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Review article

What in sleep is for memory

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Abstract

Since the seminal research by Jenkins and Dallenbach in the 1920s, it has been well proven that sleep has a major effect on the memory of pre-sleep material. However, there is still sparse knowledge about exactly which features of sleep have the most impact.

Studies which examined separately the role of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep provided largely controversial results and aroused harsh scientific debate, and the investigation of the link of specific sleep patterns to different memory systems (e.g. declarative vs. procedural) did not fully reconcile these inconsistencies.

New research perspectives have been proposed in recent years to overcome the limits of the previous ‘single state’ approach. Psychological, neurophysiological and neuroanatomical data have recently suggested that NREM and REM sleep both play a part in memory consolidation.

We here present the hypothesis that NREM and REM are complementary for memory processes during sleep, thanks to their close interaction within the NREM–REM cycle, and discuss experimental data which prove the critical role of the sleep cycle for the morning recall of verbal material.

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The relationship between sleep and memory has been an object of scientific debate at least since the seminal research by Jenkins and Dallenbach [1]. Sleep as a whole, or rather its components, were in turn considered to explain the apparent positive role of sleep on memory, but few topics have turned out to be as puzzling and complicated by epistemological and methodological difficulties as this one. (See the section devoted to this topic in Ref. [2]). Recent issues of journals such as *Nature*, *Science*, and *Behavioral and Brain Sciences* have shown renewed interest in this area.

We will question the conclusions about memory consolidation during sleep of material learnt during previous wakefulness (sometimes referred to with the more general terms ‘memory’ and ‘memory processes’), reached by separately considering each sleep state, and will show the advantages of studying the interaction of non-rapid eye movement (NREM) and rapid eye movement (REM) within the sleep cycle.

1. Early steps in the research about sleep and memory: the ‘sleep effect’

Experimental studies on the role of sleep in memory processes began a long time ago. Early landmarks were the research by Patrick and Gilbert [3] and the subsequent, well known study by Jenkins and Dallenbach [1], who showed that memory recall of nonsense syllables was better when the retention period (the interval between learning and recall), independent of its duration, was spent in sleep rather than wakefulness. This phenomenon, defined ‘sleep effect’, was consistently replicated by other authors [4–7], who used various materials for recall and more solid methodological control procedures for confounding factors such as time of day and baseline learning level.

A considerable amount of research has also presented theories expanding upon the original Jenkins and Dallenbach hypothesis that the sleep effect was due to the reduction of waking interference. If the global amount of sleep and wakefulness, and thus interference, is kept constant during the retention period, the sleep effect is more pronounced when sleep immediately follows learning

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than when it is postponed [8,9]. This result suggests that sleep might be favourable to the active memory ‘consolidation’ processes.

2. What is in sleep for memory? Sleep states and memory consolidation

It is now accepted that sleep is more effective than wakefulness for memory consolidation of waking events [10,11]. However, the problem of relating the single sleep states (REM sleep and NREM sleep) with memory is much more complicated. Attempts to shed light on this issue have been made mainly by means of two approaches: (1) the analysis of changes in the amount of sleep state following intensive learning; and (2) the analysis of memory performance after sleep state deprivation or after modification of amount.

At the outset, the majority of studies were targeted at the effect of REM sleep on memory. This is not surprising, because research on the connections between sleep and cognition (mainly memory) has been largely driven by neurophysiological paradigms and concepts (see Ref. [12] for a discussion); since the outstanding discovery made by Aserinski and Kleitman [13], and at least until the 1980s, most sleep research was generally focused on REM sleep. A compelling example is the large number of papers investigating specific phasic features of REM sleep (see Ref. [14] for a review), such as the organization of REMs in bursts [15] and the ponto-geniculate-occipital waves [16,17]. Research of sleep in relation to mental activity made no exception; the equation REM sleep = dreaming was still a cornerstone of sleep research at that time, as underscored by Lairy and Salzarulo [12].

The proposed relation of REM sleep to memory began with the hypotheses that REM sleep, characterized by a higher degree of cortical activation and a different aminergic–cholinergic balance in the central nervous system than NREM sleep, would represent the optimal time for an active consolidation of memory traces [10,18].

2.1. Animal studies

Many studies, extensively reviewed elsewhere [18–20], assessed the features of sleep on animals (usually rats) after intensive training sessions, often finding an increase of post-training REM sleep; in particular, the effect of REM sleep on memory was attributed to specific REM periods, named ‘REM windows’ and characterized by a more intense phasic activity [19,20].

Several studies that used either drugs or the ‘swimming pool’ technique to selectively deprive animals of REM sleep showed consequent memory impairment [19,21]. However, Vertes and Eastman [22], focusing on a number of methodological flaws and unsolved problems that pointed to the unreliability of evidence of a REM sleep–memory

link, observed that learning might deteriorate in an animal due to the intense stress provoked by the REM deprivation studies themselves. They stated, “...reports are equally divided in showing that REM deprivation in animals does, or does not, disrupt learning/memory’.

2.2. Human studies

Human studies have provided even more inconsistent results. In initial studies focusing on post-training REM sleep changes many found an increase of REM sleep after perceptual [23], motor [24] and verbal tasks [25], but many others did not [26–28].

Focus then shifted to NREM, namely slow wave sleep (SWS), in light of its crucial role in human sleep regulation [29–31]. Thus, specific comparisons of REM sleep vs. NREM sleep emerged. Whereas some research pointed to a more beneficial effect on memory enhancement of REM sleep than NREM [32,33], other studies found no difference between the two states [6,34,35], or demonstrated better recall of verbal material associated with predominant NREM sleep compared to REM sleep [36–38].

Overall, although several authors have insisted over the years that only REM sleep could play a role in memory [21,39,40], inconsistencies in the results have been made clear by those who carried out thorough reviews of the literature. Tilley et al. [10], for instance, noted that only half of the studies found an increase in the amount of REM sleep following a heavier information-processing load.

As a methodological remark, we want to stress the difficulty of extending results based on relatively simple tasks to more complex material, as is also underscored by Gais et al. [41].

3. The dual process hypothesis

The distinction made in the psychology of memory between procedural and declarative memory has been proposed as a key to finding a unitary model for the deeply inconsistent results provided by the literature.

Declarative memory, also referred to as ‘knowing that’ [20], includes notions, ideas or events which may be recalled in a conscious manner as verbal propositions and/or mental images. Procedural memory is unconscious and expressed by changes in behaviour. It includes perceptual and motor skills, but also simple responses such as habituation and conditioning, and is usually referred to as ‘knowing how’ [20].

It has been hypothesized that the effect of sleep state on memory process would be task-dependent. That is, procedural memory would benefit from REM sleep [19,20], whereas declarative memory would be linked to NREM sleep [42]. This model, referred to as the ‘dual process’ hypothesis [43], was the starting point for a set of studies which specifically explored procedural and declarative tasks. For

instance, it was shown that a perceptual learning task (which was considered equivalent to procedural memory), usually improved by sleep, is not improved following REM sleep deprivation [44]. Furthermore, a study by Plihal and Born [42] compared the effects of early and late nocturnal sleep, showing a preferential effect of the former (richer in SWS) on declarative memory, and of the latter (richer in REM) on procedural memory. However, much of the experimental evidence has not confirmed this hypothesis, in particular with respect to the NREM sleep-declarative memory link.

First, the proposition was contradicted by previous studies that found either no difference between REM and NREM [6,34,35] or a positive effect of REM sleep in declarative memory tasks [32,33]. Furthermore, it has been demonstrated that there is a functional difference in the content of the material to be remembered; in a recent study, only neutral material benefited from early night sleep, whereas emotional memory formation was selectively enhanced by late night sleep [45]. In addition, some results have failed to support the widely upheld connection between REM sleep and procedural memory; it was ascertained that motor tasks are actually improved by stage 2 NREM sleep [18,46,47].

This body of evidence reflects the difficulty of attributing specific psychological properties to single sleep components; there is no actual evidence explaining why different memory systems should follow different paths. We believe that the straightforward one-to-one link (REM-procedural, NREM-declarative) is not able to fully reconcile the inconsistencies of the results in the literature because the model tends to support an opposite role for each state but fails to consider the cooperation between the two for memory processing.

4. The two-step hypothesis

Alternatively, much evidence at different levels consistently suggests cooperation between NREM and REM for memory consolidation.

Ambrosini and Giuditta's group carried out a series of experiments on rats, focusing on the sequence of sleep and waking states [48,49], and proposed a 'sequential hypothesis' [50,51] requiring the participation of both SWS and REM. SWS is associated with both adaptive and non-adaptive memories, whereas adaptive memories are strengthened during REM sleep.

At the neurophysiological level, experiments on the electroencephalographic correlates of SWS [52–55], as well as Buzsáki's work [56,57], give strong support to the importance of close interaction between the two states for memory: a tight 'neocortex–hippocampus dialogue' would take place during sleep, with information flowing in one direction (from neocortex to hippocampus) during SWS, thanks to the synchronous firing of neocortical neurons, and

reversing its pathway during REM sleep as indexed by the sharp theta waves facilitating long-term potentiation.

In a recent review, Peigneux et al. [43] underscore that neuroanatomical correlates of these electrophysiological events have been identified on the basis of neuroimaging (mainly, PET) studies: for example, Maquet [58] claims that deactivation in the mesio-temporal areas reflects slow synchronous oscillation reaching the hippocampus in SWS, whereas the intense activation during REM sleep of the amygdala (which is anatomically connected with the cortical areas active during REM sleep) is an expression of the hippocampal *replay* towards the neocortex.

However, there have been few behavioural data in support of an actual link between these physiological events and memory. Some important contributions came from Stickgold et al. [59], who found that the entire night is more favourable than REM or SWS alone in a visual texture discrimination task. Moreover, Stickgold and collaborators [60] observed, in subjects trained at a visual search task, that the improvement in morning performance of the task was highly correlated to both the amount of NREM sleep in the first quarter and of REM sleep in the fourth quarter of an 8-h night of sleep. The authors speak of a 'two-step model', assuming a role for SWS in the first part and for REM sleep in the last part of the night. Discussing their results, they also refer to evidence from Steriade et al. and Buzsáki [56,57] and clearly state that "...studies of sleep physiology provide considerable circumstantial evidence for both REM and NREM playing important roles for memory consolidation".

5. A role for the sleep cycle

We have recently put forward the hypothesis that memory consolidation during sleep in humans may be tightly linked to sleep organization; the cooperation between REM sleep and NREM sleep, serving complementary functions for memory consolidation, would be naturally exerted through their regular alternation within the basic functional unit of sleep, i.e. the sleep cycle [61–63].

The importance of sleep cycles has been often emphasized in the past [64–68]. A newly published paper by Franken [69], for instance, maintains REM sleep and NREM sleep reciprocally interact through the alternation in cycles, ensuring that "both behaviors are adequately expressed during the time allotted for sleep".

As indicated in Fig. 1, the sleep cycle is an important level of what we have called 'sleep organization', together with the episode, at a higher level, and the state, at a lower one [70]. Among other things, we showed that sleep becomes more and more organized during early development, as expressed by the increase in the amount and duration of NREM–REM cycles over the first year of life [71,72]. Attention is drawn to sleep cycling with regard to memory consolidation because an adequate build up of NREM–REM cycles is favourable to basic biological

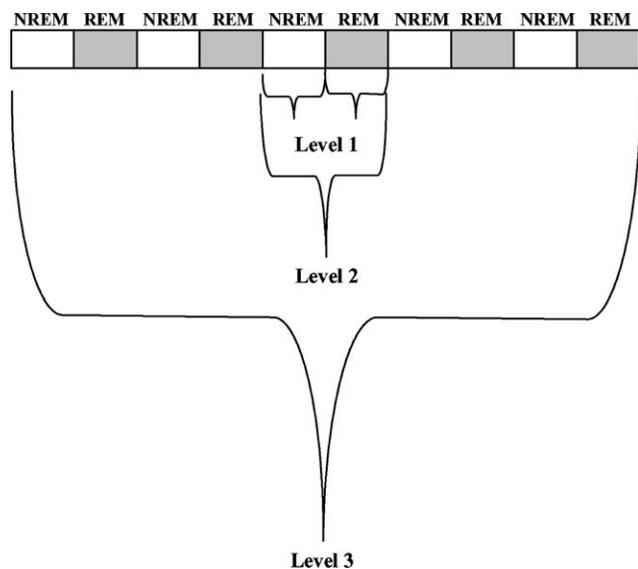


Fig. 1. Different levels of sleep organization. Level 1, sleep state (either NREM sleep or REM sleep); level 2, sleep cycle; level 3, sleep episode.

processes such as protein synthesis and anabolism [71,73] and, in turn, these might be essential for long-term potentiation and memory [74–76].

The first support for the role of NREM–REM cycles in memory consolidation in humans came from our group's investigation of elderly subjects [62,77], in which we studied morning recall of words presented before sleep in relation to measures of the previous night's sleep. Word recall was significantly correlated with the average duration of NREM/REM cycles and with the proportion of time spent in cycles over total sleep time, whereas it was not related to other sleep measures, including amounts of REM sleep and NREM sleep. We argued from this evidence that spontaneous conditions, such as aging, leading to the diminution of NREM–REM cycles and to poorly organized sleep (what we called 'functional uncertainty' [78]) may weaken memory functioning during sleep. A startling clinical conclusion is that memory may benefit very little from sleep when these conditions are chronic.

Further encouraging experimental evidence was obtained by a later study [63] in which the subjects were subjected to experimental manipulation of sleep, which either preserved or disrupted NREM–REM cycles (Fig. 2A). Better retention of memory material is found when sleep is characterized by many NREM–REM cycles, compared to sleep with few cycles (Fig. 2B). Again, as in the study by Mazzoni et al., the role of the sleep cycle appears difficult to dispute, because the C+ and the C- conditions are different only in the number of sleep cycles but there is no significant difference in duration of either REM sleep or NREM sleep. In particular, this result strongly disputes the previously hypothesized link between declarative neutral material and NREM sleep [42].

Some of the research reviewed in the previous sections could be re-thought in the light of the role of sleep cycling.

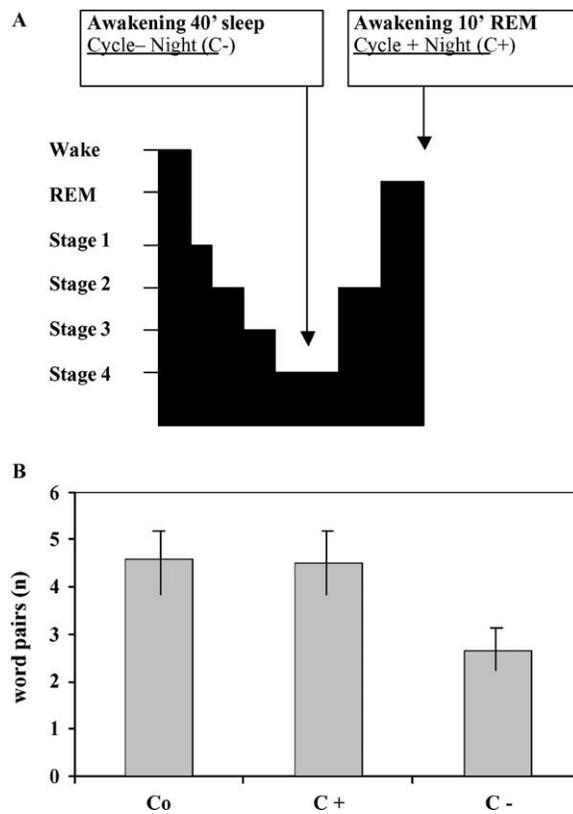


Fig. 2. (A) Research protocol adopted to interrupt sleep, either preventing or disrupting the NREM–REM cycles. In the Cycle + Night (C+), an awakening is provoked 10 min after each REM onset. In the Cycle – Night (C-), an awakening is provoked 40 min after each sleep onset. (B) Word pairs (mean ± SD) recalled in the morning after final awakening in the three experimental conditions (Co, continuous night; C+, fragmented sleep with preserved sleep cycles; C-, fragmented sleep with disrupted sleep cycles) [63,72].

One might wonder, for instance, whether the results based on the 'early sleep–late sleep comparison' [41,42,45] are better accounted for by a different number of awakenings disorganizing the NREM–REM cycle rather than by different amounts of sleep states.

In our opinion, although we currently have experimental evidence concerning only simple, declarative tasks (i.e. the recall of paired words), there is no particular reason to rule out a contribution of the sleep cycle to procedural learning. For instance, the sleep cycle perspective does not seem to us contradictory to the numerous contributions that have recently been made by Stickgold's group [59,60] on the topic of memory consolidation processes. It may be the case that those parts of a given sleep state, which in Stickgold's study [60] are significantly correlated with visual task performance improvements (NREM sleep in the first quarter, REM sleep in the fourth quarter), are also the ones which are properly followed/preceded by the other sleep states to constitute the complete sleep cycle.

The same observation could be made concerning the interesting data presented by Mednick et al. [79,80], who assessed the effect of naps on the learning of a visual

discrimination task. They show that perceptual thresholds are higher at 19.00 compared to the baseline values at 9.00. However, deterioration does not occur when a 60-min nap is administered, and there is even significant improvement after a 90-min nap. The authors claim that the differential effects between the short and the long naps are accounted for by the presence of REM sleep in the latter. An alternative possibility might be that the sleep cycle is completed only in the long naps [81].

In conclusion, it may not be enough to consider the role of both REM and NREM sleep if one overlooks their reciprocal interactions within the sleep cycle. Memory during sleep does not simply depend on the overnight 'loading' of a given state, i.e. on the total amount of that state over the entire night. Instead, it might be tightly linked to a dynamic (perhaps continuous) process reflected by the alternation of the sleep states in cycles.

We believe it would be of great clinical interest to further assess our hypothesis; if adequate cycling plays a crucial role in memory consolidation during sleep, we have a promising line of research to better understand cognitive deficits occurring in conditions associated with reduced sleep continuity and organization (for instance, old age and pathologies fragmenting sleep).

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