

Even if we cannot rule out the possibility that increases in REM sleep and, to a lesser extent, NREM sleep also reflect aspects of the task other than consolidation (such as extended presleep practice), overall these results indicate the existence of learning-dependent modifications of these sleep stages. These changes in the amount of NREM or REM sleep may be conducive to memory consolidation.

Stimulations during sleep

Another way of demonstrating memory processing during sleep consists in investigating whether a relevant stimulus can be recognized, or if new associations can be established during sleep and transferred to the waking state. Evidence of such phenomena would indicate that active plastic changes occur during sleep.

Using non-awakening intra-cerebral stimulations, Maho and Bloch (1992) showed that simple conditioning could be established during REM sleep, but not during SWS. In addition, the conditioning acquired during REM sleep could be transferred to the waking state. Similar conclusions have been reported with a second-order conditioning procedure (Hennevin and Hars, 1992). Thus, the brain keeps during REM sleep the ability to respond to a given stimulus and this response can also be elicited during the subsequent waking state, indicating that memory encoding is possible during sleep. It also suggests that the memory trace created during sleep can be consolidated during the rest of the night.

Hennevin *et al.* (1989) examined whether, during REM sleep, the memory trace to be consolidated remains in a similar state to the one it was in immediately after acquisition. To answer this question, the authors applied, during postlearning

REM sleep, a light electrical stimulation of the mesencephalic reticular formation (MRF), known to enhance memory performance when delivered just after learning. Rats were trained to run in a maze for food reward. Half of them received non-awakening MRF stimulations during the first six phases of REM sleep following learning, while control animals did not receive any stimulation at all. Stimulated rats showed a marked improvement in performance, in terms of error number reduction, confirming the facilitative effect of MRF stimulations on learning. Similar stimulations during SWS had no effect on memory performance. These results suggest that dynamic processes, comparable with those operating immediately after training, take place during REM sleep. Like the conditioned stimulus applied during SWS in Hars and Hennevin's (1987) study, the stimulation, during this sleep stage, of the MRF, which is non-specific to the task, was not detrimental to learning, indicating that the impaired performance observed in the latter study could be specifically attributed to the introduction of the conditioned stimulus. These results suggest that the presentation of the conditioned stimulus during SWS interfered with an ongoing consolidation process, whereas stimulation during REM sleep had a facilitative effect on the processing of the memory trace (Peigneux *et al.*, 2001, for review).

Hennevin *et al.* (1998) performed simultaneous recordings in the lateral amygdala and geniculate nucleus in rats that had acquired a fear conditioning associating a sound and a foot shock. The sound was then presented alone during post-training REM sleep. The conditioned responses were maintained during post-training REM sleep both in the lateral amygdala and the geniculate nucleus. These changes in firing were not observed in pseudo-conditioned rats. These results indicate that the neural response to a stimulus can still be elicited during REM sleep. In another study, Maho and Hennevin (2002) examined whether neurons in the medial division of the medial geniculate nucleus and the dorsal part of the lateral amygdala respond to the presentation of a stimulus during REM sleep after appetitive conditioning, as they do after fear conditioning. Over three sessions, rats learned to associate a sound with the presence of food. After each session, the sound was presented at a non-awakening intensity during REM sleep. The authors simultaneously recorded the activity of neurons in the geniculate nucleus and the amygdala. During wakefulness, the discharge of neurons increased in response to the sound in both areas. During REM sleep, this conditioned response occurred solely in the geniculate nucleus, demonstrating an inhibited amygdala response during sleep. The comparison between these data and those obtained during fear conditioning (Hennevin *et al.*, 1998) suggests that the elicitation of a neural response to a stimulus in the amygdala depends on the emotional valence of this stimulus.

Overall, these data support two major conclusions: (1) memory association can develop or can be acquired during REM sleep; (2) electrical stimulation of certain brain areas can facilitate these associations.

Neuronal reactivations during post-training sleep

Several studies have investigated spontaneous neuronal reactivations during post-training sleep. Thus, Pavlides and Wilson (1989) found that when place cells (i.e. hippocampal cells which fire selectively when an animal occupies a specific location), discharge during spatial exploration behaviour, they increase their firing activity in subsequent sleep states. A few years later, using large ensemble recordings of place cells in the CA1 field of the hippocampus, Wilson and McNaughton (1994) showed that cells which fired together when the animal occupied particular locations in the environment exhibited an increased tendency to fire together again during SWS. This cellular activity during SWS reproduced the pattern of discharge observed when the task was performed, suggesting that information acquired during active behaviour is re-expressed during sleep and may represent a neurophysiological substrate of memory consolidation.

Several authors have shown that the temporal sequence of neuronal discharges observed in hippocampal CA1 neurons during spatial exploration is repeated on a faster timescale during SWS (Nadasdy *et al.*, 1999; Shen *et al.*, 1998; Skaggs and McNaughton, 1996). Using ensemble recordings of cells in the CA1 field of the hippocampus and the posterior parietal neocortex, Qin *et al.* (1997) showed that traces of recent experience were re-expressed in both the hippocampus and the neocortex during sleep. Temporally organized firing patterns, reflecting seconds to minutes of active behaviour, were also reproduced in the hippocampus during REM sleep on an equivalent timescale (Louie and Wilson, 2001). In the same vein, similar temporal activity patterns of single neurons in the motor cortex of the zebra finch were elicited not only during daytime singing and song playback, but also during subsequent sleep, suggesting that the song is replayed during sleep (Dave and Margoliash, 2000).

Neuronal reactivations have been observed during SWS (Kudrimoti *et al.*, 1999; Lee and Wilson, 2002; Shen *et al.*, 1998; Skaggs and McNaughton, 1996) as well as during REM sleep (Louie and Wilson, 2001; Poe *et al.*, 2000). These discrepancies may be partly related to the timescale on which the authors focused on, as some of them examined firing patterns on a timescale ranging from milliseconds to seconds while others studied longer periods (up to few minutes). Nevertheless, these results suggest the existence of complementary processes taking place during SWS and REM sleep.

In rodents, Siapas and Wilson (1998) have found temporal correlations during SWS between hippocampal ripples (high frequency waves, 140–200 Hz) and spindle activity recorded in the prefrontal cortex, reflecting co-activation of hippocampal and neocortical pathways. A similar correlation of neuronal discharges between the somatosensory cortex and the hippocampus has also been found (Sirota *et al.*, 2003). This co-activation of hippocampal and neocortical areas may be important for the process of memory consolidation. Indeed, according to the standard model of memory consolidation (Squire and Alvarez, 1995), the hippocampus, and more

largely medial temporal lobe, serve as a temporary index of multiple aspects of the memory trace. This trace will be then gradually consolidated by strengthening the links between the different neocortical regions subserving the memories.

In a recent study, Ribeiro *et al.* (2004) demonstrated, in rats, that large-scale neuronal firing patterns observed during the tactile exploration of novel objects can recur over several hours after the end of the task in most of the forebrain areas, whereas firing patterns associated with familiar stimuli are substantially less detectable over time. This reverberation of previously-generated patterns was strong during SWS and decreased during waking. REM sleep provided more variable results across the animals studied. Even if the majority of studies have implicated SWS, there is also evidence that reactivation can occur during REM sleep (see above Louie and Wilson, 2001; Poe *et al.*, 2000) leading Ribeiro and colleagues to suggest that both SWS and REM sleep may play distinct and complementary roles in the slow process of memory consolidation.

There is evidence that, in both animals and humans, the theta rhythm is associated with enhanced learning and memory during waking (Bastiaansen and Hagoort, 2003, for review) and that, in rodents, it is highly correlated with specific behaviours, such as exploration and movement (Buzsaki *et al.*, 1983). Accordingly, it has been suggested that the transfer of information between the hippocampal formation and cortical association areas (where memories will be durably stored) may be mediated by rhythmic activity in the theta frequency range. Although the theta rhythm is not prominent during SWS, it returns to its waking level during REM sleep and hippocampal cell discharge is then modulated at the theta frequency. These data provide further evidence of the role of REM sleep (when theta activity is maximal) in memory consolidation. This activity may be a potential mechanism for memory processing during sleep (Graves *et al.*, 2001; Louie and Wilson, 2001; Poe *et al.*, 2000, for review), with theta oscillations during wakefulness and REM sleep enabling information to flow from the superficial layers of the entorhinal cortex and thus, indirectly, from neocortical areas into the hippocampus. During the sharp-wave and ripple activity of SWS, information may also flow in the opposite direction, that is, out of the hippocampus to the deep layers of the entorhinal cortex and so back to the neocortex (Buzsaki, 1996, 1998). This dialogue presumably serves to strengthen synaptic connections between neurons that process information in a manner relevant to perform the task and may engage mechanisms such as long-term potentiation for circuitry modelling (see Paller and Voss, 2004, for review).

At the subcellular scale, a wealth of cellular and molecular studies has provided evidence in favour of learning-dependent modifications during sleep [up-regulation of genes involved in synaptic plasticity during REM sleep (see Ribeiro *et al.*, 1999, 2002), etc.]. We will not go into these studies here, as this review is intended to focus on the psychological level. However, further information on this particular topic can be found in two detailed reviews (Benington and Frank, 2003; Graves *et al.*, 2001). Work still needs to be done in order to

find out which cascades of cellular events are triggered and whether these processes induce subsequent behavioural modifications (Maquet, 2001, for review).

The results presented in this review of the animal literature provide additional proof of the existence of learning-related processes during sleep, which may support the consolidation of memory traces. Indeed, REM sleep deprivation has a detrimental effect on learning, especially so when the learning task is complex. In addition, training to a complex task generally results in an increase in the amount of REM sleep (increase in the number of episodes of this sleep stage), as well as, in the case of conditioning with positive reinforcement, for example, in an increase in the amount of SWS. Several studies have also shown that conditioning acquired during the waking state is re-expressed during REM sleep and, in some cases, during SWS. Vice-versa, conditioning acquired during REM sleep can be transferred to the waking state. These data therefore argue in favour of the existence of synaptic plasticity phenomena during sleep. Lastly, patterns of discharge of neuronal ensembles observed during active behaviour may be re-expressed mainly during SWS, but also, according to some authors, during REM sleep. However, a link has yet to be established between these neuronal reactivations and subsequent behavioural modifications. Peigneux *et al.* (2004) recently provided, in humans, evidence of such a link after an episodic learning task (see the following section).

HUMAN STUDIES

Memory is not regarded as a unitary cognitive function but as the interaction of several systems. In humans, we can now go beyond the classic declarative versus non-declarative memory dichotomy and differentiate between these memory systems more accurately. Thus, according to Tulving (1995), human memory encompasses a short-term memory system (or working memory) and four systems of long-term memory: procedural memory, the perceptual representation system, semantic memory and episodic memory. Procedural memory can be defined as a system dedicated to the encoding, storage and retrieval of the procedures subtending perceptual-motor, perceptual-verbal and cognitive skills (Cohen and Squire, 1980). The perceptual representation system is involved in non-conscious expressions of memory, particularly priming effects (Tulving and Schacter, 1990). Procedural memory and priming effects are commonly designated as non-declarative (or implicit) memory, while the concept of declarative memory refers to semantic and episodic memory. Semantic memory encompasses knowledge about the world regardless of the spatio-temporal context of acquisition (I know that Rome is the capital of Italy, but I cannot say where and when I learned this fact). Semantic memory is characterized by a noetic awareness of the existence of the world, objects and events that also reflects a feeling of familiarity. Lastly, episodic memory refers to a system that stores events located in time and space (I remember our visit to the royal palace in Prague last Saturday). Episodic memory is characterized by auto-noetic

consciousness, which gives a subject the conscious sensation of travelling back in time to relive the original event and thus provides a means of linking events in the past, present and future (Tulving, 2001, 2002). Auto-noetic consciousness enables us to recollect vivid spatio-temporal and phenomenological details of the event.

In Tulving's model, information is encoded into systems serially, that is, the registration of information in one system is contingent on the successful processing in another system. For example, this model predicts that encoding in semantic memory can be efficient even if encoding processes in episodic memory are deficient, but not the reverse situation. Storage is parallel in the different systems and information from each system can be retrieved independently of information in other systems. Tulving's SPI model is the one that prevails in the neuropsychology of human memory, bearing in mind that memory is a dynamic process based on the interaction between the different systems.

Before getting to the heart of the matter, we first need to discuss a methodological issue raised by the studies relating sleep to memory. Numerous studies in this field have used sleep deprivation paradigms, where deprivation may either be total, selective of a given sleep stage or partial (of the first or second half of the night). Researchers first performed selective deprivation, in particular of REM sleep. The results obtained using this methodology must be viewed with some caution. Indeed, the numerous arousals needed to bring about selective deprivation may split sleep up and induce modifications of sleep patterns, emotional and attentional disorders, stress, a reduction in motivation and disturbances in biological rhythms (Cipolli, 1995; Horne and McGrath, 1984). These non-specific disturbances could affect behavioural performance and mask the real effects of sleep deprivation (Born and Gais, 2000). Stress response is often put forward to explain memory impairment after sleep deprivation. Indeed, corticotrophin-releasing hormone is a major component of the stress response and it has been shown that changes in the concentration of corticosteroids can affect consolidation (Plihal and Born, 1999b). The partial sleep deprivation paradigm could reduce these non-specific effects, as sleep is uninterrupted during the first or second half of the night. In this sense, this method is probably less disturbing than selective deprivation. However, this technique also has its drawbacks, as it means that part of the night is missed, resulting in a compensatory need for the lacking sleep stage. Hence, the results from sleep deprivation studies should be taken cautiously and confirmed by findings obtained using different paradigms.

Sleep and procedural memory

The various studies performed in the field of sleep and procedural memory have essentially focused on procedural learning. Procedural learning does not only involve procedural memory but also implies others memory systems and cognitive functions such as working memory, episodic memory and executive functions.

Perceptual-motor skills

Smith and MacNeill (1994) studied the acquisition of a perceptual-motor procedure, the pursuit rotor task, which consists in maintaining the contact for as long as possible between a stylus and a constantly-rotating light, using the non-dominant hand. The subjects were sleep-deprived after a training session. Total sleep deprivation on the night following the training resulted in poorer performance at retest 1 week later, whereas neither 3-h of partial sleep deprivation on the same night nor sleep deprivation carried out several days after the training had any detrimental effect. Like the control subjects, subjects who were selectively REM sleep-deprived had excellent performance on this task. By contrast, subjects who were sleep-deprived during the second half of the night (during which REM sleep prevails, rather than SWS) performed significantly worse than the controls. Considering that the second half of the night is mainly composed of stage 2 sleep and REM sleep in virtually equivalent amounts, the authors concluded in favour of a beneficial role of stage 2 sleep for this procedural type of learning (Smith, 1995, for review). Further, the individual scores correlated significantly with the amount of stage 2 sleep (Smith and MacNeill, 1992, 1994). This involvement of stage 2 sleep has seldom been reported in the literature. Nevertheless, these results suggest that motor-based tasks may depend more on stage 2 sleep than on REM sleep. It is important to note that these results do not raise any doubts about the relevance of 'early versus late sleep' comparisons. Indeed, both parts of the night contain comparable amounts of stages 1 and 2, differing only with respect to SWS and REM sleep. In this sense, the 'early versus late sleep comparison' mainly assesses the effects of SWS and REM sleep deprivation respectively. More recently, Walker *et al.* (2002) administered a finger-tapping task to subjects, requiring them to reproduce five-element sequences as quickly and accurately as possible, by pressing keys with the non-dominant hand. After a night of sleep, motor speed increased significantly, without any loss of accuracy, while an equivalent period of wakefulness brought no significant benefit. In addition, the overnight improvement in performance correlated with the amount of stage 2 sleep, particularly in the last quarter of the night. Further evidence for the correlation between performance improvement and the amount of stage 2 sleep takes the form of data indicating an increased number of spindles, a prominent feature of stage 2, after procedural training (Brière *et al.*, 2000; Fogel *et al.*, 2001). Moreover, some authors have suggested that sleep spindles play a role in synaptic plasticity, a phenomenon that may subtend memory consolidation (Sejnowski and Destexhe, 2000; Steriade and Amzica, 1998; Steriade, 1999).

In a recent study, Robertson *et al.* (2004) used a serial reaction time (SRT) task, in which awareness of learning could be manipulated to determine whether the implicit–explicit distinction influences off-line learning. Subjects faced a computer screen where several permanent markers were displayed. They were asked to react as quickly and accurately as possible

to the appearance of a stimulus below one of the markers, by pressing the spatially corresponding key. Subjects were trained on the task with either explicit instructions (a change in the colour of the visual cues indicated the introduction of the sequence to learn) or implicit ones (the cues remained the same throughout the training session with no mention of a particular sequence to learn) and were then tested after a 12-h retention interval, with or without a period of sleep. In the explicit condition, off-line skill improvement was only observed when the retention interval included sleep. By contrast, in the implicit condition, off-line learning occurred regardless of whether the retention interval did or did not contain sleep. These results are in keeping with previous studies which have recorded off-line improvements after a period of sleep in subjects who are usually fully aware of the skill they are being taught (Fischer *et al.*, 2002; Walker *et al.*, 2002, 2003a). Robertson and colleagues' findings indicate that off-line learning of implicit and explicit skills is subserved by two distinct mechanisms: one time-dependent, the other one sleep-dependent. Moreover, the overnight improvement observed in the explicit condition correlated with the amount of NREM sleep. This study also underlines the fact that awareness is a crucial factor that determines what is stored in memory in a sleep-dependant way.

Huber *et al.* (2004) administered a complex procedural motor adaptation task requiring hand-eye coordination to subjects, prior to sleep. During post-training sleep, slow-wave activity only increased in the right parietal lobe, known to be involved in this kind of task. The extent of the local parietal increase in slow-wave activity in the first 90 min of sleep also strongly correlated with the subsequent amount of learning enhancement observed the next day.

Two studies have provided evidence in favour of a beneficial role of REM sleep on motor-procedural learning. Thus, Plihal and Born (1997) assessed the consolidation of mirror-tracing skills using a partial sleep deprivation paradigm developed by Ekstrand and colleagues in the 1970s (Yaroush *et al.*, 1971). In this paradigm, illustrated in Fig. 1, the retention interval (period between learning and retesting) is either placed in the first or the second half of the night, dominated by SWS and REM sleep respectively (Hartmann, 1966), or covers an equivalent period of wakefulness. These authors found that recall of mirror-tracing skills improved more after REM sleep than after SWS (see Fig. 2a). Fischer *et al.* (2002) used a similar task to Walker *et al.* (2002) and largely replicated their findings, except they reported a correlation between the improvement in performance and the time spent in REM sleep, suggesting that REM sleep may also be involved in procedural learning.

In recent years, the study of the relationships between sleep and memory processes has benefited from a new source of inference: functional neuroimaging. Maquet *et al.* (2000) conducted a Positron Emission Tomography (PET) study using a SRT task in which stimuli appeared according to a probabilistic sequence. Several brain areas (such as the cuneus bilaterally and the left supplementary motor area) that had been activated during training were significantly more active

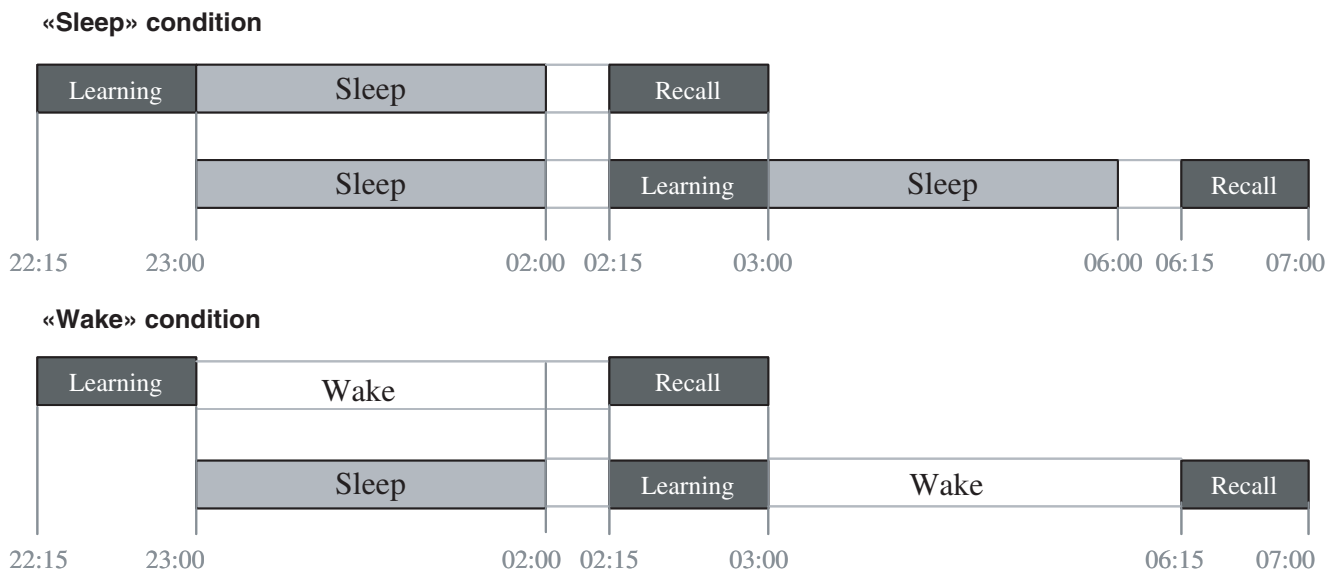


Figure 1. Partial sleep deprivation paradigm. Subjects are divided into two conditions. In the 'sleep' condition, subjects in the first of two subgroups learn the information between 22:15 hours and 23:00 hours. Their retention interval, the period during which they tried to consolidate what they learned, corresponds to a sleep period placed in the first half of the night (between 23:00 hours and 3:00 hours), rich in SWS. Fifteen minutes after awakening, subjects proceed to the recall phase. Subjects in the second 'sleep' subgroup learn the information after a period of sleep, between 2:15 hours and 3:00 hours. The retention interval is, this time, a period of sleep in the second half of the night, where REM sleep prevails. These subjects proceed to the recall between 6:15 hours and 7:00 hours. For the two subgroups in the 'wake' condition, the organization is exactly the same, except that retention intervals are filled with wakefulness.

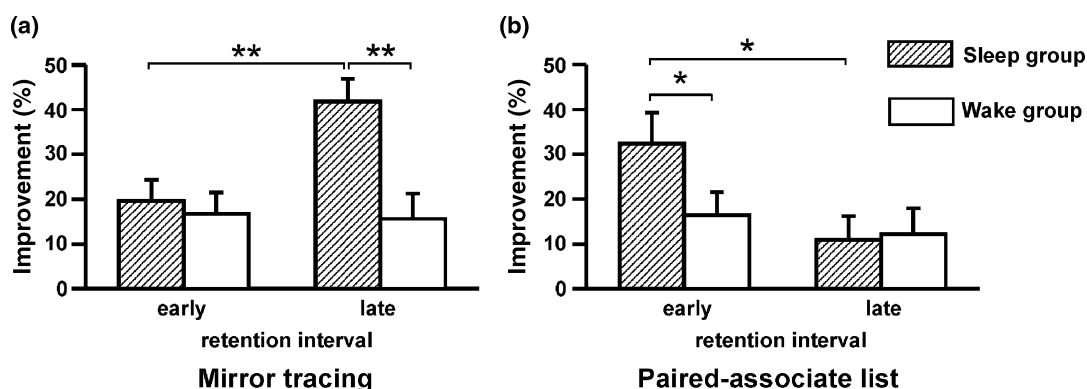


Figure 2. Mean improvement (\pm SEM) in performance after early and late retention sleep (grey bars) and after corresponding wake retention intervals (empty bars) for a procedural (mirror-tracing, a) and a declarative (paired-associate list, b) memory tasks. While procedural memory benefits from late, REM sleep-rich sleep, declarative memory relies instead on early sleep, during which SWS prevails. * $P < 0.05$; ** $P < 0.01$. Adapted with permission from Plihal and Born (1997).

during REM sleep in subjects who had previously trained on the task than in untrained ones (see Fig. 3). This study was the first demonstration, in humans, that the regional activity recorded while practising a learning task is re-expressed during subsequent sleep. In a later study, the authors considered the functional connectivity of the reactivated areas (Laureys *et al.*, 2001). The left premotor cortex was functionally more correlated with the left posterior parietal cortex and the bilateral presupplementary motor area during the REM sleep of subjects previously trained on the SRT task than during that of untrained subjects. According to Laureys and collaborators, this increase in functional connectivity during post-training

REM sleep supports the hypothesis that the cerebral areas do not act in isolation but take part in the optimization of the neural network subserving the subjects' visuomotor response. This optimization would explain the improvement in performance observed the following day. These results thus confirm the beneficial role of REM sleep in consolidating implicit information, although they do not exclude a potential contribution from SWS. As Maquet *et al.* (2000) obtained their results by comparing subjects trained on the SRT task and untrained subjects, the authors examined whether the reactivations observed during REM sleep reflected the reprocessing of the visuomotor skills or rather the implicit acquisition of the

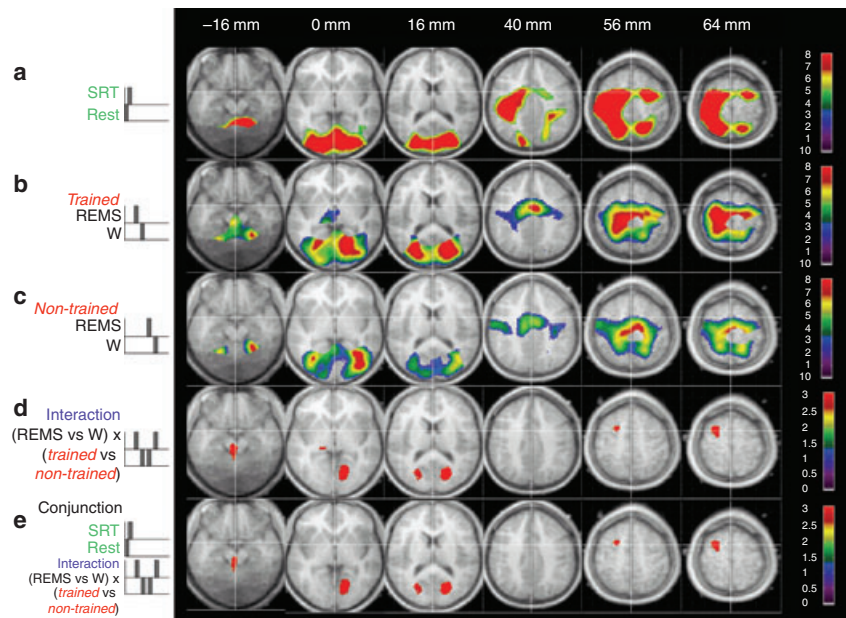


Figure 3. Experience-dependent changes in cerebral activity during REM sleep (Maquet *et al.*, 2000). Statistical parametric maps (SPM) of the cerebral areas activated while practicing a serial reaction time (SRT) task during wakefulness (a), and during REM sleep in trained subjects (b) and untrained subjects (c). Brain regions activated more in trained subjects than in untrained ones during REM sleep (d). Brain areas that were not only activated in subjects scanned while performing the task during wakefulness but were also more activated in trained than in untrained subjects scanned during REM sleep (e). Thus, certain cerebral areas activated while practicing an implicit task in the waking state are reactivated during subsequent post-training REM sleep. Reproduced with permission from Maquet *et al.* (2000).

rules that defined the stimulus sequence. To answer this question, Peigneux *et al.* (2003) measured the regional cerebral blood flow (rCBF) during the REM sleep of subjects trained on a SRT task using randomly defined stimuli and compared their results with those obtained by Maquet *et al.* (2000) using a probabilistic sequence. The authors showed that, during post-training REM sleep, the rCBF of the right and left cuneus increased more in subjects who had been trained on a probabilistic sequence of stimuli rather than a random one. The two groups of subjects were exposed to identical tasks, differing only in the underlying sequential structure of the stimuli. These results thus suggest that the reactivation of the cuneus during post-training REM sleep is not simply because of the acquisition of a visuomotor skill but rather reflects the reprocessing of information about the rules defining the sequences of stimuli to learn. Moreover, the level of acquisition of probabilistic rules achieved prior to sleep correlated with the increase in rCBF in the cuneus during subsequent REM sleep, suggesting that post-training cerebral reactivations are modulated by the strength of the memory trace developed during the learning phase. These data are also the first experimental evidence of a link between improvements in performance on an implicit task, measured during training prior to sleep, and cerebral reactivations during subsequent REM sleep.

Sensory perceptual skills

To investigate the acquisition of a perceptual skill, Karni *et al.* (1994) used a visual discrimination task whereby subjects had

to locate a target texture (three parallel diagonal lines) within a large square array of irregular lines during very short exposure times. The subjects who slept during a whole night or who were selectively SWS deprived by forced arousal improved their performance when retested in the morning. Conversely, selective disruption of REM sleep did not induce any improvement in performance, indicating that REM sleep is mandatory for consolidating this kind of learning. Using the same task, Stickgold *et al.* (2000a) showed that there is no improvement in performance during a day without any sleep episode. Deprivation of the first night's sleep after the training also strongly disturbed acquisition, even if the following nights are complete. The process of memory consolidation, i.e. the optimization of the skill, thus goes on beyond the end of the training, the first night of sleep being necessary to observe any improvement in performance.

In another study, Gais *et al.* (2000) provided evidence in favour of the involvement of both SWS and REM sleep to consolidate this kind of procedural learning. Indeed, using Karni's discrimination task and a partial sleep deprivation paradigm, these authors showed that performance improved significantly after early sleep. The improvement was even more important after a whole night's sleep. If performance improves less after early sleep (rich in SWS) than after a whole night containing both SWS and REM sleep, both sleep stages may be necessary for an optimal consolidation process. This finding is consonant with the sequential hypothesis proposed by Giuditta *et al.* (1995) which postulates that SWS and REM sleep are both required for memory consolidation.

Performance failed to improve not only after an equivalent interval of wakefulness but also after a period of late sleep, rich in REM sleep, this latter result being different of those reported by Karni *et al.* (1994). The methodological approaches used in these two studies (selective versus partial sleep deprivation) may, at least in part, account for the different results. Confirming evidence of this involvement of SWS and REM sleep comes from Stickgold *et al.* (2000b) who found that performance improvement on the visual discrimination task correlated with the amount of both SWS in the first quarter of the night and the amount of REM sleep in the last quarter (see Fig. 4). Mednick *et al.* (2002) tested subjects on this task four times a day. These authors observed a progressive deterioration in performance, attested by a progressive increase in perceptual thresholds across the four test sessions. This performance decline could be prevented by allowing the subjects to have a midday nap between the second and third sessions. These authors (Mednick *et al.*, 2003) also showed that the performance improvement observed after a 60- or 90-min nap containing both SWS and REM sleep was comparable, in terms of magnitude, sleep stage dependency and retinotopic specificity, with that previously observed after a night's sleep (Stickgold *et al.*, 2000b).

So, performance on a visual discrimination task improves slowly over the following days in the absence of further practice. To be optimal, this slow learning process requires a certain amount of sleep, especially during the first night after training. This consolidation process also appears to depend on both SWS and REM sleep. While most of the studies investigating the effects of sleep on sensory-perceptual skills have so far focused on the visual system, many studies have also described evidence of both time- and sleep-dependent memory consolidation in the auditory domain. Thus, using a pitch memory task, Gaab *et al.* (2004) showed, in subjects trained on the task in the morning or in the evening, that delayed improvement in performance occurred only across a night of sleep and not across equivalent periods of wake, whether the sleep or wake episode came first. Atienza *et al.* (2002, 2004) have also provided evidence of both time- and sleep-dependent auditory memory consolidation, notably showing sleep-dependent changes in event-related potentials (ERP). Fenn *et al.* (2003) studied the effect of sleep on a perceptual learning of spoken language. Subjects were asked to recognize phonetically similar words generated by a synthetic speech machine. After a single training session in the morning, subjects showed an increase in accuracy to identify new items. A 12-h period of wakefulness reduced this increase by half whereas an equivalent interval including a period of sleep did not decrease accuracy. Nevertheless, the decrease in accuracy observed after 12-h awake could be reversed by a sleep episode such as a nap, suggesting a process of sleep-dependent consolidation capable of re-establishing previously learned auditory skills. These four last studies extend the findings obtained with visual tasks and suggest that the influence of sleep may be ubiquitous, whatever the sensory modality.

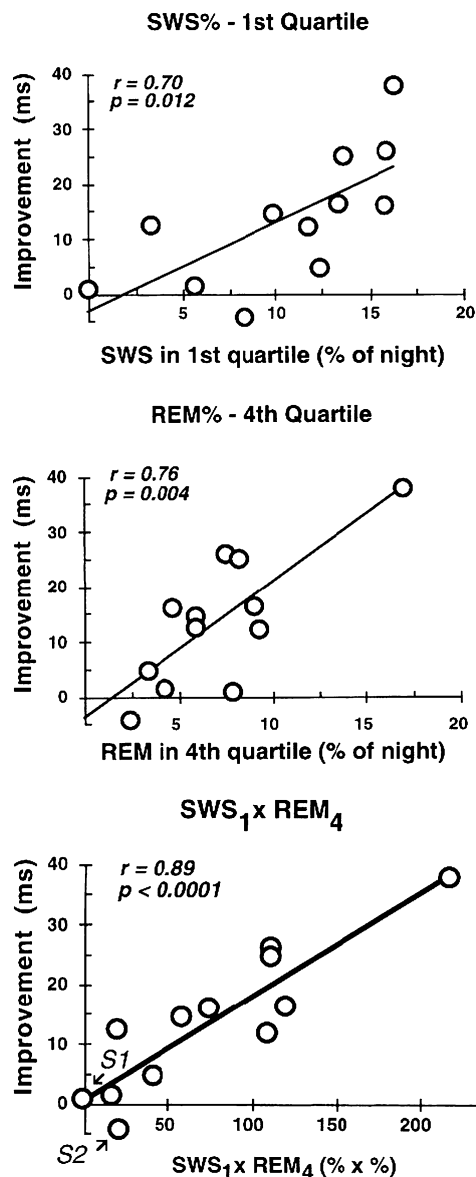


Figure 4. Correlations of overnight improvement in performance on the visual discrimination task with SWS in the first quarter of the night (top) and with the amount of REM sleep in the last quarter (middle). When combined (bottom), these two parameters were more significantly correlated with improvement than either SWS₁ or REM₄ alone, and explained 80% of the inter-subject variance. Adapted with permission from Stickgold *et al.* (2000b).

Cognitive skills

Few studies have investigated the acquisition of cognitive skills, although Wagner *et al.* (2004) have demonstrated that sleep facilitates insight. These authors designed a number reduction task in which the final solution could be reached by applying two simple rules. However, this task could also be solved in a much simpler way if subjects discovered a third, hidden rule. After all the subjects had been trained on this task, the training period was followed by an 8-h interval of nocturnal sleep, nocturnal wakefulness or daytime wakeful-

ness. Wagner *et al.* observed that sleep more than doubled the probability of discovering the hidden rule (i.e. gaining insight), compared with wakefulness. Moreover, in the sleep group, reaction times only decreased in subjects who did not discover the hidden rule. This last result indicates that changes that occurred in 'solvers' (subjects who discovered the third rule) resulted from an effect of sleep on memory representations, but did not originate from an effect on the procedural component of this task.

Only one study has tried to specify the potential role of SWS and REM sleep in consolidation of cognitive skills. Thus, Conway and Smith (1994) examined the effects of various types of sleep deprivations on performance on the tower of Hanoi, a test classically used to assess the acquisition of a cognitive procedure. The acquisition of this procedure was impaired in subjects who had been totally sleep deprived or had undergone selective REM sleep deprivation during the first post-training night. Conversely, this learning was not sensitive to selective SWS deprivation (Smith, 1995, 1996). These results indicate that consolidation of cognitive skills requires sleep, specially REM sleep.

To conclude, we report substantial evidence here for the role of REM sleep in the consolidation of cognitive skills. Concerning perceptual-motor learning, most of the studies carried out indicates a relationship to NREM sleep and features of NREM sleep, whereas the consolidation of sensory-perceptual skills (notably visual-perceptual skills) appears to rely more consistently on an association of SWS and REM sleep. In combination with results from animal studies, this last finding may suggest the existence of REM sleep windows during which memory consolidation is enhanced. This hypothesis is still speculative and needs to be confirmed, as such phenomena have only been identified with the visual discrimination task. Nevertheless, the overall data, including findings based on the latter task, underpin the hypothesis of a memory consolidation process consisting of several steps (sequential hypothesis, Giuditta *et al.*, 1995). According to this assumption, SWS and REM sleep would contribute jointly to the memory consolidation process, regardless of the memory system the trace belongs to. The particular sequence of the sleep stages during the night reflects the succession of neural processes operating on the still labile memory trace in order to turn it into a more permanent form. This theory nevertheless gives SWS a more important role than REM sleep. SWS would appear to prompt the consolidation process, while REM sleep acts on the memory traces later on, once the consolidation process has been initiated (Gais *et al.*, 2000; Stickgold *et al.*, 2000b).

In a recent review, Walker (in press) (see also Walker *et al.*, 2003a,b) proposed a neurocognitive framework of procedural learning, consisting of acquisition, followed by two specific stages of consolidation: stabilization and then an enhancement phase, whereby delayed learning occurs. During the stabilization phase, the memory trace becomes more resistant to interference. This phase results in the maintenance of performance level (i.e. no improvement in speed or accuracy)

without further practice. This stabilization process occurs in a time-dependent manner across periods of wakefulness following the acquisition of a procedural skill and does not require sleep. Then a phase of memory trace enhancement occurs, requiring sleep and leading to additional improvements in performance, rather than simple maintenance. Despite the stabilization phase, reactivation of a learned sequence at retest weakens the memory trace, which becomes labile once more and sensitive to interference, requiring a reconsolidation phase (Walker *et al.*, 2003a).

Walker's model of memory consolidation does not contradict the sequential hypothesis – it is 'simply that the sequential hypothesis of Giuditta and Stickgold focused specially on sleep, without detailed discussion of the differential effects of initial wake/time in producing behaviourally unique forms of consolidation. Indeed, it may be that for certain tasks (e.g. a visual discrimination paradigm), consolidation-based enhancement is achieved by a successive, early and late sleep-stage mechanisms as proposed by these authors' (Walker, in press). However, it remains to determine whether the beneficial effect of sleep reported here depends on the explicit or the implicit processes [see the studies performed by Robertson *et al.* (2004) and Peigneux *et al.* (2003), respectively] involved, at learning, in procedural tasks.

Sleep and perceptual representation system

The assessment of the perceptual representation system relies on the demonstration of the existence of perceptual priming effects. Priming refers to facilitative changes in the ability to identify, generate or process an item due to a prior encounter with this item or a similar stimulus (Tulving and Schacter, 1990). Priming does not require conscious or explicit recollection of the prior encounter with the item and, in this respect, is regarded, as a form of implicit (or non-declarative) memory (Graf and Schacter, 1985). Priming and procedural memory are therefore both expressions of implicit memory, but they differ in the nature of the stored representations and their neural substrates. In tasks assessing perceptual priming, stored information corresponds to items (i.e. drawings, words) presented only once, whereas procedural memory involves the storage of procedures acquired over several training sessions. In addition, priming and procedural memory refer to different memory systems, as attested by neuropsychological dissociations, particularly in subcortical dementias, and are subserved by different brain areas, as evidenced by neuroimaging studies (subcortical areas such as the striatum for procedural memory (see for example Hikosaka *et al.*, 1998) versus neocortical areas for priming (see for example Buckner *et al.*, 1995). In the light of these differences, these systems could well be differentially affected by sleep.

Studies assessing the effects of sleep on priming are relatively scarce. Plihal and Born (1999a) used a wordstem completion task to assess the effects of a partial sleep deprivation on implicit memory. The use of this completion task is always controversial, as it does not specifically assess the perceptual

representation system. In an initial, study phase, subjects were shown a word list and instructed to rate the nouns according to their melodious sounds. This instruction was considered to induce an incidental encoding of the items. After a distraction task, subjects were invited to complete a list of wordstems with the first noun that came into their head. Priming was attested by an increased percentage for the completion of previously-seen words, compared with novel ones. After a 3-h interval, during the first or second half of the night and filled with either sleep or wakefulness, the authors administered the completion task again, using wordstems derived from the remaining words in the initial list and the same number of items derived from a novel list. Priming effects were greater after late sleep than after early sleep. In other words, subjects who had slept during the second half of the night gave significantly more items belonging to the initial list than those who had slept during the first half. Hence, REM sleep appears to enhance the consolidation of implicit information.

Using the same partial sleep deprivation paradigm, Wagner *et al.* (2003) investigated the impact of nocturnal sleep on implicit memories for unknown faces. During the study phase, subjects had to indicate the gender of the individuals as quickly as possible, by pressing keys. During the test phase, they were instructed to indicate the gaze direction of the faces. Priming would normally correspond to shorter reaction times for the previously-seen faces than for new ones. Surprisingly, in subjects who had slept during the second half of the night, the authors observed longer reaction times for previously-encountered faces, which they termed an inverse priming effect. According to Wagner and his colleagues, this inverse priming effect reflected a facilitated identification of previously-encountered faces after REM sleep, thereby producing interference with the response generation during the test phase which required subjects not to identify faces but to determine the direction of their gaze. This explanation was confirmed by a complementary experiment in which subjects were required, in the study phase, to indicate gender and then, in the test phase, to decide whether a face was familiar or not. In this second study, no interference was found and priming effects were stronger (i.e. shorter mean reaction time for previously-encountered faces) when the retention interval was dominated by REM sleep (late night sleep).

These studies assessing the effects of sleep stages on priming effects have provided concordant results in favour of a beneficial role for REM sleep on the consolidation of implicit information. These results nevertheless have to be confirmed, taking care to design tasks that only involve implicit processes.

Sleep and semantic memory

Relationships between sleep and the consolidation of semantic information have seldom been investigated. Nonetheless, one series of studies has shown that semantic processing may occur during certain sleep stages. During wakefulness and different sleep stages, Brualla *et al.* (1998) recorded electrophysiological responses (event-related potentials) to the presentation of

words, some semantically associated, others not. During the waking state, the presentation of words elicited a N400 response (an electrophysiological marker of semantic discordance) which was greater in magnitude for words that were semantically unrelated to the preceding word than for items that were semantically associated. This decrease in the N400 response for semantically associated words reflected semantic priming. These priming effects were observed when items were presented during stage 2 sleep or REM sleep, but not during SWS. In a similar vein, Perrin *et al.* (1999) recorded auditory evoked potentials to the subject's own name and to other first names during wakefulness, stage 2 sleep and REM sleep. These authors underlined that a differential response to the subject's own name, comparable with that observed during wakefulness, was elicited during stage 2 and REM sleep. These results suggest that the brain retains the ability to identify a pertinent stimulus among others during these sleep stages.

Stickgold *et al.* (1999) also explored semantic priming effects using a lexical decision task. This task is classically used to assess implicitly semantic memory but, in this study, the authors sought to investigate the impact of the subjects' cognitive state when awakening (after a stage 2 NREM sleep or a REM sleep episode) on the strength of associative links between pairs of items. To this end, the task was administered to subjects four times: once prior to bedtime, twice immediately after awakening from stage 2 NREM sleep and REM sleep respectively, and 5 min after waking up in the morning. This task featured lists of prime-target pairs comprising unrelated, weakly related or strongly associated words, as well as word/non-word pairs. For each list, subjects were required to decide, as quickly as possible, if the second word of the pair (i.e. the target) was a word or a non-word. Priming was attested by shorter reaction times for items that were preceded by a semantically linked prime, than for weakly related ones. Subjects waking up from NREM sleep (stage 2) displayed priming effects whereas subjects waking up from REM sleep presented different responses i.e. shorter reaction times for weakly associated items. These results suggest that cognitive processes occurring during the waking state, NREM and REM sleep are qualitatively different and that the automatic spread of activation believed to underlie semantic priming is strongly hindered during REM sleep. This hindering of normal cognitive processing helps to explain the bizarre and hyperassociative nature of REM sleep dreaming.

The following studies had a different purpose and mainly assessed postlearning sleep modifications. De Koninck *et al.* (1989) monitored native English-speaking students during a 6-week French immersion course. Their knowledge of this language was limited to secondary-school level. While the proportion of REM sleep increased in these subjects during the course, the other sleep stages were not modified. This increase in REM sleep correlated with improvements in performance. Thus, subjects who did not really progress during the course (improvement <4%) did not have any significant modification in REM sleep. These results must, however, be viewed with caution. Indeed, this task consisting in acquiring new

information in semantic memory (reason why we class it as a semantic task), is not a pure-process task since it also involves, at least, an episodic component. Likewise, Mandai *et al.* (1989) studied modifications in REM sleep after a Morse code learning session. Subjects underwent a 90-min training session that consisted in identifying and reproducing sets of Morse code signals. This training session was administered before sleep and subjects were retested on the same task after awakening. Learning Morse code led to an increase in the amount of REM sleep and of the number of REM sleep episodes. Moreover, performance correlated with the density of REMs during REM sleep. Once again, these results suggesting a beneficial effect of REM sleep must not be taken at face value, as this task also involves a major procedural component. In this sense, learning Morse code could also be regarded as a cognitive skill which also depends, as previously shown, on REM sleep.

The results of the studies presented in this section indicate (1) that cognitive processes occurring during the waking state and the diverse sleep stages are qualitatively different and (2) that the amount of REM sleep increases after the acquisition of new semantic knowledge. The importance of these results remains, nonetheless, limited by the fact that the tasks used in the literature to assess semantic memory are not pure and involve procedural and/or episodic memory. Hence, it is hard to say whether the consolidation in semantic memory truly benefits from REM sleep or depends instead on the other processes involved.

Sleep and episodic memory

Literature dealing with episodic memory consolidation during sleep is particularly abundant but reveals several discrepancies. Yaroush *et al.* (1971) studied the retention of a word list across retention intervals located either during the day (waking state) or during the first or the second half of the night. The authors found a beneficial effect of sleep in the first half of the night (i.e. SWS) on recall performance. By the same token, Barrett and Ekstrand (1972) explored the consolidation of a word list in three groups of subjects. To eliminate circadian effects, the retention interval was placed between 2:50 hours and 6:50 hours for all subjects. This interval corresponded to a wakeful period for the first group and, for the second and third groups, to early sleep (rich in SWS) and to late sleep (rich in REM sleep) respectively. Recall was better after sleep than after wakefulness and better when the retention interval was filled with SWS rather than with REM sleep. More recently, Plihal and Born have confirmed these results. Using a partial sleep deprivation paradigm, they showed that SWS enhances declarative memory, as assessed via two distinct tasks: a verbal paired associate task (Plihal and Born, 1997; see Fig. 2b) and a mental spatial rotation task (Plihal and Born, 1999a).

Gais *et al.* (2002) have also supported the involvement of NREM sleep in the consolidation of episodic or declarative memories, measuring learning-dependent sleep modifications after paired-associate learning. The authors administered a

cued recall task immediately after learning and after a whole night's sleep. Spindle density was higher in subjects who performed the learning task than in control subjects. This effect was maximal during the first 90 min of sleep. In addition, spindles density correlated with performance on immediate and delayed cued recall. Spindle activity during non-REM sleep therefore appears to be particularly sensitive to the learning consolidation and thus successful recall of episodic information.

However, other studies have brought conflicting results. Thus, the recall of words, grammatically correct but meaningless sentences, and prose passages is significantly impaired after selective REM sleep deprivation (Empson and Clarke, 1970). Likewise, the recall of short stories is sensitive to REM sleep deprivation (Tilley and Empson, 1978). A beneficial effect of REM sleep has also been found for the recall of words belonging to different semantic categories (Tilley, 1981) as well as for the retention of emotional texts (Wagner *et al.*, 2001). Only one study (Chernik, 1972) has failed to find any significant impairment of word-pairs retention after REM sleep deprivation. Lastly, Ficca *et al.* (2000) have shown that the recall of pairs of unrelated words is impaired after fragmented sleep leading to a disruption of the sleep cycle, but not if awakenings during the night preserved the sleep cycle. This emphasizes the importance of sleep organization, i.e. the regular occurrence of NREM-REM sleep cycles, rather than of specific sleep states *per se*.

Studies concerning episodic memory consolidation present a degree of heterogeneity in their results, probably because of the nature of the stimuli used (e.g. neutral/emotional) and the cognitive processes involved. Moreover, many of the tasks used to assess episodic memory do not truly fit the current definition of this memory system. As previously mentioned, episodic memory refers to a system which stores events located in time and space, and is characterized by auto-noetic consciousness. Auto-noetic consciousness corresponds to a feeling of re-experiencing or reliving the past and mentally travelling back in subjective time. It differs from noetic consciousness, which characterizes semantic memory and corresponds to the subject's ability to be aware of information about the world in the absence of any recollection (Tulving, 1985, 2001, 2002; Wheeler *et al.*, 1997). Auto-noetic consciousness is usually assessed during recognition tasks with the Remember/Know (R/K) paradigm (Gardiner *et al.*, 1998). 'Remember' responses are based on the subject's ability to re-experience the source of acquisition of the event (spatio-temporal and phenomenological details) and reflect auto-noetic consciousness. By contrast, 'Know' responses, reflecting noetic consciousness, are based on a feeling of familiarity in the absence of conscious recollection. The tasks used to assess episodic memory in sleep studies are generally restricted to learning lists of words. The different components of episodic memory (factual, spatial and temporal) are rarely dissociated, and the state of consciousness is given little consideration. Some recent studies of episodic memory have used original tasks which fit more comfortably within current theoretical

frameworks. Accordingly, we will now focus on this handful of studies that have assessed episodic memory via purer tasks than the aforementioned.

Peigneux *et al.* (2004) recently performed a neuroimaging study using a virtual route-learning task. These authors discovered that hippocampal areas that were activated while exploring the 3D environment were re-activated during subsequent SWS (Fig. 5a). In addition, the hippocampal activity expressed during SWS was positively correlated with the improvement in route retrieval on the following day (Fig. 5b). These results support the view that re-expression of hippocampal activity during post-training SWS reflects the off-line processing of recent spatial episodic traces, which may lead to the plastic changes underlying the overnight improvement in performance.

Recently, in a partial sleep deprivation paradigm, we investigated the consolidation of episodic memories using an original task that takes into account the three components

(factual, spatial, and temporal) of episodic memory, as well as the state of consciousness of the subject performing the task (Rauchs *et al.*, 2004). This task, called the ‘What–Where–When’ test (Guillery *et al.*, 2000) consists in memorizing two lists of words (factual information or ‘What’), their location (at the top or the bottom of a page; spatial information or ‘Where’) and the list to which they belong (temporal information or ‘When’). Immediately after subjects have learned this information, free recall is tested. The second part of the task took place after a 4-h retention interval and comprised another free recall, followed by a forced choice recognition task for the word and each feature (spatial and temporal). For each response during this recognition task, subjects also had to indicate their subjective experience by means of the R/K paradigm (Gardiner *et al.*, 1998). Thus, subjects give either an R response, if they are able to bring to mind some recollection of what occurred when the item was encoded (i.e. thoughts, feelings or perceptions) or a K response, if retrieval is achieved without this access. Our main results indicated that spatial aspects of episodic memory (including the number of spatial features remembered and R responses associated with a correct recognition of the location of the items) benefit from late REM sleep, whereas SWS appears to be more beneficial to the temporal dimension of episodic memory (see Fig. 6). Hence, we suggest that the consolidation of a genuine episodic memory, i.e. including all its dimensions, requires both SWS and REM sleep, these stages probably dealing with distinct aspects of the memory.

Fosse *et al.* (2003) have examined the relationships between dreaming and episodic memory, focusing on the degree of similarity between the events that have occurred during the recent waking life and the dreams. Subjects kept a diary in which they reported their activities and dream reports. Recent episodic memories, assessed using very strict criteria, were replayed in less than 2% of the dreams. So, while elements of memories of recent waking life are reactivated during sleep, they do not take the form of intact episodic memories. For these authors, reactivation of episodic memories appears to be actively blocked during sleep. This finding, which suggests that sleep does not act on the memory traces to be consolidated, must be viewed with caution, as this study does not specifically assess retention. Nonetheless, the fact that only a few elements of an episodic memory are reactivated during sleep provides new insights into the process of consolidating episodic memories. Indeed, in a discussion of the study performed by Fosse *et al.* (2003), Schwartz (2003) provides a possible explanation for episodic memory consolidation during sleep. During the waking state, information flows to the hippocampus, which links together the various elements of an episodic memory that will be stored in different neocortical areas. According to some authors (Buzsaki, 1996; Hasselmo, 1999), the memory trace is transferred during SWS to the neocortex through neuronal bursts initiated in the hippocampus. By contrast, during REM sleep, the hippocampal outflow to the neocortex is blocked, and information flows mainly in the opposite direction. During this sleep stage, the information arriving in the hippocampus,

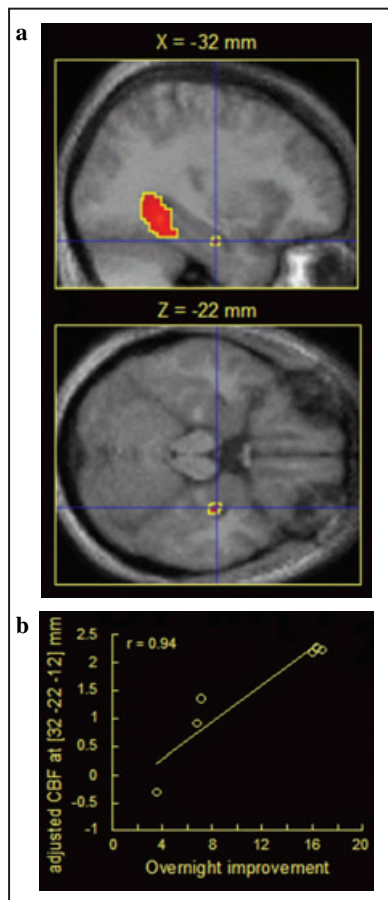


Figure 5. Hippocampal reactivation during slow-wave sleep and consolidation of spatial episodic memories. (a) Regression between regional cerebral blood flow increases during SWS and overnight improvement in performance (distance left to the target in presleep minus postsleep session) superimposed on sagittal (top) and transverse (bottom) cross-sections of the average T1-weighted MR image. Activations are located in the right parahippocampal gyrus (top cross-section) and right hippocampus (visible on both cross-sections). Adapted with permission from Peigneux *et al.* (2004).

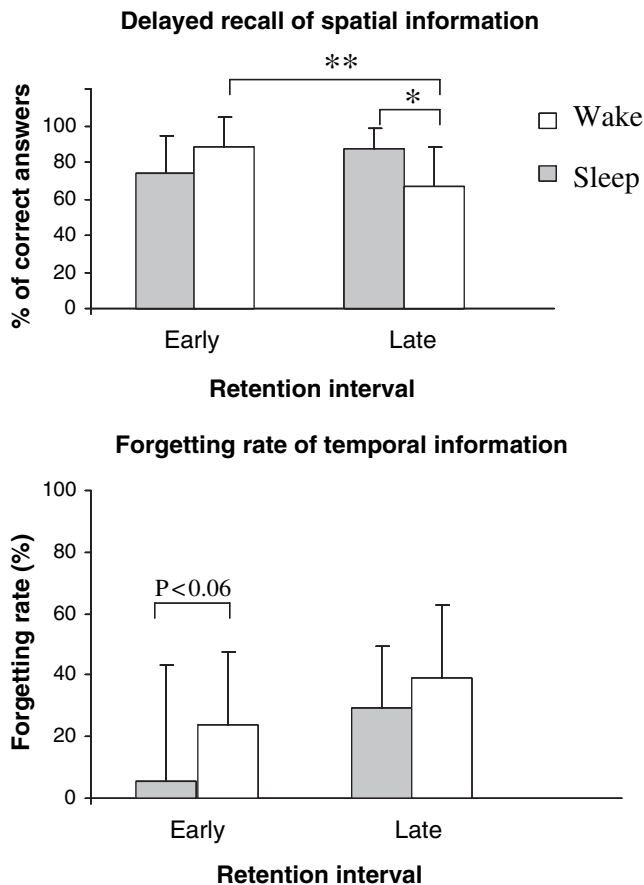


Figure 6. Mean performance (\pm SD) on delayed free recall for spatial information (top) and mean forgetting rate (\pm SD) of temporal information (bottom) after early and late sleep (grey bars) and corresponding wake control groups (white bars) for an episodic memory task: the 'What, Where, When' test. While consolidation of spatial information benefits from REM sleep, consolidation of temporal features appears to rely instead on SWS. * $P < 0.05$; ** $P < 0.01$. Adapted from Rauchs *et al.* (2004).

at least for recent memories, probably flows from independent cortical modules. Because of this, there is no reason to expect a report of complete and integrated episodic memories during REM sleep. The results would be different for older, consolidated memories, i.e. stored within inter-connected cortical modules. Moreover, recall processes depend on the integrity of the prefrontal cortex, which is deactivated during sleep. Thus, one can assume that episodic elements will be reactivated during sleep in a fragmented fashion, rather than in the form of an integrated life episode (Schwartz, 2003).

This model of memory consolidation proposed by Buzsáki (1996) and Hasselmo (1999) has recently been tested in humans (Gais and Born, 2004). In this study, the authors showed that an injection of the cholinesterase inhibitor physostigmine during SWS prevents the consolidation of declarative memories but has no effect on the consolidation of a motor skill. Thus, while the acquisition of declarative (or episodic) memories requires high levels of acetylcholine during the waking state (Hasselmo, 1999), the consolidation needs a low

cholinergic tone, which results in the cholinergic suppression of excitatory feedback synapses in the hippocampal CA3 field and on efferent projections spreading activation from CA3 to CA1, the entorhinal cortex and neocortex. Thus, the reduction of acetylcholine levels may provide an ideal window for transferring memory traces that have been recently encoded and indexed in the hippocampus to the neocortex.

Results concerning episodic memory consolidation have provided heterogeneous results, most of them arguing in favour of the role of SWS, others in favour of REM sleep. This heterogeneity can be explained, at least in part, by the material used and the processes involved while performing the task. Further investigations would appear to be necessary, in order to find out whether these partially discrepant results can be explained by the fact that episodic memory consolidation depends, like the consolidation of implicit information, on the alternation of both SWS and REM sleep episodes. Virtual reality techniques seem to be particularly useful in assessing contextual memory (spatial and temporal context) more accurately.

CONCLUSION

The results of the various studies outlined in this review have provided evidence in favour of both dual-process and sequential theories. Hence, these results suggest that SWS and REM sleep, as well as stage 2 NREM sleep, may all be involved in memory consolidation. Fig. 7 illustrates the relationships between sleep stages and Tulving's long-term memory systems. Based on our current knowledge, it is hard to reach a consensus on the role of specific sleep stages in memory consolidation. Nevertheless, it appears that within procedural memory, consolidation of perceptual-motor skills relies mainly on NREM sleep and features of NREM sleep (Fogel *et al.*, 2001; Huber *et al.*, 2004; Robertson *et al.*, 2004; Smith and MacNeill, 1994; Walker *et al.*, 2002, 2003a), with some evidence also suggesting a possible involvement of REM sleep (Fischer *et al.*, 2002; Plihal and Born, 1997). REM sleep may also have a beneficial effect on consolidation of cognitive skills whereas consolidation of sensory-perceptual skills appears to rely more consistently on a combination of SWS and REM sleep (Gais *et al.*, 2000; Stickgold *et al.*, 2000b). Results indicating that semantic memory and the perceptual representation system also benefit from REM sleep require replication using more pure-process tasks. The relationship between sleep stages and episodic memory is obviously more complex, as the literature contains mixed results. Thus, according to the tasks used, consolidation in this memory system may depend on NREM sleep, SWS, REM sleep or on a combination of SWS and REM sleep. Nevertheless, tasks involving emotional material (Wagner *et al.*, 2001) or mental travel in time to relive the original event (Rauchs *et al.*, 2004) appear to rely on REM sleep.

Even if the reference to Tulving's SPI model does not clarify all the relationships between the different sleep stages and memory systems, it does help us to understand some seemingly

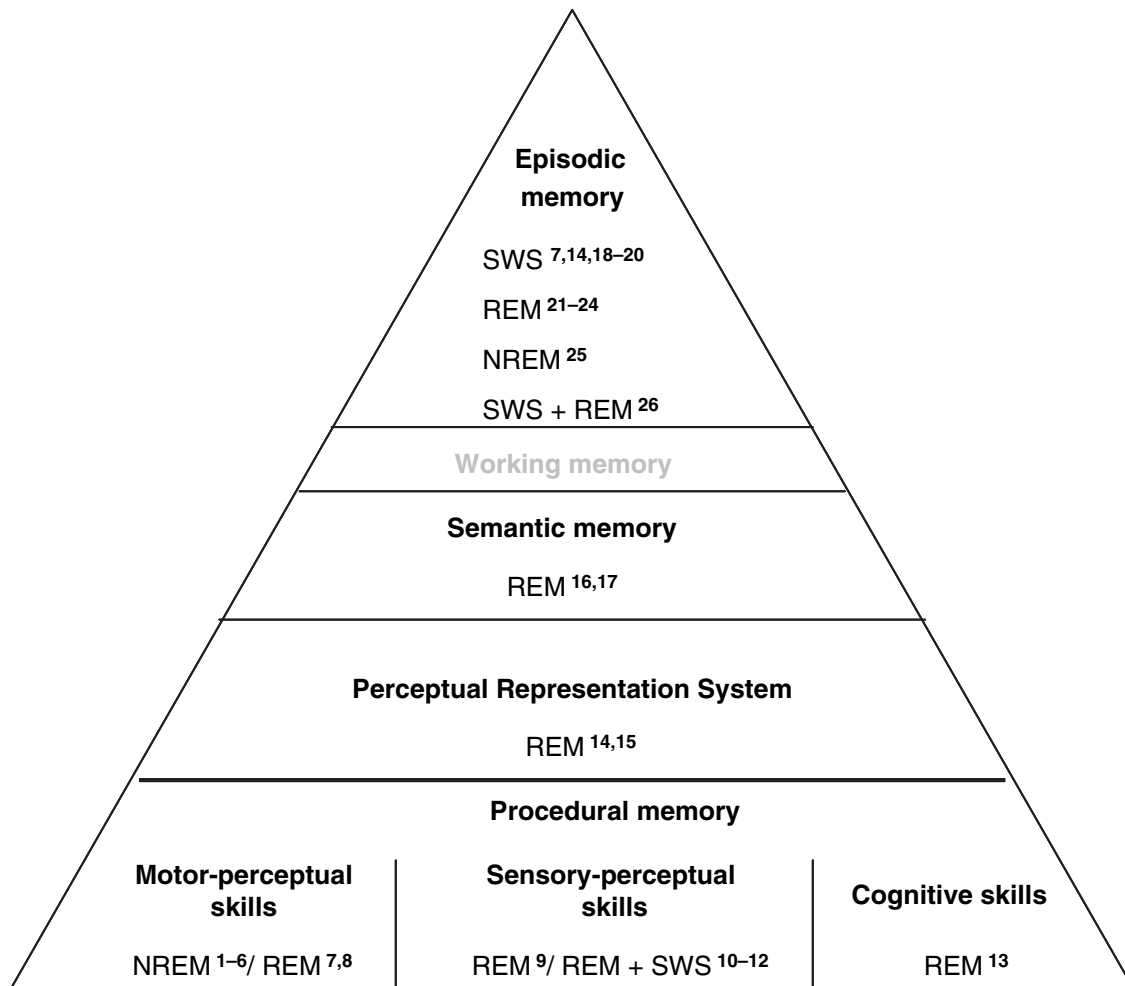


Figure 7. Relationships between sleep stages and Tulving's memory systems. Summary of the main studies dealing with sleep and memory systems. This figure is based on sleep deprivation, correlations and functional imaging studies in humans. The various studies have provided evidence in favour of a beneficial effect of REM sleep on procedural memory consolidation. However, few studies have provided elements in favour of stage 2 sleep for motor learning and of both SWS and REM sleep for tasks such as the visual discrimination paradigm. Both the perceptual representation system, which subserves perceptual priming, and semantic memory appear to rely on REM sleep as well, but these systems have not yet been extensively investigated. By definition, working memory (which is also a component of Tulving's SPI model) is not assessed when dealing with long-term memory consolidation. As for episodic memory, the numerous studies assessing this memory system have provided mixed results: beneficial effect of NREM sleep (including SWS), REM sleep or both. The use of tasks that do not truly fit the definition of episodic memory and the fact that different aspects of episodic memory (temporal/spatial) rely on different sleep stages may account for these inconsistencies. 1. Smith and MacNeill (1994); 2. Fogel *et al.* (2001); 3. Walker *et al.* (2002); 4. Brière *et al.* (2000); 5. Robertson *et al.* (2004); 6. Huber *et al.* (2004); 7. Plihal and Born (1997); 8. Fischer *et al.* (2002); 9. Karni *et al.* (1994); 10. Gais *et al.* (2000); 11. Stickgold *et al.* (2000b); 12. Mednick *et al.* (2002); 13. Conway and Smith (1994); 14. Plihal and Born (1999a); 15. Wagner *et al.* (2003); 16. De Koninck *et al.* (1989); 17. Mandai *et al.* (1989); 18. Yaroush *et al.* (1971); 19. Barrett and Ekstrand (1972); 20. Peigneux *et al.* (2004); 21. Empson and Clarke (1970); 22. Tilley and Empson (1978); 23. Tilley (1981); 24. Wagner *et al.* (2001); 25. Gais *et al.* (2002); 26. Rauchs *et al.* (2004). REM sleep, rapid eye movement sleep; NREM sleep, non-rapid eye movement sleep; SWS, slow wave sleep.

discrepant results. Indeed, this model explains the dissociation observed within declarative memory between semantic memory relying on REM sleep and episodic memory benefiting from SWS – as well as, in some aspects, from REM sleep. Likewise, this model shows why the consolidation of various kinds of skills (motor, sensory or cognitive) may not benefit from the same sleep stages since these skills are not necessarily subserved by the same cerebral areas.

Despite the considerable advances that have occurred during the last 10 years, contradictions remain to be resolved,

particularly with regard to the impact of REM sleep deprivation on the consolidation of prose passages, texts or words, or the contribution of SWS and REM sleep to the consolidation of implicit visual discrimination learning.

Lastly, the studies described in this review highlight the need to develop and validate tasks in which the respective contribution of the various cognitive processes involved can be more clearly defined. These tasks will then help us to determine which processes really benefits from a given sleep stage.

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