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The Modulation of Memory by Sleep

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Glossary

Declarative memory: Memory for items that can be verbally declared, including autobiographical memories (episodic memories) and knowledge-based facts (semantic memories), dependent largely upon structures in the medial temporal lobe.

Functional magnetic resonance imaging (fMRI): A neuroimaging technique allowing for the measurement of functional changes in brain activity measured by the response of regional blood-oxygen to changes in magnetic field strength.

Long-term potentiation (LTP): One possible cellular mechanism of long-term memory, indicated by long-standing change in the excitability of a neuron, following original stimulation; LTP is modulated by both sleep and sleep deprivation.

Medial temporal lobe (MTL): Medial surface of the temporal lobe of the cerebral cortex, consisting of the hippocampus, entorhinal cortex, parahippocampal gyrus, and perirhinal cortex, along with the amygdala. Regions within the MTL are considered crucial for processing of long-term declarative memory.

Memory consolidation: Period of memory stabilization resulting in greater stability of the learned memory in the face of interference, and greater ability to retrieve the memory at a later date.

Memory encoding: The stage of originally learning the information constituted in a memory.

Memory recall: Ability to retrieve some or all of the information stored in memory.

Nonrapid eye movement sleep (NREM): Collective stages of sleep characterized by increasingly cortical de-activity, and characteristic slow waves and sleep spindles.

Positron emission tomography: A neuroimaging technique using small doses of radioactive isotopes to measure regional changes in brain metabolism.

Procedural memory: A form of nondeclarative memory (e.g., motor skills).

Rapid eye movement sleep (REM): The stage of sleep, commonly associated with dreaming activity, characterized by acetyl cholinergic desynchronized electrical brain activity, peripheral muscle atonia and phasic eye movement bursts.

Slow-wave activity (SWA): Quantitative measure of the power (strength) of slow (~0.5–4 Hz) frequencies in the sleeping EEG.

Introduction

Despite the vast amount of time sleep takes from our lives, we still lack consensus on its function. In part, this is perhaps because sleep, like its counterpart wakefulness, may serve not one but many functions, for the brain and body alike. Centrally, sleep is a brain phenomenon, and over the past 20 years, an exciting revival has taken place within the neurosciences, focusing on the question of why we sleep, and specifically targeting the role of sleep in a number of cognitive and emotional processes. This article aims to provide a synthesis of these recent findings in humans, with the goal of extracting consistent themes across domains of brain functions that appear to be regulated by sleep. Section ‘Memory Processing and Brain Plasticity’ will explore the role of sleep in memory and brain plasticity, and also examine competing models of sleep-dependent learning. Section ‘Association, Integration, and Creativity’ will address the role of sleep beyond memory consolidation, particularly in processes of association, integration, and creativity.

Memory Processing and Brain Plasticity

When considering the role of sleep in memory processing, it is pertinent to appreciate that memories evolve over time. Specifically, memories pass through discrete stages in their ‘lifespan.’ The conception of a memory begins with the process of encoding, resulting in a stored representation of an experience within the brain. However, it is now understood that a vast number of postencoding memory processes can take place. For memories to persist over the longer time course of minutes to years, an off-line, unconscious operation of consolidation appears to be necessary, affording memories greater resistance to decay (a process of stabilization), or even improved recollection (a process of enhancement). Sleep has been implicated in both the encoding and consolidation of memory.

Sleep and Memory Encoding

Early human studies in the 1960s, that described the impact of sleep deprivation on declarative memory encoding, indicated that ‘temporal memory’ (memory for when events occur) was significantly disrupted by a night of pretraining sleep loss. Subsequent studies replicated and extended this work, demonstrating impaired learning and retention of fact-based information in subjects deprived of sleep for 36 h, even in subgroups that received caffeine to overcome nonspecific effects of lowered alertness. Furthermore, the sleep-deprived subjects often displayed significantly worse insight into their memory encoding performance, resulting in lower predictive ability of their performance.

Cognitive neuroscientists have examined the neural basis of such memory impairments using functional magnetic resonance imaging (fMRI). In one of the first such studies, sleep
deprivation significantly impaired learning activity in the medial temporal lobe (MTL), while the prefrontal cortex actually expressed greater activation. Most interesting, the parietal lobes, which were not activated during learning in the control group that had previously slept, were significantly active in the deprivation group. Such findings suggest that inadequate sleep (at least following one night) prior to learning produces bidirectional changes in episodic encoding activity, involving the inability of the MTL to engage normally during learning, combined with potential compensation attempts by prefrontal regions, which in turn may facilitate the recruitment of parietal lobe function.

The impact of sleep deprivation on memory formation may be especially pronounced for emotional material, depending on whether it is emotionally negative, positive, or neutral. For example, a recent report demonstrated that when collapsing across all types of emotional stimuli, sleep-deprived subjects exhibited a striking 40% reduction in the ability to form new human memories under conditions of sleep deprivation. When these data were separated into the three affective categories (negative, positive, or neutral), the magnitude of encoding impairment differed. In those who had slept, both positive and negative stimuli were associated with superior retention levels relative to the neutral condition, consonant with the notion that emotion facilitates memory encoding. However, there was severe disruption of encoding and hence later retention for neutral and especially positive emotional memory in the sleep-deprived group. In contrast, a relative resistance of negative emotional memory was observed in the deprivation group. These data suggest that, while the effects of sleep deprivation are directionally consistent across memory subcategories, the most profound impact is on the encoding of positive emotional stimuli, and to a lesser degree, emotionally neutral stimuli. In contrast, the encoding of negative memory appears to be more resistant to the effects of prior sleep loss, at least following one night.

The impact of sleep deprivation on the neural dynamics associated with declarative memory encoding has also been examined using event-related fMRI. In addition to performance impairments under the condition of sleep deprivation, and relative to a control group that slept, a highly significant and selective deficit was identified in bilateral regions of the hippocampus – a structure known to be critical for learning and selective deficit was identified in bilateral regions of the hippocampus – a structure known to be critical for learning new episodic information. When taken together, this collection of findings indicates the critical need for sleep before learning in preparing key neural structures for efficient next-day learning. Without adequate sleep, hippocampal function becomes markedly disrupted, resulting in the decreased ability for encoding new experiences, the extent of which appears to be further governed by alterations in prefrontal encoding dynamics.

While these findings describe the detrimental impact of a lack of sleep, recent work has conversely characterized the proactive benefit of sleep, and specific sleep physiology, on restoring episodic memory encoding ability. Episode learning capacity was assessed twice across a 6-h waking interval. Following the first learning session at 12.00, half of the subject remained awake, while the other half obtained a 100 min nap opportunity. Both groups then performed the second learning session at 18.00. Learning capacity deteriorated in those who remained awake, yet sleep blocked this deterioration and restored episodic encoding ability. Moreover, the extent of learning restoration in the nap group was correlated with both the amount of stage-2 nonrapid eye movement sleep (NREM), and specifically the number of fast sleep spindles over the prefrontal cortex. Taken together with the neuroimaging results above, these demonstrate an important role for sleep, and specific NREM oscillations, before learning in preparing the hippocampus for efficient episodic encoding ability.

Sleep and Memory Consolidation

Using a variety of behavioral paradigms, evidence for the role of sleep in memory consolidation has now been reported across a diverse range of phylogeny. Perhaps the earliest reference to the beneficial impact of sleep on memory is by the Roman rhetorician, Quintilian, stating that:

…[it] is a curious fact, of which the reason is not obvious, that the interval of a single night will greatly increase the strength of the memory… Whatever the cause, things which could not be recalled on the spot are easily coordinated the next day, and time itself, which is generally accounted one of the causes of forgetfulness, actually serves to strengthen the memory.

A robust and consistent literature has demonstrated the need for sleep after learning in the subsequent consolidation and enhancement of procedural memories. Early work focusing on the role for sleep in declarative memory processing was somewhat less consistent, but more recent findings have now begun to reveal a robust beneficial effect of sleep on the consolidation of declarative memory, which is our focus here.

Several studies have now demonstrated off-line consolidation on a word-pair associates task following sleep, attributed to early night sleep, rich in slow-wave sleep (SWS), and more recently, slow delta waves (0.5–4 Hz) and the very slow cortical oscillation (<1 Hz). Following learning of a word-pair list, a technique called ‘direct current stimulation’ was used to induce slow oscillation-like field potentials in the prefrontal cortex (in this case, at 0.75 Hz) during early night SWS. Direct current stimulation not only increased the amount of slow oscillations during the simulation period (and for some time after), but also enhanced next day word-pair retention, suggesting a critical role for SWS neurophysiology in the off-line consolidation of episodic facts.

Rather than simply testing memory recall, others have since revealed that the extent of sleep has the ability to protect declarative memories using experimentally induced learning disruption. Taking advantage of a classic interference technique called the A-B–A-C paradigm, subjects first learned unrelated word-paired associates, designated as list A-B (e.g., leaf-wheel, etc.). After overnight sleep, or wakefulness during the day, half of the subjects in each group learned a new, interfering list containing a new associate paired with the first word, designated as list A-C (e.g., leaf-nail, etc.), before being tested on the original A-B list (e.g., leaf-wheel, etc.). In the groups that did not experience the interfering challenge—simply being trained and then tested on list A-B – sleep provided a modest benefit to memory recollection. However, when testing the groups that were exposed to the interfering list learning (list A-C) prior to recalling the original list...
(list A-B), a large and significant protective benefit was seen in those that slept. Thus, memories tested after a night of sleep were significantly more resistant to interference, whereas across a waking day, memories were far more susceptible to this antagonistic learning challenge. Yet, it was only by using an interfering challenge, the A-C list, that the true benefit of sleep’s protection of memory was revealed; a benefit that would not necessarily have been evident in a standard study-test memory paradigm.

One mechanism proposed to underlie these effects on hippocampal-dependent learning tasks (and see next section) is the reactivation of memory representations at night. A considerable number of reports have investigated the firing patterns of large networks of individual neurons across the wake–sleep cycle in animals. The signature firing patterns of these hippocampal and cortical networks, expressed during waking performance of spatial tasks and novel experiences, appear to be ‘replayed’ during subsequent SWS (and in some studies, also rapid eye movement (REM)). Homologous evidence has been reported in the human brain using a virtual maze task in combination with positron emission tomography scanning. Daytime learning was initially associated with hippocampal activity. Then, during posttraining sleep, there was a reemergence of hippocampal activation, specifically during SWS. Most compelling, however, the amount of SWS reactivation in the hippocampus was proportional to the amount of next-day task improvement, suggesting that this reactivation is associated with off-line memory improvement.

It is well known that memory can be strongly modulated by smell; most of us have associated the smell of a certain perfume or cologne with a particular person, and when we encounter that same perfume again, it often results in the powerful cued recall of memories of that particular person. In one such example, however, following learning of a spatial memory task that was paired with the smell of rose, the odor was not represented again at retrieval, but instead, during subsequent SWS that night – a time when consolidation was presumed to be occurring. Relative to a control condition where the odor was not presented again during SWS, the reperfusion of the rose scent at night resulted in significantly improved recall the following day. Moreover, the representation of the odor resulted in greater (re)activation of the hippocampus during SWS. These findings support the role of SWS in the consolidation of individual declarative memories, and may indicate an active reprocessing of hippocampal-bound information during SWS. Extending these findings is the demonstration of similar sleep-dependent reactivation of memory using auditory rather than olfactory cues, describing a selective ability to manipulate individual item memory consolidation during SWS.

Counter to the classical notion of sleep universally benefiting all previously encoded memories, emerging findings are beginning to describe a more nuanced and selective role for sleep in off-line memory consolidation. For example, sleep, often REM sleep, has been demonstrated to preferentially consolidate negative emotional memories relative to neutral items. Beyond emotion, sleep has recently been demonstrated to selectively enhance memories weighted toward monetary rewards.

Interestingly, and in line with the view that sleep may actively play a role in targeted forgetting as well as remembering, the most recent work has described a differential role for sleep in remembering and forgetting using a directed forgetting learning paradigm, where individual items (words) are cued during initial encoding to either be remembered, or forgotten. Compared to a wake control group, sleep, and specifically fast sleep spindles over left parietal cortex, preferentially enhanced those items previously cued to be remembered during learning, but did so without strengthening those items previously cued to be forgotten: indicative of specific preference based on prior waking instruction (Figure 2). Collectively these studies suggest that sleep does not universally consolidate all episodic memories learned during the day. Instead, sleep appears to be more ecologically attuned to qualitative aspects of encoded experiences (e.g., emotionality, reward potential, or explicit cue instructions and intentions), resulting in discriminatory off-line memory processing.

Models of Sleep-Dependent Memory Processing

Elucidating the neural mechanisms that control and promote sleep-dependent human memory consolidation remains an active topic of research, and debate. It is perhaps unlikely that multiple different memory systems, involving diverse cortical and/or subcortical networks, require the same underlying neural mechanisms for their modulation. Even if they do, it is not clear that this process would rely on just one type of sleep-stage physiology. At present, two intriguing models of sleep-dependent plasticity, relevant to declarative memory, have been offered to account for the overnight facilitation of recall, which build on different aspects of neural activity during sleep: (1) hippocampal–neocortical dialog; (2) synaptic homeostasis hypothesis.

Hippocampal–neocortical dialog

There is considerable agreement that structures within the MTL, most notably the hippocampal complex, are crucial for the formation and retrieval of new declarative memories. These structures are believed to guide the reinstatement of recently formed memories by binding together patterns of cortical activation that were present at the time of initial learning. A classical model of declarative memory consolidation suggests that information initially requires MTL binding, but over time, and by way of slow off-line processes, is eventually integrated into neocortical circuits (Figure 3). Neocortical structures thus become the eventual storage site for consolidated episodic memories through cross-cortical connections, and as a consequence, the MTL is not necessary for their retrieval. Therefore, the classical model of memory consolidation holds that neocortical structures become increasingly important for the retention and retrieval of successfully consolidated episodic memories, while the corresponding contribution of the hippocampus progressively decreases. In addition to its role in binding distributed cortical memory components, the hippocampus plays a critical role in reactivating these networks, specifically during sleep. This process of reactivation would, over multiple sleep cycles across a night, and/or multiple occurrences of sleep over many nights, gradually strengthen the initially weak connections between neocortical sites, thereby reinforcing them (Figure 3). Eventually, this strengthening would allow the original information to be activated in the cortex, independent of the hippocampus.
Interestingly, these models make two predictions about the impact of sleep on declarative memory. The first is that declarative memories from the day prior should be more resistant to interference the next day, due to the increased corticocortical connections formed during overnight consolidation (Figure 1). This prediction has been demonstrated by the finding of greater postsleep resistance to interference, using the A-B–A–C paired-associate paradigm. A second and far less considered benefit of this sleep-dependent dialog is the encoding capacity of the hippocampus (Figure 3). If the strengthening of corticocortical connections takes place during sleep, albeit iteratively, then blocking sleep after hippocampal learning should negate this off-line transfer, preventing the development of independence from (or ‘refreshing’ of) the hippocampus, and by doing so, decrease the capacity for new hippocampal learning the next day. This second premise appears to accurately explain the findings discussed in the memory encoding section above, which describe a significant impairment of hippocampal encoding activity when sleep has not taken place (through deprivation), being associated with a decreased ability to form new episodic memories.

Recent evidence has provided further support for this sleep-dependent dialog and neural transformation of declarative memory. One such study examined the benefit of daytime naps on episodic declarative memory consolidation. In addition to a long-term evaluation of memory over 3 months, there was also a short-term evaluation of memory across the first day, which included an intervening nap period (90 min) between training and testing of the original studied (‘remote’) stimuli. Interestingly, the duration of NREM SWS during the intervening nap correlated positively with later recognition memory performance, yet negatively with retrieval-related activity in the hippocampus. Expanding on these findings is the demonstration that one night of posttraining sleep

![Figure 1](image1.png)

**Figure 1** Impact of sleep on the consolidation and stabilization of declarative memory. Percent correct recall for B words from the original A-B pair after a 12-h retention interval of either wake or sleep following no interference or interference learning (list A-C). *p < 0.10, **p < 0.05, ***p < 0.001; error bars indicate S.E.M. Modified from Ellenbogen et al. (2007).

![Figure 2](image2.png)

**Figure 2** Role of sleep on directed remembering and forgetting. (a–b) Behavioral data. Memory performance: (a) number of words recalled based on prior cue instruction (remember, R-words; forget, F-words) in the nap and no-nap groups and (b) the efficiency measure of directed forgetting, calculated as the subtraction of these scores (R–F; expressed as a proportion of total recall). Between group comparisons (line across bars) reflect significance at: *p < 0.05 and **p < 0.01. Error bars represent S.E.M. Modified from Ellenbogen et al. (2007). (c–d) Physiological data. Relationship between memory performance and sleep spindles: (d) correlation topographical plot demonstrating strength of relationship between fast sleep-spindle density and R–F score. Note spindle activity at the P3 (left parietal) electrode site showing the strongest relationship (color bar indicates r value, with noted corresponding critical p value increments). Modified from Saletin JM, Goldstein AN, and Walker MP (2011) The role of sleep in directed forgetting and remembering of human memories. *Cerebral Cortex* 21(11): 2534–2541, http://dx.doi.org/10.1093/cercor/bhr034.
deprivation, even following recovery sleep, significantly impairs the normal modulation of hippocampal activity associated with episodic memory recollection. Furthermore, first-night sleep deprivation also prevented an increase in hippocampal connectivity with the medial prefrontal cortex, a development that was only observed in those that sleep after learning.

While no one study has yet demonstrated that the neural signature of learning during the day is subsequently reactivated and driven by characteristics of SWS at night, and that the extent of these properties are consequently proportional to the degree of next-day recall and memory reorganization; collectively, they offer an empirical foundation on which to entertain this possibility.

**Synaptic homeostasis hypothesis**

In recent years, an orthogonal theory of SWS and learning has emerged, which postulates a role for sleep in regulating the synaptic connectivity of the brain – principally the neocortex. The synaptic homeostasis model considers NREM SWS, and specifically the magnitude of slow-wave activity (SWA) of SWS, as a brain state that promotes the decrease of synaptic connections, not their increase. Accordingly, plastic processes, such as learning and memory occurring during wakefulness, result in a net increase in synaptic strength in diffuse brain circuits. The role of SWS, therefore, and the slow oscillation in particular, is to selectively downscale or 'de potentiate' the synaptic strength back to baseline levels, preventing synaptic overpotentiation, which would result in saturated brain plasticity. In doing so, this rescaling would leave behind more efficient and refined memory representations the next day, affording improved recall. A number of human studies have provided evidence supporting their model. For example, it has been shown that learning of a motor-skill adaptation task during the day subsequently triggers locally specific increases in cortical SWA at night, the extent of which is proportional to both the amount of initial daytime learning and the degree of next-day improvement (Figure 4).

How can the two concepts of neural reactivation (such as increased fMRI activity during SWS) and neural homeostasis (such as increased slow-wave EEG activity) be interpreted at a neural synaptic level? It could be argued that both these reported changes reflect either an increased neural reactivation, or an increase in SWA associated with homeostasis and synaptic downscaling. Furthermore, both hypotheses, while distinctively different, mechanistically, could offer complementary benefits at the network level in terms of signal-to-noise ratio (SNR), and may account for overnight memory improvements. Specifically, homeostatic synaptic downscaling could result in the removal of superfluous neural connections, resulting in improved SNR. However, neural reactivation and strengthening of experience-dependent circuits, without removing redundant synaptic connections, may equally improve SNR. Therefore, both mechanisms, while different, could produce a similar outcome – enhanced fidelity of the memory representation. Presumably the combination of both would perhaps produce the most optimal and efficient memory trace, yet a careful delineation of these possibilities remain an important goal for future studies.

Interestingly, the homeostasis model would also predict that sleep deprivation, specifically the prevention of SWS, would also negate effective new learning the next day, due to over potentiation of the synaptic connections. Thus, any region that exhibits SWA, and is involved in representing memory (e.g., hippocampus), would display a corresponding inability to code further information beyond a normal waking duration (~16 h in humans). Such a premise may offer an alternative explanation to the marked hippocampal encoding deficits reported under conditions of sleep loss.

**A role for sleep spindles?**

Independent of both these models, which consider the role of SWS in memory processing, a number of reports have also described an association between learning and the hallmark feature of stage-2 NREM – sleep spindles; short (~1 s) synchronous bursts of activity expressed in the EEG in the 10–16 Hz frequency range. For example, following learning of a motor-skill memory task, posttraining sleep spindles over the motor cortex were recorded, evaluating the difference in spindle activity in the right, learning hemisphere (since subjects perform the task with their left nondominant hand), relative to the left, nonlearning hemisphere. Remarkably, when sleep-spindle
power at electrode sites above the primary motor cortex of the nonlearning hemisphere (left) were subtracted from those in the learning hemisphere (right), representing the within-subject, between-hemisphere difference in spindle activity following learning, a strong predictive relationship with the amount of memory improvement emerged.

Such findings indicate that the enhancement of specific memory representations is associated with electrophysiological events expressed at local, anatomically discrete locations of the brain. Contrasting with the proposed impact of SWS, the mechanistic benefit of sleep spindles may be related to their faster stimulating frequency; a range suggested to facilitate long-term potentiation (LTP; a foundational principal of synaptic strengthening in the brain), and not synaptic depression. This increase in spindle activity may represent a local, endogenous trigger of intrinsic synaptic plasticity, again corresponding topographically to the underlying memory.

Increases in posttraining spindle activity are not limited to procedural memory tasks. For example, significantly higher sleep-spindle density has been reported in subjects that underwent a daytime episodic learning session (encoding of word-pair associates) compared to controls that did not perform the learning session. Moreover, the spindle density was associated with the proficiency of memory recalled the next day in the learning group.

**Reconciling models**

None of these models necessarily need to be wrong. Instead, aspects of each may afford complementary and synergistically beneficial outcomes for memory. Clues to this possibility lie within the ordered structure of human sleep, with NREM SWS dominating early in the night, and stage-2 NREM and REM prevailing later in the night. When placed in this temporal framework, a progression of events emerges that may be optimal for the neuroplastic modulation of memory representations. From a reactivation perspective, the predominance of hippocampal-neocortical interaction would take place in the early SWS-rich phase of the night, leaving corticocortical connections on offer for later processing during stage-2 NREM and REM. Similarly, and even in coincidence, SWS may downscale cortical (and possibly subcortical) plasticity, and do so in a learning-dependent manner, again leaving only those representations (or aspects of these representations) which are strongest – including those strengthened by hippocampal-neocortical interplay – for processing during these latter periods of sleep, dominated by faster frequency oscillations.

This concept is analogous to the art of sculpture. During the day, through experience, substantial informational ‘clay’ is acquired on the cortical pedestal; some relevant, some not. Once accumulated, the next step is to carve out and select the strongest and most salient memory representations (‘statues’) for the organisms – a mechanism that SWS, occurring first and predominately early in the night, may be ideally suited for. Following such downscaling and/or dynamic selection of memory through translocation, the remaining cortical representations – the rough outline of the sculpted form – may finally be strengthened by faster frequency oscillations.
including those of sleep spindles (and potentially PGO-wave burst during REM), more associated with the potentiation of synaptic connections, not their depotentiation. This final step is akin to polishing and improving the detailed features of the memory statue; which in terms of computational modeling would offer improved signal-to-noise quality within the system. Such a cooperative mechanism, which appreciates the temporal order of the wake–sleep cycle (acquisition, followed by postprocessing), and within sleep, the ultradian pattern of sleep-stage progression across a night (selection and removal, followed by strengthening), would produce a network of stored information that is not only more efficient, but for those representations remaining, more enhanced. Both these processes would predict improved recall of remodeled individual memories from the prior day, and further afford the synaptic capacity for efficient acquisition of new ‘information clay’ the next day.

**Association, Integration, and Creativity**

As critical as consolidation may be – an operation classically concerned with individual memory items – the association and integration of new experience into preexisting networks of knowledge is equally, if not more, important. The resulting creation of associative webs of information offers numerous and powerful advantages. Indeed, the end goal of sleep-dependent memory processing may not be the enhancement of individual memories in isolation, but instead, their integration into a common schema, and by doing so, facilitate the development of universal concepts; a process which forms the basis of generalized knowledge, and even creativity.

**Association and Integration**

Perhaps the earliest demonstration that sleep may be involved in a form of memory generalization was described using an artificial grammar task, where subjects trained and later tested on the ability to transfer phonological categories across different acoustic patterns. The task required forming new mappings from complex acoustical sounds to preexisting linguistic categories, which then generalized to new stimuli. As such, it involved both a declarative process of forming specific memories associated with the learned stimuli, together with a procedural component involving mapping across the set of learned sounds that supports generalization to novel stimuli. During the initial training session there was a significant improvement in recognition performance on the task. However, when retested after a 12-h waking interval, performance had decayed. Yet, if subjects were retested following a night of sleep, this ability for memory generalization was restored. Supporting this concept, others have also demonstrated that sleep, and not equivalent time awake, can integrate related but novel phonemes into preexisting long-term lexical memory stores overnight.

Similarly, infants when exposed to ‘phrases’ from an artificial language during a learning session – for example, phrases like ‘pel–wadim–jic’ – until the infants became familiar (as indexed by look responses). These three syllable units had an embedded rule, which was that the first and last unit formed a relationship of nonadjacency; in this case, pel predicts jic. The infants were then retested several hours later, yet some infants took normally scheduled naps, while others were scheduled at a time when they would not sleep after learning. At later testing, infants again heard the recordings, along with novel phrases in which the predictive relationship between the first and last word was new. Infants who did not sleep recognized the phrases they had learned earlier, yet those who had slept demonstrated a generalization of the predictive relationship to new phrases, suggesting that the intervening process of sleep allowed the reinterpretation of prior experience, and supported the abstraction of commonalities – that is, the ability to detect a general pattern in new information.

This sleep-dependent hypothesis of integration was recently tested by examining human relational memory – the ability to generalize previously acquired associations to novel situations. Participants initially learned five ‘premise pairs’ (A>B, B>C, C>D, D>E, E>F). Unknown to subjects, the pairs contained an embedded hierarchy (A>B>C>D>E>F). Following an off-line delay of 20 min, 12 h across the day or 12 h containing a night of sleep, knowledge of this hierarchy was tested by examining relational judgments for novel ‘inference’ pairs, either separated by one-degree of associative distance (B>D, C>E pairs), or by two-degrees of associative distance (B>E pair). Despite all groups achieving near identical premise-pair retention after the off-line delay (i.e., the building blocks of the hierarchy), a striking dissociation was evident in the ability to make relational inference judgments. Subjects that were tested soon after learning in the 20 min group showed no evidence of inferential ability, performing at chance levels (Figure 5(a)). In contrast, the 12 h groups displayed highly significant relational memory development. Most remarkable, however, if the 12 h period contained a night of sleep, a near 25% advantage in relational memory was seen for the most distantly connected inferential judgment (the B>E pair; Figure 5(a)). Together, these findings demonstrate that human memory integration takes time to develop, requiring slow, off-line associative processes. Furthermore, sleep appears to preferentially facilitate this integration by enhancing hierarchical memory binding, biasing the development of the most distant/weak associative links amongst related yet separate memory items (Figure 5(b)). It is also interesting to note a further advantage of this sleep-dependent assimilation process. When stored as individual premise pairs (top row, Figure 5(b)) the size/number of items (‘bits’) of information to code is ten (A–B, B–C, C–D, D–E, E–F). However, when formed into a hierarchy, the informational load is compressed, reduced by nearly 50% to just six bits (A–B–C–D–E–F). Therefore, a supplementary benefit of sleep-dependent memory association may be the improved efficiency of memory storage, in addition to a more generalized representation.

Thus, the overnight strengthening and consolidation of individual item memories (reviewed above), may not be the ultimate objective of sleep-dependent memory processing, especially when considering that declarative (nonemotional) memories decay over the long term. It is then interesting to speculate whether sleep serves to facilitate two complimentary objectives for declarative memory, which span different time courses. The first may be an initial process of consolidating individual item (episodic) memories that are novel, which may
occurs in the relative short term. Over a longer time course, however, and utilizing these recently consolidated item memories prior to their fading, sleep may begin the process of extraction (of meaning) and abstraction (building associative links with existing information), thereby creating more adaptive semantic networks. Ultimately, individual item memories would no longer be necessary for the goal that sleep is trying to achieve, and only the conceptual meaning of such experiences would remain. Whether the subsequent loss of item memories is passive, or whether sleep plays an active role in this process remains to be examined, but this is a testable hypothesis, that is, forgetting (individual items) is the price we pay for remembering (general rules).

**Creativity**

One potential advantage of testing associative connections and building cross-linked systems of knowledge is creativity—the ability to take existing pieces of information and combine them in novel ways that lead to greater understanding and offer new advantageous behavioral repertoires. The link between creativity and sleep, especially dreaming, has long been a topic of intense speculation. From the dreams of both August Kekulé which led to the conception of a simple structure for benzene, and Dmitri Mendeleev that initiated the creation of the periodic table of elements, to the late night dreaming of Otto Loewi which inspired the experimental demonstration of neurochemical transmission, even scientific examples of creativity occurring during sleep are not uncommon.

Quantitative data have further demonstrated that solution performance on tests of cognitive flexibility using anagram word puzzles is more than 30% better following awakenings from REM sleep compared with NREM awakenings. Similarly, a study of semantic priming has demonstrated that, in contrast to the situation in waking, performance following REM sleep awakenings shows a greater priming effect by weakly related words than by strong primes, while strong priming exceeds weak priming in NREM sleep, again indicating the highly associative properties of the REM sleep brain. Even the study of mental activity (dreams) from REM sleep indicates that there is not a concrete episodic replay of daytime experiences, but instead, a much more associative process of semantic integration during sleep.

Yet, the most striking experimental evidence of sleep-inspired insight was elegantly demonstrated when using a mathematical ‘number reduction task,’ a process of sleep-dependent creative insight. Subjects analyzed and worked through a series of eight-digit string problems, using specific addition rules. Following initial training, after various periods of wake or sleep, subjects returned for an additional series of trials. When retested after a night of sleep, subjects solved the task, using this ‘standard’ procedure, 16.5% faster. In contrast, subjects who did not sleep prior to retesting averaged less than a 6% improvement. However, hidden in the construction of the task was a much simpler way to solve the problem. On every trial, the last three response digits were the mirror image of the preceding three. As a result, the second response digit always provided the answer to the problem, and using such
‘insight,’ subjects could stop after producing the second response digit. Most dramatically, nearly 60% of the subjects who slept for a night between training and restesting discovered this short cut the following morning. In contrast, no more than 25% of subjects in any of four different control groups that did not sleep, had this insight. Sleeping after exposure to the problem, therefore doubled the likelihood of solving it (although it is interesting to note that this insight was not present immediately following sleep, but took over 100 trials on average to emerge the next day).

In summary, substantial evidence now suggests that sleep serves a meta-level role in memory processing that moves far beyond the consolidation and strengthening of individual memories, and instead, aims to intelligently assimilate and generalize these details off-line. In doing so, sleep may offer the ability to test and build common informational schemas of knowledge, providing increasingly accurate statistic predictions about the world, and allowing for the discovery of novel, even creative next-day solution insights.

Conclusions

While not fully complete, we will soon have a new taxonomy of sleep-dependent memory processing, and one that will supersede the polarized all-or-none views of the past. With such findings, we can come to a revised appreciation of how both wake and sleep unite in a symbiotic alliance to coordinate the encoding, consolidation and integration of our memories, the ultimate aim of which maybe to create a generalized catalog of stored knowledge that does not rely on the verbose retention of all previously learned facts.

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See also: Associations and Consequences of SRBD: Sleep-Related Breathing Disorder (SRBD) – Attention and Vigilance.

Further Reading


