

Sleep-dependent memory consolidation

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The concept of ‘sleeping on a problem’ is familiar to most of us. But with myriad stages of sleep, forms of memory and processes of memory encoding and consolidation, sorting out how sleep contributes to memory has been anything but straightforward. Nevertheless, converging evidence, from the molecular to the phenomenological, leaves little doubt that offline memory reprocessing during sleep is an important component of how our memories are formed and ultimately shaped.

The question of how sleep might contribute to learning and memory consolidation is an old one. In the first century AD, the Roman rhetorician Quintilian, commenting on the benefits of sleep, noted that, “what could not be repeated at first is readily put together on the following day; and the very time which is generally thought to cause forgetfulness is found to strengthen the memory”¹. Although this may have been obvious to him, it has been less obvious to the research community, and, until a seminal paper by Karni, Sagi and colleagues in 1994 (ref. 2), the topic received relatively little attention within either the sleep or memory research communities. But over the past 10 years, the rate of publication of research papers on sleep-dependent learning and memory consolidation has increased fivefold³. Evidence supporting sleep-dependent memory consolidation has come from a range of molecular, cellular, physiological and behavioural studies (for a review, see ref. 4; for an opposing view, see ref. 5).

One of the major problems facing this area of research is that the terms sleep, memory and memory consolidation all refer to complex phenomena, none of which can be treated as a singular event. I begin this review by clarifying my use of these terms, and then present some of the more convincing evidence from studies of procedural learning in humans. I then review more broadly the behavioural evidence for sleep-dependent consolidation of perceptual and motor skill procedural memories, declarative memories and complex cognitive procedural memories. I follow this by outlining converging evidence from molecular, cellular, neurophysiological, brain-imaging and dream studies, all of which support an important, and sometimes essential, role for sleep in memory consolidation.

Sleep and memory

There is more than one type of memory. Consider, for example, the capital of France, what you had for dinner last night and how to ride a bicycle. All three of these recollections require information that you have learned and stored, but they are very different types of memory. Multiple memory systems store different classes of memory in different brain regions and, quite probably, in different formats.

Memories are most commonly divided into declarative memories, which are those that a person can call to mind (for example, the capital of France or last night’s dinner), and non-declarative memories, which are those that are normally used without conscious recollection (for example, how to ride a bicycle or how to talk your way out of a parking ticket) (Fig. 1)⁶. Declarative memories are further divided into episodic memories, that is, memories of specific events (such as what you had for dinner last night), and semantic memories, in other words memories of general information (such as the capital of France). Non-

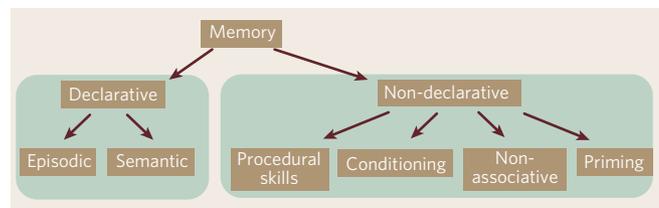


Figure 1 | Categorization of memory systems.

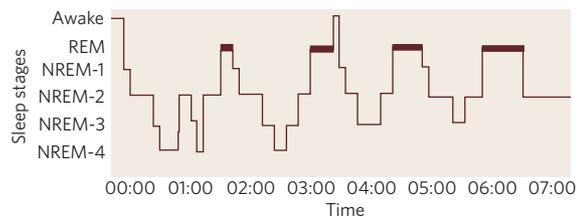


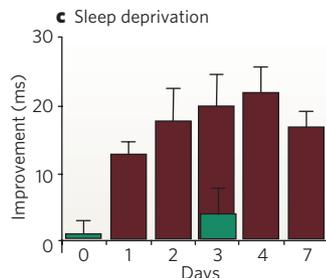
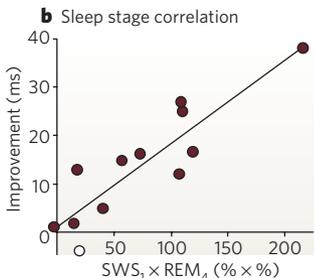
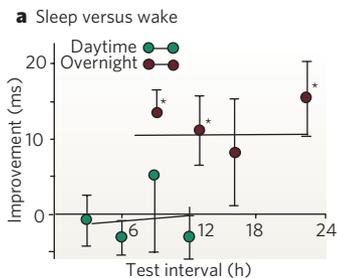
Figure 2 | Categorization of sleep stages.

declarative memories are also divided into several subcategories, such as procedural skills. Others in the field use the term memory in a more restricted manner, such as limiting it to episodic memories (see the commentary by Hobson in this issue, p. 1254).

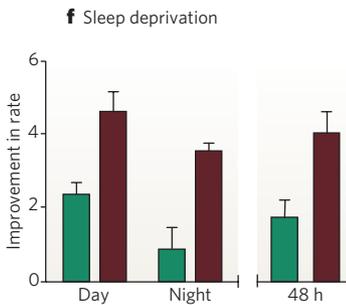
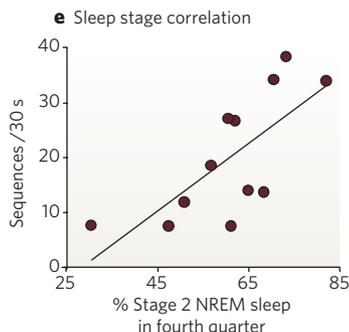
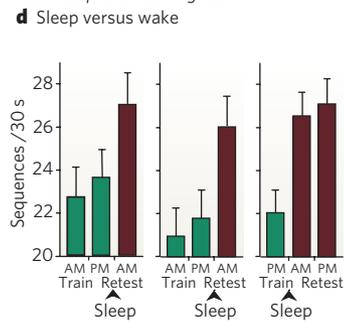
There is no consensus on what processes should be covered by the term ‘memory consolidation’. The term memory consolidation originally referred to a process of memory stabilization, through which memories become resistant to interference^{7,8}. But after the initial encoding of a sensorimotor experience, a series of cellular, molecular and systems-level alterations develop over time, automatically and outside of awareness, that stabilize and enhance the initial memory representation, converting it into a long-lasting and optimally integrated memory. These include not only cellular and molecular processes occurring at the local synaptic level, but systems-level reorganizations of individual memories as well (see refs 9, 10, for example). These additional memory-consolidation processes show the greatest evidence of sleep dependence, and I include all of them under the umbrella term memory consolidation. It is important to note that there is no consensus on how many distinct post-encoding processes exist, how they should be defined, and which should be considered under the rubric of memory consolidation. For example, memory stabilization cannot be considered absolute, because that would mean that other consolidation processes, such as enhancement and reorganization of memories, would not be possible.

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Visual texture discrimination task



Motor sequence learning task



Motor adaptation learning task

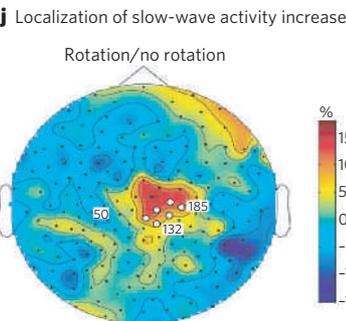
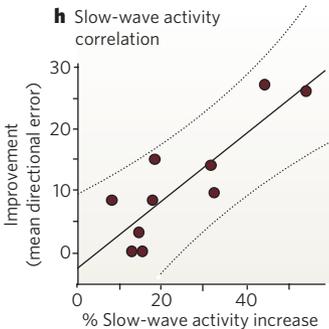
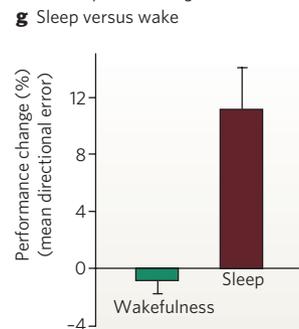


Figure 3 | Sleep-dependent consolidation of procedural memories. **a–c**, Participants in a visual texture discrimination task show improvement only after post-training sleep, even when finger movement was suppressed with mittens during wake periods (**d**). Improvement correlated with early-night slow-wave sleep and late-night REM sleep. **d–f**, Participants in a motor sequence finger-tapping task show similar sleep-dependent improvement, correlated with late-night stage 2 non-REM sleep. **g–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 s.e.m. See the text for further details. Green bars, performance without intervening sleep or without sleep on the first post-training night. Dark red bars, performance after normal sleep. See the text for further details. Panel J is reproduced with permission from ref. 21.

When we speak of consolidation processes as being ‘sleep dependent’, we are hypothesizing that they occur primarily during sleep. But most sleep-related processes can occur during periods of wakefulness and vice versa (for example, waking hallucinations and sleep walking). Nonetheless, in most cases, experimental studies have found sleep-dependent processes occurring only during sleep.

Unlike the nature of memory and memory consolidation, the structure of human sleep is clear. A night of sleep is composed of ~90-minute cycles divided into periods of rapid eye-movement sleep (REM) and non-REM sleep (NREM), with NREM further divided into stages 1 to 4 (Fig. 2). Stages 3 and 4 are the deepest stages of sleep, and are referred to collectively as slow-wave sleep (SWS) on the basis of the patterns of large, slow (0.5–4-Hz) oscillations observed on the electroencephalogram (EEG). Sleep stages differ not only in depth of sleep but also in the frequency and intensity of dreaming, EEG oscillations, eye movements, muscle tone, neuromodulation of cortical circuits, regional brain activation and communication between memory systems¹¹. REM, stage 2 and SWS have all been implicated in sleep-dependent memory processing, as have specific patterns of synchronous cortical neuronal activation associated with these stages, including ponto-occipitogeniculate waves and theta rhythms in REM, sleep spindles in stage 2 and the slow-wave activity of SWS.

Sleep-dependent memory enhancement

Results from three laboratories who asked volunteers to perform three different tasks, a visual texture discrimination test^{12,13}, a motor

sequence test^{14,15} and a motor adaptation test¹⁶, demonstrated that all subjects show post-training improvement after a night’s sleep but not during an equivalent period of being awake. The results also demonstrated that the amount of overnight improvement correlates with the amount of specific sleep stages or sleep events, and that total or partial sleep deprivation can prevent the normal overnight improvement.

These results leave little doubt that sleep contributes to the consolidation of memories, especially their enhancement. But the details of these processes remain unclear. Although improvement on the visual texture discrimination task correlates with the levels of REM and SWS, improvements in the motor sequence task correlate with lighter stage 2 NREM. With the motor adaptation task, improvement was linked, using EEG patterns, to SWS. Thus, even for these procedural skill tasks, sleep-dependent consolidation does not seem to depend consistently on one specific aspect of sleep. Instead, each stage of sleep seems to contribute differently to these processes, and we have proposed that the multiplicity of sleep stages has evolved, in part, to provide optimal brain states for a range of distinct memory consolidation processes. I will now look at each of the tests in more detail.

Visual texture discrimination

Several studies have supported the sleep-dependent enhancement of a foreground–background discrimination task (Fig. 3a–c). In this task, subjects must identify the orientation of an array of diagonal bars against a background grid of horizontal bars. Although an initial study found overnight improvement blocked by REM deprivation, but not

by SWS deprivation², subsequent studies suggested roles for both SWS and REM^{12,17}. For example, overnight improvement is strongly correlated with both the amount of SWS in the first quarter of the night ($r = 0.70$, $P = 0.01$) and the amount of REM in the last quarter ($r = 0.76$, $P = 0.004$), leading to the suggestion that a two-step process is necessary, the first during SWS and the second during REM¹². The product of these two sleep parameters, SWS1 \times REM4, produces an even stronger correlation ($r = 0.89$, $P < 0.0001$; Fig. 3b)¹². In addition, sleep deprivation the night after training prevents normal improvement, even when measured 72 hours after training, following two nights of recovery sleep (Fig. 3c, 3 days, green bar)¹³. Significant improvement is also seen after the first 3 hours of the night, rich in SWS (means: SWS = 74 min, REM = 24 min) but not across the last 3 hours of REM-rich sleep (SWS = 32 min, REM = 58 min)¹⁷. But an entire night, including both SWS-rich and REM-rich periods, shows more than three times as much improvement as the early night period¹⁷.

After consolidation takes place during this first post-training night, no improvement is seen throughout the second day (Fig. 3a). But additional nights of sleep produce further improvements (Fig. 3c). Thus, the sleep-dependent process of memory enhancement continues for at least 48–96 hours, an order of magnitude longer than the time thought to be required for the stabilization component of consolidation.

Motor sequence task

In this finger-tapping task, subjects type a simple numeric sequence, such as 4–1–3–2–4, on a computer keyboard, as quickly and accurately as possible. Alternative versions require subjects to touch fingers to thumb in a particular order. In the keyboard version, subjects improve steadily over the first minutes of practice, and then approach an asymptote, with a ~60% improvement in speed over twelve 30-second trials¹⁴. Subsequent retesting, 4–12 hours later the same day, shows no significant improvement (4%, $P = 0.13$; Fig. 3d, left panel, green bars). In contrast, after a night of sleep a significant 20% increase in speed is seen ($P > 0.0001$; Fig. 3d, left panel, red bar)¹⁴, an increase that correlates with the amount of stage 2 NREM in the last quarter of the night ($r = 0.72$, $P = 0.008$; Fig. 3e). Although daytime wake produces no improvement, a 90-minute midday nap leads to a significant 16% improvement¹⁸. Retesting after 72 hours shows even more improvement than after 24 hours (26% compared with 17%; $P = 0.07$), suggesting that, as with the visual discrimination task, improvement continues beyond the first night¹⁹. With the finger-thumb opposition version, sleep deprivation the night after training reduces the amount of improvement by over 75% ($P < 0.001$) after one night of recovery sleep (Fig. 3f, right panel). Again, sleep during the day produces significantly more improvement than an equivalent period of daytime wake ($P < 0.001$; Fig. 3f, left panel)¹³.

In addition to improvements in speed, sleep also leads to an increase in accuracy. Although subjects show no significant improvement in either speed or accuracy during 12 hours of daytime wake (speed: +4%, $P = 0.13$; error rate: +9%, $P = 0.46$), they improve significantly across a night of sleep (speed: +20%, $P < 0.0001$; error rate: -36%, $P = 0.01$)¹³.

Compared with memory enhancement, the issue of memory stabilization is more complex. Cross-training on a second finger-tapping sequence 10 minutes after training does not affect the speed or accuracy of performance on the initial sequence when retested shortly thereafter²⁰. From this perspective, consolidation seems complete within 10 minutes of training.

But when retesting is performed the next day, a different picture is seen. Now, the prior cross-training is seen to interfere with normal overnight enhancement of accuracy. Although both sequences show normal overnight improvement in speed the next day (sequence 1 = 12%, $P < 0.005$; sequence 2 = 6%, $P < 0.001$), the original sequence no longer shows the normal decrease in error rate (sequence 1 = -1%, $P = 0.90$; sequence 2 = -39%, $P < 0.001$). Thus, cross-training seems to

interfere not with the subject's recently gained ability to perform the task, but rather with the subsequent sleep-dependent enhancement of that ability. This susceptibility to interference seems to be time limited, because cross training 6 hours after the initial sequence fails to block overnight improvement in either speed or accuracy. In this case, both sequences show overnight improvement in accuracy (sequence 1 = 20%, $P < 0.05$; sequence 2 = 37%, $P < 0.005$). Whether stabilization is complete at 6 hours is unclear; the first sequence showed only half (54%) of the increase in accuracy seen in controls, but the difference was not statistically significant²⁰. But in either case, this stabilization now occurs over a period of wakefulness rather than sleep. When sleep can similarly support this stabilization is unknown.

Thus, this procedural motor sequence task shows features of sleep-dependent enhancement similar to those reported for the visual texture discrimination task. Performance improves significantly over a night of sleep, but not over either an equivalent period of wake during the day or a night of sleep deprivation; overnight improvement correlates with amounts of one or more specific (but different) sleep stages; and performance improves with a daytime nap. In contrast, memory stabilization can occur during periods of wakefulness.

Motor adaptation task

In this rotation adaptation task, subjects use a digital tablet (similar to an oversized Palm Pilot) to draw a line displayed on a computer screen from a starting point to a target while overcoming a virtual force 'pushing' the line to one side. As in the previously described tasks, subjects improve over a night with sleep, but not over an equivalent period of daytime wake (Fig. 3g)¹⁶. As with the visual discrimination task's nap studies, training on the task alters subsequent sleep¹⁶, in this case leading to a localized increase in the strength of SWS-associated EEG slow waves recorded over portions of the right parietal cortex implicated in task performance of this task (Fig. 3j)²¹, and this increase correlates with subsequent sleep-dependent improvement in performance ($r = 0.86$, $P < 0.005$; Fig. 3h)⁹. These 0.5–4-Hz EEG oscillations characterize SWS and may themselves facilitate memory consolidation²².

Additional findings and caveats

Studies with other learning tasks help clarify the range and limits of these findings. For example, the serial reaction-time task is a visuo-motor procedural learning task, in which four lights, placed above four response keys, flash in a complex order. As each light flashes, subjects must press the key beneath it. The sequence of lights displayed contains an embedded pattern, which subjects gradually learn. Positron emission tomography (PET) brain imaging studies have demonstrated that on the night after training, regions active during task performance are specifically reactivated during REM²³, a finding similar to the selective regional EEG activation seen during SWS after training on the motor adaptation task¹⁶.

A striking feature of all of the tasks described above is that the enhancement of performance seen over time seems to develop only during sleep. Although one might have expected both wake and sleep to support enhancement, that has not been the case. None of the volunteers showed significant improvement in the task over time awake. But this is not universally true. Training on a complex auditory tone sequence task leads to further improvement after 24 hours even in the absence of sleep²⁴. But, even here, recordings of event-related potentials (ERPs) suggest that subtle sleep-dependent processing is occurring. ERPs measure the EEG activity in response to a specific stimulus, in this case the auditory tone sequence, and allow high temporal resolution of the brain's processing of such stimuli. Here, where no overt sleep-dependent improvement is seen, post-training changes in the ERP, which are thought to be linked to systems-level consolidation processes, are sleep dependent. Thus, some sleep-dependent 'consolidation' seems to be taking place, although it is not reflected in performance gains²⁴. A second auditory discrimination task, in which subjects learn to identify vowel-consonant combinations against a background of white noise, also shows sleep-independent improve-

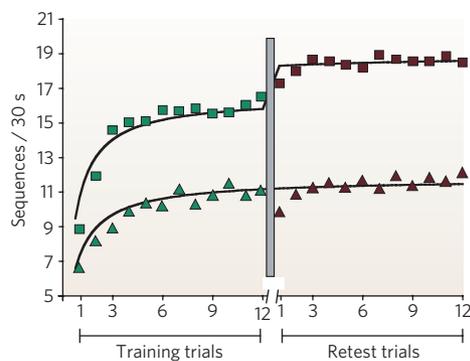


Figure 4 | Fit of data to exponential model of motor learning. Controls ($n = 14$, squares) showed a significant ($P < 0.0001$) 15% overnight improvement, whereas schizophrenia patients ($n = 20$, triangles) showed no improvement ($M < 0.1\%$; $P = 0.998$). The gray bar represents a 24-hour interval between training and retest. Reproduced from ref. 32.

ment, developing over 12 hours, across a day of wake or a night with sleep²⁵.

To make matters more complicated, the serial reaction-time task described above shows very different sleep dependence depending on exactly how the task is implemented²⁶. When subjects are informed at the start of the task that a repeating pattern of stimuli will be presented, they tend to learn the pattern explicitly, within awareness, and can report at least part of the pattern after completion of the protocol. By contrast, when subjects are not so informed, they tend to learn the sequence implicitly, without awareness, and cannot report it. Although both groups show sleep-dependent improvement, the implicit, but not explicit, learners also show improvement across an equivalent period of daytime wake²⁶. Only the explicit version of the task shows exclusively sleep-dependent improvement. Thus it is becoming clear that although we know of no offline procedural performance enhancement that occurs exclusively during periods of wakefulness, some tasks show such improvement during both wake and sleep.

There is one final caveat. Although there is now something close to a consensus that procedural memories are enhanced by sleep (but for a different opinion see ref. 5), there are very few data concerning sleep's role in the stabilization phase of consolidation. Although there is some evidence for stabilization across periods of wake^{20,27}, so far there is no clear evidence of stabilization across periods of sleep.

One important conclusion from this collection of studies is that whether or not sleep-dependent consolidation is observed depends on how training is carried out and how consolidation is measured. Thus interference training on the finger-tapping task blocks sleep-dependent improvements in accuracy, but not in speed²⁰. Post-training sleep deprivation had no effect on post-training enhancement of a complex tone sequence task but does block post-training consolidation measured as ERP changes²⁴. And time-dependent improvement in the serial reaction-time task can be switched from sleep independent to sleep dependent by simply informing subjects that a response pattern exists²⁶.

In summary, procedural learning of perceptual and motor skills are clearly enhanced across periods of sleep, in some cases only across periods of sleep, and most probably only during specific stages of sleep. But what characteristics of a memory control the exclusivity of this sleep-dependent consolidation, as well as which sleep stages are involved, remain unclear, as does the identity of which components of memory consolidation are sleep dependent for any given task.

Clinical considerations

All major psychiatric disorders, the so-called Axis I diagnoses²⁸, such as schizophrenia, bipolar disorder and major depression, have associated sleep disturbances that are considered sequelae to, but never contributors to, the psychiatric condition. But this interaction might be bi-directional. For example, it has been suggested that cognitive deficits

in people with schizophrenia arise in part from an inability to automate simple procedural learning²⁹, a function potentially related to sleep-dependent consolidation. Indeed, chronic, medicated schizophrenia patients show normal practice-dependent improvement in the finger-tapping task discussed above, but show no overnight improvement (Fig. 4)³⁰. Thus, in one major psychiatric illness, at least, one process of sleep-dependent memory consolidation seems to be totally dysfunctional.

Declarative and hippocampal learning

Although sleep-dependent consolidation of procedural learning seems certain, the evidence for declarative memory is weaker. Declarative memory, the formation of which is dependent on the hippocampus and medial temporal lobe, consists primarily of memories for events and facts. Studies of its sleep-dependent consolidation have commonly used tasks such as memorization of nonsense syllables³¹ or word-pair associates³².

As early as 1885, sleep was known to sustain declarative memory more effectively than daytime wake. But this superiority was ascribed to an absence of destructive interference that weakens memories during periods of being awake³¹. Because such memories do not normally show improvement with time, studies measure a balance between stabilization and enhancement on the one hand and interference and passive loss on the other. Until recently, most studies of word-pair associates showed no benefits from sleep (for a review see ref. 32). But a recent series of studies has argued that early night sleep, rich in SWS, supports declarative memory stabilization, and, perhaps, even enhancement³³, although it is not clear what role SWS plays in this consolidation. The stress hormone cortisol is at its lowest early in the night, and infusing cortisol during this time blocks sleep's beneficial effects on these word-pair associates³⁴. Similarly, levels of acetylcholine are lowest early in the night, and consolidation is blocked by cholinesterase inhibitors, which increase acetylcholine levels³⁵. Other studies have found that overnight retention of verbal memory correlates with sleep spindles, an EEG signature of stage 2 NREM^{36,37}. Despite this, others have argued that this sleep benefit merely reflects passive retention in the absence of interfering stimuli during SWS³⁸. Thus, the question of consolidation of word-pair learning remains unresolved.

A second approach to declarative memory has been through the study of hippocampus-dependent spatial memory³⁹. Subjects who train on a virtual navigation task show overnight improvement correlated with increased hippocampal activation during SWS ($r = 0.94$, $P = 0.005$)⁴⁰. This reactivation, measured using PET, parallels a wealth of animal data showing that temporal patterns of activity across networks of hippocampal neurons during performance of a spatial task are repeated during subsequent SWS and REM^{41,42}. In a pattern reminiscent of the human visual discrimination task data¹², replay is seen during SWS hours earlier than in REM. Furthermore, replay during SWS, but not REM, is on a highly compressed timescale. Additional studies have shown REM-dependent consolidation of spatial memory on both radial arm⁴³ and Morris water⁴⁴ mazes in rats. Thus, there is consistent evidence for sleep-dependent consolidation of hippocampus-dependent spatial memory tasks, although relatively few of the data are from humans.

It is striking that, although human studies have implicated SWS in hippocampus-dependent declarative memory consolidation (for examples see refs 33, 40), rat studies suggest that REM is crucial. A possible explanation for this apparent discrepancy comes from a human study suggesting that REM contributes to the consolidation of emotionally charged declarative memories. In this study, recall of emotion, but not neutral, text was enhanced by REM-rich, late-night sleep (emotional, $P < 0.001$; neutral, $P = 0.58$)⁴⁵. Thus, the REM dependence of consolidation in the rat might reflect increased emotional stress.

We thus can draw conclusions concerning declarative and hippocampal memories similar to those for procedural memories, albeit with less confidence. At least some forms of declarative and hippocampus-mediated memory seem to be consolidated across periods of sleep, and, in some cases, preferentially during specific stages of

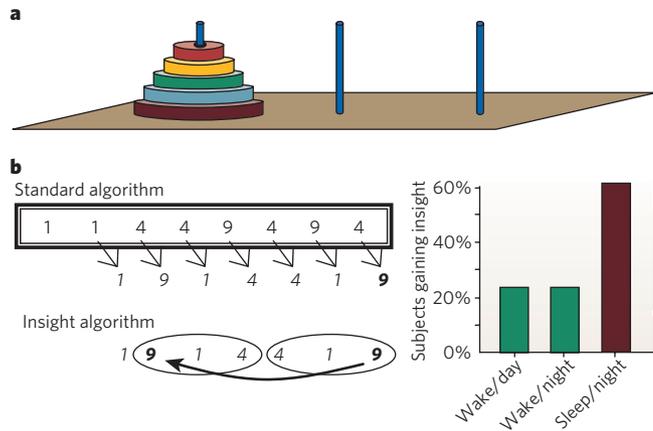


Figure 5 | Complex cognitive procedural learning. **a**, Tower of Hanoi task. Subjects must move one disk at a time, from one pole to another. Disks can be placed only on empty poles or on disks of larger diameter. The goal is to move all the disks to the right-hand pole in the fewest number of moves. For n disks, the optimal score is $2n - 1$ moves. **b**, Mathematical insight. The standard algorithm: subjects are taught a standard algorithm for reducing an eight-digit sequence to a final answer (the bold, italic '9' at the right), through six intermediate calculations (in italics). The 'insight' algorithm: the design of the task is such that the last three calculations form a mirror image of the preceding three, so that the second intermediate calculation always matches the final answer. Right, subjects allowed to sleep between the training and retest showed significantly higher rates of insight compared with those not allowed sleep. Reproduced from refs 49, 50.

sleep. But, again, the characteristics that determine this sleep-dependent consolidation of such memories and the sleep stages involved remain unclear. Even more basic is our uncertainty concerning the effect that sleep has on providing active consolidation, as opposed to merely preventing the negative effects of interference.

Complex cognitive procedural learning

The data presented thus far suggest that the more complex and sophisticated a task, the less confident we are of its sleep-dependent consolidation. Does sleep simply not contribute to more complex forms of human learning? The answer is no. Aside from the fact that motor skills form the basis of dance and music, distinctly human forms of expression, and that more complex motor learning shows more sleep-dependent improvement⁴⁶, several studies suggest that sleep contributes to the consolidation of uniquely human, complex cognitive procedural learning.

The Tower of Hanoi task (Fig. 5a) involves moving five disks from the leftmost pole to the right-most pole, following two rules: first, only the top disk on any pole can be moved at one time, and second, a disk can be moved to a pole only if that pole has no disks or if the disk is smaller than all the disks on the destination pole. When subjects are retested a week after training, a significant ($P = 0.03$) 40% improvement in performance is seen. But if REM is experimentally reduced the night after training, no such improvement is seen.

In another example of complex procedural learning (Fig. 5b)⁴⁷, subjects were taught a complex algorithm for solving a group of mathematical problems. Unknown to the subjects, a simpler solution also exists, which none discovered during training. But at retest, 12 hours later, a subset of subjects discovered this simpler method of performing the task. The probability of discovering it was more than doubled after a night of sleep (Fig. 5b, right, $P = 0.01$)⁴⁷. Thus, sleep enhanced the probability of gaining novel insight into the task, even though subjects did not know that there was an insight to be gained.

These studies suggest a more sophisticated role for sleep in memory consolidation, one that involves the discovery and clarification of complex rules within one's environment, forming and strengthening

associations within memory networks. Such processes are arguably among the most sophisticated human cognitive functions.

Converging evidence

So far, we have focused on human behavioural evidence of sleep-dependent memory consolidation. But several additional lines of investigation provide converging evidence of an important role for sleep in experience-dependent brain plasticity.

Molecular studies

In rats, gene expression during wakefulness and sleep displays state-dependent regulation. High-density microarray studies demonstrate that ~10% of genes expressed in both the cerebral cortex and cerebellum of rats undergo day–night fluctuations, and half of these are specifically dependent on wake–sleep states⁴⁸. Several genes upregulated during sleep, including those encoding calmodulin-dependent protein kinase IV and calcineurin, are believed to contribute to brain plasticity and memory consolidation. Others contribute to the synthesis and maintenance of cell membranes and myelin⁴⁸. In addition, genes are upregulated during sleep in a behaviour-dependent manner. The immediate early gene *zif-268*, which participates in activity-dependent synaptic plasticity, is induced during REM after exposure to enriched environments⁴⁹ (Fig. 6), and experimental induction of hippocampal long term potentiation induces *zif* expression during subsequent REM, first in the amygdala, entorhinal and auditory cortices, and, during subsequent REM periods, in somatosensory and motor cortices⁵⁰.

Cellular studies

Sleep contributes to normal experience-dependent plasticity in both the cat and rat visual systems. In young kittens, monocular deprivation of visual input for 6 hours reduces the responsiveness of cortical neurons to input from the deprived eye. When such deprivation is followed by 6 hours of sleep (but not 6 hours of wake in the dark), the effect is enhanced, producing as much additional change as another 6 hours of active monocular deprivation would⁵¹. Similarly, a crucial period of experience-dependent plasticity in the rat visual system can be extended by REM deprivation⁵².

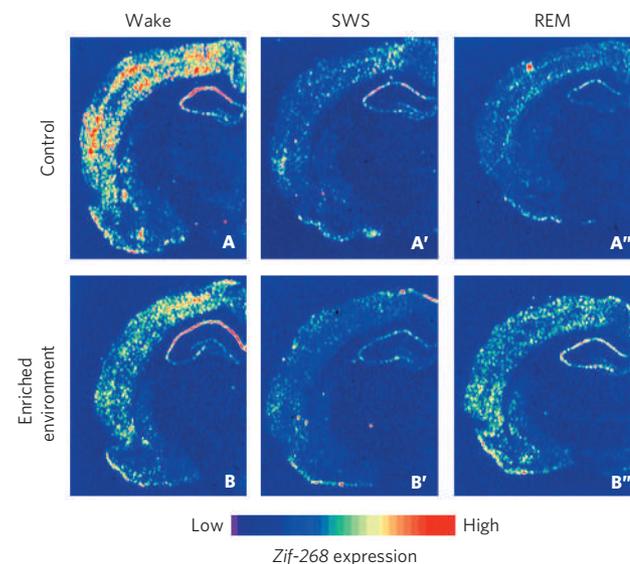


Figure 6 | Experience-dependent upregulation of the synaptic plasticity related immediate early gene *zif-268* during periods of wakefulness, SWS and REM sleep in the rat. Autoradiograms of frontal coronal brain sections in which gene-expression levels best represent the means for each group studied. In controls, *zif-268* expression decreased from wake (A) to SWS (A') and REM (A''). In enriched-environment animals, *zif-268* levels decreased from wake (B) to SWS (B'), but increased from the latter to REM (B''). This effect was particularly noticeable in the cerebral cortex and the hippocampus. Reproduced with permission from ref. 52.

Table 1 | Correlation of sleep-dependent learning and brain measures

Brain measure	Learning/memory task	r	r ²	P	Refs
Quantitative EEG	Motor adaptation	0.86	0.74	<0.005	9
PET	Virtual navigation	0.94	0.88	0.005	62
Time in SWS and REM	Visual discrimination learning	0.89	0.79	<0.0001	5
Time in stage 2	Motor sequence learning	0.72	0.52	<0.01	63
PGO wave density	Shuttle box avoidance (rats)	0.95	0.90	<0.001	64
Spindle density	Paired associates learning	0.56	0.31	<0.05	65
Means and combined probability		0.82	0.69	10 ⁻¹⁵	

Correlation coefficients are between post-sleep improvement and brain measures, including quantitative EEG and REM-related pontogeniculo-occipital (PGO) brain waves, taken during sleep. The combined probability of 10⁻¹⁵ reflects the likelihood of all six studies providing such low probabilities for the null hypothesis.

Neurophysiological studies

As noted earlier, patterns of hippocampal neuronal activation seen during spatial navigation are replayed during subsequent sleep. A similar process of replay is seen in the song system of the Zebra finch, where patterns of neuronal excitation seen during song rehearsal are replayed during sleep⁵³. In this case, sleep leads to a temporary deterioration in song quality⁵⁴, but this deterioration correlates with overall improved learning. This suggests that sleep plays an important role in balancing stabilization of the rehearsed song against the continued plasticity required for further improvement⁵⁴.

Brain imaging studies

Both the visual texture discrimination task^{55,56} and the finger-tapping task⁵⁷ show changes over time in the patterns of regional brain activation associated with task performance, and a night of sleep leads to a reorganization of the brain regions involved in both visual discrimination⁵⁶ and motor sequence⁵⁷ learning. Sleep leads to increased activation in primary visual and motor regions, as expected, but regions of the limbic, frontal and parietal areas also see changes. This suggests that sleep supports enhanced performance by altering the entire strategy used by the brain and allows more automatic execution of the tasks^{24,29}.

Dream studies

An unexpected source of evidence for sleep-dependent memory consolidation comes from the study of dreaming. Dream reports, in common with microarray analyses of gene expression, single-cell and neural network recordings and human brain images, can provide a window into the activity of the sleeping brain, albeit a subjective one. Two such studies^{58,59} suggest, perhaps counterintuitively, that episodic memories are not reactivated during dreaming.

When subjects identified waking sources for dream elements⁵⁸, less than 2% of the elements seemed to be possible replays of episodic memories. In a second study of sleep-onset dreams⁵⁹, subjects who have been playing the computer game Tetris report images from the game, but in a stereotyped form not consistent with a replay of episodic memories. This conclusion is reinforced by similar reports from densely amnesic patients who have no conscious memories of playing the game. Both studies suggest that dream construction occurs without activation of hippocampus-mediated episodic memories; instead they show abstracted images of key elements of the waking events.

Such an absence of episodic memory replay is supported by human PET studies showing that the dorsolateral prefrontal cortex, normally involved in memory recall, is deactivated during sleep, and especially during REM sleep⁶⁰. It is also supported by animal studies suggesting that the flow of information from the hippocampus to the cortex is blocked during REM⁶¹.

Summary

The past 10 years have shown an explosive growth in our knowledge of the relationship between sleep and memory, providing consistent

and strong support for the existence of sleep-dependent memory consolidation. For example, Table 1 summarizes several studies correlating delayed improvement in procedural memory tasks with various measures of intervening sleep. What is noteworthy is that for these six studies, correlation values of 0.56–0.95 were reported, explaining an average across studies of 69% of the variance, a remarkable achievement for any factor contributing to memory consolidation!

Future directions

But several major questions remain. What types of memory are consolidated during sleep? There is strong evidence for some, but not all, forms of procedural learning being consolidated, and more modest evidence for forms of declarative memory, but the rules determining which are consolidated during sleep remain unclear. In addition, what types of consolidation occur during sleep are largely unknown. When sleep-dependent consolidation occurs, both in terms of sleep stages and the time of night, also remains poorly understood. And finally, why these processes are preferentially or exclusively restricted to sleep is completely unknown. The search for answers to these questions is the task of the next decade of research into sleep-dependent memory consolidation. And we still do not know what it means to 'sleep on a problem'. ■

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Acknowledgements This work was supported by grants from the US National Institutes of Health.

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