Published in: Neuroreport (2001), vol. 12, issue 18, pp. A111-A124
DOI: 10.1097/00001756-200112210-00001
Status : Postprint (Author's version)

Sleeping brain, learning brain. The role of sleep for memory systems

Philippe Peigneux[1], Steven Laureys[1], Xavier Delbeuck[1], Pierre Maquet[1,2]

[1]*Cyclotron Research Center, University of Liège, Bat. B30, Sart Tilman, B-4000 Liege, Belgium;*

[2]*Wellcome Department of Cognitive Neurology, University College London, UK*

KEYWORDS: Learning; Memory consolidation; Memory systems; Paradoxical sleep; REM sleep; Sleep; Sleep function; Sleep Stages; Stage 2 sleep; SWS

ABSTRACT

The hypothesis that sleep participates in the consolidation of recent memory traces has been investigated using four main paradigms: (1) effects of post-training sleep deprivation on memory consolidation, (2) effects of learning on post-training sleep, (3) effects of within sleep stimulation on the sleep pattern and on overnight memories, and (4) re-expression of behavior-specific neural patterns during post-training sleep. These studies convincingly support the idea that sleep is deeply involved in memory functions in humans and animals. However, the available data still remain too scarce to confirm or reject unequivocally the recently upheld hypothesis that consolidations of non-declarative and declarative memories are respectively dependent upon REM and NREM sleep processes.

WHAT IS SLEEP?

Sleep is operationally defined as a specific behavior during which the organism adopts a recognizable posture (usually characterized by the relaxation of the antigravity musculature), during which the responsiveness to external stimuli is decreased and which is regulated by a homeostatic process whereby the deprivation of sleep subsequently leads to a sleep rebound. In Homeotherms, distinct polygraphic patterns characterize the sleep episodes [1] (see below). While the homeostatic process maintains the duration and intensity of sleep within certain boundaries, the circadian rhythm determines its timing [2]. Sleep is not a unitary process, but is composed of at least two substrates, each named after its main distinctive features. One is characterized by the presence of rapid eye movements (REMs) despite global muscular tonus abolition and is therefore often referred to as REM sleep. It is also known as paradoxical sleep [3] (PS) because the phasic activity of the eye muscles and the high-frequency pattern of the electroencephalographic (EEG) recording give to REM sleep some resemblance to the awake state. In animals, a further distinguishing feature of PS is the recording of ponto-geniculo-occipital (PGO) waves, i.e. prominent phasic bioelectrical potentials that occur in isolation or in bursts just before and during PS [4]. PGO waves are closely related to rapid eye movements [5] and are recorded the most easily in the pons [3], the lateral geniculate bodies [6] and the occipital cortex [4], hence their name. In humans, functional equivalence of animal PGO waves has been suggested [7- 9], a hypothesis recently

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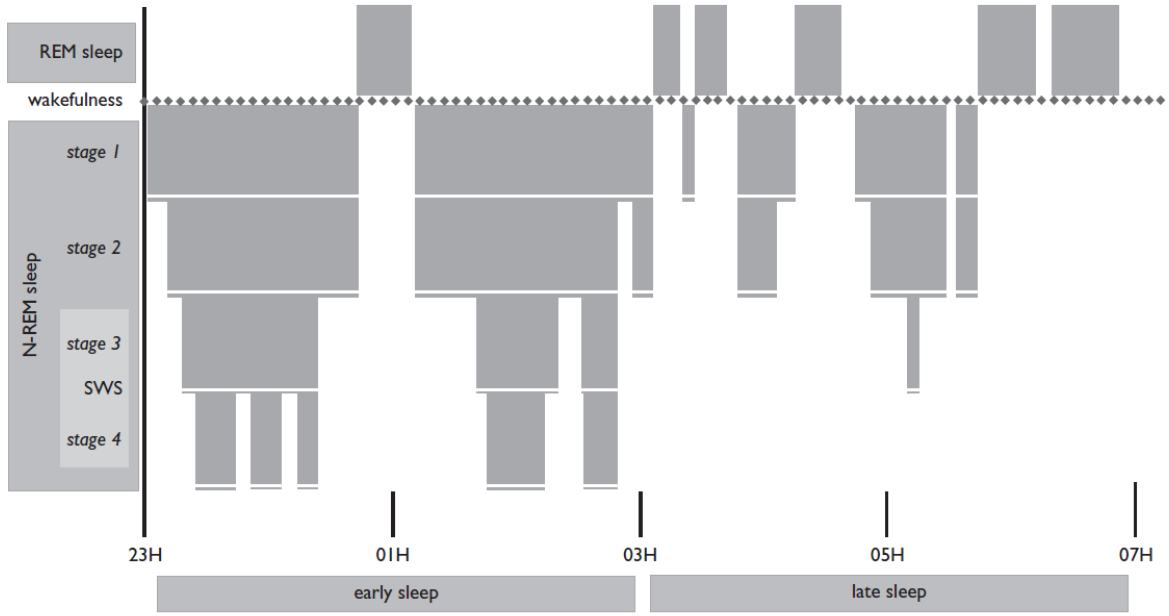
reinforced by the finding of rapid eye movements correlation with geniculate body and occipital cortex blood flow during REM sleep but not during wakefulness [10]. The other main sleep type is known as non REM (NREM) sleep. In primates, NREM sleep is divided into several stages, corresponding to increasing sleep depth [11]. Stage 2 sleep corresponds to light sleep and is characterized by K complexes and sleep spindles. While sleep deepens, the amount of slow oscillations increases leading to stages 3 and 4 sleep, or slow wave sleep (SWS). In carnivores such as cats or dogs, NREM is subdivided into light and deep SWS; and in rats or mice only one NREM stage is usually defined. This categorization of sleep stages is however somehow arbitrary. There is physiologically a continuum in the cellular activities subtending the NREM sleep stages [12]. This continuum is better characterized by spectral analysis that allows specifying slow (< 1Hz) and delta (1-4 Hz) rhythms, that probably correspond to specific discharge patterns observed at the cellular level [13,14]. Sleep is also characterized by a number of specific neurotransmitter and neurochemical changes [15-18] which profoundly modify cellular functions and interactions throughout the brain.

All through the night, the NREM and REM sleep periods alternate following an ultradian cycle, SWS invariably preceding REM sleep in healthy subjects. In humans, the ultradian cycle is about 90-100 min, but it is important to note that SWS is most abundant during the first half of the night (up to 80% of the sleep time), while in the second half of the night, the proportion of REM sleep dramatically increases [19] and alternates with stage 2 sleep (Fig. 1).

Figure 1. *Distribution of the sleep stages across a canonical night of human sleep. Horizontal axis: time elapsed from 23:00 h to 07:00 h. Vertical axis: stages of REM and NREM sleep. The shaded bars below the dotted line cover the periods of NREM sleep, and the length of the shaded bars represents the depth of the NREM sleep period, from stage 1 to stage 4. Stages 3 and 4 are usually grouped under the SWS label. Shaded bars above the dotted line represent periods of REM sleep. Periods of wakefulness correspond to periods of time in which the shaded bar is not below or above the dotted line. Note that SWS periods are mainly present during the first half of the night, while the number and duration of REM sleep episodes increases during the second half of the night.*



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INTRODUCTION

Despite our increasing understanding of the semiology, the mechanisms and the regulation of sleep [20], its function remains elusive. Among several hypotheses [21 - 29], it was suggested that sleep is involved in the processes of brain plasticity for memory consolidation. Brain plasticity, i.e. the capacity of the brain to modify its structure and function along time [30], could support several functions during sleep [31- 38]. Memory consolidation is defined as the time dependent process that converts labile memory traces into more permanent and/ or enhanced forms [39]. In this hypothesis, the information acquired during wakefulness would be actively altered, restructured and strengthened during sleep. The ensuing robust memory trace would enduringly adjust the behavioral responses to the recent environmental changes thereby enlarging the organism's behavioral repertoire [39- 43].

However, the picture becomes more complex when it is kept in mind that sleep and memory are both heterogeneous entities. Memory is not a unitary phenomenon, and long-term memories belong to multiple memory systems, primarily delineated between declarative, i.e. explicit, and non-declarative, i.e. procedural or implicit, memory in man [44, 45]. Sleep is composed of two prominent stages (see above), namely REM sleep and NREM sleep, the latter being subdivided into SWS and Stage 2 sleep in humans. These stages of sleep differ by many factors [20] including their temporal distribution and regulation [2], the pattern of neuronal activity [46], the specific neurotransmitter and neurochemical changes [47,48], and regional brain activity [49,50].

Up to now, four experimental approaches have been used to test the hypothesis of the processing of memory traces during sleep: (1) the effects of post-training sleep deprivation on memory consolidation, (2) the effects of learning on post-training sleep, (3) the effects of within- sleep stimulation on the sleep pattern and overnight memories, and (4) the reexpression of behavior-specific neural patterns during post-training sleep. These studies, which we review here, actually suggest that REM and NREM sleep stages could have memory-related functions. On this basis, not all types of memories seem to rely on the same stage of sleep for consolidation.

The role of sleep stages for memory has been interpreted in two different ways. The dual-process hypothesis argued that REM sleep and NREM sleep act differently on memory traces, depending on the memory system they belong to. An example is the hypothesis that SWS facilitates consolidation of declarative memory [51], whereas REM sleep facilitates consolidation of non-declarative memory [51, 52]. The other position is that particular sequences of sleep substates reflect the succession of brain processing events supporting memory consolidation [53]. In this view, SWS and REM sleep play complementary roles and have to act serially in order to consolidate the memory trace, in a double-step process [54].

Some caution is needed in discussing this issue because many of the published data deserve methodological considerations, which may obscure or overestimate the relationship between specific sleep processes and memories. Some of these issues have lead some authors to cast doubt on the role of sleep in memory processes, while others have argued that despite some

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methodological flaws in particular paradigms, a close observation of the entire bulk of available data did not actually allow to discard this hypothesis (see [55-67] for a recent contradictory debate on this topic). We will first detail several general reservations related to the study of memory functions, and will then comment on particular experimental approaches along with the data themselves.

METHODOLOGICAL ISSUES RAISED BY SLEEP/ MEMORY STUDIES

There are three important notes of caution concerning the interpretation of data relating to the relationship between different memory systems and sleep: (1) the need and definition of pure-process explicit or implicit memory tasks, (2) the use of animal models of human memory, and (3) the neuroanatomical segregation of memory systems in the brain.

Declarative versus non-declarative memory tasks in human studies: One of the distinguishing features of declarative memory is that information encoding and retrieval is carried out explicitly [68], i.e. the subject is aware that the stored information exists and is being accessed. Conversely, non-declarative memories can be acquired and re-expressed implicitly [45], i.e. although the subject is not necessarily aware that a new information has been encoded or is retrieved, its behavioral performance is affected by the new memory. Capitalizing on this distinction, human studies have shown modifications of sleep architecture after training to several reputedly non-declarative and declarative learning tasks, or selective memory deficits after REM or NREM sleep deprivation (see below).

However, learning Morse code, learning BASIC language or memorizing textbook passages, to cite but a few examples, are undoubtedly explicit verbal tasks, but they involve far more than a mere declarative memory component. For instance, language learning not only entails consciously memorizing dozens of new words and their meaning, but also entails to develop a learning strategy and continuously restructure the newly acquired information in a fashion coherent with the preexisting knowledge base. Moreover, one could correctly formulate a sentence while being unable to report the appropriate grammar rules, showing that a part of the language structure has been learned implicitly. This task type is definitely not process-pure, as explicit or implicit contributions to the performance cannot be segregated, and it is therefore unclear if subsequent sleep changes should be merely attributed to the presence of a declarative component or to the activation of other inherent processes.

More recent studies have proposed less complex tasks, the performance of which can be more easily attributed to declarative or non-declarative processes (e.g. declarative recall of paired-associates lists of words *vs* non-declarative perceptual learning), although it is claimed that, in fine, implicit and explicit processes both contribute to the observed performance in any task [69]. Future research should carefully control task parameters in order to specify the respective role of NREM sleep and REM sleep on the various human memory systems.

Animal hippocampal dependent memory as a model of human declarative memory: It is tempting to relate the effect of sleep on declarative memory systems in humans to what is known from cellular

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activities in the rat hippocampus during sleep. However, this tacit assumption holds only if memory systems in humans are adequately modeled by memory systems in animals. In humans, declarative memory is composed of episodic memory, i.e. autobiographical memory for events that occur in a specific spatial and temporal context, and of semantic memory which refers to general knowledge about the world [68]. It remains debated whether declarative-like memory exists also in animals. Some authors have claimed that only humans are capable of declarative memory [68], because retrieval of information is carried out explicitly and subjects are aware that the stored information is being accessed. However, others have argued that elements of episodic memory should exist also in animals in tasks in which singular events happen in a specific context [70] and which require to form relational representations between several kinds of stimuli [71]. With regard to the latter proponents, it is hypothesized that human episodic memory builds upon a system used for spatial learning in animals [72 - 75], dependent upon the hippocampal and medial temporal formation. Arguably, spatial tasks could be good markers of hippocampal function because their performance depends on the ability to form relational representations between stimuli [71]. In addition, recent findings suggest that a key feature of episodic-like memory tasks is their neuroethological relevance to the animal species [76] an example being food-cache retrieval in jays [77].

Hippocampal-dependent spatial memory tasks could therefore represent, at least in rats, a good animal model for human spatial episodic memory [78]. Nevertheless, even performance to animal tasks that require establishing other types of relationships could also be viewed as an expression of the plastic properties of the functional circuits underlying declarative-type memory in the brain [71].

Distinct neuroanatomical structures support distinct memories: In the previous section, we emphasized the role of the hippocampal formation in episodic memory. With regard to semantic memory, the other component of declarative memory, some authors have argued that the hippocampal formation selectively supports episodic memory while the surrounding entorhinal, perirhinal and parahippocampal cortices play the main role in semantic memory [79]. On the other hand, it should be kept in mind that the memory abilities aggregated under the nondeclarative label gather very different cognitive forms such as skills and habits, priming, and simple conditioning. Importantly, these various processes are subtended by distinct neuroanatomical structures both in human and animal [80, 81]. For instance, the striatum is important for habit formation [82] and interacts with the cerebellum for motor-based skill learning [83] while modality-specific neocortical regions mediate modality-specific perceptual priming [81] and the critical role in unconscious emotional learning is played by the amygdala [84]. The effects of sleep on each of these various cerebral systems might be different and await more systematical characterization.

In the following sections, we introduce the data gained in sleep studies using the different paradigms. Mainly animal data published subsequently to existing reviews will be presented here. For a complete presentation of prior studies, the interested reader is referred to reviews on the effect on memory of sleep deprivation in animals [52,85-89] and humans [52,86,90] on post-training sleep modifications in animals [52,85-88,91,92] and humans [52,86,88,90] and the effect of within-sleep stimulation in animals [87,91,92].

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POST-LEARNING SLEEP DEPRIVATION

An important part of the work relating sleep to memory processes used sleep deprivation paradigms. The classical procedures are as follows. First, the awake subjects learn a new material. Then, part of the subjects are allowed to sleep normally; the remaining part of the group either do not sleep at all (total sleep deprivation), is woken at specific occurrences of the sleep stage under study (selective sleep deprivation), or is kept awake during the period of the night in which the sleep stage is predominant (partial sleep deprivation). Finally, pre- and post-night memory measures are compared between sleeping and sleep-deprived subgroups. Sleep deprivation studies in animals, mostly laboratory rats or mice, have mainly investigated the effect of partial or selective paradoxical (REM) sleep deprivation on memory. To selectively deprive the animal of PS, animals are usually housed on small platforms over water during the sleep period. When in paradoxical sleep, but not in NREM sleep, they tend to fall to water from their platform, due to the characteristic muscle atonia in PS. Hence, they have no opportunity to resume normal PS episodes, while NREM sleep is less disturbed. Other methods are drug-induced sleep deprivation, or gentle manual awakening at each occurrence of the sleep stage under study, defined on-line according to electrophysiological criteria. Drug-induced and mechanical deprivation methods do not seem to elicit different effects when using similar tasks [93, 94].

Although the data showing detrimental effects of sleep deprivation on memory are usually interpreted in terms of a need for sleep in memory consolidation, it should be mentioned that alternative interpretations are possible. Indeed, any sleep deprivation method can result in non-specific side effects such as stress, neuronal excitability alteration, emotional and motivational modifications, and biological rhythm disturbance [87, 95]. Stress response in particular has been proposed to explain the effect of sleep deprivation on learning and memory. Indeed, corticotrophin releasing hormone (CRH) constitutes a major component of the stress response, and steroids can modify memories [96]. Moreover, lack of sleep per se could also be detrimental to cognitive performance on the post-deprivation days. Fishbein [97] showed that although 3 days of deprivation prior to learning did not affect retention of the task when tested 1 h after, the performance was impaired when tested 24 hours later, suggesting that prior PS deprivation might prevent long-term memory consolidation. More recent studies suggest that PS deprivation prior to training impair performance in avoidance conditioning tasks [98-100] and delayed alternate version of the Morris water maze test [101]. In humans, REM sleep deprivation has a profound effect on mood [102] more than total sleep deprivation which seems to particularly impair tasks depending upon the integrity of the prefrontal cortex [103], e.g. word fluency [104], decision making [105] or short term memory [106] tasks. Therefore, lack of sleep could simply affect the recall of the learned information independently of the quality of the consolidation process during the sleeping period. Prior total sleep loss also impairs the implicit, but not explicit, acquisition of sequences in a serial reaction time task [107] and alters the characteristic pattern of brain activity during verbal learning tasks [108,109]. The partial sleep deprivation technique could reduce these side effects, because sleep is uninterrupted during the first or the second half of the night. However, this technique also disorganizes the sleep cycle, as half of the sleep period is missing. In addition, early sleep deprivation entails a need for compensatory SWS during the second part of the night, which is not the case

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during late sleep deprivation. Hence, comparisons between early and late sleep deprivation are difficult. Despite various attempts to circumvent these different problems, results from deprivation studies should be considered with caution and confirmed by parallel findings using different approaches. Future research should disentangle the respective role of deprivation, stress, and other factors on memory in sleep deprivation paradigms.

Animal deprivation studies: A large number of animal studies have shown that post-learning REM sleep deprivation (usually referred to as paradoxical sleep deprivation or PSD) exerts a detrimental effect on memory tasks. PSD is effective only when applied during specific periods of time, called paradoxical sleep windows (PSW), in which PS actually increases over normal level after training, and whose latency to onset ranges from hours to days after the end of training [52,85]. PSD applied after partial learning did not alter, or even enhanced [110] performance improvement across sessions when the level of learning was below a minimal threshold [86 - 88].

Simple tasks which did not involve significant modifications of the behavioral repertoire (e.g. passive avoidance, one-way active avoidance, simple maze) are generally not affected by PSD, while performance in more complex tasks (e.g. shuttle box avoidance, discriminative and probabilistic learning, complex maze, instrumental conditioning), which entail adaptive behavioral changes and assimilation of unusual information, is impaired after PSD [88,111]. In addition, more recent studies using the Morris water maze place test or the eight arm radial maze [52] have shown that PSD deteriorates spatial reference memory in maze learning [112 - 116], but not cued [114], working [114] or non spatial memory using the visible version of the maze [116]. Hence, the effect of PSD depends not only on task complexity, but also involves the reference (spatial) component of long term memory in tasks commonly used to examine hippocampal functions in memory.

The very fact that PSD detrimental effects depend upon the task type and its memory components, on the level of learning and on the time period at which it is applied after learning suggests that REM sleep indeed plays a role in the post-learning information processing leading to memory consolidation. Nevertheless, animal deprivation studies are not informative on the role of NREM sleep for memory, which was nearly never investigated using this paradigm.

Sleep deprivation in humans: Many results from human experiments support the dual process hypothesis, but they are challenged by discrepant results, some of which support the double step hypothesis. Several studies indicate that the recall of paired-associate lists of words [51,117121] is better after sleep during the first part of the night (early sleep; SWS predominant) than after sleep during the second half of the night (late sleep; REM sleep predominant). By the same token, the recall of spatial memory in a declarative mental spatial rotation task is better following early than late sleep [122] while non-declarative wordstem priming is more effective after late than after early sleep [122,123], suggesting that the declarative aspect of the task is more relevant than its verbal content in post-training SWS processing.

However, recall of sentences and prose passages was systematically impaired following selective REM sleep deprivation [124] and likewise poorer recall of short stories [125] or list of words of various categories [126] was observed following REM sleep, but not SWS, deprivation. In this respect, an important variable in text recall could be the emotional salience of the material [127] since

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emotional material is better recalled after REM than NREM sleep [128,129].

Concerning non-verbal tasks, Plihal and Born have shown that mirror tracing skills [51,121] (acquired through a non-declarative procedural learning task) improved more after late (mainly REM) than early (mainly SWS) sleep. Likewise, Karni and colleagues [130] have shown that selective REM sleep deprivation, but not SWS deprivation, abolishes the overnight performance improvement during visual perceptual learning (a texture discrimination task). No effect of REM sleep deprivation was observed when the task was previously learned, suggesting that the mechanisms of memory consolidation and formation strongly depend on REM sleep in this task. Moreover, no performance improvement was observed after one night of sleep deprivation followed by two full nights of recovery [131], suggesting that the first night after the learning episode is mandatory to the formation of the memory trace in this perceptual task.

The conclusions of Karni *et al.* [130] were recently challenged by another study comparing the effects of early, and late sleep deprivation [132]. Here, using the same task, the improvement in discrimination skills was not affected by late sleep deprivation, but rather by early sleep deprivation and even more so by total sleep deprivation. In line with the hypothesis of a sequential processing of memory between sleep stages [53] these data suggest that SWS prompts memory formation, which is possibly, but not necessarily, consolidated during REM sleep. Accordingly, it was recently pointed out that morning recall of pairs of unrelated words is only impaired after fragmented sleep leading to cycle disorganization, but not when awakenings during the night preserved the sleep cycle [133]. This reinforces the importance of whole night organization of sleep rather than of specific sleep stages *per se.*

Finally, one study provides indirect evidence that motor memory in the pursuit rotor task is dependent of stage 2 sleep [134]. In this study, it was shown that subjects totally deprived of the second part of the night failed the task while others submitted to REM sleep deprivation did not. As stage 2 is the main component to alternate with REM sleep in the second half of the night, its role for supporting this type of memory was inferred. It should be noticed here that the results of human studies which have shown a better performance after late than early sleep [51, 121,123,129] could be interpreted as reflecting the involvement of stage 2 as well than of REM sleep, as the time spent in both stages is quasi-equivalent during the second half of the night. It could be, for example, that motor-based tasks like pursuit rotor [134] and mirror tracing [51,121] depend more on stage 2 than on REM sleep. However, this implies also that sleep stage 2 is more important for certain types of memory consolidation during the second than during the first part of the night. At present, these views remain speculative and should be investigated in future studies.

In sum, human deprivation studies provide evidence for both the dual-process and the double-step hypotheses. They suggest that all stages of sleep (REM, SWS and stage 2 sleep) might be involved in the processes of learning and memory consolidation. Contradictions remain to resolve with regard to the influence of REM sleep deprivation on text material memorizing [124 - 126] and with regard to the relative implication of REM sleep and SWS in the visual discrimination task [130,132]. Future research should systematically investigate the reasons for these discrepancies using pure-process learning paradigms, in which influences of sleep stages on explicit and implicit learning post-processes can be sorted out.

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POST-LEARNING SLEEP MODIFICATIONS

The effects of training on subsequent sleep have usually been assessed using absolute or relative duration of NREM and REM sleep phases. It remains possible that these crude measures are insensitive to important aspects of sleep regulation. For instance, in NREM sleep, and especially in its deepest stage (SWS), the power spectrum of slow activities (< 4 Hz) might be the relevant parameter to be used in order to assess experience-dependent changes in post-training sleep. Use-dependent modifications in power density during sleep have been reported [135,136], and similar changes could be observed in learning paradigms. There is no comparable measure for REM sleep. In contrast to the theta rhythm in the rat, which is a prominent marker of REM sleep, power density in the theta band (5-8 Hz) in human seems rather related to the homeostatic process during wakefulness [137]. Likewise, rapid eye movement number [138] and density [138 - 141] are sometimes used as a measure of REM sleep intensity. This postulate is sensible, given that rapid eye movements in animals are related to PGO waves, which, in turn, have been related to memory processing during sleep (see below). However, other interpretations cannot be ruled out. For instance, the density of rapid eye movements during REM sleep has been proposed as a measure of sleep need [142].

Sleep in itself is also characterized by distinct hormonal and neuromodulatory changes, which could by themselves interact with memory processes. For example, there is a strong inhibition of glucocorticoid release from the adrenals during NREM sleep [143], while a prominent cholinergic drive contrasted with a decrease of the adrenergic and serotoninergic influences characterizes REM sleep [15]. As molecular mechanisms of memory and learning are themselves also characterized by acetylcholine modulation [47,144] or cortisol levels [145] these variables should be accounted for when investigating the relationship between sleep and memory systems. Also, other aspects inherent to training sessions could significantly affect the subsequent sleep. Indeed, it is known that stressful situations, such as sustained immobilization, can lead to an increase in REM [146]. Likewise, CRH and the corticotropic axis, which constitute a major component of the stress response, are also known to increase REM sleep [147]. Future research should sort out the respective influences of the cellular firing pattern, hormonal and neuromodulatory changes observed during sleep stages.

Animal studies: In agreement with studies using the sleep deprivation paradigm, animal studies showed that post-training increases in PS duration are generally found for complex, but not simple, tasks; in animals who achieved a sufficient level of learning; in good, but not poor, learner mice strains; at specific post-learning time windows (PSW) during which PSD is detrimental to subsequent memory performance, and that variations in these parameters depend on the task type and the animal species.

Other characteristics have been highlighted, suggesting that the modifications occurring during post-training PS reflect a dynamic process, which contributes to the elaboration of memories. Studies conducted in the laboratory of Hennevin *et al.* [86, 87] and Smith *et al.* [52] have shown that an increase in the amount of PS not only appears at critical stages of learning but also is predictive of learning achievement. For example, during distributed learning, the highest increase in PS duration is observed in the nights preceding performance stabilization, when the learning curve

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approached an asymptote, after which the amount of PS returns to baseline. Moreover, when subsequent modifications are introduced in the task, leading the animal to adapt its behavior to face new learning conditions, another increase is observed in PS duration. Onset time of post-training PS increases is highly variable, depending on the number of trials per session, the task type, and the mice strain. This suggests that temporal characteristics of PS increases depend upon the time course of the memory process, which varies with the nature and amount of information acquired during the training sessions [87].

Post-training increases in PS duration are generally due to an increase in the number of PS episodes rather than their lengthening, at least in rats and mice. Another interesting feature is the increase of the density of rapid eye movements (REMs), which was actually [94] found to precede the increase in PS duration which takes place during the PS window. In rats, REMs are known to be triggered by ponto-geniculo-occipital (PGO) waves, thought to contribute to brain plasticity [5,148]. When PGO waves are recorded from the pons, these are called pontine-waves (P-waves [149]), and it is known that P- wave generator cells widely project to the hippocampus, amygdala, entorhinal and visual cortex among other regions [150]. It has been hypothesized that P-waves generating cells may serve as a trigger or cue for sleep-dependent cognitive processes such as learning and memory. In a recent study [151] a significant increase of P-waves density was found in the first four episodes of post-training PS in rats trained on an avoidance task. Moreover, the P-wave density change between the first and third PS episode was proportional to the performance improvement observed between pre- and post-night testing sessions (Fig. 2). This could suggest that activation of P-waves generating cells in this mesencephalic reticular formation during PS reactivates the forebrain and cortical memory processing structures to reprocess recently stored information, in order to help maintaining the memory trace and enhancing memory processing efficiency [151].

With regard to NREM sleep, it was shown in two studies to increase, together with PS, after a positive reinforcement conditioning [152,153]. More importantly, in rats failing the first day to learn a two-way active avoidance task, performance improvement on the second day was related to an increase in the duration of SWS episodes [154-157]. It was shown that these increases are part of significant sequences of SWS-wake or SWS-PS episodes, and these results were reinterpreted in the framework of the sequential hypothesis [53] which posits that particular sequences of sleep stages reflect the succession of brain processing events supporting memory consolidation. Further studies identified other sleep sequences in the same rat strain [158 - 161] some of these associated with a high level of avoidance in fast learning rats [159 - 161], and correlating with the performance level in the training session [162] suggesting that memory consolidation during sleep not only depends upon particular sleep stages, but also on their temporal organization.

Human studies: Although initial studies failed to show any SWS or REM post-training sleep modifications in various verbal [163,164] and non-verbal [165,166] tasks, further studies more consistently found that sleep is affected by prior experience.

Post-training REM sleep modifications were found after sustained visual field inversion [167 - 169], acquisition of complex motor skills in trampoline learning [170,171], Morse code [172], foreign language [173] and BASIC [139] learning, textbook passage study [140], intensive learning period in college students [138], word recall in the elderly after donezepil-induced REM increase [141] and

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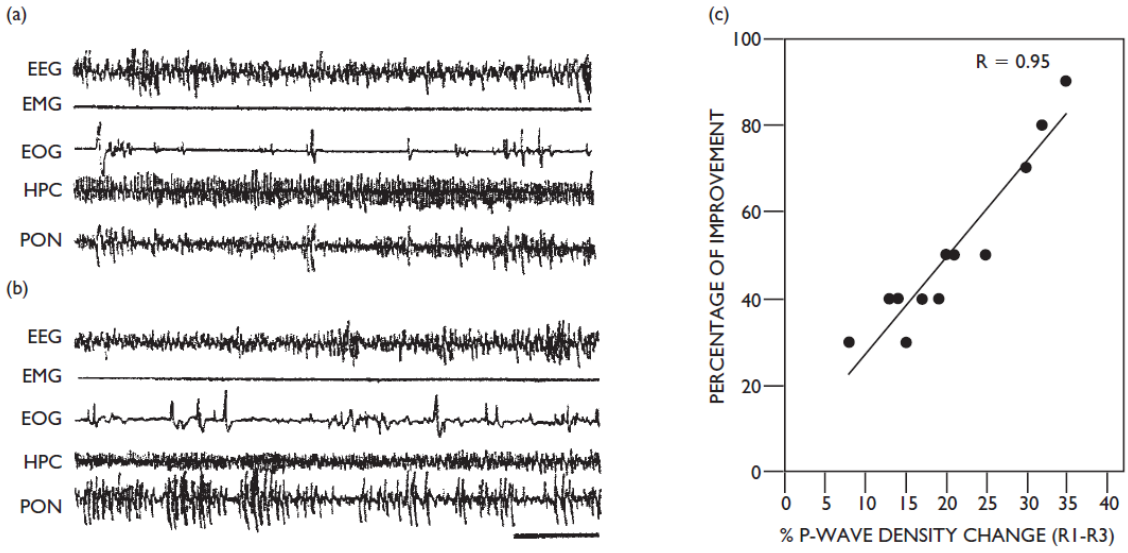
conditioning in 6-month-old infants [147]. However, it should be noticed that these modifications were found using various criteria, i.e. increases in REM duration [170,172,174], in the number of REM episodes [172] or in REM percentage of sleep time [140,147,171,173], but also rapid-eye movement density [138 - 141] and number [138] or even dream con tents [169] which make it difficult to conduct comparisons in this heteroclite task collection. Incidentally, it was also found that ocular saccades performed prior to sleep could actually occur less often in subsequent REM sleep than when not trained before [175,176].

Figure 2. *P-wave density changes during REM sleep after a two-way avoidance learning task [151], (**a**,**b**) Polygraphic appearance (sample) of the third episode of REM sleep after the first session (a) of control trials, i.e. unpaired presentation of conditional (CS) and unconditional (UCS) stimuli and (b) of learning trials (CS—UCS paired presentation). Although both records show characteristic electrographic signs of REM sleep, P-waves are more frequent in post-learning trials REM sleep than in post-control trials REM sleep. Polysomnography shows REM sleep cerebral activity recorded on frontal cortex electroencephalography (EEG) recordings, muscle atonia on electromyography (EMG), rapid eye movements on electrooculography (EOG), hippocampal waves in the hippocampal EEG (HPC), and P-waves (spiky waves) in the pontine EEG (PON). (**c**) Relationship between the P-wave density change between the first (R1) and third (R3) episodes of REM sleep after the first session of active avoidance learning trials and the improvement in learning. Data show that the level of improvement of learning in the retrial session depends positively on the percentage of the P-wave density increase between the first and third episodes of REM sleep immediately after the first session of learning trials. Adapted with permission from [151] (figure 2, p. 8610 and figure 5, p. 8611).*



Effects of learning on subsequent NREM sleep in humans are even scarcer. In one study, intensive

Published in: Neuroreport (2001), vol. 12, issue 18, pp. A111-A124
DOI: 10.1097/00001756-200112210-00001
Status : Postprint (Author's version)

maze learning or in a virtual environment enhanced subsequent EEG sleep spindles activities and increased the time spent in stage 2 sleep [177]. Another study, using the Karni et *al.* [130] visual discrimination task, showed that overnight improvement is a direct function of both the amount of SWS in the first quarter of the night and the amount of REM sleep in the late quarter of the night [54], suggesting that the memory information is not solely processed during REM sleep, but also during SWS. Note here that no improvement was observed for an equivalent amount of time spent awake, or unless subjects obtained > 6 h sleep, in which case the improvement was proportional to the amount of sleep in excess of 6 h. As this extra sleep period falls by definition in the last quarter of the night, in which REM sleep predominates, this indirectly confirms prior findings according to which late sleep deprivation significantly affects performance in this non-declarative task [51]. Finally, two studies have found that the performance in a paired associates word recall task is positively correlated with the number and duration of sleep cycles [178], the average duration of NREM/REM cycles, and the proportion of time spent in cycles over total sleep time [179].

It is intriguing to note that post-training modifications were observed in maze learning only when the maze was simple enough to allow the subject to form a cognitive map [177], in conditioning only when babies have successfully learned the response [174] and in verbal material learning only when the textbook passage to study was meaningful [140], which suggests that sleep post-training processing is allowed only if a coherent information to process has emerged from the training experience. This actually could be related to animal findings showing posttraining increases only in animals demonstrating a sufficient amount of learning [52, 86, 87].

In sum, human studies have shown post-training REM sleep increases in several reputedly non-declarative tasks (visual field inversion, conditioning, motor learning), but also in word recall (although the task could be considered implicit as subjects were not instructed to memorize the word lists overnight [141]), and various declarative learning tasks. On the other hand, no study has clearly isolated post-training SWS modifications alone (i.e. parallel changes have occurred in other sleep stages), although the involvement of SWS in paired-associates word recall [171,179] is consistent with the results of other human studies suggesting that SWS plays a significant role in declarative memory processing [51,96,121,122].

WITHIN-SLEEP STIMULATIONS

Another approach to demonstrate memory processing during sleep stages is to investigate whether a significant stimulus could be recognized, new associations can be formed and transferred to the awake state, or whether presleep learning is modified by non-awakening stimulations occurring during this stage of sleep. Indeed, evidence for such phenomena would indicate that active plastic processes are taking place during sleep.

Animal studies: Simple conditioning can be obtained in rats during PS, but not during SWS [180] using intracranial brain stimulation as conditioned (CS) and unconditioned (UCS) stimuli [180,181], and this conditioning can be transferred to the awake state [180]. Nevertheless, using a second-order conditioning procedure, the pairing of nonawakening tone and electrotactile stimulations, leading to a lick suppression response to the tone, could be established both during SWS or PS as efficiently as during wakefulness [182]. Conversely, a heart response conditioned during

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Status : Postprint (Author's version)

wakefulness could be expressed during subsequent PS, and evoked discharges in the medial geniculate nucleus in response to a conditioned tone during wakefulness could be obtained at the same level during PS on CS tone presentation [183]. Finally, using multiunit electrodes recording in the rat hippocampus, Maho *et al.* [184] demonstrated that a hippocampal response to a foot shock, paired to a specific CS (a tone) during wakefulness, could be elicited during PS on CS presentation, showing that not only the significant value of the stimulus had been detected during sleep, but also that the neural response occurs at least partly in the same hippocampal location. Hence learning-induced plasticity could be expressed both during PS and SWS stages, although more easily during the former.

In an active avoidance conditioning task, when the CS (slight ear shocks) used during a conditioning procedure was presented during the six PS periods following initial learning at wake, a significant performance increase was observed the following day. This performance gain was larger than when the same CS was presented during six periods of wakefulness [185]. In contrast, presentation of the same CS during the six SWS periods following learning significantly deteriorated the performance to the same task, but not presentation of another stimulus (a tone) unrelated to the conditioning [186]. Similar facilitation effects were found using mild electrical stimulation of the mesencephalic reticular formation (MRF) applied during the first six phrases of PS [187]. Note that here MRF stimulation, which is non specific to the task, was not detrimental to learning as was cueing when applied in SWS, showing that the impaired performance observed in the study mentioned above [186] after SWS cueing was specifically related to the introduction of the CS. This paradoxical result suggests that CS presentation during SWS had interfered with an ongoing memory process related to the post-training episode, while PS stimulations simply had a global facilitative effect on the processing of the memory trace.

Human studies: Few studies have investigated the possibility of initiating a conditioning procedure during NREM sleep in humans [188-190]. Preliminary results, which remain to be confirmed, indicate the possibility of a heart rate conditioning either during stage 2 [189] or SWS [190]. Nevertheless, several studies have demonstrated that automated discrimination of external sensory events is possible during various stages of sleep. ERPs to infrequent stimuli, presented among repeated stimuli, were recorded during REM [191,192], stage 1 [191], stage 2 [191] sleep and SWS [192]. Furthermore, the mismatch negativity (MMN) component for auditory ERPs was elicited in response to deviant tones in trains of tone bursts during REM sleep [193,194], unless the interval was > 3 s [194]. As MMN is hypothesized to reflect automatic detection of changes in the environment through current sensory input versus stored neuronal representation matching [195], it suggests that memory traces of external stimuli could survive > 3 s during REM sleep. No learning effect was found for lists of paired-associate words presented during either PS or stage 2 sleep and tested immediately afterwards [196]. Responsiveness to one's own name during sleep is a long-known phenomenon [197]. More recent studies [198,199] have shown that auditory ERPs after the presentation of one's own name are similarly elicited during wakefulness and REM sleep and with distinctive features during stage 2 sleep. Using combined EEG and fMRI techniques, it was shown that the presentation of auditory stimuli activates the bilateral auditory cortex, thalamus and caudate, both during wakefulness and NREM sleep. Moreover, hearing one's own name (as

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compared to hearing a neutral pure tone) additionally activates the left amygdala and prefrontal cortex [200]. Unfortunately, REM sleep examination and a more precise definition of the stage of NREM sleep were not allowed in this latter study. The results support, however, the idea that external events can be processed during sleep, and that stimulus significance can affect this processing.

Prior training also modulates brain responses during sleep. After a semantic priming initiated during wakefulness, greater ERPs were observed for pairs of unrelated (i.e. not primed) than for semantically related (i.e. primed) words during stage 2 and REM sleep, but not SWS [201]. Likewise, after having learned to discriminate complex auditory patterns, the MMN increase found during wakefulness was also present during REM sleep when stimuli were presented even 2 days later [202], suggesting that the information held in long-term memory has been rehearsed during REM sleep at a sufficient level to facilitate the detection of the deviant auditory stimuli.

On the other hand, within-sleep stimulations could enhance the performance for a previously learned task and modify the sleep architecture under some circumstances. When non awakening auditory stimulations (brief white-noise) are presented at random during post-training REM sleep after Morse code learning, there is an increase in REM sleep duration but only a marginal effect on memory [203,204], while presentation of the same auditory stimulations time-locked to the rapid eye movements did not modify REM duration but significantly enhance memory [204]. Likewise, a significant improvement in performance was demonstrated in subjects who had learned a complex logic task with constant auditory clicks in the background, when the same auditory clicks were displayed during posttraining REM sleep in coincidence with rapid eye movements [205]. As no performance improvement was found when auditory clicks were randomly distributed during the REM period, i.e., falling between rapid eye movements during the quiet period of ocular movements, the effect could hardly be explained by a simple elevation of the functioning level during REM sleep. It is known that REMs are closely related to the occurrence of PGO waves during REM sleep in animals [4] and possibly to their putative equivalent in humans [10]. PGO waves synchronize high frequency (20±50Hz) oscillations when induced by brain stem stimulation [206]. These fast oscillations involve thalamic and widespread cortical areas during REM sleep and wakefulness [207] and are presumed to play a substantial role in cognitive functions during wakefulness [208]. Hence, it could be that PGO activities during human PS synchronize fast oscillations that would convey experience-dependent information in thalamo-cortical and intra-cortical circuits to process recent memory traces.

REACTIVATION STUDIES

One of the most exciting contributions of the scientific research for the understanding of the mechanisms underlying memory consolidation during sleep has been brought in the last decade with the growing evidence that neural structures engaged in the process of learning during waking could be re-activated during subsequent stages of sleep. Most of this research was done in animals and it should be kept in mind that it has not yet been shown that the spontaneous reactivations of neuronal ensembles are related to any subsequent behavioral modifications. It remains to be shown that these cellular processes are actually behaviorally relevant for memory systems.

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DOI: 10.1097/00001756-200112210-00001
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Animal studies: Most studies have investigated posttraining neuronal spontaneous reactivations during sleep in the so-called place cells in rats, i.e. hippocampal cells selectively firing when the rat occupies a specific location in space [72, 73]. After having shown that the individual place cells activated during training increase their firing rate during the subsequent sleep episode [209], it was further shown using simultaneous recordings from a large ensemble of hippocampal cells that those cells that fired together when the animal occupied particular locations in the environment exhibit an increased tendency to fire together [210,211] and that the order in which they fired during the spatial exploration is re-expressed [212 ± 214] during subsequent SWS, not only within the hippocampus but also within the neocortex [215].

Firing rate and temporal sequences of activity in the hippocampal CA1 region were differentiated between neighboring neurons during PS following familiar versus novel experiences [216,217]. After exposure to a familiar experience, the firing of place cells during PS occurs preferentially at a phase of the local EEG theta rhythm 180° reversed from the peak firing phase during waking behavior. In contrast, for new memories, place cells discharge in phase with the theta rhythm during post-training PS. At variance, experience-specific patterns of firing correlations for familiar locations were found during post-training quiet wakefulness or SWS, but not PS [218]. Interestingly, another study demonstrated that the co-activation of cell pairs in CA1 remains highly correlated across sleep-wake-sleep sequences for both PS and NREM sleep stages, unless a novel task is introduced during the intervening waking period [219]. Lastly, hippocampal multi-neuron ensemble activity was recorded on a large time-scales up to minutes, during a spatial locomotor task in which the rat has to walk on a circular circuit from its place to a target with food reward systematically located 270° from the start. During post-training PS, the temporally sequenced ensemble firing rate patterns reflecting the training experience are reproduced at an equivalent timescale [220]. Likewise in the zebra finch, temporal activity patterns of single neurons in the motor cortex are active both during daytime singing, song playback, and the subsequent sleep phase, suggesting that the song is replayed back during sleep [221]. It should be noted that neural reactivations were found in rat hippocampus either in post-training SWS [212,213,218] or PS [217,220] using similar type of tasks. On the one hand, this apparent discrepancy could be explained by the different time-scales of the analyses and the working hypotheses of the different authors. On the other hand, it is likely that it reflects complementary processes, which take place during SWS and PS. It has been suggested that neo-cortical spindle activity and hippocampal discharge correlations during SWS [222] may be important for the initial process of memory consolidation [223] while hippocampal-cortical interactions are rehearsed during PS to consolidate the transition of recent memories from short-term hippocampal to longer-term neocortical stores [220].

Human studies: At variance with the animal field, obvious ethical reasons preclude the use of electrophysiological intracerebral techniques to prove the spontaneous reactivation of neuronal ensembles in healthy humans. Nevertheless, at the level of macroscopic cerebral systems, non-invasive brain imaging methods allow to study the regional cerebral activity in the entire brain both during wakefulness and during sleep. Although recent attempts indicate that fMRI can be combined with EEG recording and used to image human sleep [200] (despite severe technical limitations which remain to be resolved), the functional neuroanatomy of normal human sleep has been mainly

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investigated using PET and glucose metabolism ([^{18}F]fluorodeoxyglucose technique) or cerebral blood flow (CBF, $H_2{}^{15}O$) determination. Current implications, possibilities and limitations of global and regional cerebral blood flow (rCBF) measurement using PET during sleep are discussed elsewhere [224 - 226].

In SWS, as compared to wakefulness, the most deactivated areas are located in the dorsal pons and mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain/hypothalamus, prefrontal cortex, anterior cingulate cortex, precuneus and in the mesial aspect of the temporal lobe [50, 227 - 230]. During REM sleep, the most activated areas are found in the pontine tegmentum, thalamic nuclei, limbic areas (amygdaloid complexes, hippocampal formation, anterior cingulate cortex) and in the posterior cortices (temporo-occipital areas). In contrast, the dorso-lateral prefrontal cortex, parietal cortex, as well as the posterior cingulate cortex and precuneus, are the least active brain regions during REM sleep [49, 228, 231]. Stage 2 sleep *per se,* as differentiated from SWS, has received less interest. Global cerebral glucose metabolism in stage 2 did not significantly differ from wakefulness, although admittedly tending to decrease [232]. Sigma band activity (1215 Hz), maximal during stage 2 sleep, correlates negatively with the midline-medial thalamus rCBF [230].

The functional significance of these regional patterns of activations/deactivations across sleep stages and wakefulness remains a picture in development. The deactivation of mesio-temporal areas during SWS reflects local slow synchronous oscillations [225], already observed in the hippocampal formation of rats during SWS and possibly related to off-line reactivation of labile memory traces during sleep for consolidation into more permanent knowledge structures in the neocortex [45,90,210,222,233,234]. On the other hand, since amygdaloid complexes have numerous anatomical connections with the cortical brain areas activated during REM sleep, but very few with the least active regions, their strong activation observed during REM sleep [49] suggests that they modulate the activity of cortical areas during REM sleep [225] and that this amygdalo-cortical interplay reflects the processing of some type of memory traces, mainly emotional or procedural memories [235]. The hypothesis is reinforced by the demonstration that functional interactions between amygdala and occipito-temporal areas differ in the context of REM sleep compared with SWS or wakefulness [226].

Up to now, a single $H_2{}^{15}O$ activation PET study has been successful to demonstrate experience-dependent cerebral activity during REM sleep [236] using a non-declarative serial reaction time (SRT) task. These results are still preliminary and should be confirmed independently. The experiment showed that several brain areas, activated during the practice of the SRT task, were also activated during post-training REM sleep in subjects previously trained on the task, significantly more than in control subjects without prior training, suggesting a re-activation process which may contribute to overnight performance improvement (Fig. 3). Moreover, further analyses have shown that among these reactivated regions, rCBF in the premotor cortex was significantly more correlated with the activity of the pre-SMA and posterior parietal cortex during post-training REM sleep than during REM sleep in subjects without any prior experience to the task [237]. The demonstration of a differential functional connectivity during REM sleep between remote brain areas engaged in the practice of a previously experienced visuo-motor task gives further support to the hypothesis that memory traces are replayed in the cortical network and contribute to the optimization of the

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performance. These studies open a new field of research for the understanding of the functions of sleep in humans, as it remains to be demonstrated that the neural structures subtending either types of memories during wakefulness are reactivated during sleep, and possibly during specific sleep stages.

CONCLUSION

A growing body of experimental evidence relates sleep to memory processes, especially to memory consolidation.

In animals, it was suggested that hippocampal-dependent spatial memory tasks, thought to correspond to human episodic memory [78], depend on SWS sleep. Although reactivation of place cells is indeed often observed during SWS [210-215], available data do not support the hypothesis of SWS exclusivity since PSD also impairs reference spatial memory in maze learning [52,112-116] and hippocampal place cells conversely reactivate during subsequent paradoxical sleep [216,217]. Nevertheless, functional distinctions exist as place cell reactivations [216 ± 218] or co-activation of cell pairs in CA1 [219] during either SWS or REM apparently could be a function of stimulus familiarity, and within-sleep stimulations during either REM or SWS exert opposite effects during an active avoidance conditioning paradigm [186].

In humans, it should be concluded that the information still remains too fragmentary. The declarative versus nondeclarative (or explicit *vs* implicit) categorization of memory systems cannot be unequivocally superimposed to the distinction between NREM and REM sleep function for memory. Although infrequent stimuli can be detected in all stages of sleep [192], responsiveness to one's own name [198,199] and to primed semantic associates [201] is present during REM and stage 2 sleep only.

Figure 3. *Experience-dependent modifications of regional brain activity during REM sleep [236]. (**a**) Statistical parametric map (SPM) of the brain regions activated during practice of the SRT task during wakefulness, as compared to rest. (**b**) Brain regions activated during REM sleep after SRT task practice (trained group) compared with wakefulness. (**c**) Brain regions activated during REM sleep in subjects without prior experience (non-trained group). (**d**) Brain regions that showed a common activation in subjects scanned while performing the task during wakefulness (a) and that activated more in trained (b) than in non-trained (c) subjects scanned during REM sleep. SPMs are displayed on transverse planes at 6 different brain levels (from 16 mm below to 64 mm above the bicommissural plane) and superimposed on the average MRI image of the sleeping subjects. Adapted with permission from [236] (figure 2, p. 833)*

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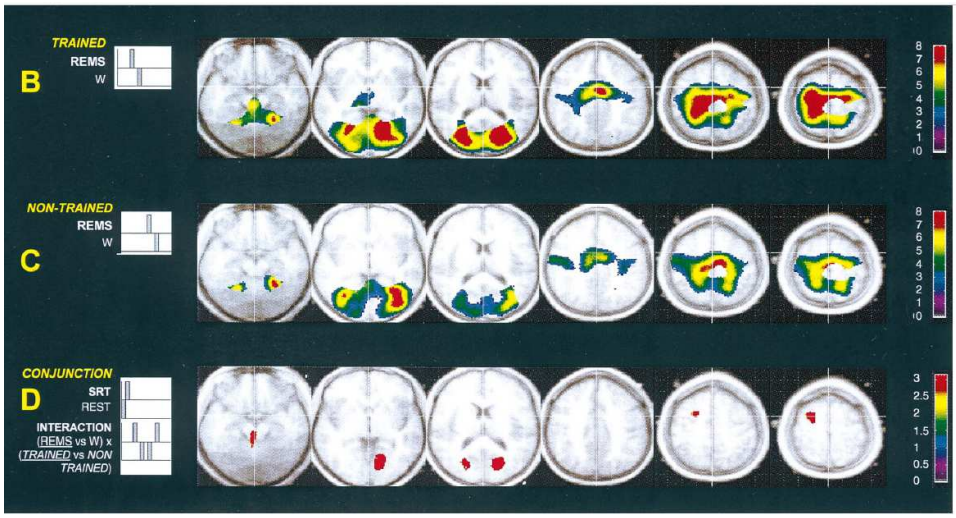
DOI: 10.1097/00001756-200112210-00001
Status : Postprint (Author's version)



This suggests that automatic semantic-like processing of externally presented stimuli can occur during these stages of sleep, but not during SWS. Several complex verbal tasks, such as text recall [124,125,138,140] and structured language learning [139,172,173,204], are affected by REM sleep deprivation or within-REM sleep stimulations and modify the post-training REM sleep architecture, while the only task using verbal material in which the performance seems clearly linked to post-training SWS or SWS deprivation is the declarative recall of paired associate lists of words [51,117 ± 121,178,179]. On the other hand, several non-verbal motor [170,171], perceptual [54,130,167 ± 169] and perceptivo-motor [51,121,236,237] procedural learning tasks have been linked to REM sleep, whereas memory for spatial mental rotations [122,123] but also a reputedly non-declarative perceptual task [54] have been shown to rely on SWS. Finally, the role of stage 2 sleep in memory consolidation remains to be resolved. Hence, we still do not clearly understand the respective role of NREM and REM sleep with regard to the consolidation processes for distinct memory types. We believe that the design of future experiments should specifically test the dual-process and double-step hypotheses, using more process-pure (explicit or implicit) memory tasks.

At a lower level of description, reactivations of neuronal ensembles seem to play an instrumental role in experience- related sleep processes. Recent studies showing experience-dependent gene-expression of gene zif-268 during paradoxical sleep in rats exposed to a rich sensorimotor environment [238] or the role of sleep for enhancing the remodeling of ocular dominance in the developing visual cortex [239] are also in line with the hypothesis that sleep participates to neuronal plasticity and memory processes. However, although neural re-expression in the hippocampus and anatomically connected cortical regions fits with theories of memory consolidation [45,222,233,234], the data available in the literature are still too scarce to conclude to a strict relationship between the consolidation process of particular memories (i.e. declarative or non-declarative) and the reactivation of dedicated brain systems. Moreover, the neural reactivations have been investigated using only a few tasks in animals, and these reactivations have not yet been shown associated to behavioral modifications on the next day. Therefore, the consequences of these reactivations should be explored in two different directions. On the one hand, the

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reactivations on the post-sleep behavior should eventually enlarge the animal's behavioral repertoire according to recent experience. On the other hand, the impact of the reactivations on the cellular and synaptic organization should lead to a better understanding of the basic mechanisms which might re-process the memory traces during sleep.

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Acknowledgements: The authors thank an anonymous reviewer for insightful comments on a prior version of this review, A. Komaromi for help in revising the manuscript, and authors and editors of refs [151,236] for their kind permission to reproduce Figures 2 and 3. P.P. was supported by the Fondation Medicale Reine Elisabeth (FMRE) and the Research Fund of the ULg during the preparation of this review. P.M. and S.L. are respectively Senior

Published in: Neuroreport (2001), vol. 12, issue 18, pp. A111-A124
DOI: 10.1097/00001756-200112210-00001
Status : Postprint (Author's version)

Research Associate and Postdoctoral Researcher at the Fonds National de la Recherche Scientifique de Belgique (FNRS).