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# A refined model of sleep and the time course of memory formation

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**Abstract:** Research in the neurosciences continues to provide evidence that sleep plays a role in the processes of learning and memory. There is less of a consensus, however, regarding the precise stages of memory development during which sleep is considered a requirement, simply favorable, or not important. This article begins with an overview of recent studies regarding sleep and learning, predominantly in the procedural memory domain, and is measured against our current understanding of the mechanisms that govern memory formation. Based on these considerations, I offer a new neurocognitive framework of procedural learning, consisting first of acquisition, followed by two specific stages of consolidation, one involving a process of *stabilization*, the other involving *enhancement*, whereby delayed learning occurs. Psychophysiological evidence indicates that initial acquisition does not rely fundamentally on sleep. This also appears to be true for the stabilization phase of consolidation, with durable representations, resistant to interference, clearly developing in a successful manner during time awake (or just time, per se). In contrast, the consolidation stage, resulting in additional/enhanced learning in the absence of further rehearsal, does appear to rely on the process of sleep, with evidence for specific sleep-stage dependencies across the procedural domain. Evaluations at a molecular, cellular and systems level currently offer several sleep specific candidates that could play a role in sleep-dependent learning. These include the upregulation of select plasticity-associated genes, increased protein synthesis, changes in neurotransmitter concentration, and specific electrical events in neuronal networks that modulate synaptic potentiation.

**Keywords:** consolidation; enhancement; learning; memory; plasticity; sleep; stabilization

## 1. Introduction

The cognitive neuroscience of sleep has undergone a remarkable resurgence in recent times. A significant proportion of work has focused on the role of sleep in relation to learning and memory. There is now a large body of data describing the dependence of certain types of learning on sleep, already complemented by cellular and molecular theories (Benington & Frank 2003; Graves et al. 2001; Sejnowski & Destexhe 2000; Steriade 1999; Tononi & Cirelli 2001). However, the field remains considerably divided, with some supporting and some repudiating the role of sleep in memory consolidation (Maquet 2001; Siegel 2001; Smith 2001; Stickgold et al. 2001; Vertes & Eastman 2000). As a result, there is still a lack of consensus regarding the precise stage or stages of memory development where sleep is considered important or unimportant.

I will begin by discussing the basic characteristics of sleep and memory formation, then consider evidence regarding the role of sleep in the process of memory development, focusing primarily on procedural learning. Based on these data, I will propose a new neurocognitive framework that separates out several discrete stages of memory formation, demonstrating the existence of at least two specific forms of consolidation following memory acquisition; one of *stabilization* and one of *enhancement*. Using this new model, we can consider three issues: (1) at what stage of memory formation is sleep important? (2) what types of sleep are important? and (3) what are the candidate biological mechanisms underlying sleep-dependent learning? By presenting this heuristic model, I firstly hope that a more clear understanding of memory stage development can be agreed on. Secondly, such discussions may also help move away from an all-or-nothing contemplation for the role of sleep in memory formation, and instead, shift to a more subtle conception of how wake, sleep, and time can all play their parts in acquiring, stabilizing, and enhancing memory representations.

### *1.1. Sleep architecture and neurobiology*

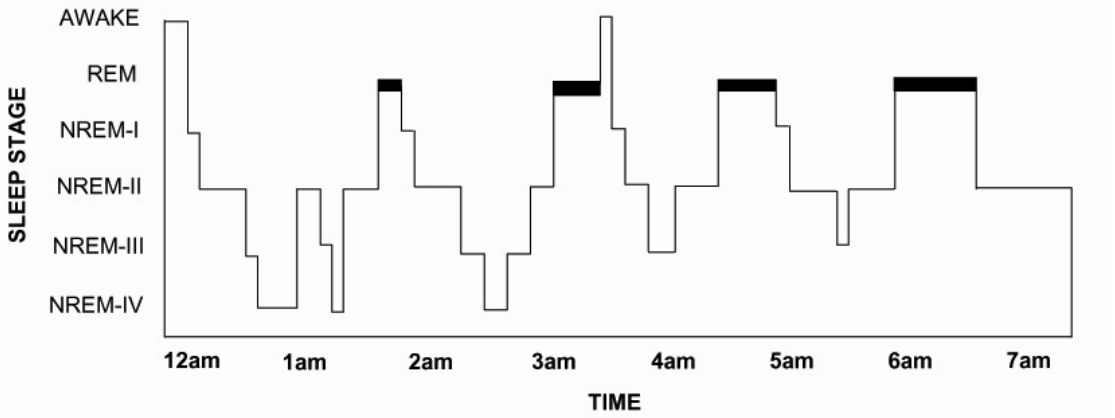
Human sleep has been broadly classified into two distinct types; non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, with NREM sleep being further divided into four substages (1–4) corresponding in that order to increasing depth of sleep (Rechtschaffen & Kales 1968). REM and NREM sleep alternate across the night in an ultradian pattern every 90 minutes, with NREM sleep (particularly stages 3 and 4) dominating the first half of the night, while REM sleep and stage 2 NREM sleep prevail in the latter half of the night (Figure 1).

During the descent into NREM sleep, electroencephalographic (EEG) activity begins to slow, with a dominance of theta activity (4–8 Hz) in the early stages. Throughout stage 2 NREM, there is also the presence of phasic electrical events including K-complexes (large electrical sharp waves in the EEG) and sleep spindles (short synchronized EEG waveform oscillations in the frequency domain of 7–14 Hz) (Steriade & Amzica 1998). Stages 3 and 4 NREM are often grouped together under the term "slow wave sleep" (SWS) because of the occurrence of high amplitude waves in the delta range (0.5–4 Hz) and below (<1 Hz), an expression of underlying cortical synchrony (Amzica & Steriade 1995).

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

The changes in brain electrical activity across different REM and NREM sleep stages are accompanied by distinct patterns of functional anatomy. During NREM SWS, rostral brain stem regions, thalamic nuclei, basal ganglia, prefrontal and cingulate cortices, together with medial regions of the temporal lobe all show decreased activity relative to waking (Braun et al. 1997; Maquet et al. 1996). In contrast, during REM sleep, significant elevations in activity are seen in the pontine tegmentum, thalamic nuclei, occipital cortex, mediobasal prefrontal lobes, and limbic regions including the amygdala, hippocampus, and anterior cingulate cortex relative to waking and NREM SWS (Braun et al. 1997; 1998; Maquet et al. 1996; Nofzinger et al. 1997). At the same time, the dorsolateral prefrontal cortex, posterior cingulate, and parietal cortex show even greater decreases in activity during REM sleep compared with both NREM and waking (Braun et al. 1997; Maquet et al. 1996)

Throughout the respective sleep stages, the brain also undergoes dramatic alterations in neurochemistry. In NREM sleep, subcortical cholinergic systems in the brain stem and forebrain become markedly less active (Hobson et al. 1975; Lydic & Baghdoyan 1988) while firing rates of serotonergic raphé neurons and noradrenergic locus coeruleus neurons are also reduced relative to waking levels (Aston-Jones & Bloom 1981; Shima et al. 1986). During REM sleep, both these aminergic populations are strongly inhibited while cholinergic systems become as active or more active compared with wake (Kametani & Kawamura 1990; Marrosu et al. 1995), resulting in a brain state largely devoid of aminergic modulation and dominated by acetylcholine. A summary of these physiological sleep characteristics is presented in Figure 1.




| Sleep Stage | Electrophysiology | Neurochemistry | Functional anatomy |
|---|---|---|---|
| **NREM:** Stage I<br>Stage II<br>*SWS* { Stage III<br>Stage IV | - Loss of α-EEG<br>- Spindles/k-complex<br>- Slow wave synchronous EEG | Aminergic & cholinergic conc. LOW | ↓ Activity in pons, thalamic, limbic, frontal, temporal regions |
| **REM:** | - Increased EEG frequency<br>- PGO waves<br>- Muscle atonia | Aminergic conc. LOW, cholinergic conc. HIGH | ↓↓ Activity in lateral pre-frontal cortex, ↑ activity in visual, medial frontal, limbic system, anterior cingulate. |

Figure 1. The sleep cycle and respective biological properties.

Across the night, NREM and REM sleep cycle every 90 minutes in an ultradian manner, although the ratio of NREM to REM sleep shifts so that early in the night stages 3 and 4 of NREM dominate, while stage 2 NREM and REM sleep prevail in the last 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, and slow delta waves developing in NREM SWS (slow wave sleep). Synchronized electrical events are also proposed in REM sleep, expressed in the pons (P), geniculate nuclei of the thalamus (G), and the occipital cortex (O), termed *PGO waves.* In addition, significant changes in neurochemistry take place across the sleep cycle. Relative to the wake state, activity of aminergic and cholinergic neurons is reduced during NREM. During REM sleep, aminergic activity continues to fall, while activity of cholinergic neurons now returns to similar levels observed during the wake state. The functional anatomy of sleep is also nonhomogeneous, with NREM SWS exhibiting marked deceases in activity throughout subcortical regions important for arousal as well as regions of the limbic system. However, in REM sleep, areas of the occipital and medial frontal cortices increase in their activity, together with the anterior cingulate and temporal lobe structures, while lateral regions of the prefrontal lobe undergo continued decrease in activation.

## 2. The time course of learning and the contributions of different brain states

### *2.1. Memory systems in the brain*

The process of acquiring information (such as facts, experiences, actions, skills, etc.) and modifying that knowledge over time can be considered the process of memory formation, expressed behaviorally as learning. Once developed, the size of the mammalian cerebral cortex is largely fixed, placing anatomical and functional limitations on information storage (Kass 2000). Therefore, to maintain the ability for continued memory formation, the adult cortex must, by necessity, continually modify its central representations in a dynamic balancing act to ensure that the most salient information is retained and available in the organisms behavioral repertoire.

A widely accepted mechanism of memory formation is brain "plasticity," a lasting change in neuronal properties (such as structure or function) in response to a stimulus (such as an experience). There now exists an abundance of mechanisms that can provide the foundation of brain plasticity, ranging from the reorganization of cortical networks at a macroscopic level, to the disinhibition of existing circuitry, the modification of synaptic strengths, and the structural remodeling of synaptic connections at a microscopic level (Buonomano & Merzenich 1998; Martin et al. 2000; Pascual-Leone 2001).

While several theories have offered common underlying mechanisms of memory, it is important to note that memory is not a single entity, at least not in humans. Human memory has been subject to several different classifications, many of which include discrete neuroanatomical regions. The most popular of these taxonomies is based on the distinction of declarative versus nondeclarative memory (for review see Squire & Zola 1996).

Declarative memory may be considered as the conscious memory for fact-based information (i.e., knowing "what"), and is usually acquired with relatively few exposures

to the information, such as just one or two readings of a text, or one exposure to an event. Several subcategories of the declarative 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) (Tulving 1972). Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, including the hippocampus (Eichenbaum 2000), which is thought to form a temporally ordered retrieval code for neocortically stored information.

In contrast, non-declarative memory can be regarded as non conscious. The non-declarative category includes procedural memory (i.e., the knowing "how"), such as the learning of actions, habits, and skills, as well as implicit learning, which is characterized as a passive process involving the acquisition of knowledge simply through exposure (Dienes & Perner 1999). Procedural learning of perceptual and motor skills often requires longer periods of acquisition compared to declarative memory, and is usually achieved through periods of performance repetition. The neural structures involved in procedural learning are diverse, involving both cortical and subcortical networks. While different perceptual-motor skills may share some anatomical commonalities, the networks modulating specific kinds of procedural learning are often defined by the sensory (input) and motor (output) demands of the task (e.g., Grafton et al. 1998; Jancke et al. 2001; Karni et al. 1995; Schwartz et al. 2002).

### *2.2. The current status of sleep, learning, and memory*

The idea that sleep may participate in the process of learning and memory formation is not new. Some of the earliest evidence was provided by researchers such as David Hartley (1801) and Jenkins and Dallenback (1924) indicating that the strength of a memory representation ("trace") maybe more preserved by periods of sleep compared with equivalent periods of time awake. Following the discovery of discrete sleep stages (Aserinsky & Kleitman 1953), research investigating the influence of sleep on memory has become gradually more complex at both a behavioral and mechanistic level.

Studies using animal models have provided evidence for the role of sleep in primarily hippocampal dependent tasks; although these cannot be classed as declarative since no "declaration" as such can be made. Learning of spatial tasks and avoidance paradigms during waking have been shown to trigger alterations in proceeding sleep stage characteristics, relative to sleep periods without prior learning (Ambrosini et al. 1992; Datta 2000; Hennevin & Hars 1987; Mandile et al. 2000; Smith et al. 1980). Furthermore, sleep deprivation following task acquisition can result in learning impairments at future retests (Beaulieu & Godbout 2000; Fishbein et al. 1974; Hennevin & Hars 1987; Marti-Nicolovius et al. 1988; Oniani et al. 1987; Pearlman 1969; Shiromani et al. 1979; Smith & Kelly 1988; Smith & Lapp 1986). It is important to note, however, that a proportion of this early animal literature has been criticized for its lack of control regarding the confounds of sleep deprivation (Siegel 2001; Vertes & Eastman 2000). More recently, however, refined experiments have also demonstrated that selective deprivation of specific sleep stages, and even specific sleep-stage time windows, can cause significant deficits in memory consolidation (Smith & Butler 1982), as opposed to long durations of deprivation which may cause nonspecific effects on memory recall.

The majority of early work investigating sleep and learning in humans focused on classical tests of declarative memory (for detailed review see Peigneux et al. 2001a; Smith 2001). These findings offered mixed and contradictory conclusions, some in support of sleep-associated learning; others starkly against any role for sleep in memory formation. For example, Meienberg et al. (1977) found no evidence of altered posttraining sleep architecture following learning of a verbal memory task. However, De Koninck et al. (1989) demonstrated significant increases in posttraining REM sleep after intensive learning of a foreign language, with the degree of successful learning correlating with the percentage increase of REM sleep. Similar inconsistencies have been reported in the degree to which intensive learning experiences during wake can alter subsequent sleep-stage properties, as well as the learning impairments that follow selective sleep deprivation (Chernik 1972; Empson & Clarke 1970; Lewin & Glaubman 1975; Meienberg 1977; Plihal & Born 1997; Zimmerman et al. 1970; 1978).

This lack of agreement between studies may reflect inappropriate retest schedules. Alternatively, it may be a consequence of the significant differences in task characteristics, such as the degree of experimental difficulty (Empson & Clarke 1970; Tilley & Empson 1978), or the emotional salience of the test (Wagner et al. 2001), each of which may drive sleep dependency. An examination of different declarative memory categories, including episodic and semantic forms has also not been fully investigated (Cipolli & Salzarulo 1980), and may add further to the apparent contradictions in the degree to which sleep is or is not important.

It is also possible that the effects of sleep on declarative memory are more protracted, making the identification of sleep-dependent learning more difficult to measure. For example, the influence of sleep on declarative memory could be one of subtle maintenance, preventing decay over time. Therefore, retesting memory several days or weeks following sleep deprivation, rather than the next day, could prove a more informative measure of long-term retention. However, Smith et al. have tested subjects' retention for declarative material one week after first-night selective or total sleep deprivation following encoding (Smith 1995), still reporting no evidence of impairment.

Regardless of the reasons, a clear understanding of the role of sleep in declarative memory formation remains to be established in humans, and represents a significant challenge to researchers in the field of sleep and memory.

In contrast to the declarative system, evidence for the reliance of procedural memory on sleep in humans has been incredibly robust, and currently offers the most promising and informative model of sleep-dependent learning (Buchegger & Meier-Koll 1988; Fischer et al. 2002; Gais et al. 2000; Karni et al. 1994; Smith & MacNeill 1994; Stickgold et al. 2000a; 2000b; Walker et al. 2002, 2003b). In the light of this consistency, we will now focus on recent advances in understanding the specific stages of procedural memory development, and discuss the differing contributions that time, wake, and sleep offer.

### *2.3. Behavioral stages of procedural memory formation: a contemporary model*

Memory formation does not transpire as a solitary event, but instead evolves in several discrete stages (McGaugh 2000; Schacter & Tulving 1994). Classically, the process of memory formation is considered to develop in a time-dependent manner, resulting in a more permanent memory representation.

The time course of behavioral modification, and changes in brain plasticity, also appear to be diverse, with rapid changes on the order of seconds to minutes taking place during or soon after an experience; while more delayed changes can occur in the subsequent hours or days after that event (e.g. Igaz et al. 2002; Karni et al. 1998). In some cases, this latent phase of plasticity has been suggested to occur across weeks, but it may simply reflect the continued cycling of a process occurring across several hours or days, with repeated exposure to the specific experience in-between. Two of the most recognized stages of memory formation are the initial *acquisition* phase, followed by a *consolidation* phase.

**2.3.1. Acquisition: Behavioral time course and brain-state dependence.** In the procedural memory domain, acquisition can be measured by a specified performance level within an exposure period or a practice session. This usually requires a training interval involving repeated engagement with the procedure being learned (Rattoni & Escobar 2000). Training for procedural skills generally requires time periods ranging from several minutes to several hours. Rarely does engagement last longer since practice benefits will often asymptote, although this does not mean the capacity for learning has ended. Continued practice can not only render little additional improvement, because of system fatigue or decreased motivation and attention, but can even result in decreased performance, the effects of which can be reduced by brief periods of daytime sleep (Mednick et al. 2002). In general, acquisition itself involves learning, since behavioral performance often improves across the session, and by definition, successful acquisition corresponds to achieving a certain level of task proficiency.

*2.3.1.1. Mechanisms of acquisition and its brain-state dependency.* Rapid learning within brief training sessions, or shortly after, is presumably too fast for extensive structural change involving the synthesis of new proteins, and the formation of new synapses. Instead, a common mechanism underlying acquisition may be the disinhibition, or "unmasking," of already existing cortical connections. Using regional blockade of GABAergic inhibition, Jacobs and Donoghue (1991) have demonstrated the ability to rapidly disinhibit latent horizontal connections in the motor cortex, connections that are suppressed by feed-forward inhibition. Comparable effects have been described in humans using centrally acting pharmacology targeting $GABA_A$ receptors (Butefisch et al. 2000). Similar mechanisms of early learning involving the rapid alteration of intra-cortical horizontal connections have been proposed in the visual (Gilbert & Wiesel 1989; Trachtenberg & Stryker 2001), auditory (Buonomano & Merzenich 1998; Wang et al. 2000), and somatosensory cortices (Micheva & Beaulieu 1995). Such rapid removal of local inhibition would allow the fine turning of existing networks, and may explain the short-term functional and electrophysiological changes revealed at a systems level during acquisition (Müller et al. 2002; Naatanen et al.1993). At a molecular level, there is evidence that these early stages of memory formation result in the "tagging" of activity-dependent synapses (Frey & Morris 1998). As a consequence, these synaptic tags are thought to act as request signals for plasticity-related proteins that become available several hours later, meaning that only selective synaptic connections are facilitated over the long-term.

Regarding the brain-state dependency of memory acquisition, the majority of studies indicate that wake, rather than sleep, is most preferable, being a time of focused perceptual attention to external stimuli (Joseph et al. 1997), and the ability for conscious, driven motor output (e.g. Brashers-Krug et al. 1996; Karni et al. 1998; Muellbacher et al. 2002; Shadmehr & Brashers-Krug 1997). Evolutionarily, this trait for rapid improvement *during* the waking repetition of a new skill makes considerable sense, particularly if it were a beneficial procedure. It would not seem logical to have a system that requires hours or days, or periods of sleep, before the first signs of improvement emerge.

Nevertheless, this is not to say information cannot be assimilated in such a way during sleep (for recent review see Coenen & Drinkenburg 2002). Hennevin and colleagues have demonstrated that new associations can be formed when information is presented during REM sleep in rats. Furthermore, the influence of this REM sleep experience can be identified in subsequent waking behavior (Hennevin et al. 1995). At the human level, Cheour et al. (2002) have described electrophysiological evidence that human newborns are able to acquire the ability to discrimination between simple vowel sounds throughout all stages of sleep. Information not only appears to be accessible to the brain during sleep, but may be preferentially dealt with. For example, Portas et al. (2000) have provided neuroimaging data to suggest that emotionally salient auditory information (the subject's own name) is differentially processed at a higher cortical level relative to a beep tone during NREM sleep. In addition, the emotionally salient stimulus was processed in a functionally different manner in NREM sleep compared to perception of the same stimulus during wake.

Continued acquisition and further modification of information learned during prior waking also appears to be possible during sleep. Several studies (Guerrien et al. 1989; Smith & Weeden 1990) have demonstrated that auditory learning during waking can be further modified by presentation of similar auditory cues during phasic REM sleep periods (REM sleep epochs with eye movements), leading to improved waking performance. No such learning occurred during episodes of tonic REM (REM sleep epochs without eye movements).

Although intriguing, there would seem to be little advantage offered by the sleep state compared with wake for the acquisition of information, apart from perhaps a reduction in the number of competing stimuli likely to occur. Furthermore, just because acquisition can take place during sleep does not necessarily mean sleep serves that purpose. This would also seem to be the most parsimonious explanation, considering that most species seek a sleep location based not only on its degree of safety but its reduced degree of sensory stimulation, dramatically decreasing the amount of information available for learning.

**2.3.2. Consolidation: Behavioral time course and brain-state dependence.** The early changes in both behavior and neural dynamics during acquisition are often fragile and vulnerable to interference. Additional changes are required before the newly formed memory becomes more permanent. Following acquisition of a procedural skill, it is widely accepted that a specific map of that information, or *representation,* is formed within the brain. This representation appears to undergo several stages of modification, although classifying these stages can be problematic depending on the tool of measurement, for example, behavioral, neurophysiological, molecular, and so on.

On successful completion of acquisition, a slowly developing process, termed *consolidation,* is believed to evolve. Classically, consolidation has referred to a process whereby a newly formed memory becomes increasingly less susceptible to interference from a variety of amnesic agents such as trauma or experimental interventions such as electroconvulsive shock (for recent review see McGaugh 2000). Indeed it is the degree of stability or resistance to interference that is usually taken as the defining measure of successful consolidation.

Until recently, the process of consolidation was considered to evolve with the simple passage of time, albeit requiring many underlying biological mechanisms (Figure 2A). However, several new studies suggest that consolidation of procedural memory is not simply determined by *time* per se, but instead, is more strictly determined by time spent in specific brain states such as wake or sleep, or even certain stages of sleep (Brashers-Krug et al. 1996; Fischer et al. 2002; Gais et al. 2000; Karni et al. 1994; Muellbacher et al. 2002; Shadmehr & Brashers-Krug 1997; Stickgold et al. 2000a; 2000b; Walker et al. 2002; 2003b). Yet this premise rests critically on one issue: the definition of consolidation. Based on new psychophysical data, I propose here that consolidation in the procedural domain can be separated into at least two different behavioral (and possibly mechanistic) stages (1) *Consolidation-based stabilization* (CBS) and, (2) *Consolidation-based enhancement* (CBE). This contemporary model is outlined in Figure 2B. Previously, the concept of consolidation as stabilization or enhancement has been

suggested in an "and/or" proposition (Abel & Lattal 2001; Hoffman & McNaughton 2002), but a clear separation has never been outlined. As will be discussed, not only does this definition offer a new behavioral framework of procedural memory formation, it can help in dissociating wake or time-dependent learning from sleep-dependent learning.

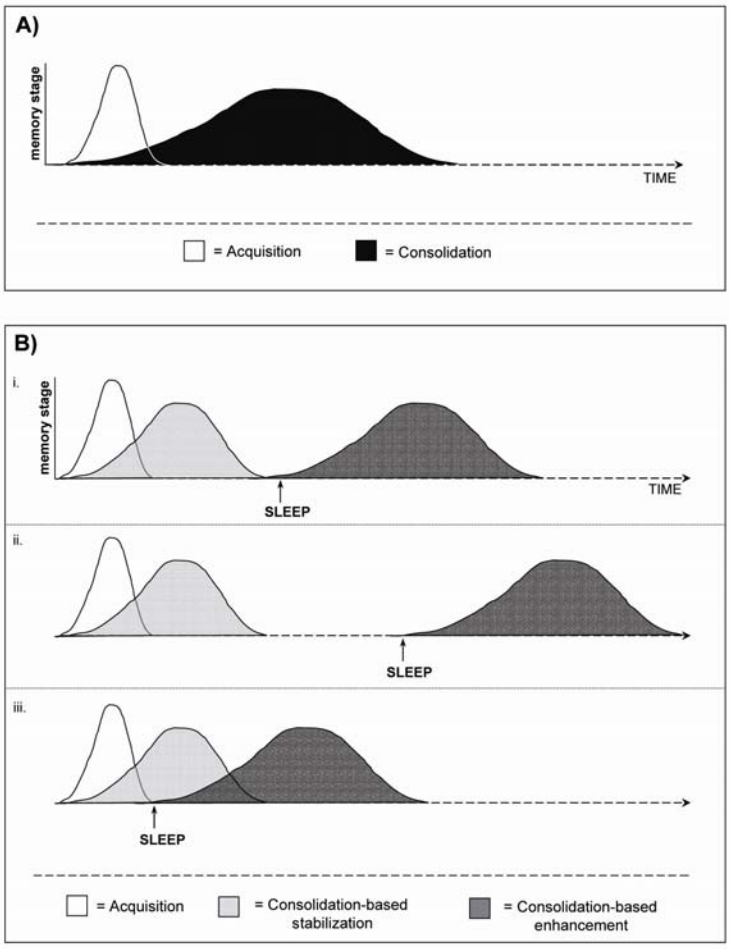



Figure 2. Classical and new models of procedural memory stage formation

(A) *Classical, time-dependent course of memory formation*: The process of memory formation begins with an acquisition stage involving engagement with an experience or task to be learned, resulting in a specific memory representation in the brain. By the end of this experience or shortly after, an additional stage of consolidation evolves in a time-dependent, but not brain-state–dependent manner. Following the passage of a specific time period, information learned during acquisition is now retained in a more permanent form.

(B) *Contemporary brain-state–dependent course of memory formation*: In this alternative model, the process again starts with an acquisition stage requiring a period of exposure to the task or experience. Following or during acquisition, another time-dependent (but not sleep-dependent) mechanism occurs, involving a process of consolidation-based stabilization. As a result, the memory representation is now resistant to interference, while behavioral performance (learning) is maintained, but not improved. However, only during periods of sleep can the additional process of consolidation-based enhancement, a brain-state–dependent process, take place, regardless of whether this is immediately after acquisition (i), or several hours later (ii & iii). As a consequence, behavioral performance indicates additional learning over and above that achieved during acquisition.

*2.3.2.1. Consolidation-based stabilization.* As noted, consolidation has historically been considered the conversion of a memory representation from an initially labile state to a more stable form, allowing information to be retained after a set period of time. Although a specific representation may have become resistant to disrupting or competing factors, this process is one of *maintenance* only, simply permitting the same expression of performance level to that accomplished during acquisition, no more.

There are now several studies demonstrating that a process of consolidation-based stabilization (CBS) can be effectively achieved during periods of wake, without requiring sleep. Using procedural visual and motor skill tasks, Stickgold et al. (2000b) and Walker et al. (2002; 2003b) have outlined the time course of behavioral improvement across subsequent periods of wake (and sleep; see below) following task acquisition. In these studies, time periods of 3–12 hours of intervening wake offered no improvement in skilled behavioral performance level on either task, only maintenance. Although not specifically testing memory stability by way of interference probes, these examples first indicate the preservation of learning across periods of wake without decrement, and second demonstrate the lack of any additional learning attributable to the passage of waking time.

Muellbacher et al. (2002) have directly addressed the question of stabilization in the human brain across periods of wake using a skilled motor task. Brief periods of practice on the task produced considerable gains in performance during the training session. Following a 15 minute rest period, subjects showed retention of that same performance

level at retesting. A second group of subjects experienced an identical training session, but during the intervening 15 minute rest, underwent repetitive transcranial magnetic stimulation (rTMS) applied to the primary motor cortex; this is a technique that can interfere with local neural activity. In contrast to the first group of subjects, when retested 15 minutes later, performance had decreased back to pretraining values, suggesting that rTMS had interfered with maintenance of the motor memory. A third group of subjects were also trained on the task, but instead of receiving rTMS to the motor cortex immediately after training, received rTMS after a prolonged 6 hour waking time period. Despite being applied in the same location, when retested after this 6 hour period, rTMS now had no interference effect, with performance levels again being maintained relative to the end of training. Therefore, a process of stabilization had occurred sometime between 15 minutes and 6 hours following the end of training, and as a result, the memory representation was no longer susceptible to the interference effects of rTMS. It is important to note, however, that neither 15 minutes nor 6 hours of time awake could offer any additional learning benefit relative to the end of training, only stability and thus maintenance of performance.

An equally clear dissection of the stabilization process has been demonstrated by Shadmehr and colleagues. In the second of several experiments (see below), subjects were trained on a skilled reaching task during functional imaging of the brain (Shadmehr & Brashers-Krug 1997). When retested after 6 hours of wake (a period that had previously been shown to be necessary for stabilization) (Brashers-Krug et al. 1996), behavioral performance was again maintained, but not improved, relative to performance levels during acquisition. In contrast to the lack of change in behavior, a significantly different pattern of regional brain activation had developed, with greater recruitment of premotor, parietal, and cerebellar regions after 6 hours. These data indicate that the functional stability offered by the passage of time awake was associated with a change in the neural representation of this skill.

Collectively, this evidence suggests that periods of wake can successfully provide a time-dependent stabilization process in the first 6 hours after acquiring certain procedural

skills. Nevertheless, while the time awake is clearly not amnesic in and of itself, it does not offer the ability for any additional learning to occur, independent of rehearsal.

*2.3.2.2. Consolidation-based enhancement.* In the current model, the process of consolidation-based enhancement (CBE) posits that a specific representation is not only more stable and impervious to interference, but is now further *enhanced* following a night of sleep. As a consequence, behavioral performance indicates that *additional* learning has taken place in the absence of any further rehearsal or experience. Several studies have now established data indicative of CBE, and each example has taken place across a time period containing a night of sleep, some of which explicitly determine sleep as the causal trigger.

As discussed above, a study by Shadmere et al. (Shadmehr & Brashers-Krug 1997) illustrated that 6 hours after the end of training on a skilled motor reaching task, subjects' behavioral performance was not changed, but the pattern of functional activity observed using brain imaging was significantly different. In a prior study using the same task, Shadmere and colleagues (Brashers-Krug et al. 1996) demonstrated that the first 4 hours following training represented a susceptible time to interference from competing behavioral movements, but that after this critical time window had passed, performance could not be altered by such competition. That is to say stabilization had been achieved, similar to the study of Muellbacher and colleagues. However, instead of being retested after 6 hours (Shadmehr & Brashers-Krug 1997), or following interference (Brashers-Krug et al. 1996), a separate group of subjects were simply retested 24 hours after training without any interference challenges (Brashers-Krug et al. 1996). Following this intervening time, containing a night of sleep, subjects now displayed additional learning relative to initial training, instead of simply maintaining performance levels, as was the case after 6 hours of waking. Similar evidence of delayed learning across 24 hours following training has been shown using a skilled hand-cursor apparatus (Krakauer et al. 1999) and a sequential finger-tapping task (Karni et al. 1998).

Thus improvement or enhancement of certain motor skills continues for at least 24 hours following training, yet the relative contributions of time spent awake and asleep were still not clear. Walker and colleagues recently addressed this question (Walker et al. 2002; 2003b), again using a sequential finger-tapping motor task (Figure 3). In their initial study, subjects were trained either at 10:00 a.m. or 10:00 p.m. and then retested at subsequent intervals across 24 hours. Initial practice on the motor skill task improved performance by nearly 60% within the training session for all groups equally, regardless of time of day. However, subjects went on to demonstrate remarkably different time courses of subsequent motor skill improvement, specifically dependent on sleep. Subjects trained at 10:00 a.m. showed no significant improvement when retested later that same day at 10:00 p.m., after 12 hours of wake (Figure 3, A & B). Yet when retested a second time at 10:00 a.m. the next morning, following a night of sleep, subjects now showed an average 20% improvement in speed and a 39% improvement in accuracy. Subjects trained at 10:00 p.m. demonstrated equally large significant improvements at 10:00 a.m. the next morning in both speed and accuracy, just 12 hours post training, following sleep, but showed no significant additional improvement after a further 12 hours of wake at 10:00 p.m. later that day (Figure 3, C & D). An alternative explanation of these results was that motor activity during the wake period prevented motor skill consolidation, and sleep was therefore simply a passive time of hand-rest allowing enhancement. To eliminate this possibility, an additional group of subjects were trained at 10:00 a.m. and then wore mittens for the duration of the waking interval to prevent skilled finger movements before being retested at 10:00 p.m. Yet again, the waking episode, with total hand rest during the day, resulted in no significant improvement in performance, and actually led to an increase in errors, while large improvements were again seen after the night of sleep.

Significant delayed improvement was therefore seen only across a night of sleep and not over an equivalent period of wake, regardless of whether the time awake or time asleep came first. Furthermore, when the degree of overnight improvement in motor skill speed was correlated with sleep-stage recordings, a significant positive correlation with the percentage of stage 2 NREM sleep was evident, particularly late in the night, further

implicating sleep in the observed learning effect. Fischer et al. (2002) have recently confirmed these findings, with the additional evidence that sleep on the first night following training is critical for these delayed improvements to develop, and that sleep during the day triggers similar performance gains to those achieved following nocturnal sleep. However, these authors reported a correlation with REM sleep and not stage 2 NREM.

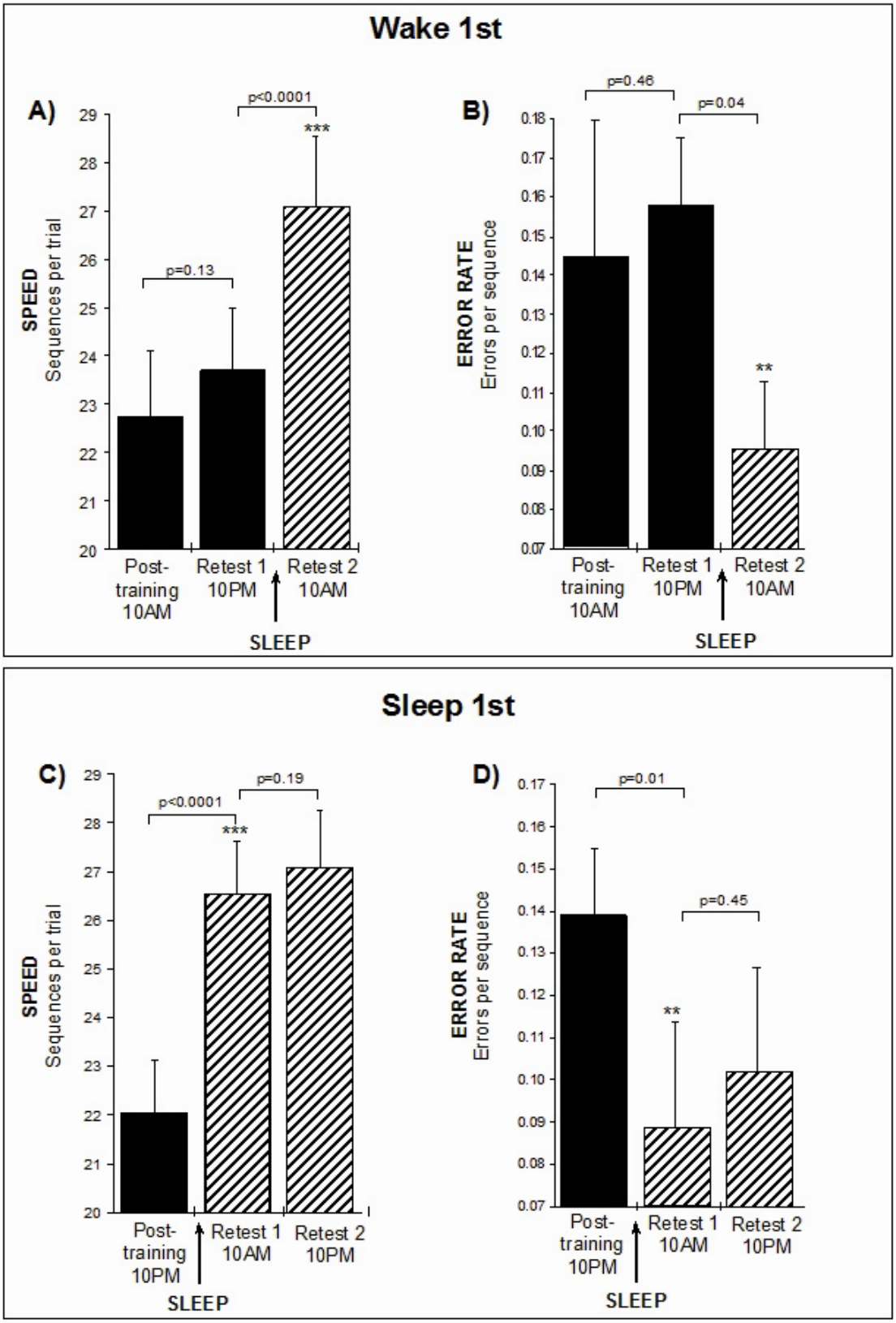

Wake 1st
A)
SPEED
Sequences per trial
p<0.0001
***
p=0.13
Post-training 10AM
Retest 1 10PM
Retest 2 10AM
SLEEP
B)
ERROR RATE
Errors per sequence
p=0.46
p=0.04
**
Post-training 10AM
Retest 1 10PM
Retest 2 10AM
SLEEP
Sleep 1st
C)
SPEED
Sequences per trial
p<0.0001
***
p=0.19
Post-training 10PM
Retest 1 10AM
Retest 2 10PM
SLEEP
D)
ERROR RATE
Errors per sequence
p=0.01
p=0.45
**
Post-training 10PM
Retest 1 10AM
Retest 2 10PM
SLEEP

Figure 3. Sleep-dependent learning on a motor skill task

(A & B) Subjects in the Wake 1st group (n=15), trained at 10:00 a.m., showed no significant change in either speed (A) or error rate (B) at the first retest following 12 hours of wake (Retest 1, filled bars). However, by the second retest, following a night of sleep (retest-2, filled hatched bars), performance improved significantly, with speed increasing by 19% and error rate decreasing by 39%.

(C & D) In contrast, subjects in the Sleep 1st group (n=15), trained in the evening (filled bars), immediately showed significant improvements in (C) speed (+20%), and (D) error rate (-36%), just 12 hours after training following a night of sleep (retest-1, filled hatched bars). Subjects displayed no further significant change in speed or error rate with an additional 12 hr of wake (Retest 2, filled hatched bars). (Modified from Walker et al. 2002; 2003b.)

Asterisks represent degree of significance.

* = *P <0.1*
**= *P <0.05*
***= *P<0.005*

Error Bars = SEM

In the second of their studies, Walker et al. (2003b) have gone on to investigate the temporal evolution of motor learning before and after sleep, the effects of different training regimens, and the long-term development of motor learning across multiple nights of sleep. These data demonstrate that overnight, sleep-dependent learning alters the capacity for rehearsal-based improvement during subsequent waking episodes, so that prior to a night of sleep, practice continues to trigger small, within-session performance benefits, but following sleep, this capacity is diminished. Secondly, doubling the duration of training does not appear to alter the amount of subsequent sleep-dependent learning. Thirdly, the amount of practice-dependent learning during training does not correlate with the amount of subsequent sleep-dependent learning, suggesting that these two stages (initial acquisition and the later sleep-dependent enhancement) are functionally distinct and regulated by different mechanisms. Finally, while the majority of sleep-dependent motor skill learning appears to occur during the first night of sleep, additional nights of sleep still offer continued improvements over time.

This pattern of sleep-dependent learning is not solely restricted to the motor system. In the perceptual domain, Karni et al. (1994) have demonstrated that learning on a visual texture discrimination task, which has been shown not to benefit from periods of 4–12 hours of wake following acquisition (Stickgold et al. 2000b), improves significantly following a night of sleep. Furthermore, Karni et al. (1994) established that selective disruption of REM, but not NREM sleep, results in a loss of this performance gain. Using the same task, Stickgold et al. (2000a) have shown that these delayed performance benefits are absolutely dependent on the first night of sleep following acquisition (Figure 4), and that the sleep-dependent gains are correlated positively with the amount of SWS early in the night, as well as the amount of REM sleep late in the night (Stickgold et al. 2000b). Also following training on this same visual skill task, Gais et al. (2000) have selectively deprived subjects of sleep early in the night (dominated by SWS), and sleep late in the night (dominated by REM and stage 2 NREM), inferring that consolidation is triggered by SWS related processes, while REM sleep may promote additional consolidation, only after periods of SWS sleep have occurred.

Although the original report of these effects demonstrated that most subjects required a night of sleep before the delayed learning was expressed (Karni & Sagi 1993), it should be noted that two out of nine subjects did display some improvement without a night of sleep, some 8 hours later. However, subsequent studies using this task have not been able to find evidence of delayed learning during wake (Stickgold et al. 2000b).

While the sleep-dependency of this visual task is now well established, the neural correlates are still relatively uninvestigated. Using functional MRI (fMRI) in humans, Schwartz et al. (2002) have recently measured brain activity 24 hours after training on the visual discrimination task. At the 24-hour retest, greater activation was observed in the retinotopic area of V1 corresponding to the trained visual field. However, these data were unable to determine whether this enhanced activity was present immediately at the end of training before sleep, or developed during the sleep period.

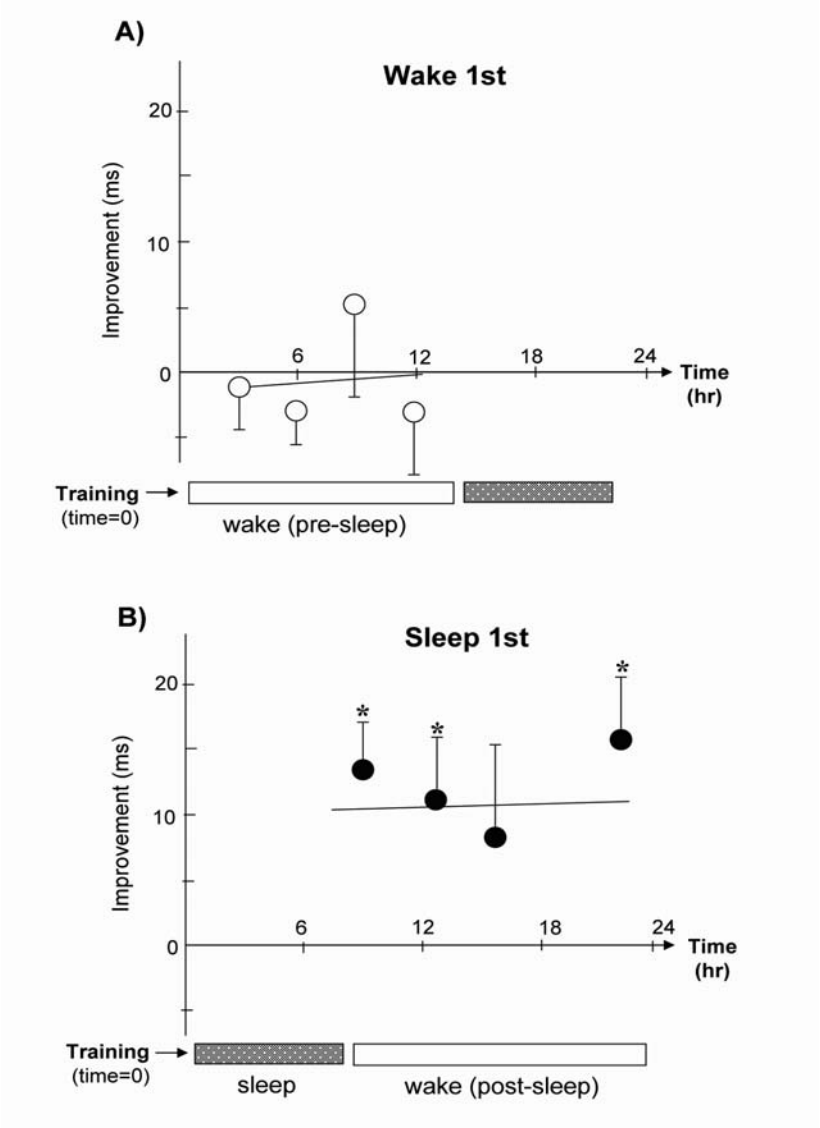



Figure 4. Sleep-dependent learning of a visual discrimination task

Subjects were trained and then retested at a later time, with the respective improvement (in milliseconds) in performance illustrated across time. Each subject was retested only once, and each point represents a separate group of subjects.

(A) *Wake 1st*: Subjects were trained and then retested either 3, 6, 9, or 12 hours later on the same day (open circles) without any intervening sleep. No significant improvement was evident as a consequence of the passage of waking time across at any of the four time points.

(B) *Sleep 1st:* Subjects were trained and then retested 8, 12, 15, or 23 hours after a night's sleep (filled circles), with a significant improvement occurring as a consequence of sleep.
In total, n=57, with n=7–9 for individual points. (Modified from Stickgold et al. 2000b.)

Asterisks represent individual groups showing significant improvement at $P < 0.001$.

Error Bars = SEM

Maquet et al. (2003) have also demonstrated evidence of sleep-dependent enhancement using a procedural visuomotor task in combination with fMRI. Subjects were trained on the task and subsequently retested three days later. Half of the subjects were deprived of sleep the first night following training, and then allowed two subsequent recovery nights of sleep before being retested. The remaining half of the subjects slept all three nights. Relative to the sleep-deprived group, subjects who slept all three nights showed both enhanced behavioral performance and a selective increase in activation in the superior temporal sulcus at the later retest, while subjects deprived of the sleep the first night showed no such change. These results are also in accordance with previous data by Smith and MacNeill (1994), demonstrating that selective late night sleep deprivation, particularly related to the loss of stage 2 NREM, can impair retention of a similar visuo-motor task.

Curiously, Eysenck and Frith (1977) have shown that, following practice on a visuomotor task, very brief periods of rest (e.g. 5–15 minutes) also result in performance enhancements relative to posttraining values without the need for sleep, an effect termed *reminiscence.* However, this rest-induced enhancement can be short lived, decreasing back to posttraining values if retesting continues for several minutes (Denny 1951). The effect of reminiscence has been considered as a form of consolidation, although alternative suggestions posit that these improvements more accurately reflect the relief of inhibitory factors that build up across training. The latter hypothesis would seem to explain why sustained retesting following the rest period quickly returns performance back to posttraining levels, arguing against instantiation of permanent learning. Of note for the current theory, there is evidence that a 24-hour rest period following training on this task (presumably containing sleep), in contrast to a 10-minute rest period, similarly enhances performance relative to the end of practice, but these improvements are instead sustainable across continued retesting, without any rapid decline over time (Holland 1963). A longer rest period, containing a night of sleep, may therefore confer a true

enhancing effect, more reflective of consolidation, rather than a temporary relief of practice-induced inhibition.

While the majority of research investigating the effects of sleep on procedural learning has so far focused on visual and motor systems, pioneering work by Atienza and colleagues have also described evidence of both time- and sleep-dependent memory development in the auditory domain (Atienza et al. 2002; 2003), suggesting that the influence of sleep maybe ubiquitous throughout perceptual sensory and motor domains.

Together, these studies show that within the procedural memory system, a process of continued (sustainable) learning can occur after training has stopped, but that this process of CBE develops only during intervening periods of sleep and not during wake.

The dependence on REM and SWS for the visual skill task is in contrast to the stage 2 NREM relationship identified in the motor domain. Such a difference may have several possible explanations. First, the degree of task complexity may be a determining factor (Tweed et al. 1999), with more complex skilled tasks showing a greater sensitivity to REM sleep deprivation, while relatively simple tasks appear more sensitive to stage 2 NREM deprivation. Second, within the procedural domain, different sleep-stage dependencies may reflect distinctions between the input (sensory/perceptual) and output (motor) roles of these systems, each of which could require functionally different brain states for effective consolidation. Indeed, if memory development is one of the many functions that sleep serves, it would seem careless *not* to exploit these multiple stages. After all, evolution has fought vehemently to preserve each of these physiologically distinct brain states, an accomplishment that has required both considerable effort and mechanistic complexity. If there are several different memory systems in the brain, why utilize only one sleep stage, such as REM? Instead, the reliance of subtly different forms of memory on different stages of sleep appears to make biologically efficient sense.

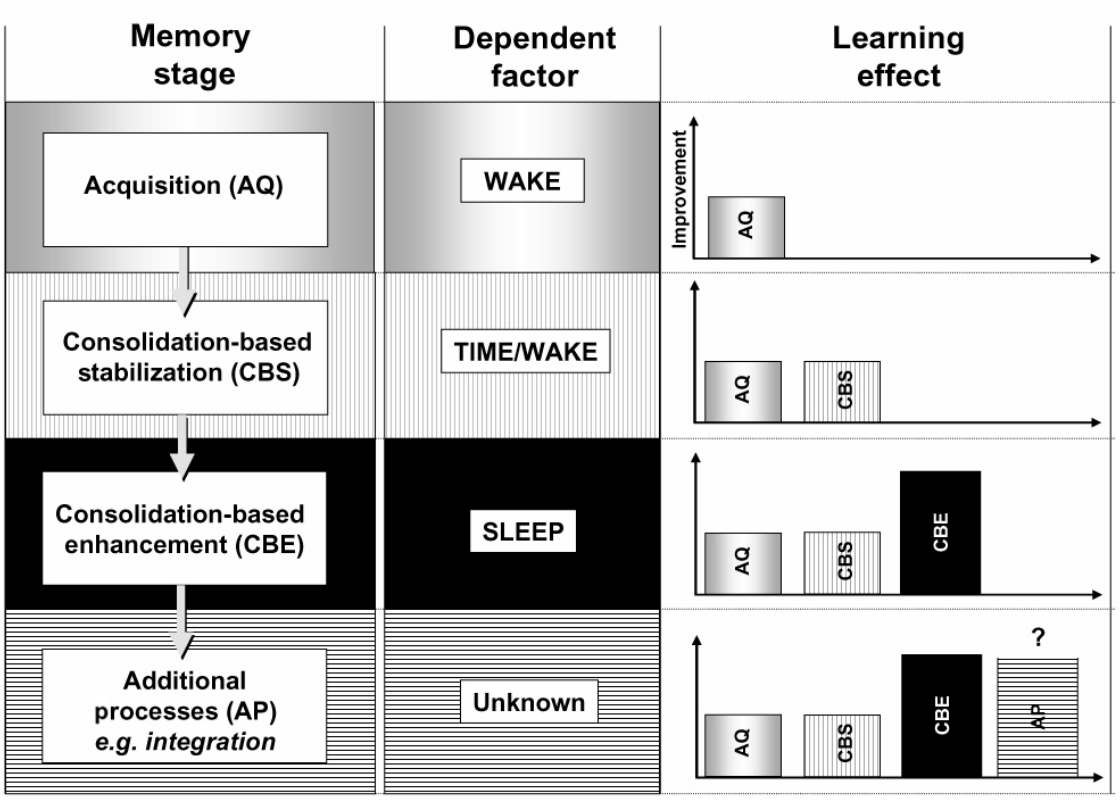



Figure 5. Procedural memory stages and the contributions of time, wake, and sleep in behavioral improvement

The initial stage of memory formation begins with acquisition (AQ), a process that occurs most commonly during waking, resulting in early behavioral improvement (learning).

Following acquisition, a process of consolidation-based stabilization (CBS) evolves in a time-dependent manner across 0–6 hours, developing efficiently during periods of being awake. As a consequence, the memory representation becomes more resistant to interference, but there is no further learning relative to the end of acquisition.

Following CBS, a process of consolidation-based enhancement (CBE) ensues. This stage of consolidation offers additional learning in the absence of further practice, and explicitly requires episodes of intervening sleep. Ancillary memory stages such as integration or reconsolidation following memory reactivation may take place either during (in parallel) or following (serial) CBS or CBE, but these additional processes (AP) are less well understood, as are the time/wake/sleep contributions.

In summary, the available evidence demonstrates the existence of two discrete stages of consolidation in the procedural memory system. The first is a process of stabilization, resulting in the maintenance of performance level, but without further learning. This stabilization process can occur effectively in a time-dependent manner across waking episodes without requiring sleep. The second process of enhanced learning involves further modification of the memory representation, resulting in additional performance gains rather than simple maintenance. This process does appear to depend on sleep. A model of the dynamics between time, wake, and sleep and different memory stages is outlined in Figure 5.

**2.3.3. The relationship to previous models of sleep and memory.** Several models of memory development that consider either time or sleep have previous been offered (Buzsaki 1998; Giuditta et al. 1995; Hasselmo 1999; Karni et al. 1998; Smith 2001; Stickgold 1998). As discussed below, the model presented here is consistent with several features of these aforementioned ideas. It also introduces several new concepts by which we are able to dissect behavioral different stages of memory and relate their dependencies to discrete brain states and time courses, the evidence for which, until recently, has not been available.

Advancing an earlier framework of Buzsaki (1998), Hasselmo (1999) has proposed a two-stage model of hippocampal episodic memory transfer based on opposing levels of acetylcholine (ACh) during wake and slow wave sleep. During wake, hippocampal levels of ACh are high, promoting a dominate flow of information into the hippocampus from the neocortex – ideal conditions for memory encoding. Then, during subsequent SWS, when ACh concentrations are low, this directional flow is reversed, and although the newly established hippocampal connections remain, novel associative connections are now established out in the neocortex. This alternating pattern of information flow during wake and sleep is therefore able to promote different network strengths throughout hippocampal and neocortical structures. In this model, the term *consolidation* refers to an

integration of newly acquired information within associative memory networks, and thus differs in its interpretation relative to the forms of consolidation proposed in the current model. While being pertinent to declarative memory, this hippocampal based model also holds less relevance to procedural memory, since learning of skilled sensory and motor tasks can occur without requiring integrity of medial temporal lobe structures (Corkin 1968; Squire et al. 1984).

Smith (2001) has argued in an impressively comprehensive manner, that simple declarative memory demonstrates no reliance on REM sleep, while procedural memory, together with a less established memory category termed *cognitive procedural memory,* does appear to require sleep for consolidation. Again, the ideas put forward in the current theory are certainly consonant with the notions of Smith, but here we separate out several unique stages of procedural memory, and relate those stages to different brain states, not only during sleep, but also across wake/time.

Giuditta (Giuditta et al. 1995), and later Stickgold (1998) have offered a two-stage model of memory development within sleep, suggesting the sequential influence of multiple sleep stages across the night. The first step towards successful consolidation takes place during SWS which predominates early in the sleep cycle. A subsequent, complementary process then develops during REM sleep, which predominates later in the night, finally completing the goal of consolidation. As can been seen, the current model does not contradict such a process; simply that the sequential hypothesis of Giuditta and Stickgold focused specifically on sleep, without detailed discussion of the differential effects of initial wake/time in producing behaviorally unique forms of consolidation. Indeed, it may be that for certain tasks (e.g., a visual discrimination paradigm), consolidation-based enhancement is achieved by a successive, early and late sleep-stage mechanism as proposed by these authors. This does not, however, appear to be the case for procedural motor learning (Walker et al. 2002).

Finally, Karni et al. (1998) have proposed an innovative model of procedural learning that also involves two successive time-dependent stages. An initial “fast” stage of

learning occurs during task engagement, similar to the acquisition stage outlined in the current theory. Following these practice-dependent improvements, a second "slow" incremental learning phase then continues for hours to weeks, which may or may not need additional task engagement to develop over the long term. In this sense, the second stage is akin to a process of general consolidation developing as a function of time per se, similar to the classical model outlined in Figure 2A. While the current model does not suggest that the tenets of this former theory are incorrect, it is uniquely different to the slow and fast learning model of Karni et al. It builds on this model both in terms of the very specific behavioral forms of consolidation that it describes – one conferring stabilization, the other enhancement – and differs also in its dissociation regarding the contributions of specific brain states and sleep stages. Based on the conception of different forms of consolidation as outlined here, it is possible to suggested that the slowest learning components described by Karni et al. over many weeks is actually the continuing cycle of task repetition followed critically by subsequent sleep and thus CBE. In this sense, there is a multiplicative effect of CBE during repeated nights of sleep with intervening task exposure over long time periods.

In summary, the model of procedural memory formation described thus far clearly supports several aspects of previously conceived theories of learning and consolidation. It also advances these concepts, adding new descriptive and mechanistic levels of memory stage formation, and separates out the unique contributions of different brain states and time.

### *2.4. Considerations on mechanisms of learning during sleep*

In the remainder of this article, I will focus on several speculative biological mechanisms, relating specifically to sleep-dependent learning, that could produce CBE. I will initially consider the basic processes that regulate synaptic modification, and follow with a discussion of several candidate mechanisms of sleep-dependent plasticity at three descriptive levels: (a) electrophysiological (b) neurochemical and (c) molecular and cellular.

**2.4.1. Regulation of synaptic plasticity.** Many neuronal models of synaptic plasticity focus on rules of Hebbian learning (Hebb 1949). While Hebbian learning remains controversial (Abbott & Nelson 2000), there is evidence that it forms at least one of the processes regulating plasticity by modulation of synaptic sensitivity, termed *potentiation* (for recent reviews see Abel & Lattal 2001; Soderling & Derkach 2000). Through the action of both neurochemical and neurophysiological signals, synapses can either be potentiated, leading to enhanced sensitivity over time (long-term potentiation – LTP) or depotentiated, leading to reduced sensitivity (long-term depression – LTD).

In the case of LTP, the release of presynaptic neurotransmitter in coincidence with the subsequent excitation of a postsynaptic action potential will strengthen a particular synapse. During this scenario, excitation of glutamate NMDA receptors allows extracellular calcium to flood the postsynaptic terminal. This triggers a variety of intracellular events such as the activation of kinase enzyme cascades, together with the release of additional intracellular calcium. As a result, key genes important to plasticity are upregulated, leading to the phosphorylation of additional receptors and enhancement of synaptic sensitivity. (Abel & Lattal 2001; Soderling & Derkach 2000).

If there is no subsequent postsynaptic action potential, or its coincidence is not tightly coupled with the presynaptic action, the synapse will instead undergo LTD. The mechanisms of LTD appear to rely on low-frequency trains of stimulation in the 0.5- to 4-Hz range (Braunewell & Manahan-Vaughan 2001; Kemp & Bashir 2001; Lisman 1989). As a result, NMDA receptors are stimulated at subthreshold levels, triggering much lower levels of calcium in the postsynaptic terminal relative to the condition of LTP. The lower concentration and prolonged calcium entry elicits a different set of chemical cascades, primarily involving phosphatase activity (Lisman 1989). Synaptic sensitivity is therefore reduced, because of dephosphorylation of postsynaptic receptors (Braunewell & Manahan-Vaughan 2001; Kemp & Bashir 2001). LTD is considered to be as important for efficient plasticity as LTP, since continued potentiation alone would eventually lead to a grossly overpotentiated and inefficient network. Subtle adjustments

of these two processes are therefore able to help regulate the synaptic anatomy of learned behaviors.

How then does the neurobiology of the sleeping brain relate to such processes? Below I consider several non–mutually exclusive mechanisms that have the potential to regulate synaptic plasticity during sleep at a variety of different levels.

### 2.4.2. Electrophysiology: Sleep oscillations, burst activity and reactivation.

Throughout the sleep cycle, both REM and NREM sleep stages contain numerous unique electrophysiological events. Many of these electrical phenomena have been implicated in the process of plasticity and learning by way of supporting mechanisms of synaptic potentiation.

Several theories have focused on low amplitude 7- to 14-Hz synchronous waveforms that propagate in thalamocortical networks, termed *sleep spindle* (Steriade et al. 1993). Steriade (Steriade 1997; 1999) and Sejnowski and Destexhe (2000) have offered learning related theories pertaining to these phasic sleep spindle oscillations, suggesting that their influence would provide strong depolarizing effects on projection targets in the neocortex, similar to spike trains normally involved in synaptic potentiation (Contreras et al. 1997; Sejnowski & Destexhe 2000). As a consequence, waves of $Ca^{2+}$ can flood into pyramidal neurons, a well recognized and highly potent trigger for plastic events that potentiate synaptic sensitivity (Soderling 1993; Soderling & Derkach 2000) (Figure 6). Indeed, Steriade and colleagues (Steriade 2001) has provided experimental evidence to show that cortical neurons driven by frequency trains similar to sleep spindles can produce lasting changes in the responsiveness of these networks. There is also indirect behavioral evidence supporting these theories. For example, in humans, Fogel et al. (2001) have demonstrated that following training on a procedural motor task, the number of sleep spindles increased by more than 40% compared with the night of sleep prior to training. Walker et al. (2002) have also demonstrated that sleep-dependent motor skill learning is correlated positively with stage 2 NREM sleep, particularly in the last quarter of the night, when spindle density peaks (De Gennaro et al. 2000).

Phasic events during REM sleep have also been associated with learning. The endogenous PGO waves of REM sleep provide a burst stimulus (300–500 Hz) throughout neuronal networks, which could triggering pronounced influxes of intracellular $Ca^{2+}$, leading to LTP (Figure 6). Datta (2000) has provided evidence that the occurrence of these REM sleep associated bursts display a strong positive relationship with successful avoidance learning in rats. Furthermore, Sanford et al. (2001) have demonstrated that fear conditioning increases the amplitude of elicited PGO waves during REM sleep in rats, indicating a homeostatic role for this REM-related event in learning related plasticity. It is also of note that PGO waves occur in a phase-locked manner with theta wave activity during REM sleep (Karashima et al. 2002). It is known that experimental burst stimulation to regions of the hippocampus at the peak of the theta phase induce LTP, but the same burst applied at the trough of the theta phase will trigger LTD (Holscher et al. 1997; Pavlides et al. 1988). As such, this PGO mechanism may serve as an endogenous mediator of synaptic regulation based on its coincidence with theta wave oscillations. Though there is some data to support the occurrence of PGO-like activity in nonhuman primates (Datta 1997), clear demonstrations of such wave forms in the human brain remain scarce (Peigneux et al. 2001b).

In contrast to the faster spindle activity or PGO bursts, slower sleep oscillations occurring in the deepest stages of NREM, expressed in the delta range (0.5–4 Hz) and below (<1 Hz), may also play a role in sleep-dependent plasticity (Sejnowski & Destexhe 2000; Steriade 1997; 1999). One possibility noted by Benington & Frank (2003) is that these slow oscillations could trigger LTD, instead of LTP. As described in section 2.4.1, synaptic depotentiation is critically regulated by low frequency stimulation trains, similar to the oscillations of SWS (Barr et al. 1995; Kourrich & Chapman 2003). The prolonged bouts of SWS activity during early night sleep may result in subthreshold stimulation of NMDA receptors, leading to the events of LTD (Figure 6). Yet this does not necessarily mean that a memory is being "erased." Instead, early night slow wave activity has the potential to actually refine and restructure neural circuits by way of synaptic depotentiation in the endeavor of *improving* synaptic efficiency. For example, a memory

representation established during waking may be unrefined in its early form. Subsequent SWS would selectively depotentiate unnecessary synapses in this verbose network, leaving only the required connections necessary for efficient use. The remaining connections would then be available for LTP during later REM or stage 2 NREM sleep.

Yet if these slow and fast synchronous events are primarily a distributed property throughout the brain, how do such global phenomena selectively assist a discrete network of neurons crucial to a specific "memory"? It is possible that the initial experience-dependent activity during acquisition primes these specific networks, leaving them with a heightened level of excitability which carries over into sleep. As such, these networks would be passive selectivity by their increased responsivity over those that had not previously been subject to waking experience-dependent activity.

At a systems level, several studies have demonstrated that the collective neuronal firing patterns recorded in the hippocampi of rats during the performance of spatial maze running are replayed during subsequent SWS and REM sleep episodes, albeit at relatively different temporal speeds (Louie & Wilson 2001; Poe et al. 2000; Skaggs & McNaughton 1996; Wilson & McNaughton 1994). In a similar paradigm, Dave and Margoliash (2000; Dave et al. 1998) have shown that waking patterns of premotor activity during song learning in the zebra finch, are replayed in a temporally and structurally similar manner during sleep.

Related evidence of neural reactivation has also been described following learning of an implicit motor task in humans. Using PET imaging, Maquet and colleagues have demonstrated that patterns of brain activity elicited when subjects practice a motor memory reaction time test prior to sleep, reappear during subsequent REM sleep episodes, while no such replay is seen in control subjects who received no daytime training (Maquet et al. 2000). Most important, when retested the next morning, subjects' performance had improved significantly relative to the evening training sessions, although there was no report that the degree of reactivation correlated with the amount of subsequent performance improvement the following morning.

These studies suggest that sleep-dependent neuronal replay is expressed throughout different memory domains including medial temporal lobe structures and procedural motor systems, as well as across different species. While there is only limited proof that these reactivations provide beneficial effects on postsleep retest performance at the human level, the function of such replay is hypothesized to allow for the adaptation of synaptic strengths within specific networks. Based on the current understanding of LTP mechanisms, is seems likely that this reactivation of pre- and postsynaptic terminals in close synchrony during sleep would trigger robust potentiation within local networks (Figure 6).

**2.4.3. Neurochemistry: Relative ratio of aminergic to cholinergic modulation.** The alternation of NREM and REM sleep is driven by marked fluctuations in the concentration of central cholinergic and aminergic neuromodulators. A substantial amount of data, independent of the sleep field, has also demonstrated the critical involvement of these transmitters in the regulation of activity-dependent synaptic plasticity (for reviews, see Foehring & Lorenzon 1999; Gu 2002).

These neuromodulators can modify the responsiveness of glutamatergic neurons by first resetting excitatory thresholds (via increasing transmitter release or postsynaptic responses) (Brocher et al. 1992; Kirkwood et al. 1999) and second triggering intracellular second messengers as a result of raised intracellular $Ca^{2+}$ levels, up regulating gene expression (Abel & Lattal 2001; Kandel 1991).

Concentrations of these neuromodulators, particularly acetylcholine, are low during NREM relative to waking. However, during REM sleep, there is a significant increase in cholinergic tone, which has been considered to play a role in sleep-dependent plasticity. For example, Graves and colleagues (Graves et al. 2001) have postulated a plasticity role for raised cholinergic activity during REM sleep through the activation of muscarinic receptor subtypes that trigger intracellular kinase cascades, leading to gene expression. They also add a tentative functional role for the lowered aminergic tone during REM sleep, highlighting the fact that certain types of serotonergic receptors are negatively

coupled to kinase mechanisms. As a result, the attenuation of aminergic activity in REM sleep may also relieve serotonergic inhibition of these kinase cascades, again leading to upregulated gene expression (Figure 6).

There is also a burgeoning literature describing a role for other nontypical neuromodulators in memory consolidation such as hormonal molecules including corticoids and melatonin (Daw et al. 1991; El-Sherif et al. 2003), cytokines (Rachal Pugh et al. 2001), and even gaseous substances such as nitric oxide (Holscher 1997). While receiving little attention regarding sleep-dependent plasticity (Plihal & Born 1999), these substances also demonstrate dramatic state-dependent shifts in concentration across the wake-sleep cycle (Pace-Schott & Hobson 2002), and may have potential influences on neuronal plasticity during REM and NREM.

Although encouraging, direct evidence implicating postsleep behavioral learning associated with changes in neurotransmitter concentration during either NREM or REM sleep remains scarce. Yet, such models do provide testable hypotheses by either facilitating or blocking the actions of these neuromodulators during sleep and then investigate the postsleep behavioral consequences.

#### 2.4.4. Molecular and Cellular processes: Protein synthesis and gene expression.

A key mechanism regulating the plastic nature of neuronal structure and function is the rapid activation of genetic machinery responsible for producing a host of synaptic molecules. Pioneering work by Cirelli and Tononi has indicated that many of the known immediate early genes (IEGs) are preferentially upregulated during wake compared with sleep, concluding that these molecular components of learning may not necessarily be sleep-dependent (Cirelli & Tononi 1998; 2000a; 2000b). Nevertheless, they do not dismiss the idea of sleep-specific gene activation, since a select number of such genes were found to be upregulated in sleep. However, the function of these genes remains uncharacterized.

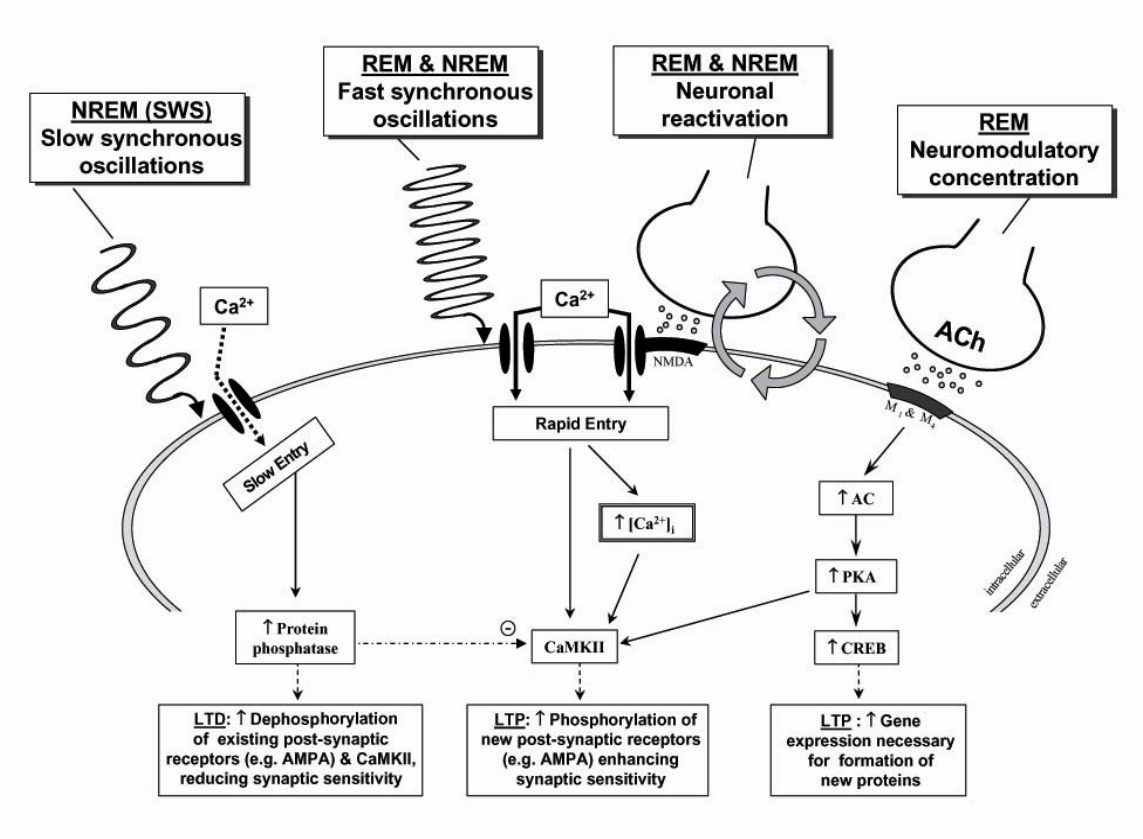



Figure 6 (Walker). Sleep-dependent influences on mechanisms of synaptic plasticity

From left to right: Low frequency synchronous oscillations (<1 Hz, and 1–4 Hz) during NREM SWS trigger slow entry of calcium ($Ca^{2+}$) into the postsynaptic cell. These conditions prompt intracellular activation of protein phosphotase enzymes, which dephosphorylate existing receptors and calcium-calmodulin dependent protein kinase (CaMKII). Together, these effects subsequently reduce neuronal sensitivity over time, resulting in long-term depression (LTD).

Faster, phasic synchronous electrical bursts during NREM, such as sleep spindles or PGO waves during REM, result in rapid, high-concentration depolarizing waves of $Ca^{2+}$ into the postsynaptic cell. The fast influx of $Ca^{2+}$ acts as a potent upregulator of CaMKII, phosphorylating new postsynaptic AMPA receptors. As a result, glutamatergic transmission is enhanced, leading to increased excitability within that circuit, and thus to long-term potentiation (LTP).
NREM and REM sleep reactivation ("replay") of local networks established during waking continues to facilitate coincident firing between pre- and postsynaptic terminals during sleep, activating glutamatergic NMDA receptors that allow rapid influx of $Ca^{2+}$. Together with the additional release of intracellular $Ca^{2+}$ ($[Ca^{2+}]_i$ ), CaMKII is again activated resulting in the above described LTP effects.

Finally, enhanced cholinergic tone during REM sleep triggers stimulation of muscarinic subtype receptors ($M_1$ and $M_4$). Subsequent intracellular signal transduction cascades begin. Activation of adenylate cyclase (AC) in turn activates proteins kinase A (PKA). PKA then activates the transcription factor cAMP response element-binding protein (CREB), a potent trigger of gene expression required for the synthesis of new proteins important for LTP.

Many of the studies profiling gene expression during sleep have done so without prior use of learning paradigms, and as such, one may therefore not expect to find evidence of learning-related, sleep-dependent gene expression. Using just such a learning paradigm, Ribeiro and colleagues have investigated the expression of zif-268, a plasticity associated IEG, in rats exposed to either rich sensorimotor experiences or benign control environments (nonexposed). As in previous studies, there was a generalized down-regulation of zif-268 during subsequent SWS and REM sleep in the nonexposed control group (although behavioral state measurements did not include surface EMG or EEG recordings). However, in the exposed group, there was a significant upregulation of zif-268 during REM sleep episodes (Ribeiro et al. 1999), indicative of increased neuronal plasticity windows during REM sleep following enriched waking experience.

Ribeiro and colleagues have also identify the temporal stage progression and anatomical specificity of zif-268 expression across intervals of wake, SWS and REM sleep following LTP induction in the hippocampus (Ribeiro et al. 2002). Interestingly they report a three-phase sequence of expression, the first of which begins soon after stimulation and peaks around 3 hour during the initial waking interval, the second during early REM sleep and the third during late REM sleep. As these stages progressed, so too did the anatomical propagation of zif-268 expression, reaching associated limbic structures during early REM, and extending to motor and somatosensory cortices in late REM. Expression of zif-268 ceased during SWS periods.

It is interesting to note the close parallels between the first wave of gene expression described by Ribeiro et al. and the initial waking stabilization time course outlined in this model, as well as the continuing expression during REM sleep and the consolidation-based enhancement stage described in this current model. Similar, discrete time windows of gene expression have been demonstrated in numerous paradigms of plasticity, suggesting the occurrence of many successive waves of gene transcription for at least 24 hours following initial synaptic stimulation (Cavallaro et al. 2002; Igaz et al., 2002). The

fact that gene transcription can continue for many hours after the initial cellular trigger means that quantifying "late" as opposed to "early" gene expression is equally critical to understanding the molecular mechanisms associated with sleep-dependent learning. This contention becomes particularly germane considering that sleep, and the associated CBE, generally occurs many hours following acquisition. Indeed, behavioral data suggest that tasks learned as much as 12 hours prior to the onset of sleep still trigger sleep-dependent enhancements in performance (Stickgold et al. 2000b; Walker et al. 2002; 2003b).

At a cellular level, the rate of cerebral protein synthesis has been positively correlated with the amount of NREM sleep in rats (Ramm & Smith 1990). Similar relationships between sleep and markers of protein synthesis have also been elucidated in numerous brain regions of the monkey (Nakanishi et al. 1997). In addition, Smith et al. (1991) have shown that administration of protein synthesis inhibitors during REM sleep windows in rats, thought to be critical for consolidation, prevents behavioral improvement following the sleep period, while groups that receive saline during this time show normal postsleep learning.

More recently, a form of sleep-dependent plasticity at a cellular level has been elegantly demonstrated during early postnatal development of the cat visual system (Shaffery et al. 1998; 1999). Brief periods of monocular visual deprivation during critical periods of development can 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 & Stryker 1993).

Frank et al. (2001) have shown that when 6 hours of monocular deprivation are followed by 6 hours of sleep, the size of the monocularity shift doubles. In contrast, if the cats are kept awake (in the dark so that there is no input to either eye) for the same 6 hours following monocular deprivation, a nonsignificant reduction in the size of the shift was observed. These studies suggest that sleep contributes as much to developmental changes in synaptic connectivity as does visual experience, presumably by modifying the initial changes which occurred during the prior period of monocular deprivation. In contrast,

sleep-deprivation results in a loss of previously formed, experience-dependent synaptic changes. Furthermore, it is not simply that a nonwaking brain state can achieve such results, since, as the authors point out, the state of anesthesia actually inhibits ocular column plasticity, in stark contrast to the effects of sleep (Rauschecker & Hahn 1987).

Complementing these findings, Shaffery et al. (2002) have demonstrated sleep-dependent modulation of plasticity in the rat visual cortex. Using electrical stimulation techniques, they have firstly been able to produce increased excitability (potentation) in specific layers of the visual cortex in young rats (up to 30 days old). After this early developmental stage, the ability to potentate these cortical layers was not possible. However, by depriving rats of REM sleep, they were able to extend this window of plasticity by as much as 7 additional days. These findings were taken to suggest that REM sleep, in conjunction with visual experience, may serve a critical function in modulating the initial course of visual cortex maturation.

Although these demonstrations of sleep-dependent plasticity were performed during the early stages of development, and any relation to mature brain function warrants caution, they represent some of the most decisive evidence yet in favor of sleep-dependent modification of cell structure and plasticity.

Therefore, while an agreement on the nature of gene expression, protein synthesis, and cellular plasticity in sleep is far from complete, the potential for sleep to trigger specific molecular and cellular events involved in synaptic plasticity clearly exists, with the relationship to behavioral learning being increasingly noted.

In summary, there appears to be a host of sleep-specific mechanisms that offer the potential for synaptic modification, based on the known mechanisms of synaptic potentation, complemented by experimental evidence of sleep-dependent plasticity at the molecular, cellular, and systems level.

## 3. Conclusions

Refined methodologies, together with increasingly detailed levels of descriptive analysis provide convergent evidence that sleep plays an important role in the processes of learning and memory formation. However, there has been significantly less of a consensus regarding the precise stage or stages of memory development where sleep is considered either a necessity, simply favorable, or not important.

This review has offered a new model of procedural learning consisting of acquisition, followed by two specific stages of consolidation, one involving a process of stabilization, the other involving a delayed or latent phase of enhanced learning. Psychophysiological evidence indicates that initial acquisition does not fundamentally rely on sleep (although demonstrations of sleep-associated acquisition do exist). This is also true for the stabilization of procedural memories, with durable representations, resistant to interference, clearly developing in a successful manner during time awake (or just time per se). However, the relative efficacy of wake and sleep in the stabilization process remains unexplored.

In contrast, the enhancing stage of consolidation resulting in additional performance improvements appears to rely on the process of sleep, with evidence for specific sleep-stage dependencies across sensory and motor domains. The factor(s) influencing the sleep-stage dependency remain somewhat unclear but may be determined by the particular sensory or motor modality of the procedural task, or the complexity of that task. Mechanistically, several candidate mechanisms that could trigger sleep-specific synaptic plasticity have been considered, ranging from the upregulation of plasticity-associated genes to the occurrence of unique electrical events throughout neuronal networks.

Separating discrete stages of memory, and identifying their relation to specific brain states, remains an essential challenge for any inclusive model of memory formation. Attempting to attribute memory processes exclusively to one single behavioral state such

as wake, or sleep, seems both intuitively misplaced and biologically inefficient. Such polarized approaches have undoubtedly contributed to the separation of those either in favor or against the role of sleep in memory, cultivated viewpoints only at each extreme. Such a separation is dangerous, and can force a once-progressive research field into a regressive state, more concerned with defense than with extension. Through distinguishing specific forms of memory, and most important, identifying unique stages of consolidation, we can begin considering a new level of appreciation of how each memory stage relates to the different brain states of wake, sleep and specific stages of sleep. In doing so, we are able to move away from the question of whether sleep is *the* key factor responsible for memory formation, and instead, begin disentangling certain confusions around the argument of exactly what sleep is or is not required for with regard to discrete stages of memory development.

While acquisition and consolidation are clearly important stages in the "life" of a memory, there are additional memory processes that have also been considered. These include the integration of recently consolidated information with past experiences and knowledge, reorganization, reconsolidation following reactivation of a memory, translocation, and even erasure of network strengths thus weakening memory representations, with which sleep has already been associated (Crick & Mitchison 1983; Hasselmo 1999; Poe et al. 2000; Stickgold 2002; Walker et al. 2003a). As our understanding of memory-stage development increases, so too should our curiosity regarding the distinct contributions that both wake and sleep may offer.

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**References**

Abbott, L. F. & Nelson, S. B. (2000) Synaptic plasticity: taming the beast. *Nature Neuroscience* 3 (Suppl.):1,178–83.

Abel, T. & Lattal, K. M. (2001) Molecular mechanisms of memory acquisition, consolidation and retrieval. *Current Opinion in Neurobiology* 11(2):180–87.

Ambrosini, M. V., Langella, M., Gironi Carnevale, U. A. & Giuditta, A. (1992) The sequential hypothesis of sleep function. III. The structure of postacquisition sleep in learning and nonlearning rats. *Physiology and Behavior* 51(2):217–26.

Amzica, F. & Steriade, M. (1995) Short- and long-range neuronal synchronization of the slow (< 1 Hz) cortical oscillation. *Journal of Neurophysiology* 73(1):20–38.

Antonini, A. & Stryker, M. P. (1993) Rapid remodeling of axonal arbors in the visual cortex. *Science* 260(5,115):1,819–21.

Aserinsky, E. & Kleitman, N. (1953) Regularly occurring periods of eye motility and concurrent phenomena during sleep. *Science* 118;273–74.

Aston-Jones, G. & Bloom, F. E. (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *Journal of Neuroscience* 1(8):876–86.

Atienza, M., Cantero, J. L. & Dominguez-Marin, E. (2002) The time course of neural changes underlying auditory perceptual learning. *Learning and Memory* 9(3):138–50.

Atienza, M., Cantero, J. L. & Stickgold, R. (2004) Posttraining sleep enhances automaticity in perceptual discrimination. *Journal of Cognitive Neuroscience* in press.

Barr, D. S., Lambert, N. A., Hoyt, K. L., Moore, S. D. & Wilson, W. A. (1995) Induction and reversal of long-term potentiation by low- and high-intensity theta pattern stimulation. *Journal of Neuroscience* 15(7 Pt 2):5,402–10.

Beaulieu, I. & Godbout, R. (2000) Spatial learning on the Morris Water Maze Test after a short-term paradoxical sleep deprivation in the rat. *Brain and Cognition* 43(1–3):27–31.

Benington, J. H. & M. G. Frank (2003) Cellular and molecular connections between sleep and synaptic plasticity. *Progress in Neurobiology* 69(2):71–101.

Brashers-Krug, T., Shadmehr, R. & Bizzi, E. (1996) Consolidation in human motor memory. *Nature* 382(6,588):252–55.

Braun, A. R., Balkin, T. J., Wesensten, N. J., Carson, R. E., Varga, M., Baldwin, P., Selbie, S., Belenky, G. & Herscovitch, P. (1997) Regional cerebral blood flow throughout the sleep-wake cycle. An H215O PET study. *Brain* 120(7):1,173–97.

Braun, A. R., Balkin, T. J., Wesensten, N. J., Gwadry, F., Carson, R. E., Varga, M., Baldwin, P., Belenky, G. & Herscovitch, P. (1998) Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. *Science* 279(5,347):91–95.

Braunewell, K. H. & Manahan-Vaughan, D. (2001) Long-term depression: A cellular basis for learning? *Reviews in the Neurosciences* 12(2):121–40.

Brocher, S., Artola, A. & Singer, W. (1992) Agonists of cholinergic and noradrenergic receptors facilitate synergistically the induction of long-term potentiation in slices of rat visual cortex. *Brain Research* 573(1):27–36.

Buchegger, J. & Meier-Koll, A. (1988) Motor learning and ultradian sleep cycle: An electroencephalographic study of trampoliners. *Perceptual and Motor Skills* 67(2):635–45.

Buonomano, D. V. & Merzenich, M. M. (1998) Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience* 21:149–86.

Butefisch, C. M., Davis, B. C., Wise, S. P., Sawaki, L., Kopylev, L., Classen, J. & Cohen, L. G. (2000) Mechanisms of use-dependent plasticity in the human motor cortex. *Proceedings of the National Academy of Sciences of the United States of America* 97(7):3,661–65.

Buzsaki, G. (1998) Memory consolidation during sleep: a neurophysiological perspective. *Journal of Sleep Research* 7(Suppl. 1):17–23.

Callaway, C. W., Lydic, R., Baghdoyan, H. A. & Hobson, J. A. (1987) Pontogeniculooccipital waves: Spontaneous visual system activity during rapid eye movement sleep. *Cellular & Molecular Neurobiology* 7(2):105–49.

Cavallaro, S., D'Agata, V., Manickam, P., Dufour, F. & Alkon, D. L. (2002) Memory-specific temporal profiles of gene expression in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America* 99(25):16,279–84.

Chase, M. H. & Morales, F. R. (1990) The atonia and myoclonia of active (REM) sleep. *Annual Review of Psychology* 41:557–84.

Cheour, M., Martynova, O., Naatanen, R., Erkkola, R., Sillanpaa, M., Kero, P., Raz, A., Kaipio, M. L., Hiltunen, J., Aaltonen, O., Savela, J. & Hamalainen, H. (2002) Speech sounds learned by sleeping newborns. *Nature* 415(6,872):599–600.

Chernik, D. A. (1972) Effect of REM sleep deprivation on learning and recall by humans. *Perceptual and Motor Skills* 34(1):283–94.

Cipolli, C. & Salzarulo, P. (1980) Sentence memory and sleep: A pilot study. *Sleep* 2(2):193–98.

Cirelli, C. & Tononi, G. (1998) Differences in gene expression between sleep and waking as revealed by mRNA differential display. *Brain Research. Molecular Brain Research* 56(1–2):293–305.

(2000a) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *Journal of Neuroscience* 20(24):9,187–94.

(2000b) Gene expression in the brain across the sleep-waking cycle. *Brain Research* 885(2):303–21.

Coenen, A. M. & Drinkenburg, W. H. (2002) Animal models for information processing during sleep. *International Journal of Psychophysiology* 46(3):163–75.

Contreras, D., Destexhe, A. & Steriade, M. (1997) Intracellular and computational characterization of the intracortical inhibitory control of synchronized thalamic inputs in vivo. *Journal of Neurophysiology* 78(1):335–50.

Corkin, S. (1968) Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia* 6:255–65.

Crick, F. & Mitchison, G. (1983) The function of dream sleep. *Nature* 304(5,922):111–14.

Datta, S. (1997) Cellular basis of pontine ponto-geniculo-occipital wave generation and modulation. *Cellular and Molecular Biology* 17(3):341–65.

(2000) Avoidance task training potentiates phasic pontine-wave density in the rat: A mechanism for sleep-dependent plasticity. *Journal of Neuroscience* 20(22):8,607–13.

Dave, A. S. & Margoliash, D. (2000) Song replay during sleep and computational rules for sensorimotor vocal learning. *Science* 290(5,492):812–16.

Dave, A. S., Yu, A. C. & Margoliash, D. (1998) Behavioral state modulation of auditory activity in a vocal motor system. *Science* 282(5,397):2,250–54.

Daw, N. W., Sato, H., Fox, K., Carmichael, T. & Gingerich, R. (1991) Cortisol reduces plasticity in the kitten visual cortex. *Journal of Neurobiology* 22(2):158–68.

De Gennaro, L., Ferrara, M. & Bertini, M. (2000) Topographical distribution of spindles: variations between and within NREM sleep cycles. *Sleep Research Online* 3(4):155–60.

De Koninck, J., Lorrain, D., Christ, G., Proulx, G. & Coulombe, D. (1989) Intensive language learning and increases in rapid eye movement sleep: evidence of a performance factor. *International Journal of Psychophysiology* 8(1):43–47.

Denny, L. M. (1951) The shape of the post-rest performance curve for the continuous rotary pursuit task. *Motor Skills Research Exchange* 3:103–05.

Dienes, Z. & Perner, J. (1999) A theory of implicit and explicit knowledge. *Behavioral and Brain Sciences* 22(5):735–55; discussion 755–808.

Eichenbaum, H. (2000) A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience* 1(1):41–50.

El-Sherif, Y., Tesoriero, J., Hogan, M. V. & Wieraszko, A. (2003) Melatonin regulates neuronal plasticity in the hippocampus. *Journal of Neuroscience Research* 72(4):454–60.

Empson, J. A. & Clarke, P. R. (1970) Rapid eye movements and remembering. *Nature* 227(255):287–88.

Eysenck, H. J. & Frith, C. D. (1977) *Reminiscence, motivation, and personality: A case study in experimental psychology*. Plenum Press.

Fischer, S., Hallschmid, M., Elsner, A. L. & Born, J. (2002) Sleep forms memory for finger skills. *Proceedings of the National Academy of Sciences of the United States of America* 99(18):11,987–91.

Fishbein, W., Kastaniotis, C. & Chattman, D. (1974) Paradoxical sleep: Prolonged augmentation following learning. *Brain Research* 79(1):61–75.

Foehring, R. C. & Lorenzon, N. M. (1999) Neuromodulation, development and synaptic plasticity. *Canadian Journal of Experimental Psychology* 53(1):45–61.

Fogel, S., Jacob, J. & Smith, C. (Oct. 2001) *Increased sleep spindle activity following simple motor procedural learning in humans.* Paper presented at the Congress Physiological Basis for Sleep Medicine, Punta del Este, Uruguay.

Frank, M. G., Issa, N. P. & Stryker, M. P. (2001) Sleep enhances plasticity in the developing visual cortex. *Neuron* 30(1):275–87.

Frey, U. & Morris, R. G. (1998) Synaptic tagging: Implications for late maintenance of hippocampal long-term potentiation. *Trends in Neuroscience* 21(5):181–88.

Gais, S., Plihal, W., Wagner, U. & Born, J. (2000) Early sleep triggers memory for early visual discrimination skills. *Nature Neuroscience*3(12):1,335–39.

Gilbert, C. D. & Wiesel, T. N. (1989) Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. Journal of Neuroscience 9(7):2,432–42.

Giuditta, A., Ambrosini MV, Montagnese P, Mandile P, Cotugno M, Zucconi G & Vescia S. (1995) The sequential hypothesis on sleep function. *Behavioural Brain Research* 69:218–22.

Grafton, S. T., Hazeltine, E. & Ivry, R. B. (1998) Abstract and effector-specific representations of motor sequences identified with PET. *Journal of Neuroscience* 18(22):9,420–28.

Graves, L., Pack, A. & Abel, T. (2001) Sleep and memory: a molecular perspective. *Trends in Neuroscience* 24(4):237–43.

Gu, Q. (2002) Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience* 111(4):815–35.

Guerrien, A., Dujardin, K., Mandai, O., Sockeel, P. & Leconte, P. (1989) Enhancement of memory by auditory stimulation during postlearning REM sleep in humans. *Physiology and Behavior* 45(5):947–50.

Hartley, D. (1801) *Observations on Man, his frame, his deity, and his expectations (1749/1966).* Scholars Facsimile Reprint.

Hasselmo, M. E. (1999) Neuromodulation: Acetylcholine and memory consolidation. *Trends in Cognitive Science* 3(9):351–59.

Hebb, D. O. (1949) *The Organization of behavior: A neuropsychological theory.* Wiley.

Hennevin, E. & Hars, B. (1987) Is increase in post-learning paradoxical sleep modified by cueing? *Behavioral Brain Research* 24(3):243–49.

Hennevin, E., Hars, B., Maho, C. & Bloch, V. (1995) Processing of learned information in paradoxical sleep: Relevance for memory. *Behavioral Brain Research* 69(1–2):125–35.

Hobson, J., McCarley R. W. & Wyzinski P. W. (1975) Sleep cycle oscillation: Reciprocal discharge by two brainstem neuronal groups. *Science* 189:55–58.

Hoffman, K. L. & McNaughton, B. L. (2002) Sleep on it: Cortical reorganization after-the-fact. *Trends in Neuroscience* 25(1):1–2.

Holland, H. C. (1963) Massed practice and reactivation inhibition, reminiscence and disinhibition in the spiral after effect. *British Journal of Psychology* 54:261–72.

Holscher, C. (1997) Nitric oxide, the enigmatic neuronal messenger: Its role in synaptic plasticity. *Trends in Neuroscience* 20(7):298–303.

Holscher, C., Anwyl, R. & Rowan, M. J. (1997) Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. *Journal of Neuroscience* 17(16):6,470–77.

Igaz, L. M., Vianna, M. R., Medina, J. H. & Izquierdo, I. (2002) Two time periods of hippocampal mRNA synthesis are required for memory consolidation of fear-motivated learning. *Journal of Neuroscience* 22(15):6,781–89.

Jacobs, K. M. & Donoghue, J. P. (1991) Reshaping the cortical motor map by unmasking latent intracortical connections. *Science* 251(4,996):944–47.

Jancke, L., Gaab, N., Wustenberg, T., Scheich, H. & Heinze, H. J. (2001) Short-term functional plasticity in the human auditory cortex: an fMRI study. *Brain Research Cognitive Brain Research* 12(3):479–85.

Jenkins, J. C. & Dallenbach, K. M. (1924) Obliviscence during sleep and waking. *American Journal of Psychology* 35:605–12.

Joseph, J. S., Chun, M. M. & Nakayama, K. (1997) Attentional requirements in a "preattentive" feature search task. *Nature* 387(6,635):805–07.

Kametani, H. & Kawamura, H. (1990) Alterations in acetylcholine release in the rat hippocampus during sleep-wakefulness detected by intracerebral dialysis. *Life Science* 47(5):421–26.

Kandel, E. R. (1991) Cellular mechanisms of learning and the biological basis of individuality. In: *Principles of neural science,* 3rd edition, pp. 1,009–31, ed. E. R. Kandel, J. H. Schwartz & T. M. Jessell. Appleton & Lange.

Karashima, A., Nakamura, K., Sato, N., Nakao, M., Katayama, N. & Yamamoto, M. (2002) Phase-locking of spontaneous and elicited ponto-geniculo-occipital waves is associated with acceleration of hippocampal theta waves during rapid eye movement sleep in cats. *Brain Research* 958(2):347–58.

Karni, A., Meyer, G., Jezzard, P., Adams, M. M., Turner, R. & Ungerleider, L. G. (1995) Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 377(6,545):155–58.

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R. & Ungerleider, L. G. (1998) The acquisition of skilled motor performance: Fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences of the United States of America* 95(3):861–68.

Karni, A. & Sagi, D. (1993) The time course of learning a visual skill. *Nature* 365(6,443):250–52.

Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J. & Sagi, D. (1994) Dependence on REM sleep of overnight improvement of a perceptual skill. *Science* 265(5,172):679–82.

Kass, J. H. (2000) The reorganization of sensory and motor maps after injury in adult mammals. In: *The new cognitive neurosciences,* 2nd edition, pp. 223–37, ed. M. S. Gazzaniga. MIT Press.

Kemp, N. & Bashir, Z. I. (2001) Long-term depression: A cascade of induction and expression mechanisms. *Progress in Neurobiology* 65(4):339–65.

Kirkwood, A., Rozas, C., Kirkwood, J., Perez, F. & Bear, M. F. (1999) Modulation of long-term synaptic depression in visual cortex by acetylcholine and norepinephrine. *Journal of Neuroscience* 19(5):1,599–609.

Kourrich, S. & Chapman, C. A. (2003) NMDA receptor–dependent long-term synaptic depression in the entorhinal cortex in vitro. *Journal of Neurophysiology* 89(4):2,112–19.

Krakauer, J. W., Ghilardi, M. F. & Ghez, C. (1999) Independent learning of internal models for kinematic and dynamic control of reaching. *Nature Neuroscience* 2(11):1,026–31.

Lewin, I. & Glaubman, H. (1975) The effect of REM deprivation: Is it detrimental, beneficial, or neutral? *Psychophysiology* 12(3):349–53.

Lisman, J. (1989) A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. *Proceedings of the National Academy of Sciences of the United States of America* 86(23):9,574–78.

Llinas, R. & Ribary, U. (1993) Coherent 40-Hz oscillation characterizes dream state in humans. *Proceedings of the National Academy of Sciences of the United States of America* 90(5):2,078–81.

Louie, K. & Wilson, M. A. (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* 29(1):145–56.

Lydic, R. & Baghdoyan, H. A. (1988) *Handbook of behavioral state control: Cellular and molecular mechanisms*. CRC Press.

Mandile, P., Vescia, S., Montagnese, P., Piscopo, S., Cotugno, M. & Giuditta, A. (2000) Post-trial sleep sequences including transition sleep are involved in avoidance learning of adult rats. *Behavioral Brain Research* 112(1–2):23–31.

Maquet, P. (2001) The role of sleep in learning and memory. *Science* 294(5,544):1,048–52.

Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., Aerts, J., Del Fiore, G., Degueldre, C., Meulemans, T., Luxen, A., Franck, G., Van Der Linden, M., Smith, C. & Cleeremans, A. (2000) Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neuroscience* 3(8):831–36.

Maquet, P., Peters J-M., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A. & Franck, G. (1996) Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature* 383(6,596):163–66.

Maquet, P., Schwartz, S., Passingham, R. & Frith, C. (2003) Sleep-related consolidation of a visuomotor skill: Brain mechanisms as assessed by functional magnetic resonance imaging. *Journal of Neuroscience* 23(4):1,432–40.

Marrosu, F., Portas, C., Mascia, M. S., Casu, M. A., Fa, M., Giagheddu, M., Imperato, A. & Gessa, G. L. (1995) Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. *Brain Research* 671(2):329–32.

Martin, S. J., Grimwood, P. D. & Morris, R. G. (2000) Synaptic plasticity and memory: An evaluation of the hypothesis. *Annual Review of Neuroscience* 23:649–711.

Marti-Nicolovius, M., Portell-Cortes, I. & Morgado-Bernal, I. (1988) Improvement of shuttle-box avoidance following post-training treatment in paradoxical sleep deprivation platforms in rats. *Physiology and Behavior* 43(1):93–98.

McGaugh, J. L. (2000) Memory – a century of consolidation. *Science* 287(5,451):248–51.

Mednick, S. C., Nakayama, K., Cantero, J. L., Atienza, M., Levin, A. A., Pathak, N. & Stickgold, R. (2002) The restorative effect of naps on perceptual deterioration. *Nature Neuroscience* 28:28.

Meienberg, P. (1977) The tonic aspects of human REM sleep during long-term intensive verbal learning. *Physiological Psychology* 5:250–56.

Micheva, K. D. & Beaulieu, C. (1995) An anatomical substrate for experience-dependent plasticity of the rat barrel field cortex. *Proceedings of the National Academy of Sciences of the United States of America* 92(25):11,834–38.

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., Boroojerdi, B., Poewe, W. & Hallett, M. (2002) Early consolidation in human primary motor cortex. *Nature* 415(6,872):640–44.

Müller, R. A., Kleinhans, N., Pierce, K., Kemmotsu, N. & Courchesne, E. (2002) Functional MRI of motor sequence acquisition: Effects of learning stage and performance. *Cognitive Brain Research* 14(2):277–93.

Naatanen, R., Schroger, E., Karakas, S., Tervaniemi, M. & Paavilainen, P. (1993) Development of a memory trace for a complex sound in the human brain. *NeuroReport* 4(5):503–06.

Nakanishi, H., Sun, Y., Nakamura, R. K., Mori, K., Ito, M., Suda, S., Namba, H., Storch, F. I., Dang, T. P., Mendelson, W., Mishkin, M., Kennedy, C., Gillin, J. C., Smith, C. B. & Sokoloff, L. (1997) Positive correlations between cerebral protein synthesis rates and deep sleep in Macaca mulatta. *European Journal of Neuroscience* 9(2):271–79.

Nofzinger, E. A., Mintun, M. A., Wiseman, M., Kupfer, D. J. & Moore, R. Y. (1997) Forebrain activation in REM sleep: An FDG PET study. *Brain Research* 770(1–2):192–201.

Oniani, T. N., Lortkipanidze, N. D. & Maisuradze, L. M. (1987) Interaction between learning and paradoxical sleep in cats. *Neuroscience and Behavioral Physiology* 17(4):304–10.

Pace-Schott, E. F. & Hobson, J. A. (2002) The neurobiology of sleep: Genetics, cellular physiology and subcortical networks. *Nature Reviews Neuroscience* 3(8):591–605.

Pascual-Leone, A. (2001) The brain that plays music and is changed by it. *Annals of the New York Academy of Sciences* 930:315–29.

Pavlides, C., Greenstein, Y. J., Grudman, M. & Winson, J. (1988) Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. *Brain Research* 439(1–2):383–87.

Pearlman, C. A. (1969) Effect of rapid eye movement (dreaming) sleep deprivation on retention of avoidance learning in rats. *Report – US Naval Submarine Medical Center* 563.:1-4.

Peigneux, P., Laureys, S., Delbeuck, X. & Maquet, P. (2001a) Sleeping brain, learning brain. The role of sleep for memory systems. *NeuroReport* 12(18):A111–24.

Peigneux, P., Laureys, S., Fuchs, S., Delbeuck, X., Degueldre, C., Aerts, J., Delfiore, G., Luxen, A. & Maquet, P. (2001b) Generation of rapid eye movements during paradoxical sleep in humans. *NeuroImage* 14(3):701–08.

Plihal, W. & Born, J. (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience* 9:534–47.

(1999) Memory consolidation in human sleep depends on inhibition of glucocorticoid release. *NeuroReport* 10(13):2,741–47.

Poe, G. R., Nitz, D. A., McNaughton, B. L. & Barnes, C. A. (2000) Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Research* 855(1):176–80.

Portas, C. M., Krakow, K., Allen, P., Josephs, O., Armony, J. L. & Frith, C. D. (2000) Auditory processing across the sleep-wake cycle: Simultaneous EEG and fMRI monitoring in humans. *Neuron* 28(3):991–99.

Rachal Pugh, C., Fleshner, M., Watkins, L. R., Maier, S. F. & Rudy, J. W. (2001) The immune system and memory consolidation: A role for the cytokine IL-1beta. *Neuroscience and Biobehavioral Reviews* 25(1):29–41.

Ramm, P. & Smith, C. T. (1990) Rates of cerebral protein synthesis are linked to slow wave sleep in the rat. *Physiology and Behavior* 48(5):749–53.

Rattoni, F. B. & Escobar, M. (2000) Neurobiology of learning. In: *International handbook of psychology, vol. xxxii,* p. 629, ed. K. Pawlik & M. Rosenzweig. Sage Publications Ltd.

Rauschecker, J. P. & Hahn, S. (1987) Ketamine-xylazine anaesthesia blocks consolidation of ocular dominance changes in kitten visual cortex. *Nature* 326(6,109):183–85.

Rechtschaffen, A. & Kales, A. (1968) *A manual standardized terminology, techniques and scoring system for sleep stages of human subjects*. U.S. Department of Health.

Ribeiro, S., Goyal, V., Mello, C. V. & Pavlides, C. (1999) Brain gene expression during REM sleep depends on prior waking experience. *Learning and Memory* 6(5):500–08.

Ribeiro, S., Mello, C. V., Velho, T., Gardner, T. J., Jarvis, E. D. & Pavlides, C. (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. *Journal of Neuroscience* 22(24):10,914–23.

Sanford, L.D., Silvestri, A.J., Ross, R.J., Morrison, A.R. (2001). Influence of fear conditioning on elicited ponto-geniculo-occipital waves and rapid eye movement sleep. *Archives Italiennes de Biologie* 139(3):169 83

Schacter, D. L. & Tulving, E. (1994) *Memory Systems*. MIT Press.

Schwartz, S., Maquet, P. & Frith, C. (2002) Neural correlates of perceptual learning: A functional MRI study of visual texture discrimination. *Proceedings of the National Academy of Sciences of the United States of America* 99(26):17,137–42.

Sejnowski, T. J. & Destexhe, A. (2000) Why do we sleep? *Brain Research* 886(1–2):208–23.

Shadmehr, R. & Brashers-Krug, T. (1997) Functional stages in the formation of human long-term motor memory. *Journal of Neuroscience* 17(1):409–19.

Shaffery, J. P., Oksenberg, A., Marks, G. A., Speciale, S. G., Mihailoff, G. & Roffwarg, H. P. (1998) REM sleep deprivation in monocularly occluded kittens reduces the size of cells in LGN monocular segment. *Sleep* 21(8):837–45.

Shaffery, J. P., Roffwarg, H. P., Speciale, S. G. & Marks, G. A. (1999) Ponto-geniculo-occipital-wave suppression amplifies lateral geniculate nucleus cell-size changes in monocularly deprived kittens. *Brain Research. Developmental Brain Research* 114(1):109–19.

Shaffery, J. P., Sinton, C. M., Bissette, G., Roffwarg, H. P. & Marks, G. A. (2002) Rapid eye movement sleep deprivation modifies expression of long-term potentiation in visual cortex of immature rats. *Neuroscience* 110(3):431–43.

Shima, K., Nakahama, H. & Yamamoto, M. (1986) Firing properties of two types of nucleus raphe dorsalis neurons during the sleep-waking cycle and their responses to sensory stimuli. *Brain Research* 399(2):317–26.

Shiromani, P., Gutwein, B. M. & Fishbein, W. (1979) Development of learning and memory in mice after brief paradoxical sleep deprivation. *Physiology and Behavior* 22(5):971–78.

Siegel, J. M. (2001) The REM sleep-memory consolidation hypothesis. *Science* 294(5,544):1,058–63.

Skaggs, W. E. & McNaughton, B. L. (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science* 271(5,257):1,870–73.

Smith, C. (1995) Sleep states and memory processes. *Behavioral Brain Research* 69(1–2):137–45.

(2001) Sleep states and memory processes in humans: Procedural versus declarative memory systems. *Sleep Medicine Reviews* 5(6):491–506.

Smith, C. & Butler, S. (1982) Paradoxical sleep at selective times following training is necessary for learning. *Physiology and Behavior* 29(3):469–73.

Smith, C. & Kelly, G. (1988) Paradoxical sleep deprivation applied two days after end of training retards learning. *Physiology and Behavior* 43(2):213–16.

Smith, C. & Lapp, L. (1986) Prolonged increases in both PS and number of REMS following a shuttle avoidance task. *Physiology and Behavior* 36(6):1,053–57.

Smith, C. & MacNeill, C. (1994) Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. *Journal of Sleep Research* 3(4):206–13.

Smith, C., Tenn, C. & Annett, R. (1991) Some biochemical and behavioural aspects of the paradoxical sleep window. *Canadian Journal of Psychology* 45(2):115–24.

Smith, C. & Weeden, K. (1990) Post training REMs coincident auditory stimulation enhances memory in humans. *Psychiatric Journal of the University of Ottawa* 15(2):85–90.

Smith, C., Young, J. & Young, W. (1980) Prolonged increases in paradoxical sleep during and after avoidance-task acquisition. *Sleep* 3(1):67–81.

Soderling, T. R. (1993) Calcium/calmodulin-dependent protein kinase II: role in learning and memory. *Molecular and Cellular Biochemistry* 127–128:93–101.

Soderling, T. R. & Derkach, V. A. (2000) Postsynaptic protein phosphorylation and LTP. *Trends in Neuroscience* 23(2):75–80.

Squire, L. R., Cohen, N. J. & Zouzounis, J. A. (1984) Preserved memory in retrograde amnesia: Sparing of a recently acquired skill. *Neuropsychologia* 22(2):145–52.

Squire, L. R. & Zola, S. M. (1996) Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences of the United States of America* 93(24):13,515–22.

Steriade, M. (1997) Synchronized activities of coupled oscillators in the cerebral cortex and thalamus at different levels of vigilance. *Cerebral Cortex* 7:583–604.

(1999) Coherent oscillations and short-term plasticity in corticothalamic networks. *Trends in Neuroscience* 22(8):337–45.

(2001) *The intact and sliced brain*. MIT Press.

Steriade, M. & Amzica, F. (1998) Coalescence of sleep rhythms and their chronology in corticothalamic networks. *Sleep Research Online* 1(1):1–10.

Steriade, M., Contreras, D., Amzica, F. & Timofeev, I. (1996) Synchronization of fast (30–40 Hz) spontaneous oscillations in intrathalamic and thalamocortical networks. *Journal of Neuroscience* 16(8):2,788–808.

Steriade, M., McCormick, D. A. & Sejnowski, T. J. (1993) Thalamocortical oscillations in the sleeping and aroused brain. *Psychiatry Research* 49(2):139–50.

Stickgold, R. (1998) Sleep: Off-line memory reprocessing. *Trends in Cognitive Science* 2(12):484–92.

(2002) EMDR: A putative neurobiological mechanism of action. *Journal of Clinical Psychology* 58(1):61–75.

Stickgold, R., Hobson, J. A., Fosse, R. & Fosse, M. (2001) Sleep, learning, and dreams: Off-line memory reprocessing. *Science* 294(5,544):1,052–57.

Stickgold, R., James, L. & Hobson, J. A. (2000a) Visual discrimination learning requires sleep after training. *Nature Neuroscience* 3(12):1,237–78.

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V. & Hobson, J. A. (2000b) Visual discrimination task improvement: A multi-step process occurring during sleep. *Journal of Cognitive Neuroscience* 12(2):246–54.

Tilley, A. J. & Empson, J. A. (1978) REM sleep and memory consolidation. *Biological Psychology* 6(4):293–300.

Tononi, G. & Cirelli, C. (2001) Some considerations on sleep and neural plasticity. *Archives Italiennes de Biologie* 139(3):221–41.

Trachtenberg, J. T. & Stryker, M. P. (2001) Rapid anatomical plasticity of horizontal connections in the developing visual cortex. *Journal of Neuroscience* 21(10):3,476–82.

Tulving, E. (1972) Episodic and semantic memory. In: *Organization of memory,* ed. E. Tulving & W. Donaldson. Academic Press.

Tweed, S., Aubrey, J. B., Nader, R. & Smith, C. T. (1999) Deprivation of REM sleep or stage 2 sleep differentially affects cognitive procedural and motor procedural memory. *Sleep* 22(Suppl. 1):H392.I.

Vertes, R. P. & Eastman, K. E. (2000) The case against memory consolidation in REM sleep. *Behavioral and Brain Sciences* 23(6):867–76; discussion 904-1,121.

Wagner, U., Gais, S. & Born, J. (2001) Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning and Memory* 8(2):112–119.

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A. & Stickgold, R. (2002) Practice with sleep makes perfect: Sleep dependent motor skill learning. *Neuron* 35(1):205–11.

Walker, M. P., Brakefield, T., Hobson, J. A. & Stickgold, R. (2003a) Dissociable stages of human memory consolidation and reconsolidation. *Nature* 425:616–20.

Walker, M. P., Brakefield, T., Seidman, J., Hobson, J. A. & Stickgold, R. (2003b) Sleep and the time course of motor skill learning. *Learning and Memory* 10(4):275–84.

Wang, J., Caspary, D. & Salvi, R. J. (2000) GABA-A antagonist causes dramatic expansion of tuning in primary auditory cortex. *NeuroReport* 11(5):1,137–40.

Wilson, M. A. & McNaughton, B. L. (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265(5,172):676–79.

Zimmerman, J. T., Stoyva, J. M. & Metcalf, D. (1970) Distorted visual feedback and augmentated REM sleep. *Psychophysiology* 7:298–303.

Zimmerman, J. T., Stoyva, J. M. & Reite, M. L. (1978) Spatially rearranged vision and REM sleep: A lack of effect. *Biological Psychiatry* 13(3):301–16.