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Sleep-Dependent Learning and Memory Consolidation

Review

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While the functions of sleep remain largely unknown, one of the most exciting and contentious hypotheses is that sleep contributes importantly to memory. A large number of studies offer a substantive body of evidence supporting this role of sleep in what is becoming known as sleep-dependent memory processing. This review will provide evidence of sleep-dependent memory consolidation and sleep-dependent brain plasticity and is divided into five sections: (1) an overview of sleep stages, memory categories, and the distinct stages of memory development; (2) a review of the specific relationships between sleep and memory, both in humans and animals; (3) a survey of evidence describing sleep-dependent brain plasticity, including human brain imaging studies as well as animal studies of cellular neurophysiology and molecular biology. We close (4) with a consideration of unanswered questions as well as existing arguments against the role of sleep in learning and memory and (5) a concluding summary.

1. Delineations and Definitions of Sleep and Memory

Before discussing interactions between sleep and memory, we must first understand what each term represents and encompasses, since misinterpretations of the literature have often arisen due to a confusion of meaning. Therefore, we will first provide an overview of sleep, its characteristic stages, and associated neurobiology. Second, we will consider the spectrum of memory categories believed to exist in the human brain. Finally, we will discuss the unique and dissociable stages of memory processing.

Sleep Stages and Sleep Biology

Mammalian sleep has been broadly classified into two distinct types: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, with NREM sleep being further divided in primates and cats into four substages (1 through 4) corresponding, in that order, to increasing depth of sleep (Rechtschaffen and Kales, 1968). In humans, NREM and REM sleep alternate or "cycle" through the night in an ultradian pattern every 90 min (Figure 1A). Although this NREM-REM cycle length remains largely stable across the night, the ratio of NREM to REM within each 90 min cycle changes, so that early in the night stages 3 and 4 of NREM dominate, while stage 2 NREM and REM sleep prevail in the latter half of the night.

As NREM sleep progresses, electroencephalographic (EEG) activity begins to slow in frequency. Throughout stage 2 NREM, there is the presence of phasic electrical events including K complexes (large electrical sharp waves in the EEG) and sleep spindles (short synchronized 7–14 Hz EEG oscillations) (Steriade and Amzica, 1998). The deepest stages of NREM, stages 3 and 4, are often grouped together under the term "slow wave sleep" (SWS), reflecting the occurrence of low-frequency waves (0.5–4 Hz and $<$1 Hz), which, in turn, are an expression of underlying cortical synchrony (Amzica and Steriade, 1995).

During REM sleep, however, EEG oscillations once again become desynchronized, and high-frequency synchronous activity in the 30–80 Hz ("γ") range emerges, similar to wake (Llinas and Ribary, 1993; Steriade et al., 1996). Periodic bursts of rapid eye movement also take place, a defining characteristic of REM sleep, while muscle tone decreases significantly compared to both NREM sleep and wake (Chase and Morales, 1990). There is evidence indicating that rapid eye movements are associated with the occurrence of phasic endogenous wave forms expressed in the pons (P), lateral geniculate nuclei of the thalamus (G), and the occipital cortex (O), and as such, have been termed "PGO waves" (Callaway et al., 1987).

As the brain passes through these sleep stages, it also undergoes dramatic alterations in neurochemistry. In NREM sleep, subcortical cholinergic systems in the brainstem and forebrain become markedly less active (Hobson et al., 1975; Lydic and Baghdoyan, 1988), while firing rates of serotonergic raphe neurons and noradrenergic locus coeruleus neurons are also reduced relative to waking levels (Aston-Jones and Bloom, 1981; Shima et al., 1986). During REM sleep, both of these aminergic populations are strongly inhibited, while cholinergic systems become as active or more active than in wake (Kametani and Kawamura, 1990; Marrosu et al., 1995), resulting in a brain state that is largely devoid of aminergic modulation and dominated by acetylcholine.

Although this summary only begins to describe the range of neuronal processes that are affected by the brain's daily transit through wake-sleep states, it clearly demonstrates that sleep itself cannot be treated as a homogeneous state, which either does or does not affect memory, instead possessing a range of physiological and neurochemical mechanisms that can contribute to memory consolidation.

Memory Categories

Although often used as a unitary term, "memory," like sleep, is not a single entity. Human memory has been subject to several different classification schemes, the most popular being based on the distinction between declarative and nondeclarative memory (Squire and Zola, 1996; Tulving, 1985).

Declarative memory can be considered as the consciously accessible memories of fact-based information (i.e., knowing "what"). Several subcategories of the de-

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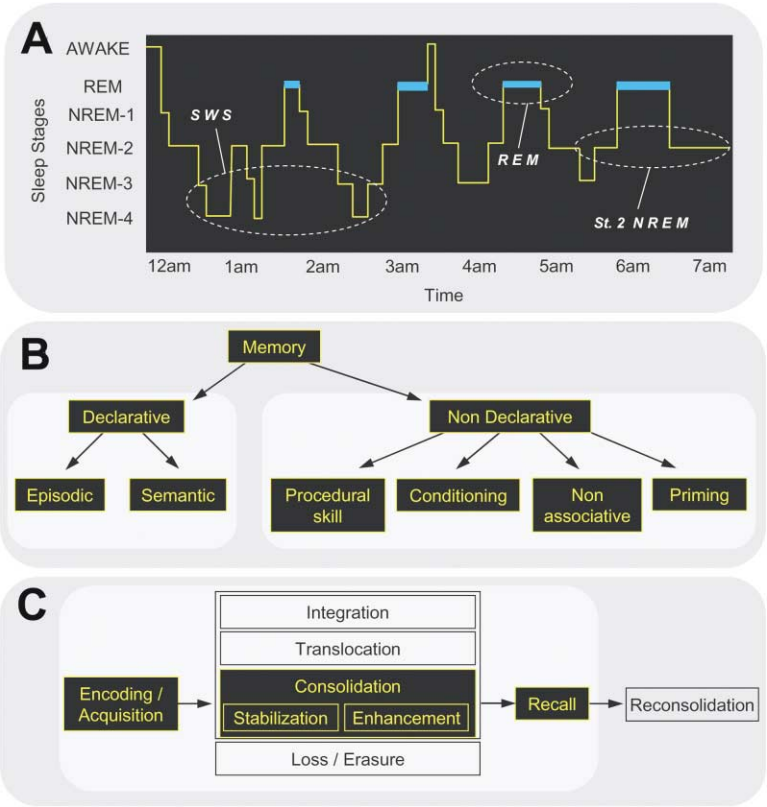

Figure 1. The Sleep Cycle, Memory Systems, and Memory Stages

(A) The human sleep cycle—across the night, NREM and REM sleep cycle every 90 min in an ultradian manner, while the ratio of NREM to REM sleep shifts. During the first half of the night, stages 3 and 4 NREM (SWS) dominate, while stage 2 NREM and REM sleep prevail in the latter half of the night. EEG patterns also differ significantly between sleep stages, with electrical oscillations such as K complexes and sleep spindles occurring during stage 2 NREM, slow (0.5–4Hz) delta waves developing in SWS, and theta waves seen during REM.

(B) Memory systems—human memory is most commonly divided into declarative forms, with further subdivisions into episodic and semantic; and nondeclarative forms, subdivided into an array of different types including procedural skill memory

(C) Developing stages of memory—following the initial encoding of a memory, several ensuing stages are proposed, beginning with consolidation, as well as integration of the memory representation, translocation of the representation, or erasure of the memory. Also, following later recall, the memory representation is believed to become unstable once again, requiring periods of reconsolidation.

clarative system exist, including episodic memory (memory for events of one's past) and semantic memory (memory for general knowledge, not tied to a specific event) (Figure 1B; Tulving, 1985). Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, including the hippocampus (Eichenbaum, 2000), a structure which is thought to form a temporally ordered retrieval code for neocortically stored information. In contrast, nondeclarative memory can be regarded as nonconscious. The nondeclarative category includes procedural memory (i.e., knowing "how"), such as the learning of actions, habits, and skills, as well as implicit learning and appears to be less dependent on medial temporal lobe structures.

While these categories offer convenient and distinct separations, in real life they rarely operate in isolation. For example, language learning requires a combination of memory sources, ranging from nondeclarative memory for procedural motor programs to articulate speech, to memory of grammatical rules and structure, through to aspects of declarative memory for the source of word selection. This, too, must be kept in mind as we consider the role of sleep in learning and memory.

Memory Stages

Just as memory cannot be considered monolithic, similarly, there does not appear to be one sole event that creates or develops it. Instead, memory appears to develop in several unique stages over time (Figure 1C). For example, memories can be initially formed by engaging with an object or performing an action, leading to the formation of a representation of the object or action within the brain. Following acquisition, the memory representation can undergo several subsequent stages of development. The most commonly recognized next stage of memory is "consolidation." Classically, the term *memory consolidation* refers to a process whereby a memory becomes increasingly resistant to interference from competing or disrupting factors in the absence of further practice, through the simple passage of time (McGaugh, 2000). That is to say, the memory becomes more stable.

Recent findings, however, have begun to extend this definition. For example, consolidation can be thought of as not only *stabilizing* memories but *enhancing* them as well, two processes which may be mechanistically distinct (Walker, 2004). The stabilization phase of consolidation appears to occur largely during wake (Brashers-Krug et al., 1996; Muellbacher et al., 2002; Walker et al., 2003a). The second, enhancement stage, appears to occur primarily, if not exclusively, during sleep, either restoring previously lost memories (Fenn et al., 2003) or producing additional learning (Fischer et al., 2002; Gais et al., 2000; Karni et al., 1994; Korman et al., 2003; Stickgold et al., 2000a, 2000c; Walker et al., 2002a, 2003b), both without the need for further practice. From this perspective, the enhancement phase of memory consolidation causes either the active retention of a memory instead of its decay, or the enhancement of a memory over its simple maintenance.

Thus, consolidation can be expanded to include more than one phase of postencoding memory processing, with each phase occurring in specific brain states such as wake or sleep or even specific stages of sleep (Brash-

ers-Krug et al., 1996; Karni et al., 1994; Muellbacher et al., 2002; Smith and MacNeill, 1994; Stickgold et al., 2000a; Walker, 2004; Walker et al., 2002a, 2003a).

It should be noted, however, that while most forms of memory appear to require consolidation following encoding, not all tasks have demonstrated time-dependent consolidation (Goedert and Willingham, 2002). But to complicate matters further, the experimental confirmation of such consolidation can depend on the manner in which learning is measured. For example, using a motor adaption task, Brashers-Krug et al. (1996) have shown evidence of delayed consolidation across the day and overnight, while Donchin and colleagues (Donchin et al., 2002), using the identical task but a different index of learning, reported no change in performance 24 hr later, either with or without sleep. Thus, differing behavioral measures may be more or less sensitive to identifying these consolidation processes.

Although this review will focus primarily on the effects of sleep on the postencoding stabilization and enhancement phases of consolidation, it is important to note that there are additional postencoding stages of memory processing that perhaps should also fall under the rubric of consolidation. These include the integration of recently acquired information with past experiences and knowledge (a process of "memory association"), the anatomical reorganization of memory representations (memory translocation), reconsolidation of memory representations following recall (memory reconsolidation), and even the active erasure of memory representations, all of which appear to occur outside of awareness and without additional training or exposure to the original stimuli. It is interesting to note that sleep has already been implicated in all of these steps (Crick and Mitchison, 1983; Stickgold, 2002; Stickgold et al., 1999; Walker et al., 2003a).

Interim Summary

There are a number of stages of memory consolidation, which use distinct brain processes to perform separate functions. When combined with the multiple classes of memories and the several stages of sleep, one is faced with a truly staggering number of possible ways that sleep might affect memory consolidation. Ignorance of these distinctions has instigated much of the current confusion surrounding sleep-dependent memory processing. It is only by asking whether a specific stage of sleep affects a particular aspect of memory processing for a given type of memory that one can ask scientifically answerable question concerning sleep-dependent memory processing.

2. Behavioral Studies of Sleep and Memory

Evidence of sleep-dependent memory processing has been found in numerous species, including human and nonhuman primates, cats, rats, mice, and zebra finch, using a variety of behavioral paradigms (for more detailed reviews, see Peigneux et al., 2001; Smith, 2001).

Human Studies of Declarative Memory

Much of the early work investigating sleep and memory in humans focused on declarative learning tasks. These studies offered mixed conclusions, some arguing for sleep-dependent memory processing and others against it. For example, De Koninck et al. (1989) demonstrated significant increases in posttraining REM sleep after intensive foreign language learning, with the degree of successful learning correlating with the percentage increase of REM sleep. Such findings suggest that REM sleep plays an active role in memory consolidation and that posttraining increases reflect a homeostatic response to the increased demands for REM-dependent consolidation. However, Meienberg et al. (Meienberg, 1977) found no evidence of altered posttraining sleep architecture following the learning of a verbal memory task. Similar inconsistencies have been reported in the degree to which intensive declarative learning experiences can alter subsequent sleep stage properties as well as the learning impairments that follow selective sleep deprivation (e.g., Chernik, 1972; Empson and Clarke, 1970; Lewin and Glaubman, 1975; Meienberg, 1977; Plihal and Born, 1997; Zimmerman et al., 1970, 1978). More recently, several studies by Born and his colleagues have shown actual improvement on a paired word associates test after early night sleep, rich in SWS (Gais and Born, 2004), and modification of sleep characteristics following intensive learning of word pairs (Gais et al., 2002). These findings are striking in the face of earlier studies that showed no effect. But this discrepancy may well reflect the nature of the word pairs used. While older studies used unrelated word pairs, such as dog-leaf, Born used related word pairs, such as dog-bone (Gais and Born, 2004). The nature of the learning task thus shifts from forming and retaining completely novel associations (dog-leaf) to the strengthening or tagging of well-formed associations (dog-bone) for recall at testing.

Thus, sleep's role in declarative memory consolidation, rather than being absolute, appears to depend on more subtle aspects of the consolidation task. Indeed, several studies suggest that factors such as task difficulty (Empson and Clarke, 1970; Tilley and Empson, 1978) and emotional salience (Wagner et al., 2001) can strongly influence the degree of sleep dependency. Furthermore, an examination of different declarative memory categories, including episodic and semantic forms, has not been fully investigated (Cipolli and Salzarulo, 1980) and may further clarify the apparent contradictions regarding the roles of both SWS and REM sleep in declarative memory consolidation (Smith, 2001).

But such studies have only begun to test sleep-related memory processes. Indeed, all of these studies have used tasks of recall and recognition as outcome measures, thereby focusing exclusively on processes of memory enhancement and resistance to normal decay, and none has looked at such processes as memory stabilization, association, translocation, or reconsolidation, discussed above. More recent studies, however, have demonstrated that the strengths of associative memories are altered in a state-dependent manner. Two reports have shown that REM sleep provides a brain state in which access to weak associations is selectively facilitated (Stickgold et al., 1999), and flexible, creative processing of acquired information can be enhanced (Walker et al., 2002b). It has also been demonstrated that, following initial practice on a numeric sequence problem-solving task, a night of sleep can trigger insight of a hidden rule and thus improve performance strategy the following morning (Wagner et al., 2004).

Interim Summary

Taken as a whole, these studies suggest a rich and multifaceted role for sleep in the processing of human declarative memories. While contradictory evidence is found for a role in the processing of simple, emotion-free declarative memories, such as the learning of unrelated word pairs, a substantial body of evidence indicates that both SWS and REM sleep contribute to the consolidation of complex, emotionally salient declarative memories embedded in networks of previously existing associative memories. In light of this evidence, pronouncements of a lack of relationship between REM sleep and "memory" (Siegel, 2001; Vertes and Eastman, 2000) appear to be unfortunate overgeneralizations, ignoring evidence that specific sleep stages play distinct roles in different stages of memory processing in separate memory systems.

Human Studies of Procedural Memory

In contrast to the declarative system, the reliance of procedural memory on sleep is a robust and consistent finding across a wide variety of functional domains, including visual, auditory, and motor systems.

Motor Learning. Smith and MacNeill (1994) have shown that selective sleep deprivation can impair retention of a rotary pursuit motor task, suggesting that the memory decrement results specifically from the loss of stage 2 NREM sleep. Walker et al. (2002a) have demonstrated that a night of sleep can trigger significant performance improvements in speed and accuracy on a sequential finger-tapping task, while equivalent periods of time during wake provide no significant benefit. These sleep-dependent benefits appear to be specific to both the motor sequence learned and the hand used to perform the task (Fischer et al., 2002; Korman et al., 2003). Furthermore, overnight learning gains correlated with the amount of stage 2 NREM sleep, particularly late in the night (Figures 2A–2C). In addition, the mechanisms of sleep-dependent learning were dissociable from those governing the initial practice-dependent learning during acquisition, as well as from the subsequent stabilization of the memory during initial waking episodes (Walker et al., 2003a, 2003b). These findings again highlight the need to consider unique contributions of different brain states for different memory stages, rather than forcing an all-or-nothing role for sleep in memory consolidation. Using the same sequential finger-tapping task, Fisher et al. have shown that sleep on the first night following training is critical for the delayed performance improvements to develop and that sleep during the day triggers improvements similar to those achieved following nocturnal sleep (Fischer et al., 2002). This report, however, described a correlation with REM sleep and not stage 2 NREM, a discrepancy that remains to be resolved.

Building on these findings, Robertson et al., (2004) have recently demonstrated that explicit awareness of a specific motor sequence being learned modifies the subsequent development of a sleep-dependent learning correlated with NREM sleep.

Visual Perceptual Learning. Karni et al. (1994) have demonstrated that learning on a visual texture discrimination task, which does not benefit from 4–12 hr of wake following acquisition (Stickgold et al., 2000c), improves significantly following a night of sleep. Furthermore, they established that selective disruption of REM but not NREM sleep resulted in a loss of these performance gains (Karni et al., 1994). Gais et al. (2000) selectively deprived subjects of early sleep (normally dominated by SWS) or late night sleep (normally dominated by REM and stage 2 NREM) and concluded that consolidation was initiated by SWS-related processes, while REM sleep then promoted additional enhancement. Using the same task, Stickgold et al. (2000c) have shown that these enhancements are specifically sleep and not time dependent, are correlated positively with the amount of both early night SWS and late night REM sleep, and that the product of these two sleep parameters can explain over 80% of intersubject variance (Figures 2D–2F). They also showed (Stickgold et al., 2000a) that these delayed performance benefits were absolutely dependent on the first night of sleep following acquisition (Figure 2E). In addition, it has been shown that daytime naps can restore performance decrements caused by repeated practice (Mednick et al., 2002) and that 60–90 min naps containing both REM and SWS can produce performance enhancements equivalent to a normal night of sleep (Mednick et al., 2003).

Auditory Learning. More recent studies have begun to explore sleep-dependent auditory skill learning. Using a pitch memory task, Gaab et al. (2004) have shown that, regardless of whether subjects trained in the morning or evening, delayed performance improvements developed only across a night of sleep and not across similar waking time periods, whether the sleep or wake episode came first. Atienza and colleagues have also described evidence of both time- and sleep-dependent auditory memory consolidation, including sleep-dependent changes in brain evoked response potentials (ERPs) (Atienza et al., 2002, 2004). While posttraining sleep deprivation did not prevent continued improvements in behavioral performance, ERP changes normally associated with the automatic shift of attention to relevant stimuli failed to develop following a night of posttraining sleep deprivation. These findings make clear the danger of presuming that a lack of change in behavioral performance is equivalent to an absence of beneficial plastic changes within the brain and highlight the importance of using combined behavioral and physiological analyses.

Finally, Fenn et al. have shown that periods of wake following training on a synthetic speech recognition task result in a degradation of task performance but that a subsequent night of sleep can restore performance to posttraining levels, suggesting a process of sleep-dependent consolidation capable of reestablishing previously learned complex auditory skill memory (Fenn et al., 2003).

Faced with such consistent and reproducible findings of sleep-dependent visual, auditory, and motor skill learning, it seems difficult to refute the claim that sleep is a necessity for the consolidation of human procedural skills, being able to restore previously decayed memory traces as well as trigger additional learning and thus improve behavioral performance without the need for further practice.

Animal Studies

Studies using animal models have provided evidence for the role of sleep in primarily hippocampally dependent tasks. Training on both spatial and shock avoidance

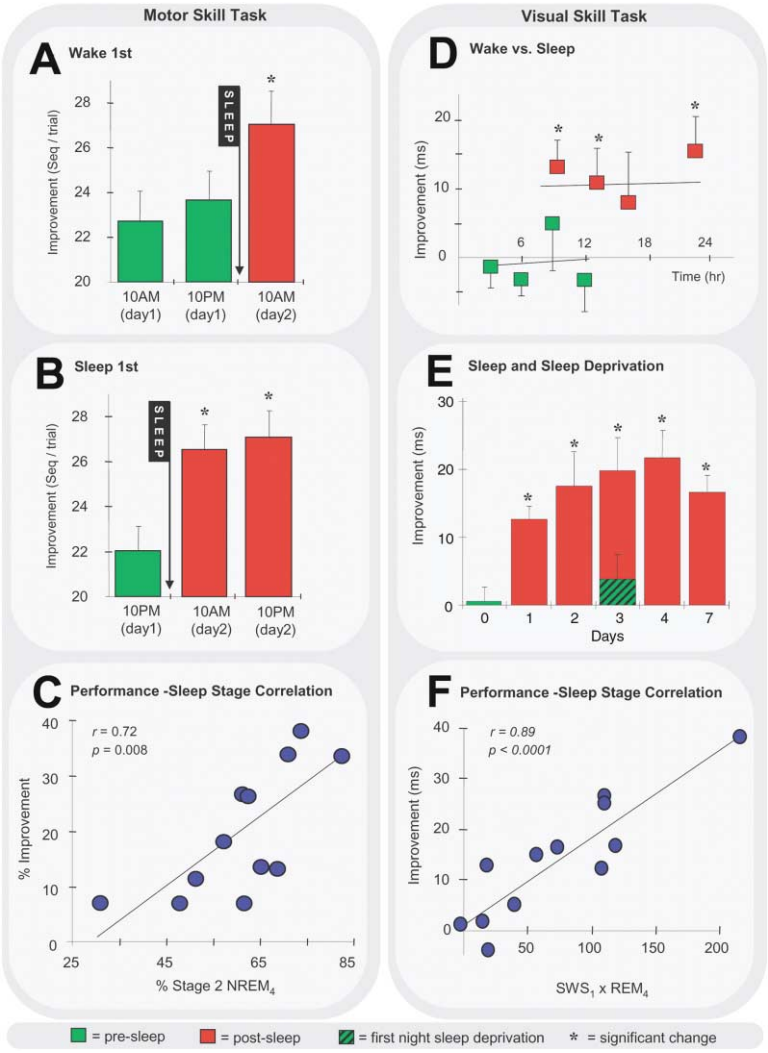

Figure 2. Sleep-Dependent Visual and Motor Skill Learning in the Human Brain

(A–C) Motor skill task. (A) Wake 1st—subjects (n = 15) trained at 10 AM showed no significant change in performance at retest following 12 hr of wake (day 1, green bars). However, by the second retest, following a night of sleep (day 2, red bar), performance improved significantly. (B) Sleep 1st—following evening training, subjects (n = 15) showed significant improvements in speed just 12 hr after training following a night of sleep (10 AM, red bar) but expressed no further significant change in performance following an additional 12 hr of wake (10 PM, red bar). (C) The amount of overnight improvement on the motor skill task correlated with the percentage of stage 2 NREM sleep in the last quartile of the night (% stage 2 NREM, fourth quartile).

(D–F) Visual skill task. Subjects were trained and then retested at a later time, with improvement (ms) in performance illustrated across time. Each subject was retested only once, and each point represents a separate group of subjects. (D) Wake versus sleep. Subjects trained and then retested on the same day (n = 33), after either 3, 6, 9, or 12 hr of subsequent wake (green squares), showed no significant improvement as a consequence of the passage of waking time for any of the four time intervals. In contrast, subjects (n = 39) trained and then retested 8, 12, 15, or 23 hr later, after a night's sleep (red squares), showed significant improvement. (E) Sleep deprivation. Subjects (n = 89) trained and retested 1–7 days later (red bars) continued to improve after the first night, without additional practice. Subjects (n = 11) sleep deprived the first night after training showed no improvement (green hatched bar), even after 2 nights of recovery sleep. (F) Overnight improvement was correlated with the percent of SWS in the first quarter of the night (SWS1) and REM sleep in the last quarter of the night (REM4). *$p < 0.05$; error bars, SEM.

tasks triggers alterations in sleep stage characteristics (e.g., Ambrosini et al., 1993, 1988; Hennevin and Hars, 1987; Mandai et al., 1989; Smith et al., 1980), suggesting, as in humans, a homeostatic response to increased demands on sleep-dependent consolidation mechanisms. In one such study, the magnitude of change in sleep architecture demonstrated a strong relationship to initial performance during acquisition, with animals who learned quickly showing the largest change in sleep structure, while those that learned poorly showed relatively little (Ambrosini et al., 1992).

Datta (2000) has suggested that, for at least some forms of learning, it is the PGO waves of REM sleep (or P waves in rats) that underlie the physiological mechanism of consolidation. In an initial study, they reported that, following initial training on an avoidance task, both the amount of REM sleep and the density of P waves increased dramatically and that the increased P wave density showed a strong positive correlation with the degree of retention of presleep learning following sleep, although not with the extent of the initial learning. These findings are particularly important from the perspective of memory, since they suggest that the increase in REM sleep and, more specifically, in the density of P waves accompanying REM sleep is critical for the effective postsleep retention of this learning.

In a more recent report (Datta et al., 2004), they have shown that the induction of PGO waves by intrapontine injection of carbachol can support postsleep retention of learning even in the face of REM deprivation, which normally completely blocks such retention. Thus, these experimentally induced PGO waves, occurring during SWS, can replace the normal requirement for REM sleep, suggesting that it is this cholinergically driven brain activity rather than REM per se that is necessary for the sleep-dependent enhancement of this consolidation.

As with humans, sleep deprivation following task acquisition has been shown to produce learning impairments at subsequent retests (e.g., Beaulieu and Godbout, 2000; Fishbein et al., 1974; Hennevin and Hars, 1987; Marti-Nicolovius et al., 1988; Oniani et al., 1987; Pearlman, 1969; Shiromani et al., 1979; Smith and Kelly, 1988; Smith and Lapp, 1986). Several of these early animal studies have been legitimately criticized for a failure to control for general effects of sleep deprivation on performance (Siegel, 2001; Vertes and Eastman,

2000). Retesting in a sleep-deprived state may mask evidence of successful consolidation due to lowered alertness and attention. Alternatively, the increased stress of prolonged wakefulness, rather than the lack of sleep itself, may be the cause of unsuccessful consolidation.

More recent studies in both humans and animals have, however, demonstrated that lower performance can still be seen several days after the end of sleep deprivation, when alertness or attention have returned to normal (e.g., Smith and Smith, 2003). In addition, selective deprivation of specific sleep stages, and even specific sleep stage time windows (some many hours to days after training), still inhibits memory consolidation (Smith and Butler, 1982; Smith and Kelly, 1988), making arguments of sleep deprivation-induced stress relatively untenable, since the stress effects would have to be uniquely produced by deprivation of specific sleep stages during specific time windows following training.

Interim Summary

Taken as a whole, behavioral studies in humans and other species leave little doubt that sleep plays a critical role in posttraining memory consolidation. Currently, the evidence is perhaps strongest for procedural learning in humans, but substantial evidence exists for conditioned learning in animals and declarative memory in humans as well. To date, all stages of sleep except sleep onset stage 1 NREM sleep (but see Stickgold et al., 2000b) have been implicated in one or more aspects of this consolidation. Still, a clear understanding of the roles of individual sleep stages remains an important future goal.

3. Sleep-Dependent Brain Plasticity

Memory formation depends on brain "plasticity," lasting structural and functional changes in neurons in response to a stimulus (such as an experience). If sleep is to be considered a critical mediator of memory consolidation, then evidence of sleep-dependent plasticity would greatly strengthen this claim. In this section, we consider a mounting wealth of data describing sleep-dependent brain plasticity at a variety of different levels in both animals and humans, complementing evidence of sleep-dependent changes in behavior.

Neuroimaging Studies

In humans, Maquet et al. (2003) have demonstrated sleep-dependent plasticity using a procedural visuomotor pursuit task in combination with functional MRI (fMRI). Subjects were trained on the task and subsequently were retested 3 days later, with half the subjects deprived of sleep the first night following training. The remaining half, who slept all three nights, showed both enhanced behavioral performance and a selective increase in activation in the superior temporal sulcus at retest. In contrast, subjects deprived of sleep the first night showed no such enhancement of behavior or brain activity.

Schwartz et al. (2002) have recently measured changes in fMRI brain activity 24 hr after training on a sleep-dependent visual texture discrimination task. At retesting, greater activation was observed in the retinotopic area of V1 corresponding to the trained visual field. However, when during this 24 hr period the enhancement of activation occurred remains uncertain.

Based on earlier animal investigations (see below), several neuroimaging studies have explored the possibility that patterns of brain activity elicited during initial task training are "replayed" during subsequent sleep. Using PET imaging, Maquet and colleagues have shown that activation patterns elicited during practice of a serial reaction time motor skill task prior to sleep reappear during subsequent REM sleep episodes, while no such activity is seen in control subjects who received no daytime training (Figure 3; Maquet et al., 2000). Furthermore, when retested the next morning, subjects' performance had improved significantly relative to the evening training sessions. Such sleep-dependent neuronal replay may allow for the adaptation of synaptic strengths within specific networks, strengthening some synaptic connections while weakening others. They have also shown that the extent of improvement during training has a direct relationship with the amount of subsequent reactivation during REM sleep (Peigneux et al., 2003). This finding mirrors previous data in animals suggesting that it is not simply experiencing the task that triggers modified sleep physiology but instead the quality of memory and magnitude of learning that determine the degree of subsequent functional replay during sleep.

Electrophysiological Studies

Both REM and NREM sleep stages contain numerous unique electrophysiological events. Many of these electrical phenomena have been implicated in the processes of plasticity by potentiating or depressing synaptic connections (Benington and Frank, 2003). For example, it has been proposed that sleep spindles, seen most commonly during stage 2 NREM sleep, can provide brief trains of depolarizing inputs to targets in the neocortex that are similar to spike trains used experimentally to induce long-term synaptic potentiation (Contreras et al., 1997; Sejnowski and Destexhe, 2000; Steriade, 1997, 1999). Indeed, Steriade and colleagues (Steriade, 2001) have shown that cortical neurons driven by impulse trains similar to those produced by sleep spindles can produce lasting changes in their responsiveness. Similarly, theta waves, seen in the hippocampus during REM sleep in both humans (Cantero et al., 2003) and other animals (Poe et al., 2000), greatly facilitate the induction of hippocampal long-term potentiation (LTP), believed to be a physiological mediator of memory formation (Huerta and Lisman, 1995; Pavlides et al., 1988).

Phasic events during REM sleep, and PGO waves in specific, have also been associated with learning. Sanford et al. (2001) have demonstrated that fear conditioning in rats can increase the amplitude of elicited P waves during REM sleep, suggesting again that they represent a homeostatically regulated component of a sleep-dependent mechanism of learning and plasticity (cf. Datta, 2000). Interestingly, these PGO waves occur in a phase-locked manner with theta wave activity during REM sleep (Karashima et al., 2002a, 2002b). Furthermore, while experimental stimulation to several regions of the hippocampus at the peaks of theta waves facilitates LTP, the same stimulation applied at the troughs of the theta waves instead leads to long-term depression of synaptic responses (Holscher et al., 1997; Pavlides et al., 1988). These findings suggest that this natural REM-PGO stimulation may serve as an endogenous mediator of synaptic plasticity, based on its coincidence

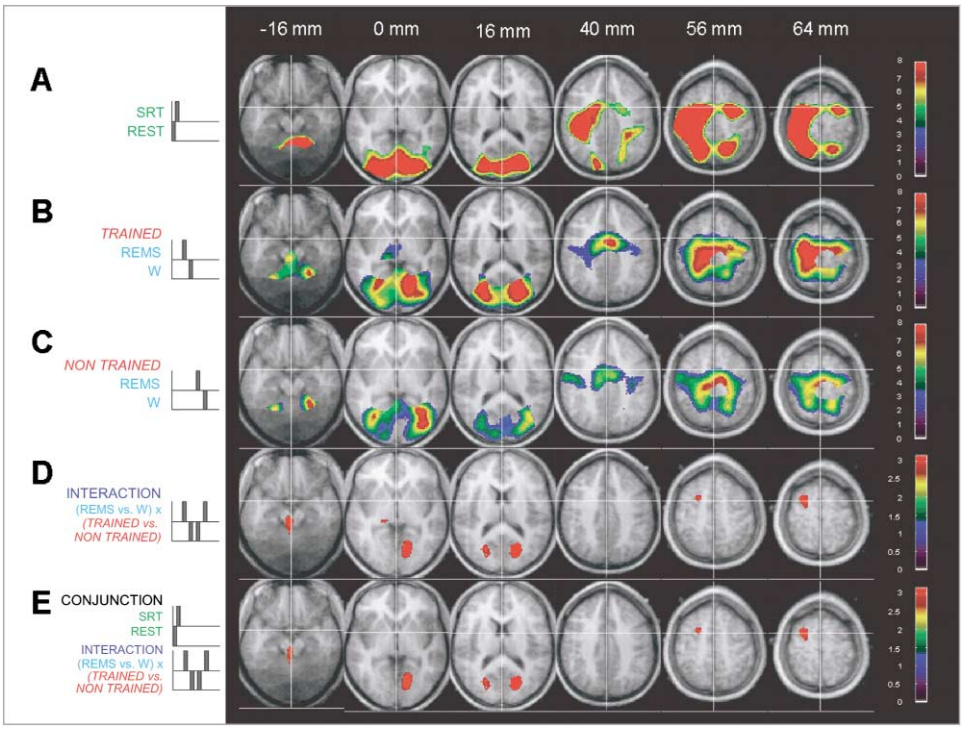

Figure 3. Task-Dependent Reactivation of Human Brain Activity, Measured Using PET, during REM Sleep

Statistical parametric maps of different experimental contrasts. Maps are displayed at six different brain levels (from 16 mm below to 64 mm above the bicommissural plane), superimposed on the average (coregistered and normalized) MRI image of the sleeping subjects. All maps are thresholded at $p < 0.001$ (uncorrected), except for (A), which is thresholded at voxel level-corrected $p < 0.05$). (A) Brain regions activated during performance of the SRT task [SRT − rest]. (B) Brain regions activated during REM sleep in trained subjects [REM sleep − rest]. (C) Brain regions activated during REM sleep in nontrained subjects [REM sleep − rest]. (D) Brain regions activated more in trained subjects than in nontrained subjects during REM sleep ([REM sleep − rest] by group [trained versus nontrained]) interaction. (E) Brain regions that showed a common activation in subjects scanned while performing the task during wakefulness and that were activated more in trained than in nontrained subjects scanned during REM sleep (that is the conjunction of the [REM sleep − rest] by group [trained versus nontrained] interaction with [SRT − rest]). With permission from Maquet et al., 2000.

with theta wave oscillations, which, depending on the phase relationship of the PGO and theta waves, could lead to either strengthening or weakening of synaptic connections, both of which are necessary for efficient network plasticity.

That such selective reactivation occurs is evident not only from the human neuroimaging studies described above, but from more precise studies of sleep-dependent network reactivation in the rat. Several groups have investigated the firing patterns of large numbers of individual neurons across the wake-sleep cycle in a variety of cortical and subcortical regions of the rat brain. The signature firing patterns of these networks, expressed during waking performance of spatial tasks and novel experiences, are replayed during subsequent SWS and REM sleep episodes, with replay during REM being at speeds similar to those seen during waking, but those in SWS being an order of magnitude faster in some, but not all, studies (Louie and Wilson, 2001; Poe et al., 2000; Ribeiro et al., 2004; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994). Dave and Margoliash (Dave and Margoliash, 2000; Dave et al., 1998) have similarly shown that waking patterns of premotor neuronal activity observed during song learning in the zebra finch are also replayed during sleep, with a temporal structural similar to that seen in wake.

Together these data indicate that sleep-dependent reactivation of temporal patterns of network activity consistently occurs following learning experiences during wake, across a broad spectrum of phylogeny. This replay of events is hypothesized to trigger distinct but complementary processes within reactivated neuronal ensembles. Ribeiro et al. (2004) have suggested that SWS reinstantiates the memory representation through network reverberation, while subsequent REM sleep then potentiates the memory for subsequent postsleep recall, through gene induction-mediated synaptic plasticity. Such a mechanism would explain the findings described above for visual texture discrimination learning, where SWS appears to stabilize and subsequent REM to enhance learning (Mednick et al., 2003; Stickgold et al., 2000c).

Cellular Studies

Recently, a form of sleep-dependent plasticity at the cellular level has been elegantly demonstrated during early postnatal development of the cat visual system (Shaffery et al., 1998, 1999). Under normal circumstances, brief periods of monocular visual deprivation during critical periods of development lead to the remodeling of synaptic connectivity, with the deprived eye's inputs to cortical neurons being first functionally weakened and then anatomically diminished (Antonini

and Stryker, 1993). Frank et al. (2001) have now shown that when 6 hr of monocular deprivation are followed by 6 hr of sleep, the size of the monocularity shift doubles. In contrast, if the cats are kept awake for these same 6 hr (in the dark, without input to either eye), a nonsignificant *reduction* in the size of the shift occurs. Thus, sleep can contribute as much to developmental changes in synaptic connectivity as does visual experience, presumably by enhancing the initial changes occurring during a prior period of monocular deprivation. In contrast, sleep-deprivation results in a loss of previously formed, experience-dependent synaptic changes, a pattern seen as well in humans, albeit at the behavioral level (Fischer et al., 2002; Stickgold et al., 2000a).

Shaffery et al. (2002) have reported complementary findings of sleep-dependent plasticity in the rat visual cortex, suggesting that REM sleep, in conjunction with visual experience, modulates the initial course of visual cortex maturation. In rats under 30 days of age, electrical stimulation produces increased excitability (potentiation) in specific layers of the visual cortex, while stimulation after this early developmental stage is unable to produce such potentiation. Depriving rats of REM sleep during this period can extend the window of plasticity by as much as 7 additional days, suggesting that events occurring during REM sleep normally control the duration of this period of experience-dependent plasticity.

Molecular Studies

At the molecular level, Smith et al. (1991) have shown that administration of protein synthesis inhibitors to rats during REM sleep windows that are thought to be critical for consolidation prevents behavioral improvement following the sleep period, while rats receiving saline injections show normal sleep-dependent learning. Such protein synthesis could reflect a fundamental mechanism regulating plasticity, namely, the activation of genetic cascades which produce key molecules for synaptic remodeling. Our understanding of such gene inductions during sleep is only now developing. In their initial studies, Tononi and Cirelli reported that several of the known "immediate early genes" (IEGs) are specifically downregulated during sleep (Cirelli and Tononi, 1998, 2000a, 2000b). These findings were subsequently used to argue that sleep is incapable of supporting plasticity and hence memory consolidation (Siegel, 2001), despite the fact that a significant number of genes were also found to be upregulated in sleep. Recently, Cirelli et al. (2004) have described approximately 100 genes that are specifically upregulated during sleep; almost the same number that are upregulated during wakefulness. Moreover, upregulation of these genes during sleep was seen only in the brain tissue.

This extensive upregulation of genes during sleep is particularly striking, as it was seen in the absence of any specific learning tasks being performed prior to sleep. Insofar as this upregulation is related to learning and memory consolidation, one might expect that such gene induction would only be seen after training on tasks that undergo sleep-dependent consolidation. Indeed, Ribeiro and colleagues have found upregulation in rats of *zif-268*, a plasticity-associated IEG, during REM sleep following exposure to a rich sensorimotor environment but its downregulation during both SWS and REM sleep in the absence of such exposure (Ribeiro et al., 1999). Thus, there appears to be a window for increased neuronal plasticity during REM sleep periods following enriched waking experience (Figure 4).

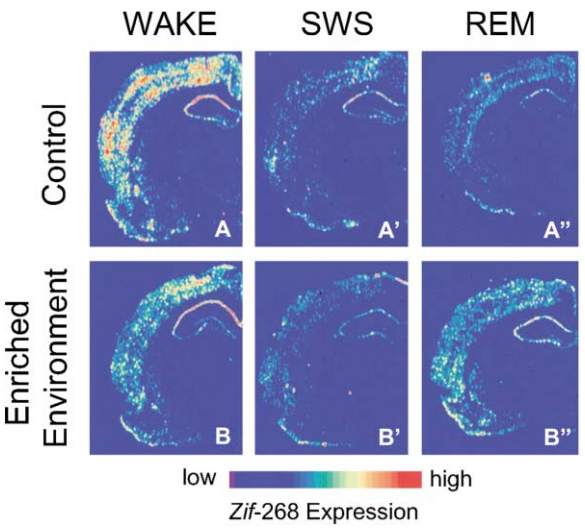

Figure 4. Experience-Dependent Upregulation of *zif-268* Gene Expression during Wake, SWS, and REM Sleep States in the Rat

Autoradiograms of frontal coronal brain sections whose 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. With permission from Ribeiro et al., 1999.

This rich-environment effect can be mimicked by brief electrical stimulation of the medial perforant pathway (Ribeiro et al., 2002). Unilateral stimulation results in a wave of *zif-286* expression during subsequent REM sleep, with expression seen predominantly in the ipsilateral amygdala and entorhinal and auditory cerebral cortices during the first REM sleep episodes after LTP induction and extending into somatosensory and cerebral cortices during subsequent REM periods (Ribeiro et al., 2002). These distinct phases of induction may correspond to the unique stages of consolidation previously reported from behavioral studies (Walker et al., 2003a).

Interim Summary

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

4. Unresolved Questions

Over the last several years, as evidence of sleep's role in learning and memory consolidation has grown, several

researchers have raised questions concerning the nature or even the existence of this relationship. Having focused our attention so far on the evidence in support of sleep's role, we turn now to objections.

Fear Conditioning and REM Sleep in Rodents

Studies described above reported increases in REM sleep in rats following fear conditioning using a shuttle box avoidance task. Such increases have been taken as indications of homeostatic increases in REM sleep driven by an increased demand on REM-dependent consolidation. In contrast, Sanford and colleagues (Sanford et al., 2001, 2003) have reported *decreases* in REM sleep in mice following fear conditioning. At first glance, these findings appear contradictory, but differences in protocol suggest a more parsimonious explanation. While the shuttle box avoidance task that was used in the studies showing increases in REM sleep involved animals learning how to successfully avoid future shocks, Sanford et al's studies (Sanford et al., 2001, 2003) involved training animals to expect future unavoidable shocks. These learned helplessness protocols permit no useful learning, and the decrease rather than increase in REM sleep makes perfect sense within this context since, for example, the magnitude of the posttraining increase in REM sleep has, in some cases, been proportional to the amount of learning (e.g., Ambrosini et al., 1992). It parenthetically provides an exemplary demonstration of the inability of stress per se to adequately explain REM increases.

Stress, REM Sleep, and Memory Consolidation

As noted earlier, several of the early findings of REM sleep-related alterations in memory have been criticized as possible confounds of stress induced both by fear conditioning paradigms and by sleep deprivation. This argument was originally presented in a comprehensive review by Horne and McGrath (1984), who made clear that they considered that this was an alternative interpretation and not evidence against sleep-dependent consolidation. A more extreme stance has since been adopted by some authors (Siegel, 2001; Vertes and Eastman, 2000), who have used these arguments as strong evidence against any role for REM sleep in memory consolidation and learning. Two distinct objections have been raised. First, that the increase in REM sleep seen after training is induced by the stress of the training and not by a need for REM-dependent consolidation, and, second, that the deterioration in performance after REM deprivation is due to stress produced by sleep deprivation. However, several findings, including (1) the previously discussed delayed "REM windows" (Smith, 1995), (2) the persistence of sleep deprivation effects for up to a week (e.g., Smith and Smith, 2003), (3) the correlation of the magnitude of the REM increase both with the degree of prior learning (Ambrosini et al., 1992) and (4) with subsequent retention (Datta, 2000), and (5) the decreased REM sleep following learned helplessness training (Sanford et al., 2001, 2003) all make it very unlikely that stress alone can explain these effects. Furthermore, the findings of performance enhancement seen (6) in humans after a nap with REM sleep (Mednick et al., 2003) as well as (7) in rats after various procedures that increase REM sleep (Wetzel et al., 2003) or even (8) increasing just PGO waves in the absence of REM sleep (Datta et al., 2004), along with (9) the suppression of enhancement by protein synthesis inhibition during REM windows (Smith et al., 1991) cannot be explained in any way by these arguments.

Table 1. Analysis of Reports Studying the Effects of REM Suppressant Drugs on Memory

Studies of REM Suppressants and Memory	
Reports	19
Reviews	3
Primary sources	16
No memory tests	5
Tested memory	11
Immediate retest (<10 min)	7
Retest at 10–30 min	3
Retest at 30 min to 5 hr	1
Sleep-dependent tasks	0
Retest following sleep	0
Sleep recorded	0

Of 19 studies that were cited as evidence that REM-suppressing antidepressants show normal learning despite REM suppression, none investigated sleep-dependent tasks, none tested memory after a posttraining night of sleep, and none confirmed the degree of REM suppression.

Miscellaneous Arguments

In addition to the substantive objections discussed above, a series of more nebulous arguments have been raised (Siegel, 2001; Vertes and Eastman, 2000). One example is the claim that studies with monoamine oxidase inhibitors (MAOIs) and other REM suppressing antidepressants have proven that REM sleep plays no role in memory consolidation, arguing that such REM suppressants could be taken for years with no deleterious effects on memory (Vertes and Eastman, 2000). But while MAOIs clearly reduce and, in some cases, even eliminate REM sleep during initial use (Landolt et al., 2001; Monti et al., 1990), REM sleep clearly reemerges with chronic drug treatment (Landolt and de Boer, 2001; Mendelson et al., 1982; Minot et al., 1993), suggesting a strongly compensatory REM mechanisms. Furthermore, there is a potent REM rebound during frequent "drug holidays," when patients temporarily suspend usage of the drug (Minot et al., 1993; Steiger et al., 1994, 1987). As a result, claims that MAOIs "can completely suppress REM sleep…throughout the period of treatment, which may continue for months or years" (Siegel, 2001) or even that they "essentially abolish REM sleep" (Vertes and Eastman, 2000) fail to reflect the reality that, after an initial period of intense REM suppression, most of these patients have significant REM sleep on a nightly basis.

A second problem arises when authors use relatively brief memory tests to argue against sleep-dependent learning. The perils of relying on such studies is evident in the interpretation of MAOI data by Vertes and Eastman (2000). Vertes and Eastman (2000) cite 29 articles, 19 of which were available in the Harvard Medical School's electronic and print libraries, to argue that REM suppression by MAOIs has no deleterious effects on memory. A review of these citations (Table 1) shows that of the 16 primary source articles (three were reviews), 5 reported no memory tests at all, 7 retested memory within minutes of training, and only 1 had a retest interval of greater than 30 min. Even more striking is the fact that none involved retesting following sleep, none tested tasks that have been reported to undergo sleep-dependent consolidation, and none recorded subjects' sleep

to determine the extent of REM suppression. In the end, such studies provide no useful information regarding the role of REM sleep in memory consolidation, let alone the role of sleep in general.

Other objections have also been raised. Siegel (2001) has argued that if REM-dependent memory consolidation exists, then species with greater intelligence should have more REM sleep than others, and individual with higher IQs should have more REM sleep than others. But there are several objections to such an inference: (1) it is unclear whether IQ and intelligence have any correlation with the efficacy of memory consolidation; (2) if such a correlation existed, it is unclear whether it would predict that lower IQ should correlate with less REM sleep (since less REM sleep produces less consolidation) or more REM sleep (since greater demands produce more REM sleep); (3) given that there are also positive correlations between SWS and stage 2 NREM sleep and memory consolidation, these should also increase, which would lead to the unreasonable conclusion that the more intelligent an individual or species, the more they would sleep; (4) since REM sleep is thought to mediate additional functions besides that of memory consolidation, it is not clear that IQ or intelligence should be the dominant determinant of baseline REM sleep amounts.

While such issues against the role of sleep in memory can feel inconsequential when taken one by one, presented as a whole, they unfortunately can produce the inappropriate impression of substantive evidence that sleep plays no role in learning and memory consolidation.

Unresolved Questions

This being said, there remain numerous important and unanswered questions regarding sleep-dependent learning and memory consolidation. Four broad categories of questions remain. First, it remains unclear exactly which types of memory undergo sleep-dependent consolidation. While procedural learning, both perceptual and motor, is clearly enhanced by posttraining sleep, the forms of declarative memory that are similarly affected are uncertain. Second, sleep's contribution to the processes of stabilization, enhancement, reconsolidation, integration, translocation, and active erasure require further elucidation. Third, the actual processes within sleep that effect consolidation are almost completely unknown. Candidate mechanisms, including (1) synchronous brain activity, such as that of PGO waves, sleep spindles, and theta rhythms; (2) changes in regional brain activation and interregional communication; and (3) shifts in global concentrations of neuromodulators, including ACh, NE, and 5-HT, and more classical hormones such as cortisol and even growth hormone, are all only beginning to be adequately investigated (Benington and Frank, 2003; Graves et al., 2001; Tononi and Cirelli, 2001). Finally, almost nothing is known about how these processes are altered in various populations, whether related to normal aging or to psychiatric and neurological disorders. Much of the excitement over the next decade will be in beginning to address these questions more fully.

5. Summary

Over the last 25 years, the field of sleep and memory has grown exponentially, with the number of publications per year listed in MEDLINE doubling every 9–10 years, faster than the growth for either sleep or memory alone, and with over 450 publications listed for 2000 through 2003. These reports, ranging from studies of cellular and molecular processes in animals to behavioral studies in humans, have provided a wealth of converging evidence that sleep-dependent mechanisms of neural plasticity lead to the consolidation of learning and memory across a range of animal species.

At the molecular level, significant number of genes appear to be upregulated specifically in brain tissue during sleep, and at least one immediate early gene related to synaptic plasticity, *zif-286*, is upregulated during REM sleep expressly in response to environmental or direct electrical stimulation of the hippocampus. In rats, patterns of neuronal activation expressed during waking exploration reappear during subsequent sleep, and, in humans, patterns of regional brain activation seen during daytime task training are repeated during subsequent REM sleep.

At the electrophysiological level, studies in rats have shown that retention of learning of a shuttle box avoidance task increases subsequent P wave density and is strongly correlated with this increase, while in humans, spindle density increases following training on a declarative memory task, and, again, this increase correlates with subsequent improvement on the task.

At the behavioral level, animal studies have found robust increases in REM sleep following task training and decrements in performance after REM deprivation, even when retesting is delayed until a week after the end of deprivation. In contrast, several animal studies have failed to find evidence of either increased REM sleep or deterioration following deprivation. Most likely this reflects a combination of methodological problems and conditions under which consolidation is, in fact, not sleep dependent. Similarly, human studies have provided examples where increases in REM sleep are seen following training, where REM, SWS, or stage 2 NREM deprivation diminishes subsequent performance, and where overnight improvement correlates with REM, SWS, or stage 2 NREM sleep.

In the end, the question appears not to be whether sleep mediates learning and memory consolidation, but instead, how it does so. The future of the field is truly exciting, and the challenge to neuroscience will be to both uncover the mechanisms of brain plasticity that underlie sleep-dependent memory consolidation and to expand our understanding of sleep's role in memory processes beyond simple consolidation, into the constellation of additional processes which are critical for efficient memory development. Work across the neurosciences will be necessary to answer these questions, but with the current rate of growth of research in the field, the next decade should provide important advances in our understanding of this critical function of sleep.

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