The idea that sleep may facilitate learning and memory consolidation has attracted considerable attention in recent years, both within the sleep research community and among the general public. Learning-related functions of sleep have been more actively investigated over the past decade than any other class of sleep functions. Yet there is by no means universal acceptance within the sleep research community that sleep facilitates learning and memory to any considerable degree. The hypothesis has strong proponents (Smith 1995; Peigneux and others 2001; Rauchs and others 2005; Stickgold 2005; Stickgold and Walker 2005), including most of the researchers actively investigating in this area, as well as no less determined and principled detractors (Vertes and Eastman 2000; Siegel 2001; Vertes and Siegel 2005).

Classic studies of sleep and learning were conducted largely at the behavioral and electroencephalographic levels of inquiry, and such approaches continue to yield interesting findings today. But increasingly, this question is being addressed also in terms of the response properties of single neurons in networks and the regulation of gene and protein expression. Sleep researchers are drawing from the rapidly growing body of work concerning cellular and molecular mechanisms of synaptic plasticity, in search of specific mechanisms that might link the neuronal activity characteristic of sleep states with modulation of synaptic connections in the brain (Benington and Frank 2003). The establishment of such links holds the greatest promise for demonstrating conclusively that facilitating memory consolidation is an important function of sleep.

In this article, we will explore what findings have already been reported, linking sleep with memory consolidation and synaptic plasticity. We will first review the behaviorally based literature and discuss how it has been analyzed by both proponents and detractors of learning-related functions of sleep. We will then review findings linking sleep with changes in neurons and consider what cellular and molecular mechanisms could explain these observations. In closing, we will discuss what work can be done in the immediate future to test specific hypotheses relating to a functional association between sleep and synaptic plasticity.

**Sleep and Learning**

Behavioral evidence for a link between sleep and memory consolidation falls into 3 broad categories: Sleep deprivation has been reported to impair memory consolidation, exposure to new environments or cognitive tasks has been reported to alter subsequent sleep, and correlations have been reported between sleep variables and next-day improvements in learning tasks. In the following sections, we will briefly review the findings of these 3 classes of studies and consider their implications for establishing a link between sleep and memory consolidation. Because this literature has already been the subject of a number of more comprehensive reviews (Smith 1995; Peigneux and others 2001; Benington and Frank 2003; Rauchs and others 2005; Stickgold 2005), we will herein cite specific findings only by way of providing examples of broader trends.

**Sleep Deprivation and Memory Consolidation**

Experimental tests of the effects of sleep deprivation on memory consolidation have used a remarkable diversity...
of experimental protocols. Both humans and laboratory animals have been used as subjects. Various types of sleep deprivation have been used, including selective rapid eye movement (REM) sleep deprivation, slow-wave sleep deprivation, and total sleep deprivation for either the first or second half of the rest period. The duration of sleep deprivation has also varied between studies as well as the intervals between learning and sleep deprivation and between sleep deprivation and testing. Studies have also used a wide range of different learning paradigms and criteria for learned improvement. In humans, effects on both declarative and procedural memories have been measured. Studies of declarative memory have tested for effects on episodic memory, semantic memory, and priming. Studies of procedural memory have tested for effects on fine motor control, perceptual skills, and cognitive operations. And even within any one of those broad categories, studies conducted by different laboratories have most often employed different specific learning protocols. A similarly wide variety of experimental paradigms has been used in animal (chiefly rodent) studies, in which a division has typically been made between hippocampal (explicit) and presumed nonhippocampal (implicit) forms of memory.

Unfortunately, no consistent picture has emerged from this impressive body of experimental work. Until about 10 years ago, there was roughly the same number of studies yielding positive versus negative findings, although positive findings have predominated since then (Stickgold and Walker 2005). In many cases, both positive and negative findings have been reported in the same article, depending on the type of sleep deprivation or learning paradigm employed. For example, REM sleep deprivation has been reported to impair memory consolidation for complex tasks but not simple ones (Peigneux and others 2001) and after animals have achieved a certain mastery of a new task but not shortly after being introduced to it (Dujardin and others 1990). In one study in humans, memory consolidation in a procedural task was impaired after total sleep deprivation for the second half of the posttraining night, when REM sleep predominates, but not after REM sleep deprivation for the entire night (Smith and MacNeill 1994). In another study, subjects’ reactions improved following a period of normal sleep in an explicit learning paradigm but not an implicit one—when color cues were used to alert subjects to which particular trials included repeated, learnable task sequences (Robertson and others 2004). Inconsistency in experimental results is a not uncommon problem during the formative stages of a scientific area of investigation (Collins and Pinch 1993). In such cases, inconsistent findings can be attributed to any of the following five causes.

1. Positive findings could result from something other than the intended treatment (in this case, sleep deprivation) that is inadvertently associated with treatment trials, whereas negative findings result from studies in which such an experimental confound is avoided.

2. Negative findings could result from inconsistencies in experimental procedures that increase within-group variability to the point at which statistically significant between-group findings do not appear.

3. The effect could be real but subtle enough to reach the level of statistical significance in only a fraction of studies, even if experimental design and execution are unchanged.

4. The analyses reported in the research literature could reach statistical significance and thus appear to be positive findings, whereas a greater number of other analyses of the same data sets may not have reached statistical significance and thus remained unreported. Analogously, studies for which apparently positive findings were achieved may have been published, whereas studies resulting in negative findings may have remained unpublished.

5. The experimental effects could be genuinely sensitive to differences in the experimental protocols (e.g., types of sleep deprivation or learning paradigms) used in studies yielding positive versus negative findings.

In offering these five possible explanations, we do not mean to imply that any one of them is especially likely in the field of sleep and memory consolidation; they merely represent the range of possible explanations for any such body of inconsistent findings in the research literature. At the moment, it is not at all clear which one or more of these causes may be responsible for the inconsistent findings in this field, although arguments have been advanced for and against one or another of them. Not surprisingly, proponents of the idea of sleep-dependent memory consolidation tend to prefer causes 2 and 5, whereas opponents tend to prefer causes 1 and 4.

In support of cause 1, opponents of the idea of sleep-dependent memory consolidation have suggested that impairment of memory consolidation is in fact caused by the stress associated with either loss of sleep in general or the specific paradigms used to deprive subjects of sleep (Horne and McGrath 1984). Indeed, sleep deprivation has been shown to increase serum levels of glucocorticoids, which have in turn been shown to affect animal and human cognition (Pliahal and others 1996). There are, however, a small number of studies in which stress can be largely ruled out as a factor (Hastin and others 2005; Ruskin and others 2005), so this criticism may wane as experimental designs continue to improve. Lingering performance deficits associated with inadequate sleep could also be responsible for poor scoring during retest in sleep-deprived conditions (Harrison and Horne 2000), although this is unlikely to apply to protocols involving very mild sleep deprivation or a longer interval between sleep deprivation and retest. The search for circumscribed time windows to which an effect of sleep deprivation on memory consolidation is restricted has likewise been geared toward undermining arguments for a performance-deficit confound (Smith 1985; Graves and others 2003). One argument that has been raised against causes 3 and 4 is the fact that, in some studies, between-group differences far exceed minimally accepted
levels of statistical significance, indicating that those cases at least are highly unlikely to represent mere statistical anomalies (Stickgold and Walker 2005).

The preponderance of positive findings in the recent research literature may indicate that researchers in the field have identified the causes of the earlier inconsistency and corrected them. The standard of expertise in administering learning tests and/or performing sleep deprivations may now be enabling researchers to get results that are consistent enough to achieve statistical significance in between-group comparison, or researchers may now be concentrating on the types of experimental protocol that yield positive findings. But in comparing the earlier and more recent experimental literature, it is not at all clear what distinguishes the more successful recent findings from the more ambiguous earlier ones. One such suggestion that has been advanced is that sleep deprivation interferes with consolidation of procedural memory in humans but not declarative memory (Smith 1995). But although procedural memory protocols have indeed predominated in the recent literature, there have also been recent positive findings concerning declarative memory (Plihal and Born 1999).

The great diversity of experimental methodologies used by researchers in the sleep and learning community is partly responsible for this impasse. What the field desperately needs is more repetition of specific experimental protocols in different laboratories. If a given protocol consistently produces positive findings in support of an effect of sleep on that type of learning, causes 2, 3, and 4 could be ruled out for that case. That well-established finding could then be used as a baseline for further explorations of the range of learning and sleep paradigms that produce similarly positive findings and in tests of candidate experimental confounds, by way of ruling out or confirming cause 1. It would obviously be too expensive and time-consuming to do this for every experimental protocol that has so far been used in the field, so researchers will have to agree on a smaller number of model systems for this more intensive approach. In the meantime, supporters of a link between sleep and memory consolidation should be cautious in drawing theoretical conclusions from variations in experimental findings with different experimental protocols, as though cause 5 were alone responsible for the inconsistencies.

Learning and Subsequent Sleep

Studies of the effects of learning on sleep have likewise produced a great diversity of findings. Learning has been reported to increase REM sleep duration, number of REM sleep episodes, REM density and ponto-geniculo-occipital (PGO) wave density in REM sleep, non-REM sleep duration, and localized increases in electroencephalograph (EEG) slow-wave activity in non-REM sleep (Smith 1995; Peigneux and others 2001; Rauchs and others 2005). This literature includes studies in humans and experimental animals following specific learning tasks, as well as studies in which experimental animals are exposed to an enriched environment. As in the case of the effects of sleep deprivation on learning described above, the cause of this diversity of findings is unclear. As each study has sampled only a fraction of the variables showing changes, it is not even clear whether this represents real inconsistency or merely the differing focus of different studies. Once again, a number of the reported findings await replication in other laboratories.

Effects of learning or an enriched environment on subsequent sleep are consistent with a role for sleep in memory consolidation, but they are equally consistent with other proposed functions of sleep by means of which novel experiments and cognitive challenges could indirectly alter subsequent sleep. For example, if sleep functioned primarily in the restoration of a metabolic deficit accumulated during waking (Benington and Heller 1995), then learning and enriched environments would be expected to enhance subsequent sleep insofar as they place greater metabolic demands on the brain during waking. Taken alone, therefore, such effects have little implication for the role of sleep in learning and memory, although they can further strengthen the case for such a role if taken in combination with other types of evidence.

**Correlations between Sleep and Memory Consolidation**

It is a truism in the natural sciences that correlation need not imply causation and that traditional experimental designs provide stronger evidence than correlative findings do. Thus, one might expect that correlations between specific sleep variables and improved performance in learning tasks following a night of sleep would provide the weakest class of evidence for a link between sleep and memory consolidation. But one could argue that correlative studies are free of some of the potential confounds of sleep deprivation experiments and enable one to test simultaneously the effects of various aspects of sleep on memory consolidation. Perhaps for these reasons, correlative data have been reported more frequently in the recent experimental literature.

Following training in a visual discrimination task in humans, overnight improvement was most strongly correlated with duration of slow-wave sleep (stages 3 and 4 in non-REM sleep) in the first quarter of the night and duration of REM sleep in the last quarter (Stickgold, Whiffbee, and others 2000). The correlation coefficient between a combination of these two sleep variables and performance improvement was an impressive 0.89, accounting for almost 80% of the variability in performance improvement. Following training in patterned finger tapping, overnight improvement was most strongly correlated with amount of stage 2 non-REM sleep ($r = 0.66$), particularly in the last quarter of the night ($r = 0.72$; Walker and others 2002). In another finger-tapping protocol, overnight improvement was most strongly correlated with amount of non-REM sleep ($r = 0.73$), but only when subjects were cued to which patterns were being repeated and thus learned (Robertson and others 2004). Following training in a procedural learning task involving hand-to-eye coordination, overnight improvement was correlated...
(r = 0.86) with localized increases in EEG slow-wave activity in non-REM sleep, in specific parts of the parietal cortex that are activated during training and reactivated during posttraining non-REM sleep (Huber and others 2004). In contrast to the above non-REM sleep–related correlations, overnight improvement in the classic Tower of Hanoi procedural learning task was correlated with REM density in REM sleep (r = 0.48–0.62; Smith and others 2004). In rats trained in an active avoidance task, improvement was highly correlated with increased PGO wave density in posttraining REM sleep (r = 0.95; Datta and others 2000).

As in the case of sleep deprivation studies, these findings are inconsistent as to whether overnight improvement is correlated with deep non-REM sleep, stage 2 non-REM sleep, or REM sleep. Each of the above studies uses a different procedural learning task, involving visual discrimination, motor actions, or a combination of visual, motor, and/or planning skills. As a result, it is impossible to determine at this point whether the inconsistencies reflect real differences in the roles of different sleep stages in different types of memory consolidation.

Memory Consolidation versus Performance Deficits

The most obvious weakness in the above-described studies is that impaired memory consolidation following sleep deprivation and correlations between memory consolidation and sleep variables could merely reflect sleep-related performance deficits during the retest period. A considerable experimental literature demonstrates that sleep loss impairs cognition on a number of levels (Harrison and Horne 2000). This explanation is most persuasive when the sleep-deprivation protocol is such as would cause subjective increases in sleepiness during the retest period, but it cannot be ruled out even when the effects of sleep loss are more subtle. In the visual discrimination and finger-tapping tasks described above (Stickgold, Whifbee, and others 2000; Walker and others 2002; Robertson and others 2004), sleep-dependent improvements in performance are measured in tens of milliseconds, between the display of a stimulus and a visual mask or between steps in a finger-tapping pattern. It is possible that such time-intensive cognitive operations are ideally suited to revealing performance deficits associated with relatively mild sleep loss, thus producing the appearance of sleep-dependent memory consolidation.

One approach that has been used to obviate this interpretation is to compare equal 12-hour intervals of normal daytime waking with normal nighttime sleep between training and retest, on the assumption that sleepiness following normal daytime waking should not interfere with performance (Stickgold, Whifbee, and others 2000; Walker and others 2002; Huber and others 2004; Robertson and others 2004). But studies in humans whose sleep-wake and circadian cycles are systematically desynchronized have demonstrated that sleep propensity increases substantially during 16 hours of waking but is masked in the late active period by a wake-inducing output of the circadian pacemaker (Dijk and Czeisler 1995). Given that performance deficits in humans have been observed following sleep deprivation, even when sleepiness is combated by caffeine administration (Harrison and Horne 2000), it is entirely possible that absence of performance improvement following 12 hours of waking reflects merely the increased sleep propensity during the retest period, in comparison with the morning following a good night’s sleep.

The obvious answer to this potential experimental con- found is to demonstrate differences in performance in equally well-rested subjects, depending on whether they slept during an earlier interval, shortly after training. For example, performance in a visual discrimination task has been reported to improve 3 days after initial training, after 2 nights of sleep, but not when subjects were sleep deprived on the first night and allowed to sleep normally on the subsequent 2 (Stickgold, LaTanya, and others 2000). Although a few such longer term findings have been published, they represent isolated reports in comparison with the much larger body of experimental findings involving retesting during periods of abiding sleep deficit.

Sleep and Synaptic Plasticity

It is unlikely that the debate over sleep’s role in learning will ever be resolved by studies that rely solely on behavioral measurements, no matter how sophisticated they become. Although behavioral assays have often anticipated the identification of neural processes by more direct means, such measurements alone cannot reveal the cellular underpinnings of the observed behavior. Only a convincing demonstration that sleep directly influences the underlying mechanisms of memory will satisfy the more ardent critics. In the following sections, we consider cellular and molecular findings that support a role for sleep in promoting synaptic plasticity. This material has been extensively reviewed elsewhere (Benington and Frank 2003; Frank 2006), and where specific citations are not provided below, the reader may consult these reviews for more information.

As is true for behavioral studies of sleep and learning, studies of sleep and plasticity can be broadly divided into 3 categories. First are studies that have identified patterns of activity during sleep that might promote synaptic remodeling. Second are studies that have examined changes in artificially induced forms of plasticity or plasticity-related molecules after sleep or sleep deprivation. A third category includes studies that have examined the effects of sleep or sleep deprivation on related processes that occur in development.

Neuronal Replay in Sleep

A number of investigators have reported reactivation or replay of wake-active neurons during sleep in rodents, primates, and even birds (Wilson and McNaughton 1994; Dave and Margoliash 2000; Hoffman and McNaughton 2002). Similarly, increased neuronal synchronization and metabolic activity in specific brain areas have been reported in humans following learning tasks (Maquet 2001; Maquet and others 2003; Peigneux
and others 2003; Huber and others 2004; Peigneux and others 2004). A few studies in rodents have also shown small but significant correlations between hippocampal events when replay is reported and thalamocortical spindles and delta waves during sleep (Benington and Frank 2003; Frank 2006).

There is strong evidence of a rich exchange between the thalamus and the cortex during sleep, which, under certain conditions, might promote plasticity (Steriade and Timofeev 2003). For example, in vivo recordings in cats have shown that anesthesia-induced spindles produce augmenting responses in cortical neurons that persist for several minutes. Similar spindle stimulus trains can depress or potentiate cortical postsynaptic responses in vivo and in vitro (Crochet and others 2005; Rosanova and Ulrich 2005). On the other hand, stimulation that mimics slower EEG rhythms does not reliably depress synapses in vitro (Perrett and others 2001), contrary to the predictions of recent proposals positing a role for non-REM sleep in Hebbian and non-Hebbian synaptic weakening (Benington and Frank 2003; Tononi and Cirelli 2003).

The significance of these findings remains unclear. In most rodent studies, reactivation is observed only after extensive training on familiar tasks, rapidly dissipates, and makes up a small proportion of total recorded activity in sleep. It also appears that sleep is not necessary for replay as replay is also detected in quiet wakefulness (Kudrimoti and others 1999; Peigneux and others 2006). The correlations between hippocampal and cortical activity during sleep are likewise interesting but may not reflect an actual transmission of information between these structures (Pelletier and others 2004). Most important, with the exception of some correlational findings in humans (Huber and others 2004; Peigneux and others 2004), there is no evidence that reactivation of waking neural activity or spontaneous sleep rhythms promote functionally important changes in circuits.

**Sleep, LTP, Long-term Depression, and Plasticity Molecules**

LTP and long-term depression (LTD) refer to use-dependent, persistent alterations in synaptic weights that strengthen (LTP) or weaken (LTD) specific synapses (Malenka and Bear 2004). Although these effects were originally identified in vitro and involved what were at the time considered nonphysiological stimulus protocols, LTP and LTD can be induced and may occur naturally in vivo (Malenka and Bear 2004). These and related forms of synaptic plasticity are now widely considered to be cellular correlates of memory. To what extent, then, does sleep influence LTP and LTD?

Beginning in the late 1980s, several investigators showed that sleep states influence LTP in vivo. Overall, it appears that hippocampal LTP can be induced during REM sleep, whereas similar stimulus protocols during non-REM sleep have no effect or produce LTD. A large number of studies have also shown that sleep deprivation inhibits the induction or maintenance of LTP in vivo and in vitro (in brain slices obtained from sleep-deprived rats; Benington and Frank 2003; Frank 2006).

Sleep and sleep deprivation are also reported to influence the synthesis of mRNAs and proteins involved in synaptic plasticity. For example, cortical mRNA transcripts for 2 genes important for LTD (i.e., calcineurin and camKIV) are specifically up-regulated by sleep (Cirelli 2005), and neuronal expression of the LTP-related gene zif-268 is increased in REM sleep following exposure to enriched environments or LTP in vivo (Ribeiro and others 1999; Ribeiro and others 2002; Ribeiro and others 2004). Sleep deprivation has also been shown to decrease hippocampal neurogenesis and neuronal concentrations of several proteins involved in synaptic remodeling (Hairston and others 2005; Davis and others 2006; Frank 2006). In a few instances, these sleep deprivation–induced changes are associated with deficits in hippocampal LTP in vitro and learning in rodents (Wright and others 2002; Davis and others 2003; Guan and others 2004; Hairston and others 2005; Chen and others 2006).

Overall, these findings suggest that sleep and sleep loss can modify synaptic plasticity and the expression of plasticity-related molecules, but a few caveats should be considered. First, only a few of these studies have controlled for circadian effects or stress. Second, the functional significance of these cellular/molecular and electrophysiological changes is not always demonstrated. For example, the fact that experimental stimuli can induce LTP in REM sleep does not mean that similar processes normally occur during REM sleep. Likewise, few of the cellular/molecular changes reported in sleep or after sleep deprivation have been conclusively linked to changes in learning or synaptic plasticity.

**Sleep and Neural Development**

Sleep amounts are higher in the neonatal period than at any other time of life, and this is also a period of rapid brain development and synaptic plasticity (Roffwarg and others 1966; Frank 2006). Therefore, if sleep contributes to synaptic plasticity, one would expect this to be especially true in developing animals. This possibility has been primarily investigated in the visual system. Development in this sensory system can be divided into 2 stages: an early experience-independent stage, in which intercellular molecular signals and endogenous neural activity form nascent circuitry, and a subsequent critical period, in which circuits are sculpted by external visual input (Berardi 2000). The critical period has historically been investigated by blocking vision in one eye (monocular deprivation [MD]), which causes a massive rewiring of cortical circuits in favor of the open eye, a process known as ocular dominance plasticity (Hubel and Wiesel 1970; see Fig. 1). This in vivo plasticity is paralleled by a type of LTP (investigated in vitro) that can be induced only in developing animals.

A role for REM sleep in brain maturation has been examined by studying the effects of REM sleep deprivation (using mechanical techniques), or the elimination of REM sleep PGO waves, on subsequent visual system development. For example, bilateral electrolytic lesions of the PGO wave generator in the rostral pontine tegmentum in the neonatal cat cause lateral geniculate nucleus (LGN)
neurons to be physically smaller and to exhibit immature response properties. These morphological and functional changes in LGN neurons are consistent with delayed development in the LGN and suggest that REM sleep neuronal activity may be necessary for normal LGN development (Davenne and Adrien 1984; Davenne and others 1989).

Total or selective REM sleep deprivation, or the deprivation of REM sleep PGO waves, is reported to augment the effects of MD on LGN neuronal morphology during the critical period. For example, Oksenberg and others (1996) found that 1 week of REM sleep deprivation in kittens combined with MD produced smaller LGN neurons innervated by the deprived eye (compared to MD alone). A similar increase in LGN neuron size disparity was found when MD was combined with brain stem lesions that eliminated PGO waves (Shaffery and others 1999).

REM sleep deprivation also appears to augment a developmentally regulated form of LTP in the visual cortex (Shaffery and others 1999). In this type of LTP, white matter stimulation in cortical slices prepared from critical period rats produces synaptic potentiation in cortical layers 2/3; however, this is not observed in cortical slices from older rats. Interestingly, a week of REM sleep deprivation appears to extend the age at which this form of LTP can be elicited (Shaffery and others 2002). The extension of the critical period by REM sleep deprivation was similar to effects produced by dark rearing, which also prolongs the period of induction of this form of LTP (Shaffery and others 2002). Subsequent studies from these investigators showed that this plasticity could be extended also if REM sleep deprivation was administered near (or overlapping) the end of the critical period (Shaffery and Roffwarg 2003; Shaffery and others 2005).

Frank and others (2001) demonstrated a role for sleep in ocular dominance plasticity by combining MD with periods of sleep or sleep deprivation (Fig. 2). Optical imaging of intrinsic cortical signals and extracellular unit recording showed that sleep nearly doubled the synaptic remodeling in the visual cortex induced by MD, whereas wakefulness in complete darkness tended to erase the effects of the preceding monocular visual experience (Figs. 3 and 4). This latter finding was particularly revealing because it showed that the effects of sleep were not simply due to a reduction of interfering signals...
and instead resulted from an active process that targeted remodeling circuits. Interestingly, no brain state other than sleep is known to have such augmenting effects on ocular dominance plasticity because anesthetic states and cortical inactivation suppress ocular dominance plasticity (Frank 2006). The precise contribution of REM and non-REM sleep to this process is still unknown, but the enhancement of cortical plasticity was highly correlated with non-REM sleep time, suggesting an important role for non-REM sleep in the rapid cortical synaptic remodeling elicited by MD (Frank and others 2001).

It has more recently been shown that this form of sleep-dependent plasticity requires cortical neuronal activity (Jha and others 2005; Frank and others 2006). Using a modified version of the experimental design described above, these investigators found that reversible inactivation of neuronal activity in cortical area V1 during sleep largely inhibited the remodeling normally observed after sleep (Fig. 4). This blockade of sleep-dependent plasticity was not due to disruption of ongoing sleep or gross alteration of visual processing, demonstrating that the loss of plasticity was specifically caused by the transient silencing of neurons during sleep. Interestingly, additional sleep (with cortical activity restored) did not rescue ocular dominance plasticity. This indicated that sleep immediately following waking experience was critical for the consolidation of this type of plasticity (Figs. 5 and 6). Subsequent findings showed that the effects of lidocaine were likely mediated by changes in postsynaptic activity. Cortical infusion of the GABA_A receptor agonist muscimol during the post-MD sleep period completely blocked sleep-dependent plasticity (Frank and others 2006). Because muscimol predominantly reduces postsynaptic activity while sparing presynaptic input, these findings indicate that the underlying

![Diagram of sleep stages and their associated EEG and EMG signals](image-url)
mechanisms, though still unknown, require postsynaptic action potentials.

To summarize, there are several intriguing findings that support a role for sleep in brain development. Although the interpretation of some of these studies is complicated by the use of prolonged sleep deprivation or secondary effects of electrolytic lesions, they suggest that sleep influences the early formation of neural circuitry and its subsequent sculpting by experience. Unfortunately, very few of these results have been replicated by independent laboratories, and only a handful of scientists are currently engaged in this line of research, even though a role for sleep in brain development was first hypothesized 40 years ago. In 1966, when Roffwarg and others first proposed such a role for sleep, much less was known about how endogenous neural activity, intercellular molecular signals, and experience shape developing circuitry. The situation has changed, and the proposal is no less interesting and important today than it was decades ago. As will be discussed further, a rapprochement between sleep and developmental neurobiology is not only timely but also may ultimately reveal precisely how sleep influences brain plasticity.

**Summary of Current Findings**

There is now behavioral, electrophysiological, cellular, and molecular evidence to support the hypothesis that sleep facilitates memory consolidation and brain plasticity. These myriad findings, however, have not been integrated in a manner that reveals by what mechanism sleep may achieve these functions. Part of the problem resides...
in the wide variety of experimental paradigms used in both humans and animals. A more salient issue is that each particular approach in isolation has limited utility. For example, even if the inconsistencies in experimental findings are eventually resolved, sleep and learning studies alone cannot reveal what happens in the sleeping brain that promotes memory consolidation. Likewise, although physiological studies have identified interesting changes in gene expression or neuronal activity in sleep or following sleep deprivation, most have not shown that these changes are functionally important for plasticity or learning. At present, only a handful of studies have attempted a more integrated approach, and these have been primarily limited to human learning studies (in which cellular mechanisms can only be grossly investigated) or rodent LTP (Frank 2006; but see below). Thus, the current situation is at once tantalizing and frustrating; it appears that many single threads of evidence exist in support of the hypothesis, yet they have not been woven into a seamless whole that irrefutably demonstrates a role for sleep in brain plasticity.

Dreaming of Integrative Models of Sleep-Dependent Plasticity

A truly integrative approach to the problem should incorporate the following criteria. First, it should focus...
on a type of plasticity that occurs in the intact brain because this would potentially allow one to measure changes in neural circuitry as they occur in natural sleep. Second, the type of plasticity should be physiologically meaningful, with known behavioral outputs that have adaptive significance. For example, several studies have shown that sleep and sleep loss modify hippocampal LTP induced by high-frequency stimulation of postsynaptic neurons, yet the adaptive significance of these findings is unclear. Naturally occurring LTP and LTD may be driven by more subtle forms of activity, and in some cases in vitro LTP/LTD is unrelated to plasticity in vivo (Malenka and Bear 2004). Third, the type of plasticity examined should be reasonably well understood on a cellular level so that one can examine the contribution of specific and well-characterized cellular signaling pathways in sleep-dependent synaptic remodeling. Fourth, the plasticity should be rapid; that is, it can be triggered over a relatively short period of time, thus allowing one to use very modest manipulations of sleep and wake in an experimental design. Last, the results should reveal basic principles by which sleep affects brain plasticity more generally. That is, the mechanisms revealed in this system should provide insights into how sleep influences plasticity in other parts of the brain and at different stages of life.

We believe that the study of ocular dominance plasticity in the developing visual system is especially promising because it satisfies the first four of these criteria and in time may satisfy the last. Ocular dominance plasticity occurs in the intact, unanesthetized brain and is triggered by natural forms of stimuli (i.e., changes in vision as opposed to artificial trains of action potentials). It is associated with behavioral outputs that have adaptive significance for the animal (stereoscopic vision and acuity) and is well described on a cellular level. Changes in ocular dominance occur within hours, which allows for minimal manipulations of sleep and wake in the experimental design. Last, the study of ocular dominance plasticity has provided important insights into synaptic plasticity in other sensory systems and has recently been shown to persist beyond the classic critical period of development (albeit in slightly different forms; He and others 2006). Therefore, by demonstrating a role for sleep in this system, one may eventually unlock the deeper mystery of how sleep interacts with specific cellular and molecular plasticity mechanisms across the life span and in many parts of the brain. A similar approach may be feasible in other sensory systems that also exhibit well-described forms of plasticity in vivo, such as somatosensory barrel cortex in rodents or auditory cortex (Berardi and others 2000).

Concluding Remarks

We cannot emphasize strongly enough the importance of resolving the current controversy regarding sleep’s purported role in memory consolidation and synaptic plasticity. Determining the function of sleep is one of the biggest unsolved problems in neuroscience today, and learning-related functions of sleep are among the most actively investigated candidate functions. If proponents of these functions are on the right track, then we stand to gain considerable insight into the nature of the vertebrate nervous system by determining how neural activity in sleep facilitates the remodeling of neural circuits. But to do so, we need to establish broadly applicable model systems that produce consistent experimental results and that link sleep-dependent changes in behavior with identifiable physiological processes on the cellular and molecular level. It is only through such an approach that we will move past an increasingly sterile debate and toward hard proof that supports or refutes this most intriguing hypothesis.

References
