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SUPPLEMENT

The Role of Slow Wave Sleep in Memory Processing

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The functions of sleep have been extensively studied and debated, but remain largely unknown. However, evidence has demonstrated the necessity of sleep; sleep is tightly regulated, it has a restorative nature and, if eliminated completely, can ultimately lead to death.[1] Perhaps the earliest reference to the beneficial impact of sleep on memory was by the Roman rhetorician, Quintilian, who stated:

"*...[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.*"[2]

In the early 18th century, it was proposed that dreaming might be associated with memory links within the brain,[3] while in the 1920s, it was demonstrated experimentally that sleep, rather than periods of time awake, may be more closely associated with the strength of a memory.[4] However, it was not until the 1950s, with the discovery of rapid eye movement (REM) and nonREM (NREM) sleep,[5] that research progressed to evaluate the relationship between the different stages of sleep and the process of memory development.

Evidence now suggests that sleep is important in the processing of newly acquired information and for the long-term storage of memory. This has become known as "sleep-dependent memory processing." Memories can be initially formed or "encoded" when the brain engages in an idea, image, thought, experience, or action, leading to the formation of a representation of this information in the brain. However, following encoding, this memory then appears to require "consolidation," which refers to the process of memory stabilization over time, making it more resistant to interference or disruption. Memories can also be reconsolidated should they become destabilized, deteriorate, or require enhancement.[6] Sleep has been implicated in all of these processes. Indeed, impaired memory consolidation has been demonstrated in patients with primary insomnia; such patients do not perform as well as healthy control subjects in tests of memory following a period of sleep.[7,8] More specifically, the ability to form and retain nonemotional, fact-based ("episodic") memories has been linked to the presence and integrity of slow wave sleep (SWS). Compared with healthy control subjects, patients with primary insomnia have diminished amounts of SWS, and this has been significantly correlated with reduced memory consolidation.[7] Similarly, increasing age (> 30 years old) is associated with diminished levels of classically scored SWS, which is associated with a decline in sleep-related memory consolidation.[9]

This review explores the evidence supporting the role of SWS in memory processing, focusing specifically on memory encoding and memory consolidation.

HIPPOCAMPAL–NEOCORTICAL MODEL OF MEMORY CONSOLIDATION

Sleep has been shown to support the consolidation of newly acquired memories, facilitating long-term storage.[6] A central model hypothesized to account for the latent facilitation of long-term memory storage is that of an interaction between hippocampal and neocortical networks.[10-12]

In the formation and retrieval of new memories, structures within the medial temporal lobe appear critical, most notably those of the hippocampal complex. According to the hippocampal–neocortical dialog model (Figure 1), during wakefulness, memory is composed of fragments or cortical modules that are encoded in the neocortical networks and predominantly into hippocampal networks.[13,14] These structures are believed to guide the reinstatement of recently formed memories by binding together patterns of cortical activation produced at the time of the initial learning.[13,14]

During subsequent periods of SWS, driven by the slow oscillations that originate in the neocortex, the newly encoded information in the hippocampus is repeatedly reactivated. The reactivations are associated with sharp wave–ripple activity in the hippocampus and spindle activity in thalamocortical circuitry.[10,11,15,16] Spindle activity refers to the short (~1 sec) synchronous bursts of oscillatory activity in the 10–16 Hz frequency range, which are generated in the reticular nucleus of the thalamus and propagate to the entire neocortex.[15-17] The relationship between sleep spindle activity and memory consolidation has been demonstrated in several studies.[18-21]

Hippocampal reactivations may facilitate the transformation of the newly encoded information from hippocampal to neocortical dependence (Figure 1). Synchronous spindle input at

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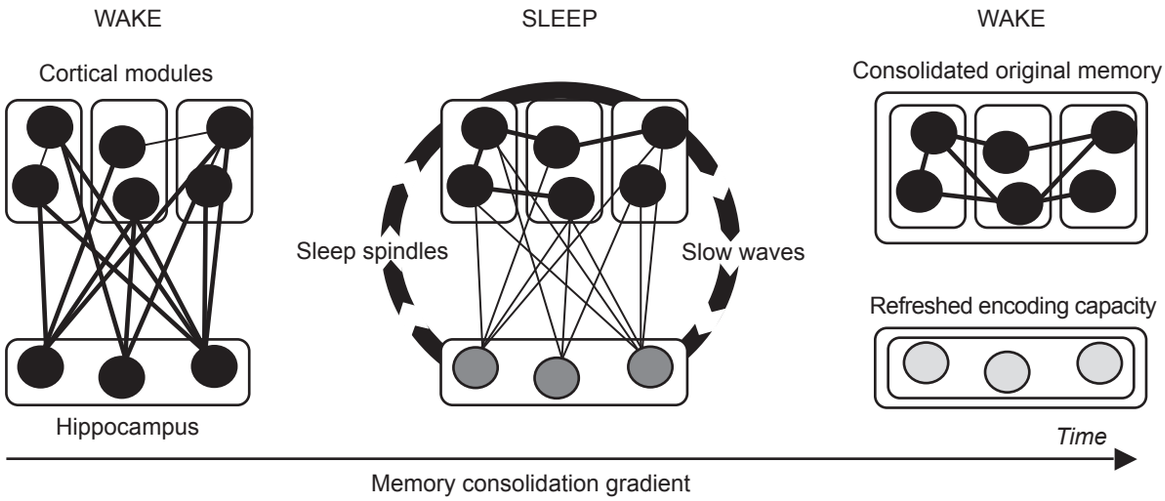

Figure 1—Hippocampal–neocortical model of memory consolidation. Reproduced, with permission, from Walker.[16]

the neocortical circuitry may lead to long-term plastic changes (long-term memory storage in the neocortex) as a result of calcium influx into cortical pyramidal cell dendrites.[22] This, in turn, may enhance the expression of specific genes and receptors that support the maintenance of long-term potentiation in these synapses.[23] Over continuous cycles of sleep or over multiple nights of sleep, it is proposed that the connections gradually dissipate, leaving the hippocampus with refreshed encoding capacity, while the connections within the neocortex build up, gradually strengthening the initially weak connections between neocortical sites. Thus, the neocortical structures become increasingly important for the retention and retrieval of successfully consolidated long-term memories, while the corresponding contribution of the hippocampus progressively decreases. This results in a consolidation and strengthening of the memory in the cortex, allowing the original information to be activated in the cortex, independently of the hippocampus (Figure 1). Importantly, however, such a model also predicts a restored hippocampal ability for new, next-day memory formation.[16]

REACTIVATION OF NEW MEMORIES DURING SWS

The covert reactivation of neuronal networks involved in consolidating newly acquired memory during sleep, as described above, has been investigated in a number of recent cognitive neuroscience reports.[16] In a study involving learning routes in a virtual town, hippocampal areas activated during the learning phase were subsequently reactivated during SWS, as measured by positron emission tomography. Furthermore, there was a positive correlation between the amount of SWS-associated hippocampal activity and the next-day improvement in route-retrieval performance, suggesting an association between reactivation and offline memory improvement.[24] Functional magnetic resonance imaging (fMRI) reports have provided further evidence in support of this sleep-dependent dialog and neural transformation of declarative memory. In one study, the benefit of daytime naps on episodic declarative memory consolidation was examined.[25] 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 minutes) between training and testing of the original test ("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. Furthermore, with increasing time following learning, there was progressively greater recall activity in medial prefrontal regions, and a continued dissipation of retrieval-related activity within the hippocampus. Advancing on these findings, it has since been demonstrated that one night of post-training sleep deprivation, even following recovery sleep, significantly impairs the normal modulation of hippocampal activity associated with episodic memory recollection.[26] 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 who slept after learning.

In a recent study, several experiments were performed to examine the offline manipulation of overnight consolidation using a "cue-dependent recall" paradigm.[27] An odor (rose scent) was provided to 18 healthy subjects while they learned a "card pairs" location memory task during the evening before sleep. This type of task was used as it is dependent on hippocampal involvement and because it is sensitive to the memory-improving effect of sleep. During the first two periods of SWS, either the rose odor was presented or odorless vehicle was used as a control.[27] After sleep, memory for "card pairs" was significantly enhanced after odor presentation during SWS compared with the use of the odorless vehicle (Figure 2A).

To demonstrate that the beneficial effect depended on the presence of the odor during learning, a second experiment was performed in which the odor was not presented during the learning phase; as before, during the first two periods of SWS, either the rose odor was presented or odorless vehicle was used as a control. After sleep, there was no significant difference in the memory for card pairs in the group that received odor compared with those receiving vehicle during sleep (Figure 2B), demonstrating that the smell became the "retrieval cue." Sleep, therefore, appears to be (re)processing/"reactivating" recently learned facts within the hippocampus during SWS, and this process can be amplified by "triggering" or cueing the reactiva-

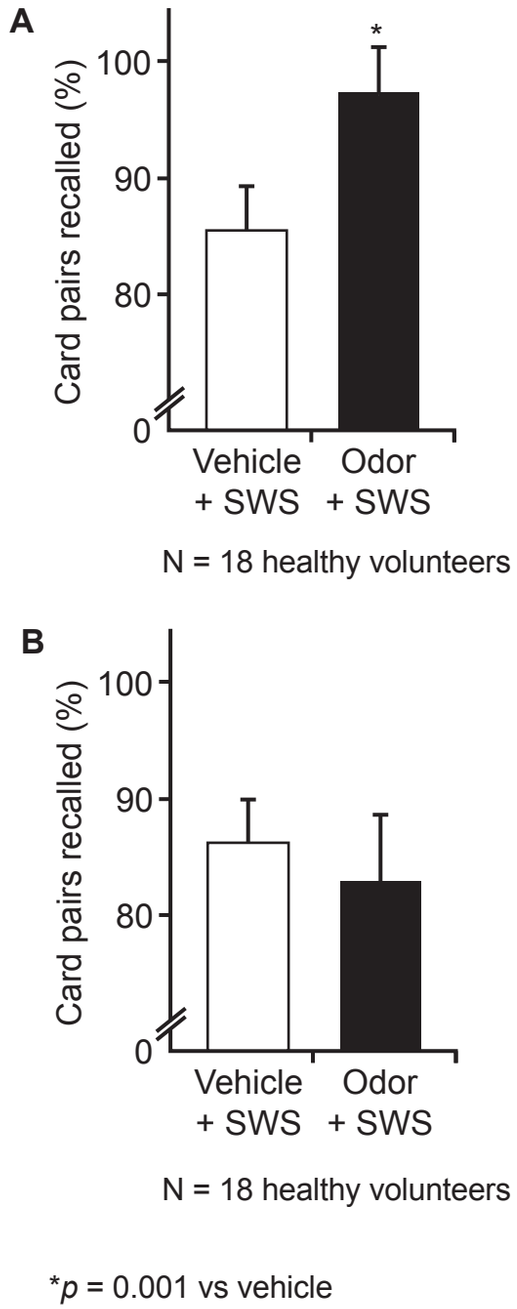

Figure 2—Retention performance in subjects receiving **A:** odor during learning and odor/vehicle during SWS; and **B:** no odor during learning and odor/vehicle during SWS. Reproduced, with permission, from Rasch et al.[27]

tion of memories at night, based on the learning received the previous day. Moreover, odor did not benefit memory during REM or during wakefulness.

fMRI scans of the brains of participants were performed to determine whether the learning stimulus of odor was able to activate the hippocampus during postlearning SWS. Odor stimulation applied during learning and SWS resulted in increased activity in the hippocampus; specifically, blood oxygenation level-dependent responses were significant in the left anterior and posterior hippocampus. Activation in response to odor presentation was stronger during SWS than postlearning wakefulness.[27] Such data imply that the odor facilitated the covert reactivation of memory more strongly during SWS. This suggests that anterior regions of the hippocampal formation are important for successful memory encoding and the degree of coordination between hippocampal and neocortical activity may predict the likelihood of subsequent memory retention.

Thus, re-exposure to the odor during SWS improved the retention of hippocampal-dependent declarative memories. This study adds additional support to the concept that offline memory consolidation can result from repeated, covert reactivation of newly encoded hippocampal-dependent information during SWS, the process of which may take place during a synchronized dialog between the cortex and hippocampus. Such an iterative model would, over time, eventually lead to the corticocortical binding of episodic memory components becoming independent of the hippocampus.

SWS STIMULATION BOOSTS MEMORY CONSOLIDATION

An implication of the data presented above is that sleep, and SWS in particular, appears to be associated with an increase in episodic declarative memory consolidation. The question now arises as to whether this memory processing can be improved by enhancing SWS, or specific components of SWS, such as slow brain oscillations. The latter reflect brain activity that is most prominent during SWS and is generated within the neocortex.

Several studies have demonstrated the ability to induce slow wave activity (SWA) in humans during sleep. Transcranial magnetic stimulation (TMS) is a noninvasive technology that delivers a magnetic pulse to a localized region of the brain. TMS pulses of 5 Hz applied to the cortex during wakefulness have been shown to induce a localized increase in SWA during the subsequent sleep episode,[28] while administering a TMS pulse < 1 Hz during sleep evoked a high-amplitude slow wave, a deepening of sleep, and increased SWA.[29]

Studies in healthy human subjects have investigated whether the induction of slow waves and slow oscillations by transcranial direct current stimulation (tDCS; a technique similar to TMS, which applies electrical rather than magnetic input) can improve memory.[30,31] One study in 30 male participants assessed repeated tDCS (over 30 min) via electrodes applied bilaterally at frontocortical locations after the subjects entered SWS, with a control group receiving sham (placebo) stimulation. A declarative memory task (word pairs) was performed before sleep and approximately 20 minutes after awakening. tDCS during SWS was shown to significantly improve the number of correctly recalled word pairs compared with placebo stimulation. On the electroencephalogram, tDCS was associated with increased slow oscillatory activity < 3 Hz, accompanied by a reduction in the power of the faster frequency bands; in addition, towards the end of tDCS, sleep depth was increased.[30]

To determine whether slow oscillation stimulation specifically can affect the consolidation of hippocampal-dependent declarative memory, a subsequent study was undertaken in 13 healthy subjects who received tDCS (0.75 Hz) via electrodes placed over the prefrontal cortical area of the brain. Stimulation was started 4 minutes after subjects had entered NREM sleep stage 2 for the first time (without transitions back to

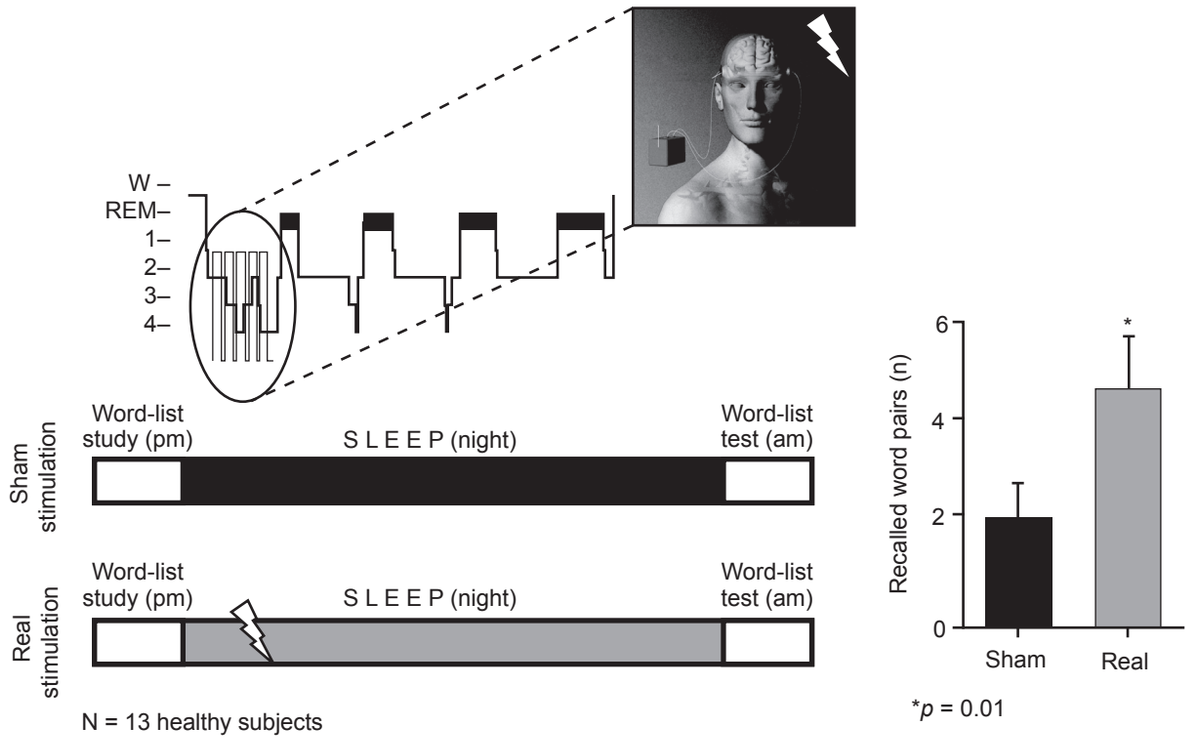

Figure 3—Effect of SWS stimulation on memory consolidation. Reproduced, with permission, from Marshall et al.[31]

stage 1 sleep or wakefulness), at the precise time when sleep is expected to progress into SWS. The control group received sham stimulation. In the evening before sleep, subjects learned different memory tasks, and the following morning, recall of memories was tested.[31]

Slow oscillation stimulation was shown to induce an increase in SWS, endogenous cortical slow oscillations, and slow spindle activity in the frontal cortex. In addition, there was a significant enhancement of the overnight consolidation of declarative memories; the number of recalled words the following morning was doubled compared with sham stimulation (Figure 3).

There was an improvement in performance on a declarative, non-verbal, paired-associate task, while performance on a non-declarative, procedural finger-sequence-tapping task and a procedural mirror-tracing task was not enhanced through slow oscillation stimulation. Together, these results showed that slow oscillation stimulation affected the formation of hippocampal-dependent declarative memory specifically.

Therefore, slow oscillation stimulation during early NREM sleep enhances the retention of declarative memory, but not that of procedural skills. This is consistent with previous observations that early SWS has a beneficial effect mainly on the retention of hippocampal-dependent memories. The results from this study confirm the hypothesis that emotion-free declarative memory is consolidated during deep NREM sleep (SWS) and that slow oscillation stimulation may enhance this process.[31]

SWS BEFORE LEARNING ENHANCES MEMORY ENCODING

Research has shown the importance of sleep after learning for the consolidation of memory. However, a number of reports now address whether sleep before learning is just as essential in preparing the human brain for memory formation. If memories of the previous day are processed during sleep, iteratively transferred from hippocampal to neocortical dependence overnight, then preventing sleep (deprivation) should negate this transaction, and result in a decreased new hippocampal-encoding ability the next day.

The effects of sleep deprivation on the ability to acquire temporal memory (memory for when events occur) have been examined.[32] The task comprised color photographs of faces (unknown to subjects), with subjects tested on distinguishing between previously presented and novel faces (recognition memory) and temporal memory (recency discrimination). Significant impairment of temporal memory was observed in a group of subjects deprived of sleep for 36 hours. Sleep-deprived groups also had poorer subjective insight into their temporal memory-encoding performance.[32]

A more recent study investigated the effect of sleep deprivation on declarative memory encoding of both emotional and nonemotional material. Subjects were either sleep deprived for 36 hours or were allowed to sleep normally, and the following day they undertook an incidental memory encoding session composed of sets of emotionally negative, positive, and neutral words.[6] After two subsequent nights of sleep, subjects returned for an unexpected recognition task. By allowing two recovery nights of sleep, the study was able to confirm that the reduction in memory encoding in subjects deprived of sleep was not confounded by concentration or alertness deficits at the time of recollection. The subjects who were deprived of sleep showed a 40% reduction in memory retention when compared with subjects who had slept normally before encoding (Figure 4).

The encoding deficit remained in the sleep-deprived group compared with controls when these data were separated into

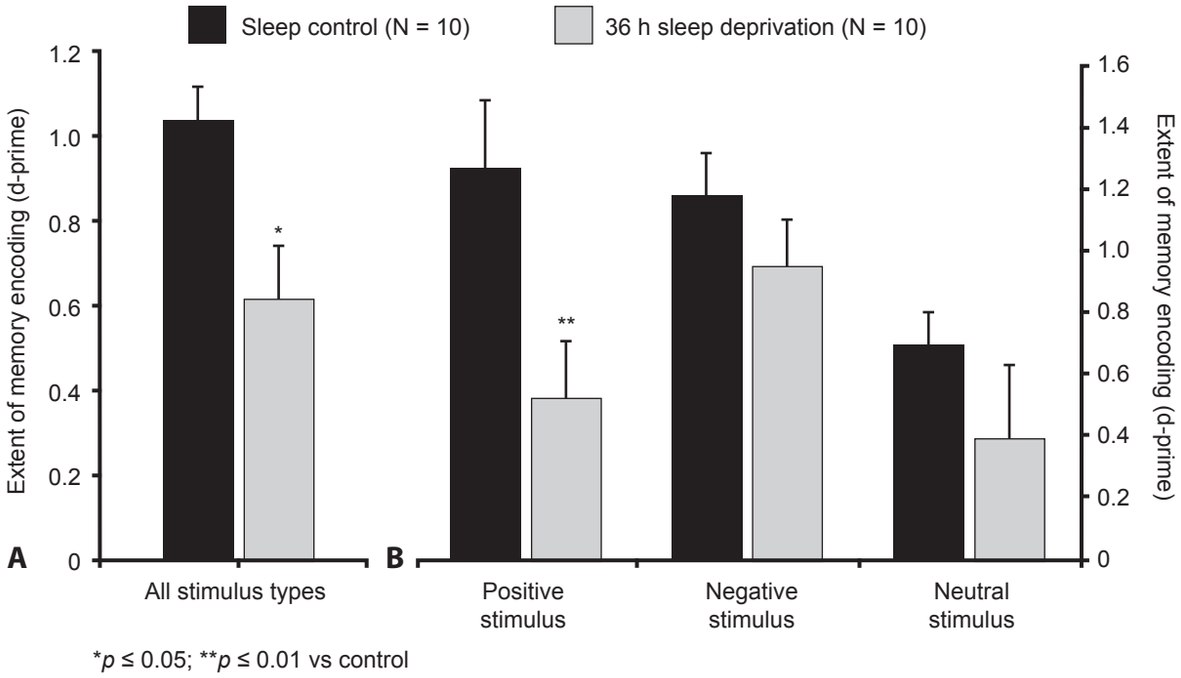

Figure 4—The impact of sleep deprivation before learning on memory encoding **A:** when combined across all emotional and nonemotional categories; and **B:** when separated in emotional (positive and negative valence) and nonemotional (neutral valence) categories. Reproduced, with permission, from Walker and Stickgold.[6]

the three emotional categories (positive, negative, or neutral) (Figure 4). However, the magnitude of the effect differed across the emotional categories. A significant difference was observed between the sleep group and the sleep-deprived group in the retention of positive emotional memory (59%), with greater retention seen in the sleep group. In the sleep-deprived group, the highest retention values were seen for negative emotional categories, whereas in the sleep group, positive emotional categories were highest. This suggests that negative emotional memories may be more resistant to the effects of sleep loss, perhaps due to their ecological salience, than positive or nonemotional events.[16]

Taken together, these data indicate the critical need for sleep before learning in preparing key neural structures for efficient next-day learning. Without adequate sleep, episodic learning capability becomes markedly impaired, resulting in decreased ability to record new experiences the next day.

Recently, a similar study was undertaken to determine the underlying neural basis of these sleep deprivation-induced encoding impairments.[33] Twenty-eight subjects were randomly assigned to either a sleep-deprivation group (deprived of sleep for a mean of 35 hours) or a sleep-control group (allowed to sleep normally), and subsequently performed an episodic memory-encoding task where they viewed a series of picture slides during fMRI scanning. All subjects returned after 2 days for a recognition test in which subjects were shown the original picture stimuli at random, together with an additional (new) number of pictures. Following the single night of sleep deprivation, a significant reduction in hippocampal activity was observed during the memory–encoding session, relative to the control group, and resulted in a significant (19%) later memory impairment. Sleep deprivation therefore caused a specific functional impairment within the hippocampal complex, a region known to be involved with encoding, as discussed previously.

While these findings indicated that, at a group level, sleep deprivation markedly impairs hippocampal memory function, when examined within each group separately, the success of encoding, from low to high, was further associated with activity in different regions of the prefrontal lobe. In those who had slept before learning, the right dorsal/middle lateral prefrontal cortex showed a strong positive relationship with the proficiency of memory encoding. In contrast, a region in the right inferior frontal gyrus displayed a significant positive, potentially compensatory, relationship with memory performance in those who were sleep deprived (Figure 5).[33]

A number of other imaging studies have also shown that sleep deprivation results in behavioral impairment in verbal memory learning, associated with increased prefrontal brain activity, combined with failure of the medial temporal lobe to engage normally and possible compensatory interactions in the parietal lobes.[34,35] Indeed, sleep deprivation diminishes prefrontal interactions with the left inferior parietal lobe, with increases in intraparietal interaction.[35]

Therefore, in addition to the benefit of sleep after learning, such data demonstrate that sleep before learning is also crucial, enabling the brain to prepare for the formation of new memories the following day.

CONCLUSIONS

Considerable advances have been made in sleep research over the past two decades, with a wealth of evidence supporting the hypothesis of sleep-dependent memory processing. This evidence comes from studies of cellular and molecular processes in preclinical models, to electrophysiologic and behavioral

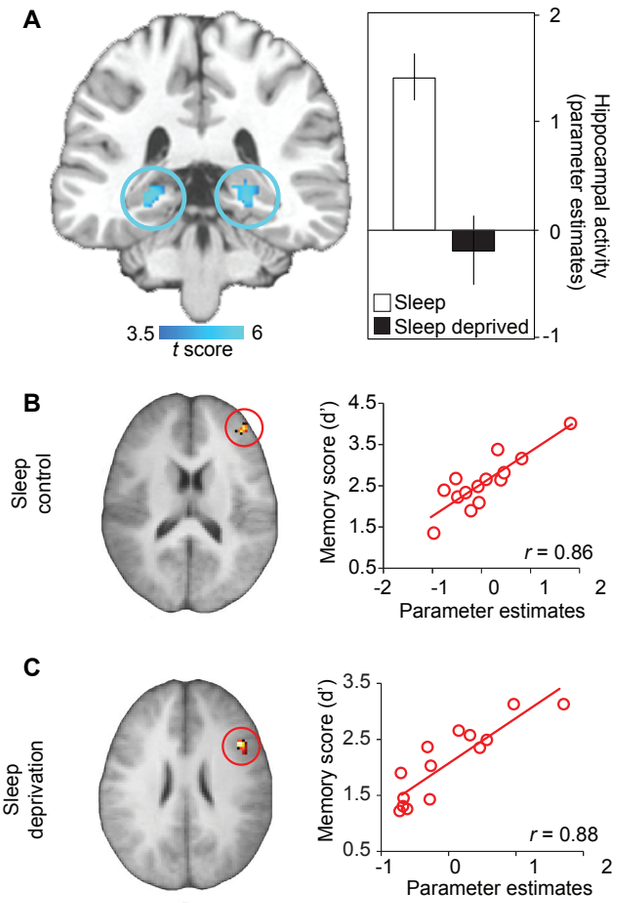

Figure 5—Neural basis of sleep deprivation-induced encoding deficits. **A:** Regions of significantly reduced activation in the sleep-deprivation group relative to the sleep-control group. **B:** Regions of significant correlation between encoding-related brain activation and memory performance in the sleep-control group. **C:** Sleep-deprivation group. Reproduced, with permission, from Yoo et al.[33]

studies in man. Sleep has been shown to be critical in both supporting the overnight consolidation of new memories, and in restoring the next-day encoding capacity of the hippocampus.

Evidence for the importance of sleep in preparing the brain for the acquisition of new memories has come from sleep-deprivation studies. Lack of sleep before a task has been shown to compromise molecular processes involved in memory formation.[6] Furthermore, imaging studies in sleep-deprived subjects have demonstrated significant alterations in brain activity during memory encoding, culminating in a reduction in performance of subsequent tasks. Therefore, adequate amounts of sleep are required before learning to fully prime the brain for the formation of new memories.

Just as important as sleep before learning is the need for adequate sleep (and particularly SWS for nonemotional episodic declarative memory) after learning. During post-training sleep, several genes appear to be upregulated in brain tissue.[6] At the electrophysiologic level, an increase in spindle density has been shown following declarative memory training, correlated with subsequent performance in the tasks. Further to this, enhancement of SWA, using amplification of slow waves during sleep, significantly improves the consolidation of declarative memories, confirming the hypothesis that certain types of declarative information can be consolidated during deep NREM sleep (SWS) and that slow oscillation stimulation may enhance this process. Central to the memory-consolidation process is the concept that repeated covert reactivation of newly encoded hippocampal-bound information during SWS is required. Cue-dependent recall studies with odor have revealed an increase in SWS-associated activity within the hippocampus in those subjects who received the odor during encoding.

Overall, this evidence supports the role of SWS in memory processing and its importance before learning, to prepare the brain for initial memory encoding, and after learning, for the offline consolidation of new memories. The precise mechanisms by which sleep mediates learning and memory processing remain to be fully elucidated, however, and further neurophysiologic studies are required to provide further advances in this area.

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