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Sleep-dependent memory consolidation and reconsolidation

Robert Stickgold [a,*], Matthew P. Walker [a,b]

[a] *Center for Sleep and Cognition, Department of Psychiatry, Harvard Medical School, Beth Israel Deaconess Medical Center E/FD 861, 330 Brookline Ave., Boston, MA 02215, USA*

[b] *Sleep and Neuroimaging Laboratory, Department of Psychiatry, Harvard Medical School, Beth Israel Deaconess Medical Center E/FD 862, 330 Brookline Ave., Boston, MA 02215, USA*

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Abstract

Molecular, cellular, and systems-level processes convert initial, labile memory representations into more permanent ones, available for continued reactivation and recall over extended periods of time. These processes of memory consolidation and reconsolidation are not all-or-none phenomena, but rather a continuing series of biological adjustments that enhance both the efficiency and utility of stored memories over time. In this chapter, we review the role of sleep in supporting these disparate but related processes.

Keywords: Sleep; Memory; Learning; Consolidation; Reconsolidation; REM; Slow-wave sleep; Visual discrimination; Motor sequence learning

1. Introduction

The question of ''sleep-dependent memory consolidation'' is a complex one. Each term in the phrase – sleep, dependent, memory, and consolidation – begs for clarification. For a start, the term ''memory'' covers a wide range of memory types, which differ in the kinds of information stored, the brain structures mediating this storage, and, in humans, whether the information is accessible to conscious awareness. There is no clear consensus at this time on how many such memory systems there are, and how they should be defined, either in terms of information content or brain structures involved in their storage [1]. The most widely accepted taxonomy divides human memories first into declarative and non-declarative, based on their accessibility to conscious recall, and then into finer and finer subdivisions of these basic categories (Fig. 1A) [2].

Similarly, the term ''memory consolidation'' refers to a poorly defined set of processes which take an initial, unstable memory representation and convert it into a form that is both more stable and more effective. At this time, it is unclear how memories are altered after initial encoding, and no consensus as to which of the processes contributing to this alteration should be included under the umbrella of memory consolidation. When the term was first introduced, it referred to as yet unknown processes which, over a period of minutes to hours, made learning resistant to degradation by, for example, electroconvulsive shock [3–5], but this notion of a single, relatively rapid process of memory consolidation has yielded to one including phases of stabilization, enhancement, and integration, extending over hours to years.

More recently, the concept ''memory reconsolidation'' has resurfaced to describe yet another aspect of post-encoding memory modification [6]. There is now evidence that when previously stabilized memories are reactivated, either by returning an animal to an earlier learning environment or by having humans briefly perform a previously learned task, the memory is

* Corresponding author. Tel.: +1 617 667 8485; fax: +1 617 667 8498.
E-mail address: rstickgold@hms.harvard.edu (R. Stickgold).

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destabilized and returns to a labile state in which it is again susceptible to destructive interference. Thus, the terms "consolidated" and "stabilized" must take on a more nuanced meaning, reflecting the *relative* consolidation and stabilization of the memory.

Many of the steps in this consolidation cascade occur preferentially or even exclusively during periods of sleep. Researchers are now focusing on identifying those types of memory, and, for each, the individual steps that show strong sleep-dependent activation. However, again, sleep does not refer to a simple unitary phenomenon, instead representing a complex array of brain states that differ in their physiology, chemistry, and phenomenological experiences. Sleep has been broadly divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep, which alternate across the night, in humans in a 90-min cycle (Fig. 1B). NREM sleep is further subdivided into NREM stages 1–4 [7], which appear to differ in their contribution to sleep-dependent memory consolidation [8].

Before describing these systems of memory consolidation in greater detail, we would like to offer an overview of our perspective on memory consolidation and reconsolidation. First, all of these processes occur over time automatically, outside of awareness and without intent. Thus, they are specifically different from changes that result from conscious reminiscing or intentional rehearsal. In this respect, they are no different from molecular cascades triggered by an initial biochemical event, but while molecular cascades are normally restricted to a single cell, the cascade of events characterizing memory consolidation range from intracellular gene inductions to brain-wide, system-level reorganizations of memories representations.

Second, while these processes occur automatically, they are, nevertheless, modulated by other factors. Again, this is not different from what is seen with intracellular molecular cascades, but the greatly extended time course allows for different forms of modulation. As a result, the multiple components of memory consolidation and reconsolidation form a coherent whole, which functions to optimally integrate initially encoded memories into an organism's existing informational networks, and which continues to refine and remodel these memories following reactivation, during wake and sleep. In short, memories do not simply form in the brain; they evolve.

For the purposes of this review, we use the term memory consolidation to refer to all post-encoding memory processing that is automatic and which occurs without intent or awareness under the rubric of "memory consolidation," while those that require either

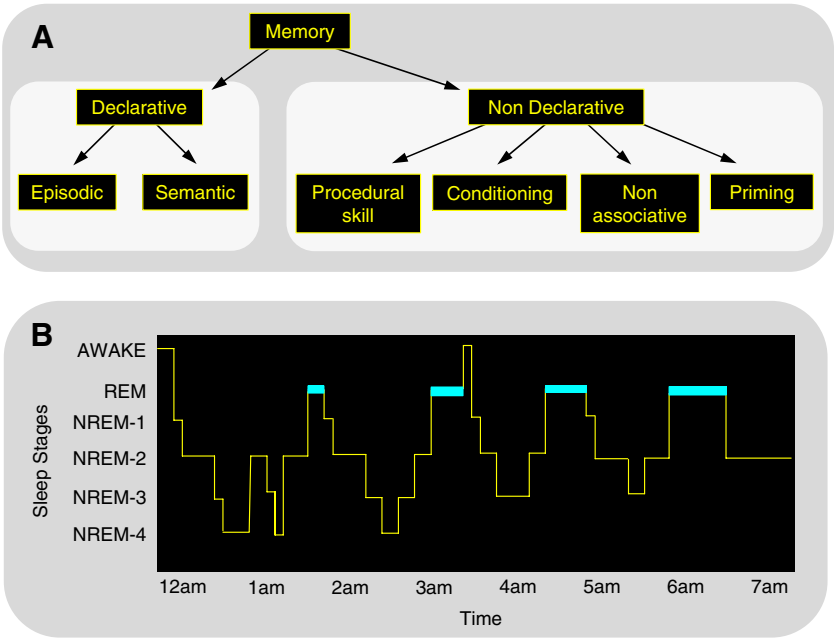

Fig. 1. Forms of memory and stages of sleep. Neither memory (A) nor sleep (B) represents a homogeneous phenomenon. (A) Declarative memory includes consciously accessible memories of fact-based information (i.e., knowing "what"), and contains several subcategories, including episodic memory (memory for events in one's past) and semantic memory (memory for general knowledge) [110]. In contrast, non-declarative memory includes all non-conscious memories, and includes subcategories such as conditioning, implicit memory and procedural memory (i.e., knowing "how"). (B) In mammals, sleep is divided into REM and NREM sleep, and in primates and felines, NREM sleep has been divided into sub-stages 1–4, corresponding to increasingly deeper states of sleep [7]. The deepest NREM stages, stages 3 and 4, are collectively referred to as slow wave sleep (SWS), based on a prevalence of low frequency (0.5–4 Hz) cortical oscillations. Dramatic changes in brain electrophysiology, neurochemistry and functional anatomy occur across these sleep stages, making them biologically distinct from the waking brain, and dissociable from one another. For example, SWS is characterized by a diminution in cholinergic activity and REM sleep by a suppression of release of norepinephrine from the locus coeruleus and serotonin from the raphe nucleus. (Reproduced with permission from [8]).

conscious or behavioral rehearsal are excluded. Thus, the development of hippocampal independence as described by McClelland and colleagues [9] would be included, but improvement through actual or imagined rehearsal would not. Similarly, all post-recall memory processing that is automatic and which occurs without intent or awareness is placed under the rubric of "memory reconsolidation."

2. Stages of memory consolidation and reconsolidation

The evolution of a memory can be a long and complex process, occurring in several distinct stages (Fig. 2). While the initial encoding of a memory is a rapid (milliseconds) process, its long-term maintenance requires processes that continue to modify it over hours to years, processes that are collectively referred to as memory consolidation [10].

Even the original view of consolidation as stabilization is now in flux. When originally proposed in 1900 [10], consolidation was defined by resistance to interference from competing memories. Animal studies in the middle of the 20th century demonstrated that such consolidation was also required for the formation of memories resistant to the more drastic actions of electroconvulsive shock (ECS) [11] and protein synthesis inhibitors [12]. More recently, the concept of memory consolidation has been simultaneously extended and challenged. Human motor skill memories have now been shown to be disrupted by training on an alternate task within the first hours after training, suggesting that such learning also requires a process of stabilization [13,14].

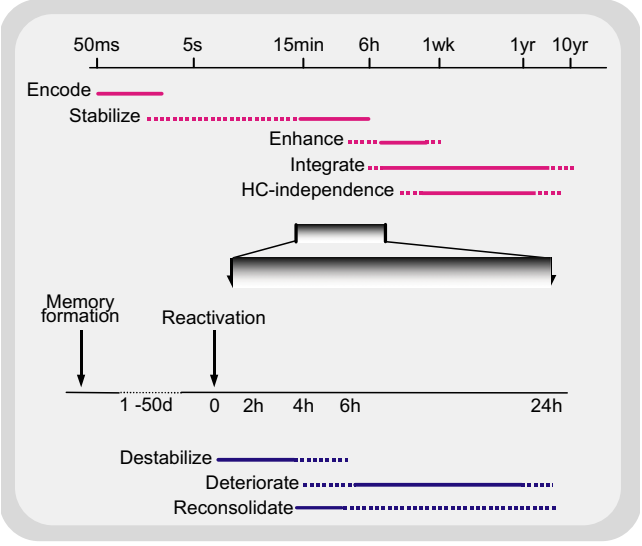

Fig. 2. Time course of memory processes. (Top) Memory formation and consolidation – after the initial rapid encoding of a sensory experience, the neural representation of the memory can go through a number of automatic processes, independent of rehearsal, intent, or awareness. These can stabilize and enhance a memory, making it resistant to interference and more effective to guiding behavior, and also integrating the memory into larger associative networks. The latter process is thought to permit episodic memories to be recalled without hippocampal (HC) involvement. The extent to which such processes affect different memory systems is unclear. Note logarithmic time scale. (Bottom) Memory reactivation and reconsolidation – after stabilization is complete, reactivation of a memory can lead to its return to an unstable form. Normally, such memories appear to be reconsolidated following this destabilization, but if such reconsolidation is blocked, degradation of the memory can ensue. (Reproduced with permission from [8]).

More importantly, these newer findings demonstrate that the time course of stabilization can be functionally significant. When initially conceptualized, consolidation was considered to be an inexorable process which, once started, continued to completion except under the most severe of insults, such as ECS. From this perspective, the length of the consolidation process could be considered irrelevant, presumably determined by idiosyncrasies of evolution. However, the finding that ecologically relevant stimuli can also interrupt consolidation suggests a functional role for this interval, where a memory is consolidated unless other similar, and competing, memories are formed shortly after the first memory. This could allow for the functional correction of inadvertently or imprecisely formed memories before they are stabilized.

The recent failure of Caithness and others to reproduce these interference effects for motor adaptation learning [15] is perhaps not surprising, since it is still unclear what the stimulus characteristics are for an effective blockade of this early consolidation. While they failed to observe interference with new learning on their tasks, it is still likely that even these memories remain sensitive to ECS and protein synthesis inhibitors for several hours [16], reflecting a required process of consolidation. Indeed, there is little objection to the view that conversion of initial memory traces into long-term memories requires protein synthesis [5].

While memory consolidation clearly serves to stabilize memories, this is far from all that it does. For a start, consolidation also *enhances* memories, for example, improving behavioral performance, independent of further practice [17]. Although these two phases of consolidation could reflect a single process, we believe that this is unlikely for at least two reasons [18]. First, the consolidation process leading to enhancement of a motor sequence learning task continues for up to 10 times as long as the earlier stabilizing phase [14,17] (Fig. 2, top), and for a visual discrimination process continues over at least 2–4 days [19]. Second, while stabilization of this motor sequence task occurs over 6 h of wake, the enhancement phase for both tasks occurs only during sleep [17,19]. Other post-encoding stages of memory consolidation include the integration of recently encoded memories into existing memory networks (memory integration/association) [20,21], the development of hippocampal independence for declarative

memories [9,22], and even the active weakening of memory representations (''memory erasure'') [23]. All of these are thought to be facilitated by sleep.

Memories can be retained for weeks to years, during which time they can be effectively recalled, but the mere act of memory recall can destabilize the memory and return it to a labile form, where it is again vulnerable to interference and degradation. Reconsolidation—the transformation of this now destabilized memory into a restabilized form—is necessary if the memory is to be retained in the face of interference [6]. Otherwise, it can degrade relatively quickly (Fig. 2, bottom). (To be more precise, it is unclear whether such degradation actually weakens the memory trace or, instead, simply makes it inaccessible to recall mechanisms, but this distinction is irrelevant for our current review).

We noted above that memories are not simply formed, but evolve over time. This time course appears to serve two conceptually distinct functions. Some post-encoding stages of memory consolidation appear necessary simply to cope with the constraints of the brain. Thus, the molecular mechanisms which support rapid memory encoding (e.g., calcium influxes) are inadequate for long-term maintenance of synaptic changes, while those processes which support long-term maintenance (e.g., protein synthesis) cannot be accomplished quickly enough to support rapid encoding [24]. Similarly, network structures that can capture an episodic memory may be incapable of supporting dense network storage of memories [9]. A recent review of off-line memory reorganization has described many of these features in detail [25].

However, processes of consolidation also serve to facilitate behavior. As examples, they could (i) automate behaviors, shifting representations from declarative to procedural systems and reducing frontal demands; (ii) extract valuable details from complex episodic memories so that one can, for example, recall the sum of five plus five without recalling an episodic memory of when and where it was learned; and (iii) integrate information, so that one associates all the ''addition facts'' with one another. For both classes of memory consolidation processes, sleep is now thought to play an important role in meeting the demands of the organism.

Our understanding of memory reconsolidation is at a much earlier stage. Although originally reported in the 1960s [3,4], the details of memory reconsolidation have only recently come under intensive investigation [6]. Its component processes, their time courses and functions, are far less well defined, and almost no attention has been paid to their possible dependence on wake–sleep states. Likewise, there has been little discussion of the significance or possible functions of these processes.

Conceptually, there are at least four processes that a consolidated memory can undergo: (i) reactivation, leading to (ii) destabilization, which in turn leads to either (iii) degradation or (iv) reconsolidation. However, the time courses of these individual steps, the mechanisms and brain states which produce them, and even their biological functions, remain unclear.

While memory reactivation can presumably occur in a fraction of a second, the destabilizing effects of such reactivation appear to depend on longer periods of reactivation. Anywhere from 30 s to 10 min can be required to produce destabilization (defined by memory degradation following the prevention of reconsolidation) [26–28], with longer times required when the intensity and duration of the initial training is increased. The duration of this destabilization appears to be on the order of 5–6 h, after which the memory becomes reconsolidated and again resistant to destructive interference [26,29,30].

Once destabilized, and in the absence of subsequent reconsolidation, degradation of a memory has generally been considered a passive process, perhaps based on molecular turnover. Alternatively, it may be that the memory is not degraded at all, but its recall ability is lost. Regardless, the nature of this degradation remains unclear. Currently, degradation is defined behaviorally as diminished performance of the learned task or response. There is little data on the time course over which this reduced efficacy, let alone its molecular correlates, develops. Following reactivation and blockade of reconsolidation, previously learned behaviors are still intact 2–4 h later [26,27,31,32]. This makes sense, since reconsolidation appears to take at least this long, and it would be counterproductive for memories to begin to degrade before reconsolidation normally has completed. By 24 h after reactivation, any degradation of the memory appears to be complete [32–34] (see also [35], Table 1).

While early studies using ECS or administration of protein synthesis inhibitors to block reconsolidation suggested that reconsolidation serves no practical purpose other than preventing the inadvertent degradation of the memory, hints of more complex mechanisms and functions are found in studies showing that inhibitors of cholinergic [33] and noradrenergic [29] neuromodulation can also prevent reconsolidation. In addition, *N*-methyl-D-aspartate (NMDA) antagonists reportedly can block the destabilization associated with reactivation [36]. Finally, training on competing tasks has now been shown to block reconsolidation as well [37]. In light of these more recent findings, we propose that destabilization and reconsolidation of memories simply represent yet another sophisticated mechanism for modulating and modifying preexisting memories.

3. Sleep-dependent memory consolidation

Over the last 10 years, a large body of evidence has been reported supporting a role for sleep in the offline (re)processing of memories. We have recently reviewed

the evidence for the critical role of sleep in memory consolidation [38] and only briefly summarize the behavioral literature here ([for an opposing viewpoint, see 39]).

Specific stages of sleep appear to be critical for discrete steps in the consolidation of various forms of memory, while for other steps sleep appears unnecessary ([for review, see 40]). For example, stabilization of some forms of procedural motor memory can develop across 3–6 h of wake [13,16,37]. In contrast, the offline enhancement of procedural sensory and motor memories has almost always been found to depend on overnight sleep, with equivalent periods of wake failing to produce any performance gains [14,17,19,37,41–52] (see Fig. 3 for examples). Such overnight enhancement has been seen for a variety of memory tasks, but individual tasks differ dramatically in the sleep stages or sleep characteristics required. Consolidation of motor skills has been connected to NREM sleep stages, stage 2 in some cases and slow wave sleep (SWS) in others, as well as to specific physiological characteristics of NREM [17,41,44,45,53]. In contrast, both SWS and REM sleep have been associated with the consolidation of memory for a visual texture discrimination task [19,46,47], suggesting that there may be more than a single phase of sleep-dependent consolidation [48,54].

In some instances, the sleep dependency of consolidation for a single task can depend on subtle features of the task. The serial reaction time (SRT) task is a procedural visual-motor task. In it, subjects watch a screen with four circles displayed across the center (Fig. 4). As individual circles light up, subjects press the key located immediately below it. As the lights flash one after another, subjects slowly learn the pattern in which they are flashing, commonly a sequence of at least 12 lights (i.e., each light three times in a complex order). If subjects are trained on this task and then retested 12 h later, enhanced performance is seen, but the sleep dependency of this improvement is not straightforward. When subjects are told ahead of time that there is a pattern to the flashing of the lights, they show time-dependent improvement across a night of sleep, but not across a day when they are awake. On the other hand, if they are simply told that it is a reaction time test, and if they do not become consciously aware of the pattern during training, then they show improvement both across the day and across the night [44]. Thus, it appears that *explicit* knowledge of the sequence is enhanced by sleep and not by wake, while *implicit* knowledge is enhanced by both. However, this still fails to fully describe the sleep dependency of the learning, since when subjects are tested after the 12-h period specifically for their knowledge of the finger sequence (e.g., right hand little finger – index finger – ring finger) or the numerical sequence (1–4–2), implicit knowledge of the finger sequence appears to improve only across the day and implicit knowledge of the numerical sequence improves only across the night [55]. Thus, the distinction between implicit and explicit knowledge might only reflect the fact that explicit knowledge is always of the numerical sequence and hence improves only across the night, while implicit knowledge is of both the numerical and motor sequences and improves across either wake or sleep.

This is not the only procedural task to show improvement during wake. An auditory procedural task has been reported to show enhancement without the need for sleep [50], although a second auditory task showed sleep-dependent changes in the brain response to test stimuli ([49]). While most procedural memories show sleep-dependent enhancements, in the end it remains unclear what determines whether a given procedural task will in fact show such enhancement.

The evidence for sleep-dependent consolidation of declarative memories is less consistent. First, it is difficult to separate processes of stabilization from processes of enhancement, since performance generally deteriorates across both wake and sleep, but when performance after equivalent periods of wake and sleep are compared, early studies split over a role for sleep-dependent memory consolidation ([for review, see 56]). More recently, Born and colleagues, using a word-pair associates task, have shown enhanced recall after periods of nocturnal sleep compared to similar periods without sleep. Furthermore, periods of early night sleep, rich in SWS, were particularly beneficial for this consolidation [57]. The fact that this effect is only seen during SWS-rich periods early in the night, rather than across all sleep periods, argues that the physiological state of sleep, and of particular stages of sleep, are critical for this consolidation process [38]. As further support, they have shown that daytime training can trigger changes in characteristics of early night SWS, with modifications reported in both the number of sleep spindles [58], and in the coherence of NREM slow-frequency electroencephalographic (EEG) oscillations [59]. In support of these findings, Peigneux and colleagues [60] have reported that overnight improvement on a hippocampally mediated spatial memory task is positively correlated with increased hippocampal activation during SWS, a finding that would seem to argue in favor of actual memory enhancement, and against the diminished interference model.

Memory destabilization and reconsolidation may also be facilitated by sleep. Although there is little data that directly pertains to this question, we propose that both degradation and reconsolidation processes can, and in some circumstances must, occur during sleep. Indeed, most rodent studies of reconsolidation are carried out during the light (sleep) phase of the circadian cycle, and it is likely that animals in all of these studies

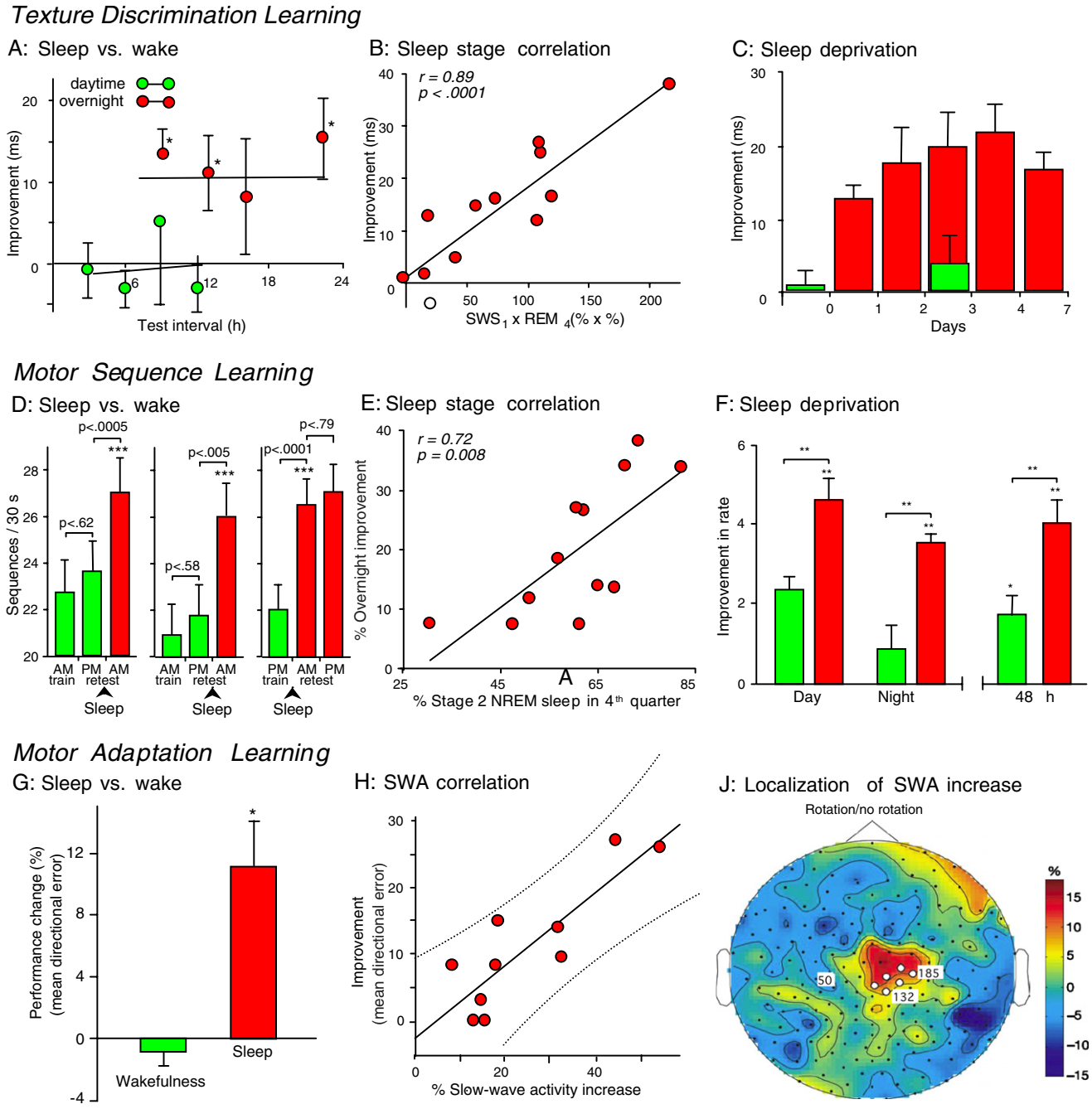

Fig. 3. Sleep-dependent consolidation of procedural memories. (A–C) Participants in a visual texture discrimination task show improvement only after post-training sleep. Improvement correlates with early-night slow-wave sleep and late-night REM sleep. (D–F) Participants in a motor sequence finger-tapping task show similar sleep-dependent improvement, even when finger movement is suppressed with mittens during wake periods (D, right panel), improvement which correlates with late-night stage 2 non-REM sleep. (G, H and J) Participants in a motor adaptation task also show sleep-dependent improvement, correlated with EEG slow-wave activity in task-related regions of the cortex. All error bars represent standard errors of the mean. Green bars, performance without intervening sleep or without sleep on the first post-training night. Red bars, performance after normal sleep. (Reproduced with permission from [8]; panel J with permission from [45]).

slept between reactivation and subsequent measurements of reconsolidation. Thus, existing evidence cannot distinguish between time-dependent and sleep-dependent reconsolidation. This is different from the situation with initial stabilization, for which there is good evidence of consolidation during wake.

Support for sleep-dependent reconsolidation comes from studies of procedural memory reconsolidation in humans [14]. Following training on a finger-tapping motor sequence task, subjects show overnight sleep-dependent gains in performance accuracy, but if subjects are taught a new competing sequence 10 min after learn-

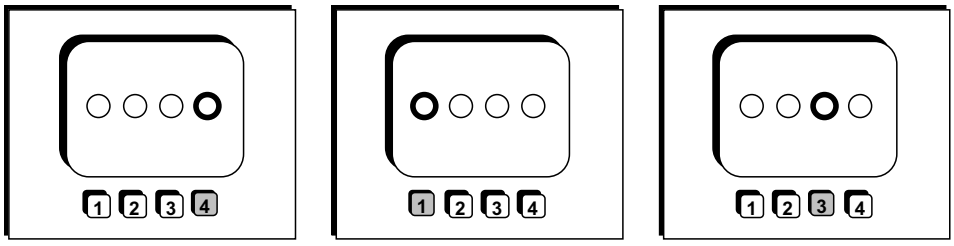

Fig. 4. Serial reaction time task. Four circles are presented on a computer screen and lit in a repeated, pseudorandom order. When each circle is lit, the button beneath it must be pressed. In this example, the fourth, then first, then third button are lit sequentially. To determine whether subjects are learning the finger movements (as a motor task) or the spatial positions (as a visual task), subjects are retested using their other hand. For example, subjects trained with their right hand are retested with their left hand. For the spatial sequence 4–1–3 shown here, during training subjects would press keys with the little, then index, and then ring finger of their right hand. If asked to type the same spatial sequence (4–1–3) at retest, subjects would have to use the index, little, and then middle fingers of their left hand. In contrast, to test for retention of learning of the motor sequence (little–index–ring fingers), subjects would be retested on the sequence 1–4–3 in place of 4–1–2.

ing the first sequence, the normal overnight improvement in accuracy is completely blocked [17]. If the time period between learning the two sequences is increased from 10 min to 6 h, no significant interference is observed the next day.

If the original memory is reactivated through 90 s of rehearsal 24 h after training, however, the memory appears to be destabilized, and now training on a second sequence leads to a complete reversal of the improvement in accuracy seen across the first night, to the level seen at the end of initial training, although not to the much lower level seen at the very start of initial training. These results suggest that the deterioration in performance seen following blockade of reconsolidation might be limited to the reversal of earlier sleep-dependent consolidation.

4. Sleep and brain plasticity

Memory formation depends on brain "plasticity"–lasting structural and/or functional neural changes in response to stimuli (such as experiences). If sleep is to be considered a critical mediator of memory consolidation, then evidence of sleep-dependent plasticity would greatly strengthen this claim. Indeed, there is now a wealth of data describing sleep-dependent brain plasticity at a variety of different levels in both animals and humans, complementing evidence of sleep-dependent changes in behavior.

4.1. Neuroimaging studies

Several studies have investigated whether daytime training is capable of modifying functional brain activation during subsequent sleep. Based on animal studies, neuroimaging experiments have explored whether the signature pattern of brain activity elicited while practicing a memory task actually re-emerges, that is, is "replayed", during subsequent sleep. Using brain imaging, Maquet and colleagues have shown that patterns of brain activity expressed during training on a serial reaction time motor task reappear during subsequent REM sleep, while no such change in REM sleep brain activity occurs in subjects who received no daytime training [61]. Furthermore, the extent of learning during daytime practice exhibits a positive relationship to the amount of reactivation during REM sleep [62]. As with previously described animal studies [63], these findings suggest that it is not simply experiencing the task which modifies subsequent sleep physiology, but the process of learning itself. Similar findings have been reported using a virtual maze task. Daytime task learning is initially associated with hippocampal activity. Then, during post-training sleep, there was a re-emergence of hippocampal activation, this time specifically during SWS. Most compelling, however, is that the amount of SWS reactivation in the hippocampus is proportional to the amount of next-day task improvement, suggesting that this reactivation leads to off-line memory improvement [60]. Such sleep-dependent replay may potentially modify synaptic connections established within specific brain networks during practice, strengthening some synaptic circuits while potentially weakening others in the endeavor of refining the memory.

A second approach, which more directly examines sleep-dependent plasticity, compares patterns of brain activation before and after a night of sleep. In contrast to measuring changes in functional activity *during* sleep, this technique aims to determine whether improved performance results from an overnight, sleep-dependent *re-structuring* of the neural representation of the memory. Using the sleep-dependent motor-skill task, Walker and colleagues have recently used functional magnetic resonance imaging (fMRI) to investigate differences between patterns of brain activation before and after sleep [64]. Following a night of sleep, and relative to an equivalent intervening time period awake, increased activation was identified in motor control structures of the left cerebellum (Fig. 5A) and right primary motor cortex (Fig. 5B)–changes which allow more precise motor output [65] and faster mapping of intention to key-press [66]. There were also regions of increased

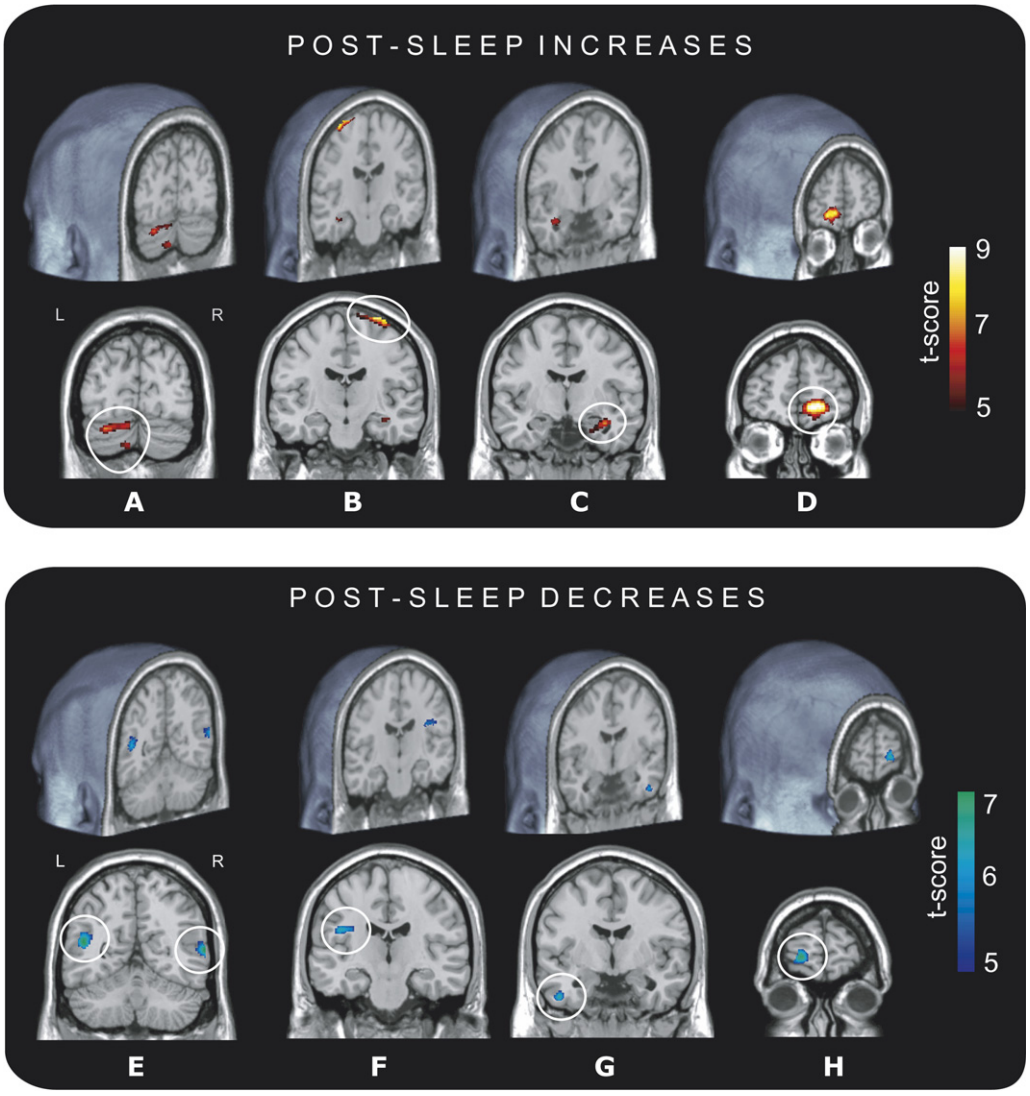

Fig. 5. Sleep-dependent motor memory reorganization in the human brain. Subjects were trained on the sleep-dependent finger-tapping motor skill task and then tested 12 h later, either following a night of sleep or a day of wake, during a functional magnetic resonance imaging (fMRI) brain-scanning session. Scans after sleep and wake were compared (subtracted), resulting in regions showing increased fMRI activity post-sleep (in red/yellow; A–D) or decreased signal activity (in blue; E–H) post-sleep, relative to post-wake. Activation patterns are displayed on three-dimensional rendered brains (*top panel* of each graphic), together with corresponding coronal sections (*bottom panel* of each graphic). Coronal sections all show left on the left; three-dimensional renderings are reversed left for right except (A). Following sleep, regions of increased activation were identified in the left cerebellum (A), the right primary motor cortex (B), the right hippocampus (C), and the right medial prefrontal cortex (D). Regions of decreased activity post-sleep were expressed bilaterally in the parietal lobes (E), together with the left insula cortex (F), left temporal pole (G), and left frontopolar area (H), all regions of the extended limbic system. All data are displayed at a corrected threshold of $p < 0.05$. (Reproduced with permission from [111]).

activation in the medial prefrontal lobe and hippocampus (Fig. 5C and D), structures recently identified as supporting improved sequencing of motor movements [67–70]. In contrast, decreased activity post-sleep was identified bilaterally in the parietal cortices (Fig. 5E), possibly reflecting a reduced need for conscious spatial monitoring [71–73] due to improved task automation [43], together with regions of signal decrease throughout the limbic system (Fig. 5F–H), suggesting a decreased emotional task burden. In total, these results suggest that sleep-dependent motor learning is associated with a large-scale plastic reorganization of memory throughout several brain regions, allowing skilled motor movements to be executed more quickly, more accurately and more automatically following sleep. These findings hold important implications for understanding the brain basis of perfecting real-life skills, and may also signify a potential role for sleep in clinical rehabilitation following brain damage.

Walker and colleagues have also used fMRI to investigate whether overnight reorganization similarly occurs in sensory-perceptual systems using the sleep-dependent

visual texture discrimination task discussed earlier [74]. Subjects were trained with or without intervening sleep. Relative to the condition without sleep, retest following sleep was associated with significantly greater activation in an area of primary visual cortex corresponding to the visual target location. However, there were also several other regions of increased post-sleep activity, throughout both the ventral object recognition (inferior parietal and occipital-temporal junction) and dorsal object location (superior parietal lobe) pathways [75], together with corresponding decreases in the right temporal pole, a region involved in emotional visual processing. Thus, a night of sleep appears to reorganize the representation not only of procedural motor but of visual skill memories as well, with greater activation throughout the visual processing streams, offering improved identification of both the stimulus form and its location in space, and with signal decreases in the temporal pole, reflecting a reduced emotional task burden that results from the overnight learning benefits.

Maquet et al. [76] have investigated the detrimental effects of sleep deprivation on underlying brain activity using a visuo-motor adaptation task – the only such study to date. Subjects were trained on the task and retested three days later, with half the subjects deprived of sleep the first night. At retest, subjects performed both the previously learned motor task and a new related task. Controls, who slept all three nights, showed both enhanced behavioral performance at retest, and a selective increase in activation in the superior temporal sulcus (a region involved in the evaluation of complex motion patterns) relative to subjects deprived of sleep the first night. In contrast, no such enhancement of either performance or brain activity was observed in sleep-deprived subjects, indicating that sleep deprivation had interfered with a latent process of plasticity and consolidation. This study offers an early indication that sleep deprivation not only disrupts consolidation but the underlying neural mechanisms that support it as well.

4.2. Electrophysiological studies

Throughout the sleep cycle, both REM and NREM sleep stages contain numerous distinct electrophysiological events which contribute to each unique physiological state. Many of these electrical phenomena have been implicated in processes of plasticity, either potentiating or depressing synaptic connections [77]. For example, it has been proposed that sleep spindles, seen most commonly during stage 2 NREM sleep, can provide brief trains of depolarizing inputs to targets in the neocortex, which are similar to spike trains used experimentally to induce long-term synaptic potentiation [78–81]. Indeed, Steriade and colleagues [82] have shown that experimental trains of impulses similar to those produced by sleep spindles can produce lasting changes in the responsiveness of cortical neurons. Similarly, theta waves, seen in the hippocampus during REM sleep in both humans [83] and other animals [84], greatly facilitate the induction of long-term potentiation (LTP) in the hippocampus, potentiation that is believed to be a physiological mediator of memory formation [85,86].

As noted earlier, phasic events during REM sleep, and ponto-geniculo-occipital (PGO) waves specifically, have been associated with learning. Sanford et al. [87] have demonstrated that fear conditioning in rats can increase the amplitude of elicited P-waves during REM sleep, suggesting again that they represent a homeostatically regulated component of a sleep-dependent mechanism of learning and plasticity [cf. 63]. These PGO waves occur in a phase-locked manner with theta wave activity during REM sleep [88,89]. This is particularly interesting because experimental hippocampal stimulation at the peaks of theta waves facilitate LTP. The same stimulation applied at the troughs of the theta waves instead leads to long-term depression of synaptic responses [86,90]. These findings suggest that natural PGO activity during REM sleep may serve as an endogenous mediator of synaptic plasticity, based on its coincidence with theta wave oscillations, which, depending on its phase relationship, could either strengthen or weaken synaptic connections, both of which are necessary for efficient network plasticity.

Selective reactivation is seen not only in the human neuroimaging studies described above but also in more precise measurements of sleep-dependent network reactivation in the rat. Several groups have investigated the firing patterns of large networks of individual neurons across the wake-sleep cycle in a variety of cortical and subcortical regions of the rat brain. The signature firing patterns of these networks, expressed during waking performance of spatial tasks and novel experiences, are replayed during subsequent SWS and REM sleep, with replay during REM at speeds similar to those seen during waking but those in SWS being an order of magnitude faster in some, but not all, studies [84,91–94]. Dave and Margoliash [95,96] have shown that waking patterns of pre-motor activity observed during song-learning in the zebra finch are also replayed during sleep, with a temporal structure similar to that seen in wake.

Together, these data indicate that temporal patterns of network activity seen during waking experiences are consistently reactivated during subsequent sleep across a broad spectrum of phylogeny. This replay of events is hypothesized to trigger distinct but complimentary processes within reactivated neuronal ensembles. Ribeiro et al. [94] have suggested that SWS reinstantiates the memory representation through network reverberation, while subsequent REM sleep then potentiates the memory for subsequent post-sleep recall, through gene-induction mediated synaptic plasticity.

4.3. Cellular studies

Recently, a form of sleep-dependent plasticity at the cellular level has been elegantly demonstrated during early post-natal development of the cat visual system [97,98]. Under normal circumstances, brief periods of monocular visual deprivation during critical periods of development lead to the remodeling of synaptic connectivity, with the deprived eye's inputs to cortical neurons being first functionally weakened and then anatomically diminished [99]. Frank et al. [100] have now shown that when 6 h of monocular deprivation are followed by 6 h of sleep, the size of the monocularity shift doubles. In contrast, if the cats are kept awake for these same 6 h (in the dark, without input to either eye), a non-significant *reduction* in the size of the shift occurs. Thus, sleep can contribute as much to developmental changes in synaptic connectivity as does visual experience, presumably by enhancing the initial changes occurring during a prior period of monocular deprivation. In contrast, sleep-deprivation results in a loss of previously formed, experience-dependent synaptic changes, a pattern seen as well in humans, albeit at the behavioral level [19,42].

Shaffery et al. [101] have reported similar findings of sleep-dependent plasticity in the visual cortex of the rat, suggesting that REM sleep, in conjunction with visual experience, modulates the initial course of visual cortex maturation. In rats under 30 days of age, electrical stimulation produces increased excitability (potentiation) in specific layers of the visual cortex, while stimulation after this early developmental stage fails to produce such potentiation. Depriving rats of REM sleep during this period extends this window of plasticity by as much as seven days, suggesting that events occurring during REM sleep modulate the duration of this period of experience-dependent plasticity.

4.4. Molecular studies

At the molecular level, Smith et al. [102] have shown that administration of protein synthesis inhibitors to rats during REM sleep windows thought to be critical

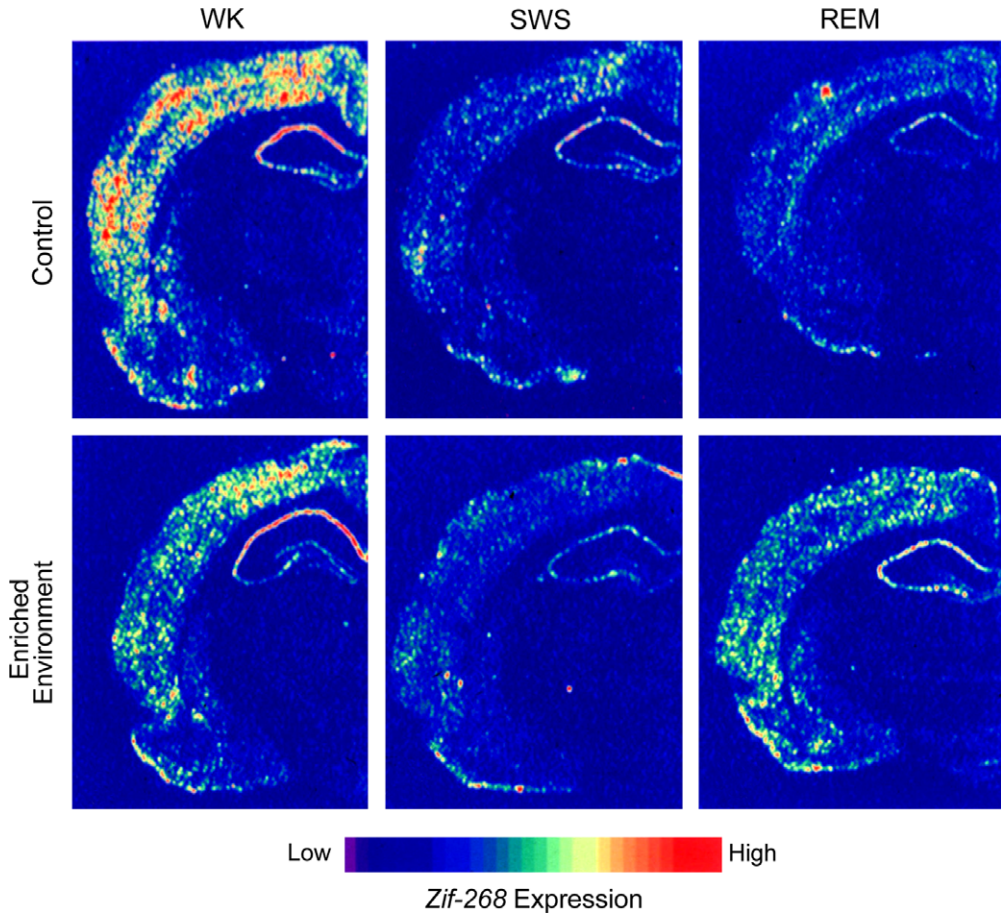

Fig. 6. Experience-dependent up-regulation of the synaptic plasticity related immediate early gene *zif-268* during periods of wakefulness and REM sleep in the rat. Autoradiograms of frontal coronal brain sections in which gene-expression levels best represent the means for each group studied. (Top panels) In controls, *zif-268* expression decreased from wake (WK) to SWS and REM. (Bottom panels) In enriched-environment animals, *zif-268* levels decreased from WK to SWS, but then increased in REM. This effect was particularly noticeable in the cerebral cortex and the hippocampus. (Reproduced with permission from [107]).

for consolidation prevents behavioral improvement following the sleep period. Such protein synthesis could reflect the activation of genetic cascades which produce key molecules for synaptic remodeling. Our understanding of such gene inductions during sleep is only beginning. Although several of the known "immediate early genes" (IEGs) are specifically down-regulated during sleep [103–105], approximately 100 genes are specifically up-regulated during sleep [106], almost the same number that are up-regulated during wakefulness. Moreover, up-regulation of these genes during sleep was seen only in brain tissue.

This extensive up-regulation of genes during sleep is seen even in the absence of any specific learning tasks being performed prior to sleep. If this up-regulation were specifically related to consolidation of recent learning and memory formation, one would expect that such gene inductions would be seen specifically after training on tasks that undergo sleep-dependent consolidation. Indeed, such learning-specific up-regulation has been observed. Ribeiro and colleagues found up-regulation in rats of *zif-268*, a plasticity associated IEG, during REM sleep following exposure to a rich sensorimotor environment, but found down-regulation during both SWS and REM sleep in the absence of such exposure [107]. This provides additional molecular evidence for the existence of windows for increased neuronal plasticity during REM sleep periods following enriched waking experience (Fig. 6), in agreement with both behavioral, physiological, and neuroimaging studies.

This rich environment effect can be mimicked by brief electrical stimulation of the medial perforant pathway [108], which normally carries signals from the cortex into the hippocampus. Unilateral stimulation results in a wave of *zif-286* expression during subsequent REM sleep, with expression seen predominantly in the ipsilateral amygdala, entorhinal, and auditory cortices during the first REM sleep episodes after LTP induction, but extending into somatosensory and other cerebral cortices during subsequent REM periods [108]. These distinct phases of induction may correspond to the unique stages of consolidation previously reported from behavioral studies [14].

5. Conclusions

Learning and memory are dependent on processes of brain plasticity, and sleep-dependent learning and memory consolidation must be mediated by such processes. Many examples of such plasticity during sleep have now been reported, with several of them specifically induced by waking experiences. What remains to be demonstrated is that these specific components of brain plasticity, aside from the overall requirement for protein synthesis, specifically mediate sleep-dependent learning and memory consolidation. Such evidence would require elegant interventions in the cellular and molecular processes of brain plasticity during the normal course of sleep-dependent consolidation, studies which most likely are already in progress.

The opposing processes of synaptic stabilization and plasticity have recently been highlighted in a review by Abraham and Robins [109], who argue that functional stability requires molecular plasticity, so that the encoding of new information necessarily modifies the storage of older memories. The processes of memory consolidation and reconsolidation offer a series of opportunities for such plastic modification to occur. As such, they may be thought of as processes of memory organization, reorganization and refinement. While some of these events, such as initial stabilization, might reflect simple strengthening of the initial memory trace, sleep-dependent stages of consolidation and possibly reconsolidation are likely more complex, integrating memories within neural networks and memory systems.

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