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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.

In this target article, I 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 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 hope, first, that a more clear understanding of memory stage development can be agreed upon. Second, 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

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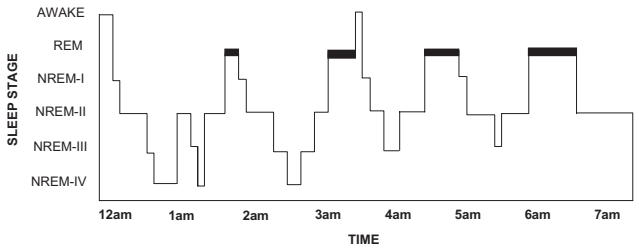
an ultradian pattern every 90 minutes, with NREM sleep (particularly stages 3 and 4) dominating the first half of the night, while REM sleep and stage 2 NREM sleep prevail in the latter half of the night (Fig. 1).

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).



Sleep Stage	Electrophysiology	Neurochemistry	Functional anatomy
NREM: Stage I, Stage II, SWS { Stage III, Stage IV	- Loss of -EEG - Spindles/k-complex - Slow wave synchronous EEG	Aminergic to Cholinergic ratio HIGH	Activity in pons, thalamic, limbic, frontal, temporal regions
REM:	- Increased EEG frequency - PGO waves - Muscle atonia	Cholinergic to Aminergic ratio HIGH	Activity in lateral prefrontal 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.

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.

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 organism's 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 a plethora of mechanisms which 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 non-declarative 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") may be more preserved by periods of sleep compared to 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 (1977) found no evidence of altered post-training sleep architecture following learning of a verbal memory task. However, De Koninck et al. (1989) demonstrated significant increases in post-training 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 activity, 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 tuning 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. (2002b) have described electrophysiological evidence that human newborns are able to acquire the ability to discriminate 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 pe-

riods (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.

Upon 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 (Fig. 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.

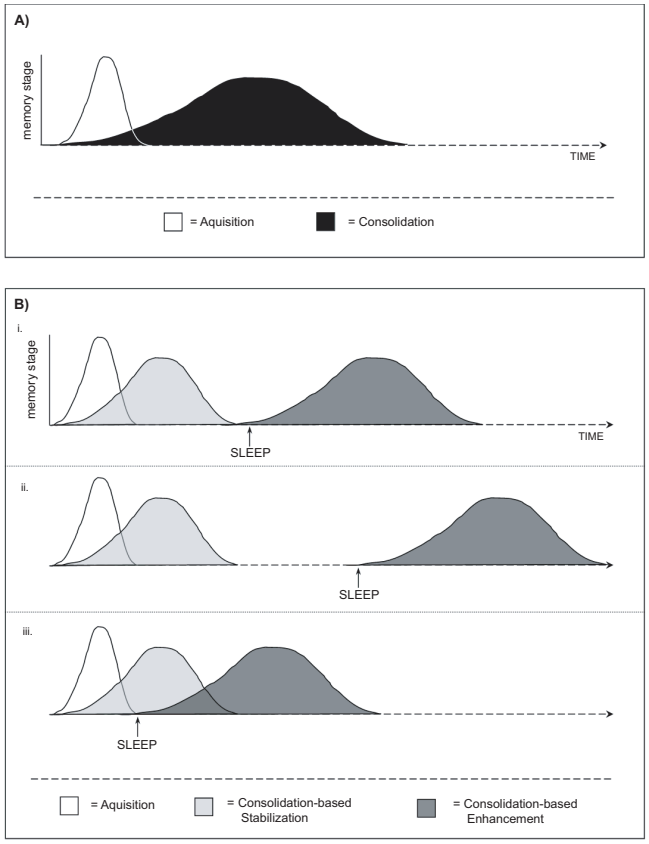


Figure 2. *Classical and new models of procedural memory stage formation.* **(A)** *Classical, time-dependent course of memory formation*: The process of memory formation begins with an acquisition stage involving engagement with an experience or task to be learned, resulting in a specific memory representation 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 and 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, and nothing 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 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 pre-training 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 Shadmehr and 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).

We thus saw that 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 (Fig. 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. In contrast, subjects trained at 10:00 in the morning showed no significant improvement when retested later that same day after 12 hours of wake (Fig. 3, A and B). Yet when retested a second time at 10:00 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 in the evening demonstrated equally large significant improvements the next morning in both speed and accuracy overnight, just 12 hours post-training, following sleep, but showed no significant additional improvement after a further 12 hours of wake later that day (Fig. 3, C and D).

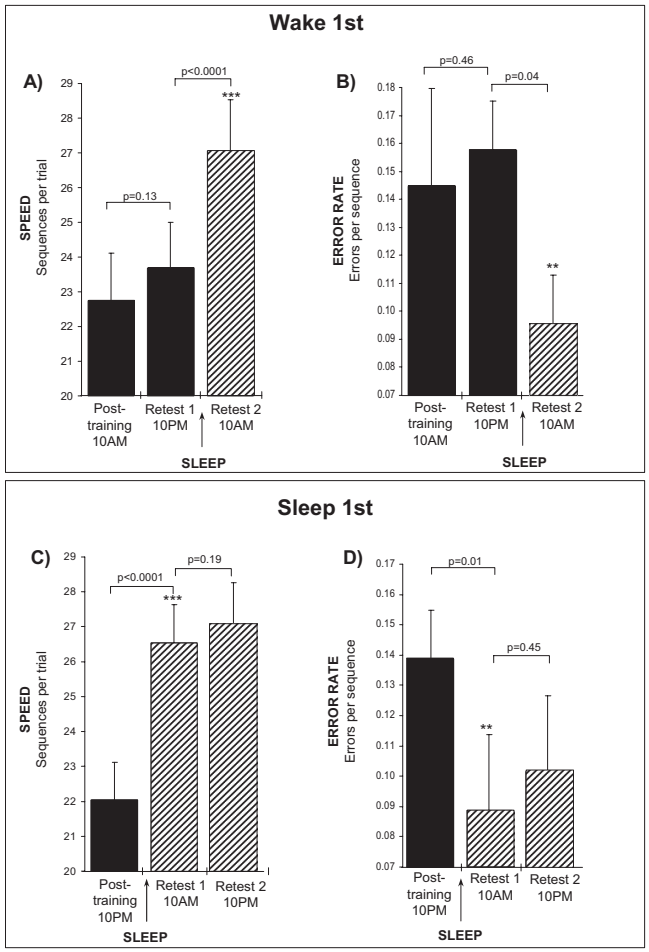


Figure 3. *Sleep-dependent learning on a motor skill task.* (**A.** & **B.**) Subjects in the Wake 1st group (n = 15), trained at 10:00 a.m., showed no significant change in either speed (A) or error rate (B) at the first retest following 12 hours of wake (Retest 1, filled bars). However, by the second 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 hours 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 (Standard Error of the Mean).

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.

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 (Fig. 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

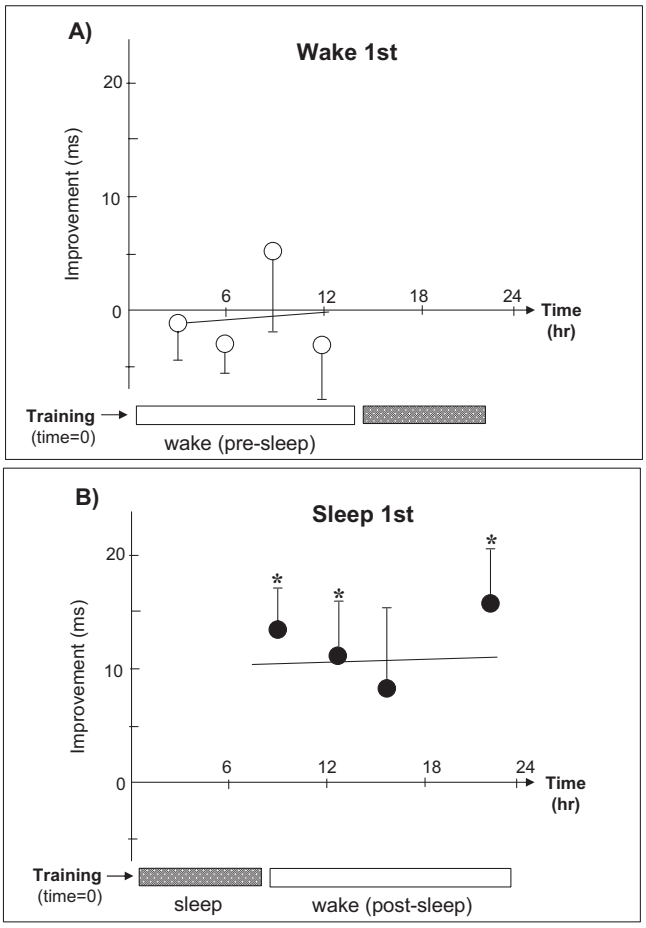


Figure 4. *Sleep-dependent learning of a visual discrimination task.* Subjects were trained and then retested at a later time, with the respective improvement (in milliseconds) in performance illustrated across time. Each subject was retested only once, and each point represents a separate group of subjects. **(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.

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.

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 post-training values without the need for sleep, an effect termed *reminiscence.* However, this rest-induced enhancement can be short lived, decreasing back to post-training 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 post-training 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 may be 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 sys-

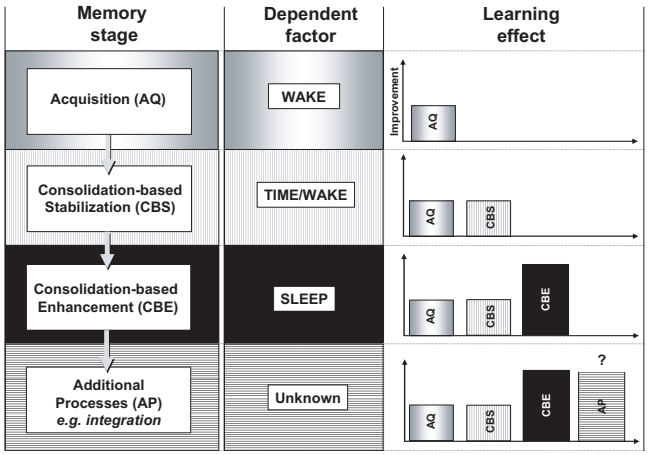


Figure 5. *Procedural memory stages and the contributions of time, wake, and sleep in behavioral improvement.* The initial stage of memory formation begins with acquisition (AQ), a process that occurs most commonly during waking, resulting in early behavioral improvement (learning). Following acquisition, 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.

tems, 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.

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 previously 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 behaviorally 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 dominant 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 focuses specifically on sleep and the temporal order of sleep stages, 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 which 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 in terms of both 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 suggest 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, which 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 a 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 over-potentiated 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 (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) (Fig. 6). Indeed, 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 associ-

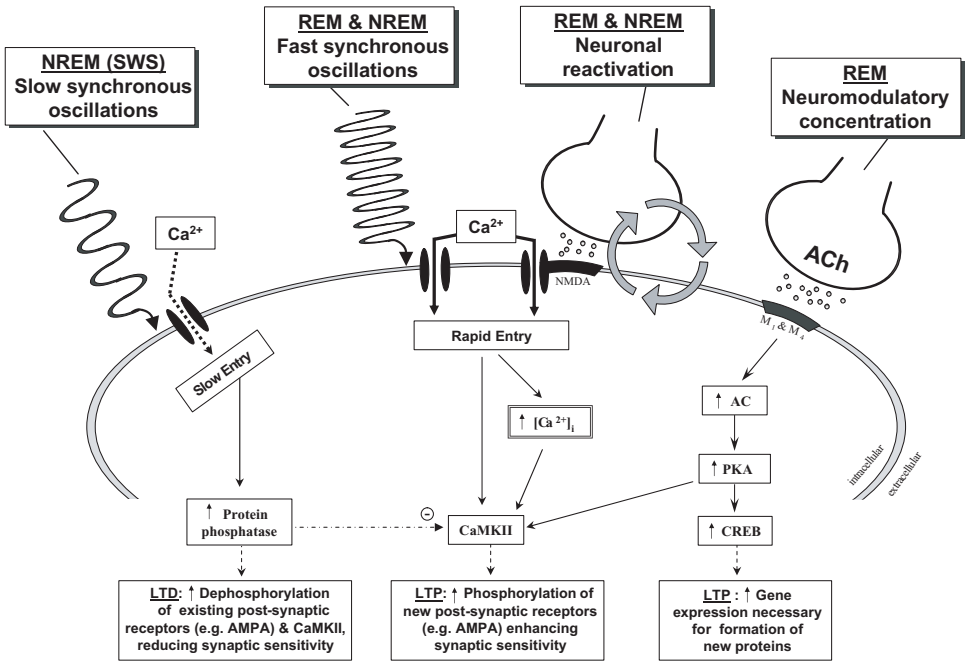


Figure 6. *Sleep-dependent influences on mechanisms of synaptic plasticity.* From left to right: Low frequency synchronous oscillations (<1 Hz, and 1–4 Hz) during NREM SWS trigger slow entry of calcium (Ca^{2+}) into the postsynaptic cell. These conditions prompt intracellular activation of protein phosphotase 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.

ated with learning. The endogenous PGO waves of REM sleep provide a burst stimulus (300–500 Hz) throughout neuronal networks, which could trigger pronounced influxes of intracellular Ca^{2+}, leading to LTP (Fig. 6). Datta (2000) has provided evidence that the occurrence of these REM sleep associated bursts displays 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 induces 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 and 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 (Fig. 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 passively selected by their increased responsivity over those which 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 hippocampus 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 post-sleep 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 post-synaptic terminals in close synchrony during sleep would trigger robust potentiation within local networks (Fig. 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, first, by resetting excitatory thresholds (via increasing transmitter release or postsynaptic responses) (Brocher et al. 1992; Kirkwood et al. 1999), and second, by 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 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 (Graves et al. 2001). 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 up-regulated gene expression (Fig. 6).

There is also a burgeoning literature describing a role for other non-typical 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). Although receiving little attention regarding sleep-dependent plasticity (Plihal & Born 1999b), 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 post-sleep 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 post-sleep 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 up-regulated 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 up-regulated in sleep. However, the function of these genes remains uncharacterized.

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 as-

sociated IEG, in rats exposed to either rich sensorimotor experiences or benign control environments (non-exposed). As in previous studies, there was a generalized down-regulation of zif-268 during subsequent SWS and REM sleep in the non-exposed 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 identified 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 hours 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 the model proposed in the present target article, 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 post-sleep 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 non-significant 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 non-waking 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 were initially able to produce increased excitability (potentiation) in specific layers of the visual cortex in young rats (up to 30 days old). After this early developmental stage, the ability to potentiate 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 so far in favor of sleep-dependent modification of cell structure and plasticity.

Therefore, although 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 potentiation, 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 up-regulation of plasticity-associated genes to the occurrence of unique electrical events throughout neuronal networks.

The separation of 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 divergence of those either in favor or against the role of sleep in memory – cultivated viewpoints only at each extreme. Such a divergence 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 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* type of sleep is or is not required 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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Open Peer Commentary

Redefining memory consolidation

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Abstract: Based on brain state-dependent behavioral changes, consolidation of sensorimotor memories has been posited to evolve in two different functional stages. Only the second of these stages requires sleep and leads to performance benefits. Recent results, however, suggest that sleep is not always crucial for the expression of delayed behavioral gains but might be critical for enhancing automaticity in the absence of attention, another expression of memory consolidation.

Little is known about the cerebral processes that culminate in the formation of permanent sensorimotor memories. Evidence from psychophysical and neurophysiological studies intimates different functional stages in perceptual and motor memory formation based on early and delayed behavioral gains, on quantitative and qualitative behavioral benefits, and on the neural correlates of time-dependent changes in behavior. *Consolidation* is one of these stages, and refers to the slow changes – in both brain dynamics and behavior – evolving after a single training session, that make learning more resistant to interference, less dependent on voluntary attention, and more long-lasting. Based on behavioral parameters and the time spent on specific brain states, Walker provides solid arguments on refining the definition of memory consolidation. In particular, he subdivides consolidation into two distinct functional stages with different time courses and different behavioral expressions, which most likely are subserved by different neuronal mechanisms. While the first stage, *consolidation-based stabilization*, is simply determined by the passage of time and might be mediated by local cellular mechanisms, the subsequent stage, *consolidation-based enhancement*, develops during intervening periods of sleep and seems to be mediated by neural reorganization. Only the latter leads to additional gains in performance, a sine qua non condition for consolidation-based enhancement.

Regardless of variations in performance, both substages of memory consolidation involve qualitative shifts in the representation of the sensorimotor experience. The neural correlates of these changes in the internal neural models differ not only from one stage to the other, but also, and contrary to what can be inferred from Walker's contemporary model, from sensory to motor learning.

With the passage of time – that is, several hours after completion of training – newly-acquired motor memories become immune to interference. At this point, performance remains unchanged, but the task becomes more automatic, as revealed by the decreased role of the prefrontal cortex and the increased contribution of the cerebellum (Shadmehr & Holcomb 1997). In the perceptual domain, neither electrophysiological changes (e.g., Atienza et al. 2002) nor additional behavioral benefits (e.g., Stickgold et al. 2000b) have been reported within the hours following completion of training, before a night of sleep. It is unknown, however, if a new representation of the sensory event emerges as a result of memory stabilization, such as in the motor domain.

Although most evidence suggests that stabilization of new memories does not require sleep, it remains to be determined whether or not sleep speeds this process. In fact, there are results that indirectly support this hypothesis. Indeed, a midday nap containing slow wave sleep has been shown to prevent performance deterioration in a texture discrimination task tested within the same day (Mednick et al. 2002). If the nap period also includes

REM sleep, it produces improvement when tested the same day and enhances performance twice as much after one intervening period of nocturnal sleep (Mednick et al. 2003). So, if the effects of diurnal and nocturnal sleep on learning are additive, sleep might facilitate stabilization of sensorimotor memories as well.

Sleep seems to be a crucial factor for additional behavioral improvement in the absence of further practice. This has been demonstrated for several motor skills and for certain kinds of perceptual skills in visual modality. Recent results, however, do raise the hypothesis that the simple passage of time might also have a consolidation-based enhancement effect on other forms of memories. For example, Donchin and colleagues (Donchin et al. 2002) trained subjects to make reaching movements while holding a robotic arm that applied forces to the hand. Contrary to any prediction, subjects tested with 24 hours of sleep deprivation performed as well as the control group. Similar results were seen in subjects trained in a sound discrimination task (Atienza et al. 2004). In that study, both control and sleep deprived subjects showed increased accuracy and speed when tested 48 hours after completion of training, without intervening practice. Changes in brain dynamics as revealed by changes in event-related potentials suggested, however, that sleep, and not simply the passage of time, plays a role in consolidation of this perceptual task. As in most studies evaluating whether different brain mechanisms subserve different stages of sensorimotor learning, performance was tested while attention was focused on the sound discrimination task, but brain electrical activity was measured while subjects directed their attention elsewhere. This original approach disentangled the effects of sleep on behavior and brain dynamics. Post-training sleep deprivation prevented neither behavioral improvement nor the slow development of cortical dynamics related to the enhanced familiarity with the task. However, those cerebral responses associated with the automatic shift of attention to unexpected sounds were evident only in subjects who slept the night following training. We conclude from these results that sleep is not always crucial for the expression of the delayed gains, but it might be decisive for enhancing automaticity in the absence of attention, another expression of memory consolidation. Should the brain mechanisms involved in sleep-induced automaticity enhancement differ from those mechanisms responsible for sleep-dependent behavioral enhancement, consolidation-based automaticity might be a new latent, intermediate stage of memory formation.

We believe the relative contributions of time, awake or asleep, to consolidation-based enhancement still remain unclear. Likewise, the neural correlates of consolidation-based enhancement need to be investigated in both the perceptual and motor domains. Psychophysical, neuroimaging, and computational studies suggest that different brain dynamics underlie consolidation of motor and perceptual memories. While consolidation of motor learning seems to require engagement of new brain regions and increased functional connectivity in the cortico-cerebellar system for performance of the learned task (e.g., Maquet et al. 2003; for a review see Ungerleider et al. 2002), consolidation of perceptual learning seems to be mainly restricted to strength of local connectivity within the cortical regions initially involved in memory acquisition (e.g., Hoshino 2004; Karni & Sagi 1991; Schwartz et al. 2002; for a review see Gilbert et al. 2001).

There are other aspects of consolidation of motor memories that need to be investigated for perceptual skills. For example, in the motor domain, the effects of consolidation-based enhancement remain for several months and are qualitatively different from the additional gains resulting from prolonged training (Korman et al. 2003). Whether or not perceptual learning results in similar multiple shifts in the representation of the memory experience has to be determined. Likewise, Walker and colleagues recently found that consolidated motor memories return to a labile state by simple rehearsal (Walker et al. 2003a). Since these labile memories seem to require subsequent reconsolidation, should we then talk of reconsolidation-based stabilization and reconsolidation-based enhancement?

Molecular mechanisms of synaptic consolidation during sleep: BDNF function and dendritic protein synthesis

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Abstract: Insights into the role of sleep in the molecular mechanisms of memory consolidation may come from studies of activity-dependent synaptic plasticity, such as long-term potentiation (LTP). This commentary posits a specific contribution of sleep to LTP stabilization, in which mRNA transported to dendrites during wakefulness is translated during sleep. Brain-derived neurotrophic factor may drive the translation of newly transported and resident mRNA.

The target article makes a valuable distinction between the role of sleep in the stabilization and enhancement of memory consolidation. Very little is known regarding the molecular mechanisms underlying these processes. Insights into the role of sleep in the molecular mechanisms of consolidation are likely to come from studies of activity-dependent synaptic plasticity, including long-term potentiation (LTP), long-term depression, and depotentiation.

Sleep: A window of opportunity in synaptic stabilization. LTP is the most ubiquitous and best understood form of synaptic plasticity. Formation of stable LTP, like memory consolidation, requires at least one period of new mRNA and protein synthesis. Does LTP stabilization require sleep? Few studies have looked at this and no clear answer has emerged. Late protein synthesis-dependent LTP can certainly be induced in brain slice preparations suggesting that sleep is not an absolute requirement for stabilization. On the other hand, LTP can last far beyond the lifespan of tissue slices and is likely to consist of multiple phases.

Protein synthesis-dependent consolidation represents a commitment of cellular resources toward macromolecular synthesis, and, presumably, a commitment in computational terms for the network in which the altered synapses are embedded. The NMDA-receptor is exquisitely designed to trigger LTP in response to coincident pre- and post-synaptic neuronal activity. Rather than responding slavishly to the intracellular events that trigger LTP, stabilization is likely be to have its own molecular controls governed at least in part by new synaptic signaling events occurring during the maintenance phase of LTP.

Brain-derived neurotrophic factor (BDNF) is a potential mediator of synaptic consolidation. First, BDNF is stored in or near glutamatergic synapses from which it is released in an activity-dependent manner. Release from dendrites has been shown in hippocampal neurons. Second, the BDNF-receptor, TrkB, is expressed on glutamatergic nerve terminals and postsynaptic spines, suggesting bidirectional signaling. Third, BDNF is capable of stimulating its own release, creating regenerative loops of BDNF-TrkB activation. Fourth, BDNF regulates gene expression and protein synthesis. Finally, several lines of evidence suggest that BDNF serves to trigger protein synthesis-dependent LTP (Kang & Schuman 1996; Kang et al. 1997; Messaoudi et al. 2002; Ying et al. 2002). Thus, BDNF acts locally to trigger a process of protein synthesis-dependent consolidation.

Our laboratory is currently exploring the idea that labile synapses are actively stabilized during sleep. Sleep may provide the conditions in which synapses, primed and readied during waking states, are actively read out and stabilized. How would such a mechanism operate at the molecular level? Recent work suggests that LTP requires synthesis of proteins locally, in dendrites, in addition to synthesis in cell bodies (Steward & Schuman 2003). In the rat dentate gyrus, LTP induced by brief high-frequency stimulation or local infusion of BDNF is associated with induction of the immediately early gene Arc (activity-regulated cytoskeleton-associate protein). Once induced, Arc transcripts are rapidly de-

livered from granule cell bodies into dendritic process, where mRNA levels remain elevated for several hours. New evidence based on local infusion of Arc antisense oligodeoxynucleotides shows that *stabilization* of LTP requires a window of Arc translation (Messaoudi et al. 2004). In addition, a handful of mRNA species are stored in dendrites in a translationally dormant state. One of these mRNA encodes the α-subunit of CaMKII, a key enzyme in synaptic plasticity. LTP is associated with translocation of preexisting CaMKII mRNA into dendritic spines (Havik et al. 2003), and mutant mice lacking dendritic CaMKII mRNA have impaired late LTP and memory function (Miller et al. 2002). Furthermore, in isolated synapses, BDNF application drives the translation of both CaMKII and Arc mRNA (Kanhema et al., submitted; Yin et al. 2002). This raises the possibility that BDNF stimulates synaptic stabilization through translation of transient (Arc) and resident (CaMKII) dendritic mRNA. As components of the post-synaptic density, these gene products are positioned to modulate glutamate receptor signaling and synaptic structure.

When in sleep would this take place? In slow-wave sleep (SWS), synchronized population events such as hippocampal sharp-waves and dentate spikes could be involved (Bramham 1998; Buzsaki 1989). The frequency of these events is increased during SWS, and this state is associated with global increases in protein synthesis (Ramm & Smith 1990) Depolarization of dendrites during these population events may facilitate BDNF release, which then drives dendritic mRNA translation. In REM sleep, synaptic inputs synchronized to the positive theta peak could have a similar role. Furthermore, cholinergic transmission during REM sleep could contribute to modulation of dendritic protein synthesis (Feig & Lipton 1993).

In addition to stabilization, sleep-related modification of synaptic strength may involve activity-dependent decay of glutamatergic transmission and depotentiation. Decay of LTP appears to be an active, NMDA receptor-dependent processes extending over several days (Villarreal et al. 2002). Synapses transiently potentiated during waking that fail to undergo protein synthesis-dependent stabilization may be depotentiated. Protection from depotentiation is protein synthesis-dependent (Woo & Nguyen 2003). These mechanisms of selective stabilization and destabilization may contribute to *enhancement* of memory consolidation during sleep.

Modulation of LTP induction during sleep. The target review also raises the question of new acquisition during sleep. Studies of LTP have shed some light on this issue. For example, LTP is powerfully modulated by sleep-wakefulness state. While readily induced during REM sleep, LTP induction is suppressed in an all-or-none manner during SWS (Bramham & Srebro 1989; Leonard et al. 1987). There must exist powerful endogenous mechanisms to inhibit new LTP induction during particular stages or events in SWS. The mechanism and physiological significance of this suppression is unclear. As detailed in the review, post-trial learning is associated with periods of enhanced REM sleep important for retention. Perhaps LTP induction is generally facilitated during these prolonged REM epochs. However, in the only work examining this issue so far, no changes were found in the magnitude or duration of LTP induced during enhanced REM sleep (Bramham et al. 1994). Thus, if *new potentiation* is facilitated during enhanced REM sleep, this potentiation is likely to be a function of REM-epoch duration and reactivation of network nodes.

Sleep is optimizing

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Abstract: It is suggested that Walker's consolidation-based enhancement of memory during REM sleep corresponds to the simulated annealing technique used for function optimization, and that robotic and AI design could benefit from inclusion of a deliberate REM-like memory optimization phase.

Scene 1: A robotics laboratory. A frustrated John Doe sits at a computer connected to a humanoid robocup soccer player. Across the room is his friend, Matthew Walker, who is visiting from the medical school.

JOHN: I don't get it. I've been able to train my robot to have all the basic skills, but it can't play worth a damn. Sometimes it makes the wrong decision, sometimes it just takes too long to choose. Either way, the other player just drives the ball by. . . .

MATTHEW: What sort of architecture do you use for memory and learning?

JOHN: It uses a neural network-based system. Recognition functions use Hebbian learning; actions are learned using the back-propagation algorithm.

MATTHEW: So it's basically patterned after the brain?

JOHN: Pretty much.

MATTHEW: So when does it sleep?

JOHN: Sleep!?

MATTHEW: Yes, sleep. My research shows that the initial acquisition and stabilization of memory do not depend on sleep, but a further process, consolidation-based enhancement, depends crucially on sleep. Since this is true of the brain, it should be true of your neural-based soccer player.

JOHN: Nonsense! Why would a humanoid robot using silicon circuits to simulate neural activity need sleep? Ridiculous! Sleep is a defect of meatware! I sleep as little as I can get away with. Avoiding those defects is one reason for our robotics research!

MATTHEW: Still, your neural networks are patterned after the functioning of the brain, so I don't think it unreasonable that they also share some of the defects as you say.

[Tom Clarke enters.]

TOM: What's the shouting about?

JOHN: Matthew here thinks that if I make my robots sleep, they will play soccer better.

TOM: Well, wouldn't they? Don't you play better after a sleep?

JOHN: But I'm – a human. My robots are silicon and algorithms . . .

TOM: I've read Matthew's latest paper in *BBS* and there's a lot to it that parallels techniques of mathematical optimization.

JOHN: [*Sputtering*] Matthew's a psychiatrist. How could psychiatric research contribute to humanoid robot design?

TOM: I think if you pay attention, quite a bit. You've heard of simulated annealing? Well, I happen to think that the REM portion of sleep is a kind of simulated annealing for the brain.

JOHN: I use simulated annealing as an optimization technique all the time. You add noise to a system being optimized, then slowly reduce the noise and the system settles into an optimum state. If the noise is reduced slowly enough, the system is guaranteed to fall into the global optimum and not get stuck in a less than optimal local state. Hence the term "annealing."

MATTHEW: Noise? Global optimum? What does this have to do with sleep?

TOM: Well I've always thought that dreaming – the random dis-

connected, illogical content of dreams – is a kind of mental noise that subjects your mind to several sessions of simulated annealing each night.

MATTHEW: Ah. I see what you are getting at. At a cognitive level the process of REM sleep and dreaming serves to stabilize and enhance memories through a process of optimization. Now that you mention it, it seems like rather an obvious idea. There must be an extensive literature on this.

TOM: Oddly, no. I've searched the web for the combination of "simulated annealing" and "REM sleep" and only get 34 hits. There doesn't seem to be much discussion of this except in a few theses. There is literature on optimization at the neural level via simulated annealing, but not at the level of memory content. I'll send you some references (e.g., Beckerman 1998; Cameron 1988; Hinton & Sejnowski 1986; Malhotra 2003; Robocup Soccer League 2004).

JOHN: So how is this going to help my robot win?

TOM: You will have to put your robot into the equivalent of sleep after training sessions. Don't just turn it off, but let it run with random inputs. I'm not sure if random inputs alone will be sufficient, I think there must be feedback from memory to sensory input. But I've never worked out a good architecture to simulate this.

MATTHEW: Don't forget to disable the outputs. Animals in REM sleep are effectively paralyzed.

JOHN: Very interesting. I think I'm getting some ideas of how I can rewire my robot to have REM-like states.

Scene 2: Several months later.

MATTHEW: Congratulations, John. Your robot won the cup. Don't you find that it performs so much better after a good night's sleep?

TOM: I could say something about how the REM sleep – er, simulated annealing – provides precomputed feasible solutions to the NP Hard problems of real world soccer play, but I think I'll quote Douglas Adams instead. "The endless dancing shapes and patterns would reach far deeper into our minds than we could manage by reason and logic. . . . Logic comes afterwards. It's how we retrace our steps. It's being wise after the event. Before the event you have to be very silly" (Adams 2002).

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Where is the classic interference theory for sleep and memory?

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Abstract: Walker's target article proposes a refinement of the well known two-stage model of memory formation to explain the positive effects of sleep on consolidation. After a first stage in which a labile memory representation is formed, a further stabilisation of the memory trace takes place in the second stage, which is dependent on (REM) sleep. Walker has refined the latter stage into a stage in which a consolidation-based enhancement occurs. It is not completely clear what consolidation-based enhancement implies and how it can be dissociated from a stage for memory-stabilisation. A more serious consideration, however, is whether a second stage in memory consolidation that is solely dependent on sleep, is really necessary. The classical, passive, interference theory is able to explain adequately the findings related to the effects of sleep and memory, and can lead perhaps better to an understanding of the highly variable data in this field.

The idea that sleep is a favourable brain condition for memory consolidation has been going around since the days of Sir John Hughlings Jackson. In 1881 he predicted that sleep had a function in stabilising the vulnerable memory trace by making "permanent rearrangements during so-called dreamless sleep" (see Taylor 1958). Although not all researchers are able to show this phenomenon, generally, subjects remember more of a learning task when tested after a period of sleep than they do when tested after an equal period of wakefulness (Benson & Feinberg 1977; Grosvenor & Lack 1984). Historically, this positive effect of sleep on memory is interpreted in terms of the "interference theory," implying that during sleep there is less new learning interfering with memory storage than during wakefulness (Underwood 1966). In the period that the labile memory trace is stabilised, it is still vulnerable for interference. Hence, in the absence of interpolated learning, in a situation with less retroactive inhibition, the remembrance is better when sleep intervenes between original learning and recall than when this interval is filled with wakefulness during an ongoing uptake of new information. This is the classical, passive, way to explain the positive effect of sleep on memory.

An alternative interpretation, however, is that sleeping might play an active, rather than a passive, role in the stabilisation of the labile memory trace (Ekstrand 1967). An experimental upswing came when animal research suggested that REM sleep in particular, rather than sleep per se, could be important for the positive effect of sleep on memory. Two lines of research dominated the field: the study towards the effects on learning on sleep with the question whether REM sleep should be increased after a period of intensive learning, and the question of whether deprivation of REM sleep after learning should impair memory consolidation. Especially popular in animal research were the deprivation experiments, and a huge number of rats were put on inverted flowerpots to deprive them from REM sleep. Inconsistent and controversial results were found, which could be ascribed mainly to inappropriate deprivation techniques and the lack of adequate controls. Studies to establish that intensive learning was followed by an increase of REM sleep were also inconclusive. Even less positive evidence could be found in human research. These disappointing outcomes resulted in a decline of these kinds of studies in the late eighties and the beginning of the nineties.

However, the findings in the paper by Karni et al. (1994) heralded an experimental revival. These authors showed, in humans, an improvement in performance of a perceptual skill dependent upon the occurrence of REM sleep. Although the focus was again on an active role of REM sleep and not of sleep per se, Giuditta et al. (1995) gathered evidence for the "sequential hypothesis" on sleep function. According to this hypothesis, REM sleep, occurring later in the night, should serve the ultimate completion of consolidation, but the earlier occurring slow-wave sleep should function in the first step towards stabilisation of the memory trace. Since then, the role of non-REM sleep has also been explored, but up to now sound evidence for an active role of non-REM sleep, as well as REM sleep, in memory organisation is weak and contradictory (Vertes & Eastman 2003).

It is against this background that Walker's model must be regarded. He has adjusted the existing two-stage model of sleep and memory, which was formulated in 1970 by Bloch. Bloch suggested a discrete two-stage model in which the acquisition of new information is followed by a short period of processing, and true consolidation occurs later, during (REM) sleep. Walker's two-stage model is quite reminiscent of Bloch's model, but it is refined in the sense that he proposes a first stage in which a time-dependent consolidation-based stabilisation takes place, followed by a second stage in which a sleep-dependent consolidation-based enhancement takes place. Walker based this refinement on data obtained with an extended version of the Jenkins and Dallenbach (1924) paradigm, among others. In this paradigm, subjects were trained to perform a motor task skill, either in the morning or in the evening. Subjects trained in the morning were tested in the evening and retested the following morning. Whereas the first (evening) test showed no significant change in performance from the training session, the second (morning) test, which was admin-

istered after a night of sleep, showed significant improvements. On the other hand, subjects trained in the evening already showed improvements in the first (morning) test, and no further improvements were demonstrated in the second (evening) test. This led Walker to conclude that a consolidation-based enhancement of performance, leading to a significant improvement, occurred only after a night of sleep. It is not fully clear to me, however, what exactly consolidation-based enhancement implies. Is there an experimental design, which can discriminate between predictions related to consolidation-based stabilisation and those related to consolidation-based enhancement?

Walker rejects the classical time-dependent second stage model of memory formation, but on what grounds? Putting aside that a circadian rhythm in performance cannot fully be excluded in the previously mentioned experiment, the good old interference theory also seems able to explain these results. Let me try to give a comparison: the role of sleep in food digestion. After food intake the process of digestion starts, independent of sleeping and waking. But sleep provides a more beneficial condition for digestion than waking. During waking, activity interferes with digestion, but during sleep bodily activity is restricted, providing a minimal interference, and the process of digestion is faster. The effect of sleep on this digestive process is variable: It depends on factors such as the kind and amount of food, the circadian time of eating, and the timing of sleep after food intake. In all, the effect of sleep on digestion is generally positive, but indirect and variable. In this way it is an interference theory, like the one which explains the positive effect of sleep on memory. Consolidation starts immediately after acquisition; it is a slow running process in which information is first stored in a labile trace, and then remodelled into a stabile memory trace. It seems unnecessary to accept that sleep has a direct and active role in memory stabilisation, simply because it creates a favourable condition for storage by preventing gross disturbances caused by newly incoming information. Retroactive interference is a main factor in inadequate memory formation and minimising interference might improve memory organisation. In this way the outcomes of the afore-mentioned experiments can also be explained.

Therefore, I do not see the necessity for a two-stage model to explain the positive effects of sleep on memory. The one-stage time-dependent model of memory formation, with fluctuating amounts of interference dependent on sleeping and waking, is simpler and, in my opinion, also able to explain the highly variable effects of sleep on memory, as described in the literature.

Motor memory: Consolidation-based enhancement effect revisited

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Abstract: Following Karni's seminal work, Walker and other researchers have recently provided gradually convincing evidence that sleep is critical for the consolidation-based enhancement (CBE) of motor sequence learning. Studies in our laboratory using a motor adaptation paradigm, however, show that CBE can also occur after the simple passage of time, suggesting that sleep effects on memory consolidation are task-related, and possibly dependent on anatomically dissociable circuits.

In this target article, Walker proposes a well-documented account of the role of sleep in both acquisition and consolidation phases of procedural memory formation. We applaud his effort to better define the nature of sleep's contribution to the consolidation of motor and perceptual learning by proposing a new model that separates this process into two stages: a consolidation-based stabilization (CBS) phase and a consolidation-based enhancement (CBE) phase. Although enlightening, we believe, however, that this model needs further refinement, especially with respect to the specificity of sleep on CBE effects in the motor domain and the possible functional neuroanatomical systems mediating this motor memory process.

First, using skill learning paradigms initially developed by Karni and colleagues (Karni & Sagi 1993; Karni et al. 1994; 1995; 1998), Walker, Stickgold, and other investigators have recently reported compelling evidence that sleep is indeed necessary after initial training to observe spontaneous gains (i.e., consolidation) in performance without additional practice on the same task (Fischer et al. 2002; Stickgold et al. 2000a; 2000b; Walker et al. 2002; 2003b). In the motor domain, for example, Walker and colleagues have elegantly demonstrated that CBE is elicited only after a period of sleep, and not after an equivalent period of time awake following the acquisition of a new sequence of finger movements (i.e., motor sequence learning). The results of a recent study in our laboratory suggest, however, that time alone is sufficient for observing CBE effects when testing for the consolidation of skills based on the capacity to compensate for environmental changes (i.e., motor adaptation) (Simard 2004). In the latter experiment, motor adaptation was measured using a version of the eight-target tracking task in which subjects were required to use a joystick to move a cursor from the center of a screen to one of eight targets following an elliptical trajectory within a time limit (see Fig. 1A). Target reaching on each trial was accomplished in a reversed mode, where the relation between movements with the joystick and direction of the cursor had been inverted. In a parametric experimental paradigm, three distinct groups ($n = 12$) of healthy volunteers were first given enough practice trials in the morning (i.e., 16 blocks of 16 trials each) to reach asymptotic performance within this training session. Without additional practice, subjects were then retested 5, 8, or 24 hours later to measure their level of performance gains on this task. Importantly, subjects in the 5-hour and 8-hour-delay conditions were told to refrain from taking a nap between the two testing sessions, while subjects in the 24-hour delay group were allowed a normal night of sleep. The results (see Fig. 1B) revealed that unlike subjects in the 5-hour delay group, those who were tested 8 hours later the same day, or 24 hours later the next day, showed a significant increase in performance between testing sessions. Furthermore, the level of between-session improvement on the task did not differ between these two groups, hence suggesting that the simple passage of time is sufficient to elicit spontaneous performance gains in a motor adaptation task, and therefore that sleep-dependent CBE effects are not universal, but task-dependent.

Second, although Walker describes potential physiological, neurochemical, molecular, and cellular mechanisms underlying the development of procedural memories, little is said about the neuroanatomical systems thought to support the different forms of motor learning (motor sequence, motor adaptation) discussed in this review paper, and about their possible role in mediating CBE effects in the motor domain. In such a model, Doyon and Ungerleider (2002; cf. Doyon et al. 2003) have recently proposed that both cortico-striatal (CS) and cortico-cerebellar (CC) systems contribute to motor learning and consolidation, and that representational changes within these two systems depend not only on the learning phase, but on the type of motor skilled behaviour acquired. In brief, this model suggests that in the fast (early) learning phase, both motor sequence and motor adaptation tasks recruit the CS and CC systems. When consolidation occurs, the subject has achieved asymptotic performance on the task, and this performance is then automatic. At this point, it is believed that the neural representation of a new motor skill is distributed in a network of structures involving the CS or CC circuit that depends on the type

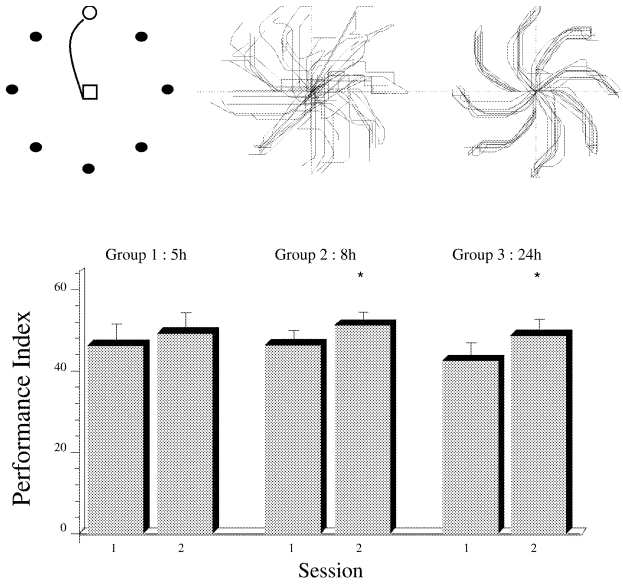

Figure 1 (Doyon et al.). Motor adaptation consolidation in normal control subjects: Method and results. Motor-adaptation learning: (A) Figure illustrates the motor- adaptation task, in which subjects are asked to reach one of the eight targets, following a curved line with a joystick in the inversed mode; that is, the x and y coordinates of the joystick had been reversed. (B) Early in training, movements of the cursor had significant deviations from the elliptical path. (C) Late in the training, movements of the cursor followed essentially a straight elliptical line. (D) Bar graph illustrating the results from Simard and colleagues (Simard 2004). Consolidation was operationally measured by comparing the subjects' performance on the last two blocks of trials in the training session to the second block of the retest session. Only subjects who were retested 8 and 24 hours after initial training revealed significant spontaneous performance gains ($p < .05$). These findings suggest that the simple passage of time is sufficient to observe significant consolidation of a motor adaptation skill, and that this physiological process may occur within a period of 5 to 8 hours after training.

of learning. Our model proposes that for motor adaptation, the striatum is no longer necessary for the retention and execution of the acquired skill; regions representing the skill are now thought to involve the cerebellum and related cortical regions. By contrast, a reverse pattern of plasticity is believed to occur in motor sequence learning, such that with extended practice the cerebellum is no longer essential, and the long-lasting retention of the skill is now believed to involve representational changes in the striatum and associated motor cortical regions. Most important for this commentary, however, this model also makes predictions about the neural systems mediating the consolidation of these two motor learning modalities. Indeed, based on previous imaging studies (Imamizu et al. 2000; Nezafat et al. 2001; Shadmehr & Holcomb 1997) that have shown that the cerebellum and its related structures are critical for the consolidation and long-term storage of a motor adaptation skill, one would expect that the striatum and its associated structures would play an equally important role in the consolidation of a newly-learned sequence of movements, as this structure contributes to the maintenance of this skilled behaviour over time (Doyon et al. 2002; 2003). Based on this model, one would also predict that sleep-dependent CBE effects observed in motor sequence learning would be associated with representational and cellular changes within the CS system, whereas the time-dependent CBE effects of motor adaptation described above would be mediated by similar changes in the CC system. To date, however, these hypotheses still remain conjectural.

In conclusion, although Walker's notion of CBE in motor learning is informative, it ought to be extended in order to explain that, depending on the type of motor skill acquired, sleep is not necessary for spontaneous performance gains to be observed, and that sleep-dependent and time-dependent CBE effects may be due to plasticity within different neural substrates.

Do words go to sleep? Exploring consolidation of spoken forms through direct and indirect measures

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Abstract: We address the notion of integration of new memory representations and the potential dependence of this phenomenon on sleep, in light of recent findings on the lexicalization of spoken words. A distinction is introduced between measures tapping directly into the strength of the newly acquired knowledge and indirect measures assessing the influence of this knowledge on spoken word identification.

Based on Walker's account, procedural memory and declarative memory seem to have little in common. The two domains would differ not only in their neural substrates and, potentially, the physiological processes underlying learning, but also by the nature of the stages that characterize memory consolidation. For most models of declarative memory (e.g., Buzsaki 1998; Eichenbaum 2000; Hasselmo 1999; McClelland et al. 1995; O'Reilly & Norman 2002), consolidation refers to the integration of newly acquired representations into long-term storage and expresses itself by the fact that decay of memory traces or interference (from another ongoing learning) can no longer be observed. In contrast, in Walker's model of procedural memory formation, integration with pre-existing knowledge is not part of the consolidation process per se; rather, it is an ancillary stage that may take place during or after stabilization or enhanced learning, which are seen as the crucial steps (see Fig. 2B [sect.2.3.2] and Fig. 5 [sect. 2.3.2.2] in the target article). Although procedural and declarative memory tap into different aspects of experience and use presumably different neural implementations, there remains the potential for an isomorphism in the stages of memory formation across the two domains. As Walker points out, little is known about the integration of procedural information, the importance of this stage, and its temporal relationship with respect to consolidation-based enhancement, which affects both perceptual (e.g., Karni et al. 1994) and motor skills (e.g., Brashers-Krug et al. 1996; Walker et al. 2002). In our view, the main reason for this state of affairs is that studies showing memory enhancement have typically used only direct measures of learning, thereby telling us about the strength of the newly acquired representations but not whether these representations would influence the access to more permanent ones. The goal of this commentary is to address the issue of integration, and the potential dependence of this phenomenon on sleep, on the basis of recent results obtained on lexicalization of spoken word forms (i.e., their integration into long-term lexical memory). Whilst the type of knowledge involved in word acquisition is initially declarative, the full lexicalization of this knowledge implies that the newly created representation should affect a well-established perceptual skill: identifying spoken words. Lexicalization of novel words, therefore, represents an ideal test case for bridging the gap between models of consolidation of declarative and procedural memory.

In models of spoken word identification, a key feature of a lexical entry is its ability to be evoked when compatible with the input, and to compete with similar-sounding entities for identifica-

tion (Gaskell & Marslen-Wilson 1997; Luce & Pisoni 1998; McClelland & Elman 1986; Norris 1994). Hence, an acid test of whether a spoken form has been lexicalized is whether or not it engages in lexical competition, and thereby affects the activity within the mental lexicon. In one of our experiments (Gaskell & Dumay 2003, Experiment 3), adults learned nonsense-speech sequences that overlapped strongly with existing words (such as "cathedruke" for "cathedral"). The influence of the newly learned words on lexical activity, our indirect measure of learning, was then assessed using the pause detection paradigm. Here, participants made speeded decisions as to whether a short silence was present towards the offset of the existing words (e.g., "cathedr_al"). Mattys and Clark (2002) demonstrated that pause detection latencies are positively correlated with the number of words activated in lexical memory on hearing the speech portion preceding the pause. As indicated by a direct two-alternative force choice recognition test (e.g., "cathedruke" vs. "cathedruce"), the 36 exposures to each novel word during learning resulted in a good immediate explicit knowledge, with no significant change when retested one week later (96% of correct responses on both occasions). More crucially, whereas no change in lexical activity was observed in pause detection immediately after learning a new competitor, a clear effect of the novel competitor had emerged during the time interval between exposure and retest, seven days later. This is strong evidence that, in contrast to phonological (episodic) storage, lexicalization (and thus integration) of spoken words requires a substantial amount of time.

In a follow-up experiment (Dumay et al. 2004, Experiment 2), we examined more closely the timecourse of lexicalization, tracking the effect of exposure on lexical activity at three time points: immediately after exposure, 24 hours later, and a week later. Again, there was no evidence of immediate lexicalization, but 24 hours after exposure as well as a week later, pause detection performance on the existing words demonstrated that the new competitor was now contributing significantly to lexical activity. Concurrently, the performance in explicit recognition and free recall improved across sessions (from 82% to 87% and from 8% to 20%, respectively).

From these results, we can therefore narrow down the critical time period for the lexicalization of a spoken word form to somewhere between one and 24 hours after exposure. Whether the integration of new representations into long-term lexical memory is primarily dependent on sleep (or some sleep-specific brain state or states) is still to be determined. However, our findings are clear evidence that both consolidation-based enhancement and integration of new declarative memory representations can be obtained after a posttraining interval that includes sleep. Rather than being a distinct stage in the process of memory formation, enhancement might be the sign that integration has taken place. In fact, it would seem quite uneconomical to engage into some sleep-dependent additional learning if it were not to integrate the corresponding representations in a long-term associative network or repertoire. Walker (sect. 2.2) speculates that the effect of sleep on declarative memory could be more protracted and one of subtle maintenance in order to prevent decay over time. Our data indicate that this may not be the case. They suggest instead that following sleep, newly acquired declarative memory representations are not only enhanced, that is, more easily accessed or specified, but also able to affect a highly automatized perceptual skill, and therefore, its underlying procedural memory system.

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What is consolidated during sleep-dependent motor skill learning?

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Abstract: Learning procedural skills involves improvement in speed and accuracy. Walker proposes two stages of memory consolidation: enhancement, which requires sleep, and stabilization, which does not require sleep. Speed improvement for a motor learning task but not accuracy occurs after sleep-dependent enhancement. We discuss this finding in the context of computational models and underlying sleep mechanisms.

Procedural learning, particularly the investigation of motor skill learning, has attracted renewed attention in memory research over the past few years. Procedural learning refers to a particular set of learning abilities that do not afford conscious memory access but may be expressed through performance. It is therefore an ideal starting point to address objectively the problem of sleep and memory. The model presented in the target article by Walker is based on experimental evidence that primarily comes from motor skill learning experiments. In this context, an important distinction to consider is the dissection of the acquisition process. Similar observations can be extended to perceptual and visuomotor experiments.

Influential computational studies of motor control (Kawato et al. 1987; Shadmehr & Mussa-Ivaldi 1994; Wolpert et al. 1995) have suggested that learning a motor skill requires the formation of an internal model of the dynamic behavior of the motor system in the task. For arm reaching movements in interaction with a mechanical device, the internal model may persist for at least 5 months without further practice, even after a single training session (Shadmehr & Brashers-Krug 1997). A computational framework could help to characterize memory-stage concepts like acquisition and consolidation in the context of neural representations.

The motor skill experiments in the target article employed a sequential motor task involving five stereotyped finger movements in the absence of dynamic constraints. It is reasonable to assume that, in adults, the internal models for each of the five movements need not be learned. It is, in fact, easy to fast finger-tap on a surface. However, this task would be profoundly different to a baby, who takes weeks to learn the internal models for skilled finger movements.

So what is "acquisition" in finger tapping? The largest improvement was obtained within the first three learning trials (3 minutes; Walker et al. 2002), suggesting that the process of acquiring a control strategy for existing internal models is fast. Karni and colleagues referred to this as "acquisition of a task-relevant routine" (fast learning; Karni et al. 1995), which additionally does not generalize even after long-term training. Fischer et al. (2002) also found that the enhancing effect of sleep on motor performance is highly specific to the practiced sequence.

This dissection is important because it helps to define constraints for the search of underlying mechanisms. It also guides thinking about the reorganization of internal motor representations during acquisition and enhancement. The enhancement component of consolidation can thus be interpreted as automatization/optimization of the new control strategy: optimization in terms of speed and/or accuracy of execution, as instructed. Note the absence of additional requirements, for example, rhythm, as would be the case for learning to play musical instruments.

Sleep may have enhancing effects on performance. However, it is not clear what aspects of performance, and consequently of internal motor representation, are enhanced exclusively by sleep. In an experiment designed to determine the effects of several interventions interfering with synaptic plasticity on the ability to learn a new motor memory, performance on day 2 after a night of sleep

did not improve compared to the last training set in day 1; in addition, total sleep deprivation between day 1 and day 2 did not alter performance compared to sleeping controls (Donchin et al. 2002). This experiment studied arm reaching in interaction with external forces, which is known to require time-dependent consolidation (Shadmehr & Brashers-Krug 1997). Interestingly, performance was quantified with a learning index that measures quality, rather than speed, on task.

Similar observations can be made for finger skills. When motor skill accuracy (error rate) was measured as absolute number of wrong sequences per 30-second trial (Walker et al. 2002), it did not change significantly between 10:00 a.m., 2:00 p.m., 6:00 p.m., and 10:00 p.m.; nor did accuracy change between 10:00 a.m., 10:00 p.m., and post-sleep 10:00 a.m.; nor did it change between 10:00 p.m., post-sleep 10:00 a.m., and post-sleep 10:00 p.m. In contrast, when error rate was redefined as number of wrong sequences relative to number of correct sequences per 30-second trial (Walker et al. 2003b), significant differences could be observed between all pre- and post-sleep conditions above. Interestingly, Fischer et al. (2002) found that performance speed, but not accuracy, significantly improved during daytime awake retention without practice. Consistent with the proposed model is the hypothesis that an adaptive, compensatory response to increased sleep need could take place during extended wakefulness (Finelli et al. 2000).

In summary, these findings suggest that sleep may not have a uniform effect on all constituents of memory. Rather, specific aspects, or types, of internal representation may be selectively enhanced by mechanisms characterizing the sleep process. Understanding which features of behavioral performance are enhanced will help uncover the specific mechanisms influenced by sleep.

Hypotheses concerning the putative mechanisms that may underlie the consolidation of memory traces during sleep have focused on the role of either REM or non-REM sleep (Maquet 2001). The evidence in favor of one or the other hypothesis requires careful consideration of experimental design and method (Peigneux et al. 2001a). Walker's (2002) hypothesis makes no a priori assumptions about the sleep state that may be exerting an effect on memory consolidation. Thus, he and coworkers were able to infer post hoc a correlation between relative amount of stage 2 non-REM sleep and performance improvement after sleep. The independent study by Fischer et al. (2002) that used a similar task and design confirmed most results, except for dependence on stage 2, showing instead a correlation between amount of REM sleep and performance gain after sleep. For both studies the amount of time spent in one sleep stage across the night at best accounted for less than 44% of the variance in performance gain (the other stage accounted for less than 14%). Therefore, none of those factors can explain entirely the relation between sleep and performance improvement (see also Gais et al. 2000; Stickgold et al. 2000b). Factors other than time related to sleep staging (e.g., electrophysiological variables) should also be tested.

It has recently been proposed that sleep spindles, by virtue of a pattern of excitation-inhibition that provokes massive Ca entry that specifically activates Ca-dependent molecular gates in the spindling cells, could open the door to subsequent long-term changes in cortical networks (Sejnowski & Destexhe 2000). This hypothesis is consistent with the correlation observed by Walker (2002). Prominent in non-REM sleep stage 2, spindles >13 Hz have been shown to have their maximal expression in an area surrounding the head vertex, that is, in close correspondence with the motor cortex (Finelli et al. 2001). Sleep is a regulated process whose timing, duration, and intensity depend on the interaction of homeostatic (the prior sleep-wake history) and circadian factors (Borbély 1982). Would a non-dramatic extension (or reduction) of some stage of sleep cause a better (or worse) improvement in performance? Sleep deprivation prior to new acquisition and sleep-induced enhancement would increase slow wave sleep, and would probably not alter stage 2. However, EEG power density in the range of spindles would be significantly reduced (Finelli et al. 2001). The concept of memory enhancement through sleep could be tested in experiments of this kind.

Sleep and memory: Definitions, terminology, models, and predictions?

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Abstract: In this target article, Walker seeks to clarify the current state of knowledge regarding sleep and memory. Walker's review represents an impressively heuristic attempt to synthesize the relevant literature. In this commentary, we question the focus on procedural memory and the use of the term "consolidation," and we consider the extent to which empirically testable predictions can be derived from Walker's model.

In recent decades, there has been increasing research focus on the topic of sleep and memory, transcending once and for all the "sleep and memory tapes" anecdotal speculation of yesteryear. Walker hails from one of the scientific hotbeds of contemporary sleep-memory research. His starting point is that neuroscientific evidence indicates that sleep plays a role in learning and memory, but that the mechanisms involved are currently unclear. In this heuristic review, Walker seeks to clarify the current state of knowledge, in the process formulating a model whereby, it is argued, sleep impacts favourably on specific elements of memory processing.

In his review, Walker focuses predominantly on procedural memory, proposing that learning in this domain comprises an acquisition phase which is followed by two specific stages of consolidation (the first involving a process of stabilization and the second involving a process of enhancement; the latter is proposed to underlie delayed learning). Walker argues that acquisition and stabilization of procedural information do not rely fundamentally on sleep. By contrast, he argues that procedural memory enhancement does appear to rely on sleep, presenting evidence for specific sleep-stage dependencies. Walker adduces relevant evidence from the sleep/memory literature and nominates potential candidate mechanisms at the molecular, cellular, and systems levels.

In the initial reading of Walker's article, there is some apparent confusion regarding the notion of consolidation. Presumably the sentence towards the end of the Abstract which begins "In contrast, the consolidation stage . . . does appear to rely on the process of sleep" should in fact read "In contrast, the enhancement phase," given that Walker has already stated that the stabilization phase of consolidation is not modulated by sleep per se.

Of interest is the manner in which Walker characterises the distinction between declarative and procedural memory; for example, in section 2.1 he refers to declarative memory in terms of "one or two readings of a text" or "one exposure to an event" and procedural memory in terms of being "passive." It is not entirely clear that these dichotomies are appropriate with respect to the extant literature. For example, a recent search of the Institute of Scientific Information Science and Social Science Citation Indexes found no association between the notions of procedural memory and passive processing. Although this point perhaps does not bear directly on the theoretical framework that is being articulated by Walker, it is germane to some of the neurocognitive mechanisms which he cites. Furthermore, we find the use of the term "consolidation" in this context to be potentially confusing, given its much more frequent use in the declarative memory literature (again evaluated via Institute of Scientific Information Science and Social Science Citation Indexes), and given the sleep-related distinction that is here being attempted by Walker between declarative and pro-

cedural memory mechanisms. How does Walker define "consolidation" exactly in the procedural memory domain as distinct from its more common application in the declarative memory domain? Moreover, how are the fundamental mechanisms of (a) declarative memory "consolidation" and (b) procedural memory "consolidation" deemed to be different with respect to their putatively contrasting interactions with the mechanisms mediating sleep?

Any scientific model worth its salt should, of course, be able to predict novel findings as well as accounting for the current body of data. With respect to Walker's further thoughts concerning procedural memory mechanisms, articulated in section 2.2, it would be interesting if (based on the tenets of his model) Walker were able to offer some novel predictions regarding the types of memory which should or should not be affected by sleep. For example, Foster and colleagues (Gagnon et al. 2004) have recently demonstrated that a form of cognitively implicit learning which has previously been associated with temporal lobe memory mechanisms can in fact be acquired in SJ, a patient with pure hippocampal amnesia (Gagnon et al. 2004). This task involves the learning of supraspan sequences (i.e. Hebb's recurring digit task).

In the test used by Gagnon et al. (2004), the participant is exposed to a series of item sequences in which one embedded sequence is presented on several occasions (amongst other item sequences that are not repeated). Each item sequence has to be recalled immediately after presentation by the participant. With respect to the points articulated by Walker in section 2.3.2.2, hippocampal patient SJ also showed learning on an implicit serial-reaction-time motor-learning task. To what extent do these tasks (which are clearly non-declarative and not critically hippocampally dependent) "fit" with respect to the framework articulated by the author?

It would be helpful if Walker were to delineate more clearly the types of memory mechanisms which he believes to be sleep-dependent. This point is underscored by his reference towards the end of section 2.4.2. to "sleep-dependent neuronal replay" being "expressed throughout different memory domains, including medial temporal lobe structures." In contrast, earlier in the piece Walker has implied that the evidence suggesting that declarative memory is associated with sleep mechanisms is inconclusive. Yet, it is declarative memory with which the hippocampus and other medial temporal lobe structures have been most strongly linked in the literature.

Regarding the proposed role of sleep in different types of memory processing, it would be interesting to know why Walker believes that sleep may be less important in declarative memory than in procedural memory. For example, could this be related to selection pressures operating in our evolutionary past? If so, what are or were the operational characteristics of these proposed mechanisms? Furthermore, how does Walker's model dovetail with the literature indicating that sleep fragmentation may cause deficits in mental flexibility, attention, and executive functioning (as well as affecting mood). The cognitive deficits induced by sleep fragmentation do not appear to be limited to the domain of memory in general (and procedural memory in particular). What are the proposed neural mechanisms underlying these other types of sleep-related cognitive deficits? Moreover, we know that cognitive capacities such as attention and executive functioning can be improved by sleep, so is it possible that some of the sleep-memory enhancement findings reviewed by Walker have in fact been confounded by sleep-mediated improvements in attention and executive capacities?

How might one test Walker's model? For example, what are the critical predictions of the model regarding interventions which influence sleep (such as the types of arousing sound pulses that have been used by Douglas and colleagues; see Martin et al. 1996) and the implications of such interventions for memory enhancement? To what extent are the different neurocognitive mechanisms which Walker imputes, truly coupled to different sleep stages? From a clinical perspective, what are the implications of Walker's model for conditions such as obstructive sleep apnea (OSA) and sleep deprivation? (A recent study by Rouleau et al. 2002 has indicated that OSA patients do not show procedural skill learning deficits, but deficits were apparent in these patients in terms of frontal dysfunction and in psychomotor efficiency and vigilance.)

Finally, given that we know that there are distinctive changes in sleep and sleep patterns across the lifespan, would Walker wish to predict that these changes should have implications for our mnemonic capacity as we age?

Old wine (most of it) in new bottles: Where are dreams and what is the memory?

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Abstract: I discuss how the work in Walker's article adds to the considerable body of research on dreaming, sleep, and memory that appeared in the early days of modern sleep research. I also consider the issue of REM-independent and REM-dependent kinds of learning. This requires including emotional issues in our discussion, and therefore emphasizes the importance of studying and understanding dreams.

Walker's article on sleep and memory is a real pleasure to see. He does a thorough job of pulling together recent work on the role of sleep in memory formation and he responds well to the many voices that still are skeptical of this relationship. This is a battle that has been going on since the early days of modern sleep research, when investigators such as Hawkins (1966), Breger (1967), Dewan (1970), Greenberg (1970), Hartmann (1970), Stern (1970), Fishbein (1971), Pearlman (1973), Glaubman et al. (1978), Hennevin and Leconte (1977), and Palombo (1978) began to publish studies related to the role of REM sleep in the integration of information or memory. Walker's summary of recent work builds on the earlier work in a most convincing manner. The criticisms of studies linking sleep, and especially REM sleep, with memory consolidation began immediately with a focus on the question of stress as the cause of the impairment of memory in REM deprivation (REMD) studies. Pearlman (1973) and Smith (1982), with their work on windows for the REM sleep relationship to memory, gave cogent reasons why stress was not a reasonable reason to discount the effects of REMD: They used the finding that there are periods when REM sleep is more related to memory processing and, studying REM deprived animals at different times, they found that only in the presumed sensitive windows of time was learning impaired. Hence, stress alone could not be blamed for the effects of REMD. Also, the fact that some studies of REMD failed to show any negative effect on learning became a reason to ignore all the positive results. By underlining the fact that there are different kinds of memory, which may or may not need the aid of sleep, Walker gets to one of the most important responses to this sort of criticism. As Walker notes:

> 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. (sect. 2.3.1.1, para. 2, emphasis in original)

This observation captures a distinction which has often been ignored in the debate. It is also very similar to one we made 30 years ago (Greenberg & Pearlman 1974): "Habitual reactions, which are closely linked to survival, are REM independent; but activities involving assimilation of unusual information require REM sleep for optimal consolidation." We compared this distinction to Seligman's (1970) ideas about prepared (hard-wired or instinctual) learning and unprepared learning. One-trial avoidance is considered prepared learning, while tasks which require both many trials and time for learning can be considered unprepared learning.

One might ask how this is different from Walker's distinction between declarative and procedural memory. While Walker's discussion is an excellent response to many of the critics, I feel that it doesn't go far enough. It is overly cognitive, and therefore leaves out a most important aspect of the problem: reference to dreams and what they tell us about the process. This is what is "missing" in the old wine.

Some would argue that dreams are not necessarily associated with REM sleep. Here I should note that the best discussion about the association of dreaming with REM sleep I have seen is the one by Walker's colleagues, Hobson, Stickgold, and Pace-Schott (Hobson et al. 2003). Furthermore, if we take dreams seriously we must include the cortex in the discussion rather than thinking of REM sleep as just pontine in origin. The idea that dreams require cortical activity led me to study how the cortex might be actively involved in REM sleep (Greenberg 1966). The role of the cortex was confirmed by Jeannerod et al. (1965) and Dorrichi et al. (1993), and has been amplified by the current work with cerebral blood flow (Braun et al. 1997) and MRI and PET scans during REM sleep (Maquet et al. 1996). We must, in light of this work, take seriously that the cortex is very much involved in REM sleep and therefore we must listen to what dreams tell us about the role of emotions and emotional adaptation in the whole process of memory consolidation and integration. If we do not do so, we will be continually hounded by those who will say that, because certain memory tasks seem unrelated to REM sleep, there is something wrong with the idea that REM sleep is involved in memory; and, furthermore, we will arrive at a constricted understanding of what is happening to memory during REM sleep.

This approach – examining the role of the cortex and, therefore, dreams – links many findings in a more meaningful way than does drawing the distinction between procedural and declarative memory or focusing on the somewhat ambiguous dimension of more complicated versus less complicated tasks. It allows us to include a fuller consideration of what is happening during sleep beyond simple physiology, namely, the EEG and chemical changes. No one can deny that dreams are a part of sleep. Therefore, why not add what dreams tell us to the rest of the information in order to develop a more complete understanding of what is happening? We could then include the work of Palombo (1978), Cartwright (1986), Reiser (1990), and Greenberg and Pearlman (1993), all of which speak to the kinds of memories that we deal with in sleep and to the role that this activity plays in the mastery, by humans, of themselves and of the environment. This approach also leads to the need to revisit classical psychoanalytic ideas about dreaming and to bring our understanding of the dream aspect of sleep more into line with what Walker has clearly and effectively elaborated in his discussion of sleep and memory (Greenberg & Pearlman 1999).

It is, finally, time for sleep researchers to look at all the information that has been developed since the beginning of modern sleep research. We need to integrate (perhaps with the help of REM sleep) this information. If we are to do this, then such findings as the activity of the limbic system during REM sleep require taking dreams and what they tell us about the emotionally significant issues in the dreamer's life as an essential part of our thinking. We will then find that our understanding of the physiology will complement and enrich our understanding of dreams and that our understanding of dreams will help us make much more sense of the kinds of findings that Walker has pulled together. I would congratulate Walker on the richness and thoroughness with which he has added to the work from the early days of sleep research, and hope we can continue to expand our understanding of an area that provides one of the clearest interfaces between what is psychological (dreaming and memory) and what is physiological (the anatomy and chemistry so ably presented here).

Consolidating consolidation? Sleep stages, memory systems, and procedures

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Abstract: We argue that by neglecting the fact that procedural memory may also have episodic qualities, and by considering only a systems approach to memory, Walker's account of consolidation of learning during subsequent sleep ignores alternative accounts of how sleep stages may be interdependent. We also question the proposition that sleep-based consolidation largely bypasses hippocampal structures.

The idea that sleep reverses the deterioration in performance which arises from extended wakefulness, is altogether less controversial than the assertion that memory is enhanced in the course of sleep, not least because the area is rife with problems that would consign most others to the academic wasteland. The resurgence of interest evident in the last decade is based on some striking empirical results that appear to dissociate waking and sleeping contributions to learning.

Before outlining our central criticism of Walker's timely and valuable target article, we wish to raise two issues which might be exploited to add to its strength. First, much is made of the differential roles that might be played by REM sleep, SWS (slow wave sleep), and sleep spindles. Both REM sleep and sleep spindles are strongly modulated by the circadian pacemaker (Dijk & Czeisler 1995), and this necessarily implies that the effect of sleep on memory enhancement must depend on where in the circadian cycle sleep occurs. It is important that future research ensures that such circadian effects are adequately taken account of, and perhaps that previous research findings, both positive and negative, are reconsidered in the light of the potential for circadian confounds (see also Laureys et al. 2002). Second, the proposed differential involvement of sleep stages in memory enhancement based on correlational evidence and partial manipulations of sleep stages is not sufficient to exclude other possibilities. Rather than accepting these as evidence for separate roles for SWS, REM, and stage 2 sleep, these findings might as easily imply that completion of the sleep process is important for consolidation. That is, completion of the sleep process is characterised by dissipation of SWS need, such that the more one has in the beginning, the more rapidly this process is completed. Once completed, what follows is a sleep-dependent disinhibition of both REM sleep and sleep spindles (Dijk & Czeisler 1995). In short, it may be that SWS or REM sleep or sleep spindles are not important in themselves; what is important is that the sleep process is completed. Careful quantification of the sleep process, through quantitative EEG analysis rather than visual staging, may be required to explore this possibility.

Our principal concern is with Walker's perhaps hasty adoption of a systems account of memory. Citing Squire and Zola's (1996) distinction between declarative and non-declarative memory, and following Tulving (1972), Walker distinguishes between declarative memory that is "episodic . . . (memory for events of one's past)" and that which is "semantic . . . (memory for general knowledge, not tied to a specific event)" (sect 2.1, para. 4). This is contrasted with non-declarative memory that is "non-conscious," requires no "declaration" and includes "procedural memory" as well as "implicit memory." This systems account of memory is perpetrated through Walker's argument. It allows an easy rejection of Buzsaki's (1998) hippocampally-mediated model of episodic transfer which is "pertinent to declarative memory" but which has "less relevance to procedural memory, since learning of skilled sensory and motor tasks can occur without requiring integrity of medial temporal lobe structures" (sect. 2.3.3, para. 2). It is also

finesses what we consider a very telling contrast between the suggested reliance of procedural memory on sleep with the lack of reliance of declarative memory on REM (following Smith 2001). We have a number of related problems with this account.

First, although Tulving's original account of episodic memory was framed in terms of the remembering of one's personal past (i.e., autobiographical memory), "episodic" is now more widely used to reflect memory which relates specific experiences that are peculiar to a given individual (e.g., see Tulving 1985; Tulving & Markowitsch 1998). Second, in the decades since Tulving's introduction of the term, it has become clear that episodic traces are formed and retrieved in the course of acquiring and subsequently repeating a wide range of tasks. For example, the retyping of simple digit strings is speeded if they are retyped using the key-configurations originally used rather than a different key-configuration (Fendrich et al. 1991). Reading of mirror reversed and inverted text is facilitated where the same reversal/inversion is reencountered (Kolers & Perkins 1975). These, together with the instance-based retrieval accounts of skilled behaviour (Logan 1988; 2002), and the proceduralist accounts of memory (Kolers & Roediger 1984; Roediger et al. 2002), stress that it is the mapping between the processing operations performed at encoding and those required by retrieval, which determine the likelihood of retrieval. Indeed, the lack of transfer of consolidated learning in both the texture discrimination task and finger opposition task requires just such specificity. Third, even accepting the crude distinctions between declarative, procedural, and semantic memory tasks offered by Smith and followed by Walker, these tasks are procedural. Moreover, at least in respect of the procedural reinstatement accounts, explicit attempts to remember or judgements of whether one is remembering are independent of whether typing-time is facilitated. That is, in a second sense these "episodic" tasks are non-declarative, because the declarations people make regarding memory are unrelated to how they perform.

Measurements and tasks that assess procedural learning and that do not assess or manipulate their episodic content risk circularity about which brain systems mediate consolidation. If we ignore the episodic content that probably necessitates hippocampal mediation, it is unsurprising that only "non-declarative" tasks appear to benefit from consolidation during sleep. For us, this begs the question as to why, as Smith (2001) reports and Walker endorses, it is that semantic tasks typically fail to show enhanced memory following sleep (see also Vertes & Eastman 2000b). Inevitably the stimulus materials used in such studies differ from those described as "procedural" by Walker, and that may indeed be the reason consolidation effects have not been widely observed. However, there are other differences between these sleep-consolidation studies of declarative and procedural learning, which might place quite different constraints on how we characterise consolidation effects. Consolidation studies of verbal learning almost invariably employ explicit or direct tests of verbal memory. Elsewhere in the memory literature, however, it is not unusual for manipulations to show effects when assessed indirectly (e.g., semantic priming) that are not obvious when people are directly asked to remember (e.g., paired-associate recall, or recognition). Finding that "implicit" but not "explicit" measures of verbal learning showed consolidation effects would presumably weaken Walker's reliance on the system-based semantic–procedural distinction. Furthermore, literate participants presumably encounter the stimuli used in verbal learning studies more frequently than they do particular visual patterns or ways of touching fingers against each other. Because it is meaningful, verbal material can be more readily incorporated within our prior knowledge and experience. It may be because of such factors, rather than any crude semantic–procedural characterisation, that stimuli for which memory traces already exist are consolidated differently, or not at all, by sleep.

Walker's excellent target article successfully offers a theoretical reformulation that serves to integrate empirical findings within a coherent cognitive structure. However, to borrow his phrasing, while the framework certainly serves to stabilise, we are less sure whether it serves to enhance.

Resistance to interference and the emergence of delayed gains in newly acquired procedural memories: Synaptic and system consolidation?

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Abstract: The progressive multistage stabilization of memory (consolidation) relies on post-acquisition neural reorganization. We hypothesize that two processes subserve procedural memory consolidation and are reflected in delayed post-acquisition performance gains: (1) synaptic consolidation, which is classical Hebbian, and (2) in some tasks, concurrently or consequently, "system consolidation," which might in some skills be sleep-dependent. Behavioral interference may affect either type of consolidation.

Consolidation has been conceptualized as a process of progressive multistage stabilization of memory, extending across hours and longer, following task acquisition. During this period of time, experience-dependent gene expression and protein synthesis may lead to long-lasting changes in synaptic efficacy, that is, synaptic consolidation (McGaugh 2000). While synaptic consolidation is considered to be a universal substrate of all memory systems, memory formation may also depend on system or circuit processes (system consolidation), as was first suggested in models of declarative memory formation (e.g., Dudai 2004). Following Karni and Sagi's (1993) paper on visual discrimination learning, and Karni et al.'s (1998) paper on motor sequence learning, results pertaining to procedural memory in different modalities suggest that nonlinear delayed gains in performance constitute an important behavioral correlate of consolidation processes. As discussed by Walker, it was suggested that synaptic consolidation processes subserve the formation of long-term procedural memory in these tasks, in accordance with Hebbian principles, and that these local synaptic changes are reflected in performance gains after some time delay (Karni 1996).

Recent results suggest that the notion of synaptic consolidation may need to be extended to accommodate the evidence that different neuronal circuits are involved in different stages of learning (Korman et al. 2003), in some analogy to declarative memory system consolidation. Delayed time-dependent performance gains may also rely on system consolidation, shifting the burden of retention of newly acquired procedural knowledge to different cortical representations (Dudai 2004; Hikosaka et al. 1999). Walker's phenomenological model nicely summarizes the differential time-course of the two behavioral measures of consolidation with respect to skill acquisition: resistance to interference and evolution of delayed gains. However, Walker's model implies that each of the above measures stands for a different process; the resistance to interference depends on time after training per se, whereas the delayed gains are sleep-dependent. We suggest that Walker's model can be improved by considering the possibility that both synaptic and system consolidation processes might be involved in the expression of delayed gains in some types of procedural learning, specifically, in motor sequence learning. While synaptic consolidation is always involved, not all skill learning requires system consolidation. The conjecture is that in tasks in which system consolidation occurs, sleep might be an important brain state determining the time of expression of delayed gains. In the case of the learning of sequential motor tasks, sleep was found

to be critical for the effective behavioral expression of delayed gains, and there is an independent indication – the generalization pattern of the acquired knowledge – which may reflect an underlying system consolidation process (Korman et al. 2003). There are, however, several reports that under certain conditions of task and training, delayed gains can evolve during a period of a few hours in the awake state following the initial training (Ari-Even Roth et al., in press; Doyon et al. 2003; Karni & Sagi 1993; Karni et al. 1994; some individuals in Fischer et al. 2002). These results raise the possibility that either synaptic consolidation processes are sufficient for delayed gains to evolve or that synaptic and system consolidation processes also occur in parallel during the awake state. Delayed gains may become effective only when both processes phases are completed (Korman et al. 2003). This, however, does not necessarily depend on sleep (see also Doyon et al.'s commentary in this issue). System consolidation may occur either in parallel to or as a consequence of synaptic plasticity, as was previously suggested for hippocampus-dependent memory (McClelland et al. 1995). Walker, following upon Karni and Sagi's proposal, suggests a local, Hebbian, synaptic-consolidation process, but with one phase that requires time per se and a slower, sleep-dependent phase to explain the time-course data. However, a non-Hebbian consolidation process such as homeostatic plasticity (Turrigiano & Nelson 2004) may be at work.

With which post-training process does behavioral interference interact: system, synaptic, or both? There are data suggesting that behavioral interference may also result in different outcomes, in terms of performance, depending on what type of consolidation process is affected. We propose that this notion may explain the discrepancy between studies showing retroactive interference in motor learning (Brashers-Krug et al. 1996) and those showing that an interfering experience only affects the evolution of delayed gains, leaving the gains acquired during the actual session intact (Walker et al. 2003a).

Thus, it is important to address experimentally the question of how the two aspects of post-acquisition time-dependent effects – the sensitivity to interference and the delayed performance gains – are functionally related to each other. For example, changes in the specificity of the knowledge gained from the training experience may serve as an independent indication of the effects that consolidation has on the representation of learned experience in memory. As discussed in our recent paper (Korman et al. 2003), in the motor sequence learning task, a sequence-specific motor representation is set up immediately after post-training and undergoes a time-dependent strengthening at an effector-independent level during the first 24–48 hours of post-training, (a hand-specific representation only evolves following multi-session training). Using a similar approach, we (Korman et al. 2003) recently found that interference during the stabilization period affects the nature of the representation of the trained sequence in motor memory. Compared to training without interference, the pattern of generalization of the acquired gains was significantly different. Given interference at 2 hours of post-training, the untrained hand showed no clear advantage in performing the trained versus the untrained sequence at 24 hours of post-training. However, immediately after post-training and even more so at 24 hours of post-training without interference, both hands showed the expected, clear advantage for the trained sequence. Interference at 8 hours of post-training resulted in an intact sequence-specific representation as well as in significant delayed gains. Thus, interference not only prevents the expression of delayed gains, but also affects the specific representation of the task in long-term memory, following a single training session.

Our suggestion that task performance may rely on different brain substrates before and after consolidation, in some paradigms of procedural learning, may extend the notion of delayed gains as merely reflecting synaptic consolidation in skill learning (Karni & Sagi 1993) and enhance Walker's model. Furthermore, it may also provide new insights into the sources of variance in the time-course of the learning of different skills.

Neurosignals – Incorporating CNS electrophysiology into cognitive process

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Abstract: This commentary reviews electrophysiological research suggesting that oscillatory electrical potentials recorded by the EEG could have function at cellular and DNA levels. Evidence supporting the potential functional significance of sleep-state-specific frequencies includes psychoactive neurochemical alteration of CNS electrophysiology, and sleep-state-specific alteration of dreaming. As Walker proposes, physiologic electrical fields are likely to have a functional role in the consolidation of memory.

The human central nervous system (CNS) is comprised of a hundred billion neurons, each with multiple synaptic connections and each with the capacity to respond to multiple neurotransmitters (Kandel 2000; Schwartz 2000). Researchers have focused on this complex interrelated network of neuroanatomy and neurochemistry to explain neuron functioning in cognitive processes. This focus has often de-emphasized the presence and the potential functional roles for physiologic electrical fields in the CNS.

Sleep differs from waking in that sleep is an electrophysiologic process that can be divided into stages based on the occurrence of synchronous physiologic EEG potentials. Drowsy, awake with eyes closed, and stage 1 (sleep onset) are defined by the presence of alpha – the frequency with the most power on spectral analysis. Stage 2 sleep is denoted by bursts of sleep spindles at sigma frequency. Deep sleep (stages 3 and 4) occurs in association with delta frequency oscillations. The perspective of REM sleep (REMS) as "desynchronized" (target article, sect. 1.1, para. 3) is at least, in part, secondary to the use of high-impedance skin electrodes on face and scalp to record the human EEG. For animal models and in human subjects using intracranial EEG electrodes, REMS is dominated by EEG runs of hippocampal theta rhythm. Recorded in this manner, REMS can be considered the most synchronous of sleep stages (Siegel 2000).

It would seem logical that the EEG-described electrical potentials are an extracellular summation of individual neuron spike potentials. It has been difficult, however, to postulate how discrete spike potentials lead to the propagated global rhythms recorded by the sleep EEG (see Table 1). Specific physiologic frequencies are likely to occur secondary to oscillatory opening and closing of ionic gateways and channels (potassium for alpha, calcium for sigma) (Cheek 1989; Christakos 1986; Steriade 2001).

An extracellular oscillating potential is likely to affect individual neurons in the CNS, and has been shown to affect the tendency of an individual neuron to produce a spike potential (John & Swartz 1978). This effect is electrophysiologically described by the classic Hodgkin, Katz, Goldman equation (Formula 1) for the interaction of potassium, sodium, and chloride ions involved in inducing a neural spike potential (Hodgkin & Horowicz 1959):

Formula 1:

$$\Delta\psi = \frac{2.3\ RT}{f} \log \frac{Pk[k+]o + Pna[na+]o + Pcl[cl-]o}{Pk[k+]i + Pna[na+]o + Pcl[cl-]I}$$

F=Faraday's constant	P=ion permeability constraints	k+=potassium
T=degrees Kelvin	$\Delta\psi$=membrane potential	na+=sodium
o=outside membrane	i=inside membrane	cl-=chloride

The extracellular oscillatory rhythms of sleep are likely to reset neural membrane ion concentrations, and affect electrically sensitive proteins and neuromessenger systems at the synapse and neuron cellular membrane (Pagel 1990; 1993a; 1993b). Formula 2 describes the effects of changing membrane potential changes on cellular kinetics. Oscillatory physiologic electrical fields are likely to have the capacity to supply energy through cyclic-AMP and ATP production at the cellular membrane (Harold 1986):

Table 1 (Pagel). *Differences between physiologic EEG rhythms and spike potentials*

	Voltage	Propagation	Time Sequence	Potential Type	Waveform Character	Cellular Effects	Functions
Spike Potential	Intracellular-(–70mv.) Extra-cellular-(3mv.)	Intracellular-(synaptic) Extra-cellular-(<500microns)	Discrete Recurrent	Spike – generally non-summating	Non-harmonic	Induction of subsequent spike potentials	Neural Transmission
EEG	.05–.15 mv.	Propagated through CNS	Periodic in Specific Sleep States	Waveform – demonstrating interference and reinforce-ment	Resonance – magnetic field inter-ference	Influences neuronal tendency to develop spike potentials	No docu-mented functions

Formula 2:

$\Delta Gp = n(-\Delta ú+) = F(\Delta \psi) - 2.3RT\ Ph$

ΔGp = Kilocalorie/mole (free energy available for ATP synthesis)

$\Delta úH+$ = difference in electrochemical potential of protons inside/outside cell membrane

n = number of protons transiting the membrane per cycle

Changes in cell membrane ion concentrations affect the major cellular transducers including the G proteins, protein kinace C's and the inositol phospholipids (Gilman 1989; Krebs 1989). Changing physiologic electrical fields are likely to affect the expression of that most electrically sensitive of protein complexes – DNA (Pagel 1993b; 1994).

The physiological functioning of these sleep-associated physiologic rhythms can be used to explain sleep stage-specific (i.e., frequency-specific) characteristics of memory consolidation. Postulating an active functional role for the electrophysiological rhythms described by the EEG introduces an attractive and logically consistent approach for the integration of DNA plasticity into the process of memory. Other evidence also exists for the potential functional significance for this system beyond that summarized by Walker in the target article.

Medications producing CNS related behavioral effects induce changes in the EEG, generally affecting background EEG frequencies (Mandema & Danhof 1992) In most cases, a consistent pattern of EEG change produced by a drug is associated with a consistent pattern of behavioral change (see Table 2) (Herrmann & Schaerer 1986).

Pharmacoelectrophysiological analysis of drug effects on the EEG has been utilized to predict behavioral activity of new preparations, drug interactions, and toxicities (Itil 1981; Pagel 2003). These findings demonstrate that CNS active pharmacological agents alter CNS electrophysiology producing drug class consistent alterations of the physiologic EEG rhythms. Many of these agents affect specific neurotransmitters. Some have known effects on memory consolidation.

The content and recall frequency of dreams (sleep mentation reported on awakening from all stages of sleep) vary consistently with the sleep stage specific electrophysiologic rhythms as described by the EEG (Pagel et al. 2001). Dream recall is generally considered to utilize the same memory processes as non-perceptual memories (e.g., intrinsic memory). Sleep-stage-specific content and recall can be affected by the time sequence till report, cognitive alertness on waking, and disease states with associated executive function deficits (i.e., obstructive sleep apnea) (Domhoff 2003; Pagel & Shocknesse 2004). The same variables are likely to affect memory consolidation, suggesting that further integration of memory and dream research will be important for the understanding of both cognitive processes (Moscovitch 1989).

Walker makes a strong argument for the integration of sleep electrophysiology with CNS neuroanatomy and neurochemistry to explain experimental characteristics of memory consolidation. An integration of electrophysiology will likely be required in order to further elucidate the cognitive states, processes, and functions of that most complex of physiologic systems: the human CNS.

Table 2 (Pagel). *Consistent quantitative alteration in physiologic EEG frequencies induced by several classes of psychoactive medications (Pagel 1996)*

	Delta – 0.5–1.5 Hz.	Theta – 5.5–8.5 Hz.	Alpha – 8.5–11 Hz.	Sigma – 12–16 Hz.	Beta – 21–32 Hz.
Benzodiazepines			↓	↑	
Tricyclic Antidepressants	↓	↓			↑
SSRI Antidepressants	↓		↑		
Amphetamines	↓	↓			↑
Opiates	↑		↓		
Classic Neuroleptics		↑	↓	↓	

Key: ↑, ↓ = direction of significant drug induced change of EEG power (Pagel & Helfter 2003)

Beyond acetylcholine: Next steps for sleep and memory research

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Abstract: We consider Walker's thorough review in the context of thinking about future research on the relation between sleep and memory. We first address methodological issues including type of memory and sleep-stage dependency. We suggest a broader investigation of potential signaling molecules that may be critical to sleep-related consolidation. A brief review of the importance of the stress hormone cortisol illustrates this point.

Walker's impressively comprehensive review of the literature on sleep and memory consolidation is a welcome advance that renders a thorny area a bit easier to grasp. Our commentary starts with methodological suggestions and then turns to mechanisms, where we encourage a focus on neuromodulators (in addition to acetylcholine) that are critical to memory function and demonstrate substantial fluctuations across the sleep cycle. We highlight the stress hormone cortisol as an important example.

Methodological suggestions. At this early stage of investigation, we encourage a diversity of designs, as well as careful replications. More attention should be paid to different types of memory consolidation across the sleep cycle. Walker's focus is largely on procedural memory, but the story of sleep and memory consolidation is likely to be quite different for episodic and semantic memory or emotional memory, which must themselves be sharply distinguished. For example, Plihal and Born (1997; 1999a) found that episodic memory (spatial memory, list-learning) is enhanced preferentially by SWS-rich early-night sleep, whereas procedural memory (mirror tracing, priming) is enhanced by REM-rich late-night sleep. While Plihal and Born's probabilistic approach to sleep stages has its own merit, the lack of replicability of sleep stage findings (e.g., using the perceptual discrimination task of Karni et al. 1994) requires additional studies that more carefully examine the relationship between performance and sleep stage specifically. If conflicting evidence continues despite stricter stage-related methodology, the field may require a deconstruction of the traditional Rechtschaffen and Kales (1968) sleep stages into more specific electrophysiological signatures (e.g., spindles or slow-wave activity).

Mechanism issues. Walker concentrates almost exclusively on acetylcholine (ACh), which is elevated during REM sleep and is thought to be involved mainly in memory acquisition (not consolidation). However, ACh is not alone in having an impact on memory function. Just to name a few examples, serotonin, norepinephrine, immune proteins, and trophic factors, as well as the stress hormone cortisol, are also important modulators of memory.

The importance of investigating other neuromodulators can be illustrated by recent studies of cortisol, which effects memory function and shows sleep-stage specific fluctuations. Cortisol secretion is at a minimum during the early portion of nocturnal sleep (when SWS is prevalent) and achieves a diurnal maximum toward the end of the night (when REM is prevalent) (e.g., McEwen 2003). Dense concentrations of cortisol receptors are found in the hippocampus, a structure critical for spatial and episodic memory function. There is considerable evidence that high plasma cortisol concentrations impair performance on episodic memory tasks in wake (deQuervain et al. 2000; Payne et al. 2002). Therefore, one complication in the investigation of sleep and episodic memory consolidation could be the high cortisol levels associated with late-night sleep.

Plihal and Born (1997; 1999a) have argued similarly that REM sleep is an inefficient time to consolidate episodes due to the deleterious effect of elevated cortisol on memory processes. SWS, on the other hand, may be an ideal physiological environment for episodic memory consolidation, because cortisol release is inhibited during early-night periods dense in SWS. Plihal and Born (1999b) found that cortisol infusions during early sleep eradicated the typical SWS-related improvement in episodic memory, but failed to disrupt retrieval of a procedural memory task. Because episodic memory, but not procedural memory, relies on hippocampal function, they concluded that cortisol inhibition during early nocturnal sleep is necessary for episodic memory consolidation. Thus, early SWS may be optimal for the consolidation of episodic memories, while the late-night cortisol-rich REM sleep may inhibit episodic memory consolidation, and account for the episodic memory difficulties often found in REM sleep.

Given the presence of high cortisol levels during late-night sleep, it may be best to test for episodic memory gains after 4 hours of early night sleep or, possibly, with the use of early afternoon naps, as Mednick et al. (2003) did, when cortisol levels are low. Mednick et al. (2003) found that brief naps containing both SWS and REM sleep enhanced visual discrimination learning equivalent to that obtained by a full night's sleep. Naps containing only SWS failed to produce enhancement. Afternoon naps, then, may be another means of isolating SWS and dissociating REM sleep from elevated cortisol.

In addition to cortisol, a number of other neuromodulators, including both immune proteins and trophic factors, may play critical roles in sleep-related memory consolidation. For example, growth hormone, which is known to play a role in memory formation by inducing gene expression for NMDA receptors in the hippocampus (Le Greves et al. 2002), reaches its peak during SWS and drops off during REM. Similarly, SWS-related decreases in the somnogenic process S candidates adenosine and interleukin-1 may play a role in memory consolidation in SWS. Adenosine modulates synaptic plasticity (de Mendonca & Ribeiro 1997) and adenosine antagonism is beneficial to memory formation (Hauber & Bareiss 2001). Interleukin-1, like cortisol, has been implicated in hippocampus-specific memory impairments (Aubert et al. 1995; Gibertini et al. 1995) and is found in high concentrations in the hippocampus (Farrar et al. 1987). If consolidation of episodic memory primarily occurs in SWS and is inhibited in REM, the systematic sleep-stage-specific fluctuations of growth hormone, adenosine, IL-1, and cortisol may contribute to this process.

Other trophic factors that modulate synapse formation and hippocampal LTP, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have been found to be related to sleep, inducing changes in sleep duration (Kushikata et al. 1999) and responding to manipulations in sleep (Peyron et al. 1998; Sei et al. 2000).

Attention to these various signaling molecules which play a role in synaptic plasticity and memory formation and fluctuate systematically during sleep would be quite informative. Many of them are poorly regulated in clinical populations that suffer from memory impairment (e.g., depression, PTSD, Alzheimer's). Investigations of sleep-related memory processes in these populations could illuminate ways in which neuromodulators influence sleep and sleep-memory consolidation interactions.

In summary, Walker has provided a comprehensive review of sleep and procedural memory that will facilitate future research. We have emphasized some methodological and conceptual issues that should be attended to by such future research.

Filling one gap by creating another: Memory stabilization is not all-or-nothing, either

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Abstract: Walker proposes that procedural memory formation involves two specific stages of consolidation: wake-dependent stabilization, followed by sleep-dependent enhancement. If sleep-based enhancement of procedural memory formation is now well supported by evidence obtained at different levels of cognitive and neurophysiological organization, wake-dependent mechanisms for stabilization have not been demonstrated as convincingly, and still require more systematic characterization.

In a laudable effort to move beyond simplistic "all-or-nothing" views on the role of sleep in memory consolidation, Walker proposes that memory traces acquired during a learning episode further undergo at least two distinct sorts of modifications after practice has ended (that is, "off-line"): consolidation-based stabilization (CBS) and consolidation-based enhancement (CBE). The first set of processes would be dependent on wakefulness, while the second would be dependent on sleep. While we certainly agree with the author that previous characterizations of the role of sleep during memory formation has tended to focus on simplistic distinctions, it also appears to us that Walker's own proposal, in which a sharp distinction is made between wake-dependent CBS and sleep-dependent CBE, falls into the same trap.

Admittedly, it is now well established that sleep plays an important role in CBE-like processes. In Walker's proposal, the enhancement component of memory consolidation is akin to what the sleep community used to characterize as a sleep-dependent memory consolidation process. In attributing a specific role to sleep for memory enhancement, however, Walker also asks us to consider that wakefulness plays a specific role in stabilization – a process during which recently acquired information stabilizes at the level attained at the end of a practice session and through which it becomes more resistant to interference. We found, however, that the evidence presented by the author in support of this otherwise interesting hypothesis is far less consistent than the evidence that supports the notion that sleep plays a significant role in memory enhancement.

Indeed, looking at the experimental data, the vigilance state-dependency of memory stabilization seems to vary according to whether the task involves perceptual or motor components. To see this, consider first the visuo-perceptual Texture Discrimination Task (TDT). Performance on this task, as measured at the end of a wake interval subsequent to the end of the training session, generally shows no improvement (Stickgold et al. 2000a), and, more important, appears to decrease with further practice unless a 30-minute nap is allowed, in which case further decay is stopped (Mednick et al. 2002). Interestingly, performance reverts to the initial levels after a longer (60-minute) nap (Mednick et al. 2002). Actual improvement is observed only after a night of sleep (Gais et al. 2000; Stickgold et al. 2000a; 2000b) or after a longer, 90-minute, nap (Mednicket al. 2003), both characterized by the orderly succession of SWS and REM periods. Because performance actually decreases across repetitions separated by wake intervals, one would tend to think that the perceptual memory trace was in fact not at all stabilized during wakefulness. On the contrary, the fact that performance only stabilizes after a nap suggests that memory stabilization takes place during the initial period of sleep, which is dominated by SWS. This interpretation may find further support in the demonstration that overnight performance improvement in texture discrimination is best explained by the amount of SWS in the first part of the night plus the amount of REM sleep in the last part of the night (Stickgold et al. 2000b). We therefore conclude that memory stabilization in a visuo-perceptual procedural task such as the TDT does not appear to depend primarily on a specific wake-dependent mechanism, but, rather, on the occurrence of specific sleep-dependent mechanisms.

Next, consider another type of task involving motor rather than perceptual procedural learning, such as the Finger Tapping Task (FTT). The time course of memory consolidation for this task follows a different course that better fits with Walker's proposal. In the FTT, a slight increase in performance is observed either with repeated practice or with elapsed wake time, albeit overnight improvement remains significantly larger (Fischer et al. 2002; Walker et al. 2002; 2003b). Most important, presentation of interfering material after 30 minutes significantly disrupts performance, which seems not to be the case anymore after a few hours (Walker et al. 2003b). Change in the robustness of a motor memory within a few hours after acquisition has been previously examined by Shadmehr and Brashers-Krug (1997), who elegantly proposed that the recruitment of activity in neuronal circuits following motor practice establishes a reverberating pattern that gradually decays in the short term, and that may serve as the teacher signal for a slower but more robust form of memory storage. Should we therefore conclude that stabilization of memory only occurs during wakefulness? Not necessarily so. Performance stabilization for procedural (or declarative) memory can also be observed after restricted periods of time mostly dominated by REM sleep (or SWS, respectively) (Plihal & Born 1997; 1999a).

A final issue that we wonder about is the functional relationship between stabilization and enhancement components. Walker et al. (2003a) have previously argued that there is a stochastic relationship between the fast components of memory formation, as revealed by the rate of improvement within training sessions and the level attained during initial practice, and the slow, off-line components, which are assumed to be specifically sleep-dependent. However, using the procedural serial reaction time task (SRTT), we have recently reported (Peigneux et al. 2003) that the reactivation of learning-related cortical areas during REM sleep is proportional to the level of performance achieved at the end of the training session. It therefore appears that the cellular processes that subtend the fast, initial "stabilization" stages modulate the subsequent consolidation-based enhancement that takes place during sleep. Understanding this interaction is clearly an important challenge for future research. Hence, while Walker has offered a comprehensive speculative discussion on the biological mechanisms of learning and of synaptic plasticity during sleep, his proposal falls a bit short when it comes to understanding the neurobiological mechanisms that support stabilization and, most important, the relationships between the latter and the mechanisms of enhancement.

New perspectives on sleep disturbances and memory in human pathological and psychopharmacological states

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Abstract: Matthew Walker's article has prompted us to consider neuropsychiatric disorders and pharmacological effects associated with sleep alterations, and aspects of memory affected. Not all disorders involving insomnia show memory impairment, and hypersomnias can be associated with memory deficits. The use of cholinergic medication in dementia indicates that consideration of the link between sleep and memory is more than academic.

In relation to insomnia, as reviewed by Roth et al. (2001), neither consistent evidence of memory deficits nor significant benefits to cognitive performance with hypnotics emerges. In enforced sleep deprivation (38 hours), working memory is not affected (Lee et al. 2003). Fatal insomnia (FI), involving degeneration in anteroventral and mediodorsal thalamic nuclei, leads to total sleep deprivation with hallucinatory episodes. FI is associated with deficits in episodic and working memory with preservation of immediate verbal and visual memory, semantic, retrograde, and procedural memory (Gallassi et al. 1996; Montagna et al. 2003). The amnesic disturbances of FI are connected to the attentional deficit (Gallassi et al. 1996). Fatality in this disorder and in total sleep-deprived animals reminds us that sleep is an essential prerequisite, involving many physiological functions not necessarily directly linked to cerebral activities. In Morvan's syndrome (agrypnia), thalamic pathology has been linked to insomnia described as "stuck" between arousal and stage 1 non-REM sleep. Hallucinations occur although cognitive function can be normal (Batocchi et al. 2001; Fischer-Perroudon et al. 1974). Whilst sleep disturbances, including night-time waking, REM-behavioural disorder and daytime somnolence, are widely reported in Parkinson's disease (PD) and associated dementia, and in dementia with Lewy bodies, these have not been directly linked to memory function. In PD, RBD can precede other features including cognitive impairment (Olson et al. 2000). Supporting Walker's hypothesis, in mania (which is associated with insomnia), inefficient encoding and consolidation of information occurs (Fleck et al. 2003), and in sleep apnea, deficits in short- and long-term memory correlate with measures of sleep disruption (Sateia 2003).

With respect to hypersomnia, there is no evidence that excessive sleep is associated with increased memory function. Schulz and Wilde-Frenz (1995) have reviewed evidence that sleepiness may be the reason for cognitive dysfunction in narcolepsy, reporting no decrements in brief tests which maintain attention; and no deficits in verbal memory (Rieger et al. 2003). In Klein-Levin syndrome, periods of hypersomnia occur with a reduction in short-term memory capacity (Landtblom et al. 2003). Excessive daytime sleepiness among elderly individuals is an important risk factor for cognitive impairment (Ohayon & Vecchierini 2002), and is associated with a decline in verbal memory in cognitively normal APOE e4 homozygotes, a group at high risk of Alzheimer's disease (AD) (Caselli et al. 2002).

In addition to pathological states, normal ageing is associated with alterations in sleep duration, but with no clear-cut evidence of concomitant variations in memory. Learning is not enhanced in infants; for example time-span auditory memory in neonates is shorter than in 8- to 12-year-old children (Cheour et al. 2002a). Although sleep duration declines in the elderly (average 5.5 hours), as does memory performance, Hayward et al. (1992) found no correlation between sleep variables and neuropsychological tests including memory in elderly individuals. Phylogenetically, sleep variations have not been linked to memory function such as consolidation enhancement. Total sleep times range from 20 hours in the brown bat and 18 hours in the giant armadillo to 3 hours in the horse and 2 hours in the giraffe (Campbell & Tobler 1984), with humans midway at 8 hours in young adults and 14 hours at 6 months. However, the lack of any correlation with memory may simply reflect the evolution of distinct species-specific consolidation mechanisms.

Drugs which reduce sleep are not necessarily associated with memory impairment. Nicotine enhances memory and attention but inhibits sleep-promotion while facilitating other wake-promoting systems in normal and AD individuals (Saint-Mleux et al. 2004; Wilson et al. 1995). Modafinil induces prolonged wakefulness in normal individuals, enabling 64 hours of sustained mental effort (Pigeau et al. 1995) and enhances cognition (Turner et al. 2003).

A diverse range of pharmacological agents which enhance sleep are generally associated with memory impairment. Benzodiazepines consistently reduce short and long term (Angus & Romney 1984) and episodic memory (Curran et al. 1998). Dose-dependent induced amnesic effects are characterised by impairment of information acquisition, consolidation, and storage (Greenblatt 1992). Benzodiazepine antagonists in contrast protect against age-related cognitive decline (Marczynski 1998). Interestingly, the phyto-hypnotic, valerian, induces reductions in awakening episodes with no effect on memory (Herrera-Arellano et al. 2001). Pramipexole (D3 receptor agonist) induces somnolence and episodes of daytime sleep (Hauser et al. 2000) and impairment of working memory in PD (Brusa et al. 2003). Effects of melatonin in the elderly include improved memory together with decreased sleep latency but with no change in total sleep time (Jean-Louis et al. 1998). The anticholinergic scopolamine induces sleep and episodic memory loss (Curran et al. 1998), and thus the use of anti-muscarinic medication in disorders such as PD, itself associated with sleep disturbances, may promote specific memory impairments. Cholinesterase inhibitors (ChEI) improve sleep and cognitive function in AD (Grace et al. 2000; Wilcock et al. 2003). In non-demented subjects, improvements in memory with ChEI are reported to relate to increased REM (Schredl et al. 2001) but with the side effect of insomnia (Jacobsen & Comas-Diaz 1999).

The role of the cholinergic system in sleep control is central, as Walker has pointed out, although how this is linked to consolidation enhancement is unknown. Graves et al. (2001) postulate a role in plasticity for acetylcholine in REM through muscarinic receptors, however deficits in avoidance responding after paradoxical sleep deprivation are not associated with M1 muscarinic receptor binding in rat brain (Moreira et al. 2003). Most interestingly, low acetylcholine in slow wave sleep (SWS) has recently been suggested to be essential for aspects of memory consolidation, on the basis of the blockade of SWS-related consolidation of declarative memory in human subjects by physostigmine infusions during SWS (Gais & Born 2004). Acetylcholine is considered essential for hippocampus-dependent declarative memory, consolidation of which is particularly strong during SWS when acetylcholine levels drop to a minimum. Physostigmine did not alter memory consolidation during waking, when endogenous cholinergic tone is maximal. These findings raise the intriguing question of whether ChEI medication in dementia patients which persists through the night could actually have detrimental effects on consolidation. Clinical benefits of these drugs wear off with time, and it might be worth considering testing chronic effects of daytime as opposed to continuous medication.

In conclusion, disease and drug effects on sleep and memory are complex. Although no consistent pattern indicating that sleep is directly correlated to memory function emerges from the examples cited, they could be related through the agency of cholinergic function, common to sleep, attention, and memory consolidation. Walker, in his seminal review, highlights the scope for dissecting different components of memory. Such developments will provide new insights into the relation between sleep and cognition relevant to understanding and treatment of human brain disorders.

Procedural replay: The anatomy and physics of the sleep spindle

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Abstract: This commentary implicates the neostriatum in the production of the EEG sleep spindle and in the processing of motor procedural learning in sleep. Whether the sleep spindle may implement not only the consolidation-based enhancement of procedural learning, but also its initial consolidation, is considered; as is the fit between (1) corticostriatal anatomy and physiology, and (2) the physical properties of the sleep spindle.

Affirming a central point of Walker's argument, this commentary will expand on his discussion of the sleep spindle as an elec-

trical event suited to the enhancement of motor procedural learning.

On one hand, as discussed in the target article (sect. 2.4.2), the sleep spindle is typically modeled as a thalamocortical network event. On the other hand, in both human and animal studies, motor procedural learning has come to be regarded as an encapsulated process that requires the participation of the neostriatum (e.g., McDonald & White 1993; Packard & Teather 1998; Reber & Squire 1998). The purpose of this commentary is to unite the two perspectives. Three arguments, bearing equally on the sleep spindle's role in motor procedural learning and on its place in neostriatal network activation, will be advanced.

(1) In anatomic terms, neostriatal projection neurons would be exempt from spindle-frequency oscillation in sleep only if their receipt of thalamic and cortical input – in each case massive, ordered, and glutamatergic – were prevented. If these excitatory afferent pathways are functional in sleep – and no evidence exists to suggest their silence[1] – then synchronous voltage oscillation at spindle frequencies in thalamus and cortex will rhythmically excite large assemblies of GABAergic striatal projection cells at their spiny dendrites. In turn, thalamocortical projection targets of pallidal and nigral GABAergic efferent neurons will be disinhibited, completing any number of (cortico)striatothalamocortical (CSTC) "loops" in sleep. If a motor procedural task has been recently learned and practiced, activation of its CSTC circuit in sleep should tend to replicate that motor procedure at acquisition-primed ("tagged") synapses.

(2) Whether spindle-based procedural replication serves consolidation-based enhancement exclusively, as Walker suggests, or both enhancement and consolidation per se, is unknown. It is reasonable, I think, to argue in favor of some role for neostriatal spindling in the process of motor procedural task consolidation. Striatal projection cells – "medium spiny neurons" – are heavily endowed with dendritic spines and thus highly susceptible to dendritic modification. In my view this susceptibility, and the complexity and prolonged time course of dendritic modification, do implicate spindle-generated replay in the consolidation (per se) of motor procedures. It is known that in the hippocampus and amygdala, various learning tasks induce relatively enduring but impermanent cytoskeletal changes at dendritic spines. These changes, effected by actin polymerization prior to nuclear (or dendritic) protein synthesis, increase synaptic efficacy – for instance, by augmenting dendritic response to glutamate – and yet remain modifiable for many hours (Lamprecht & LeDoux 2004). If practicing a motor procedure produces early and modifiable changes in, say, the number and shape of dendritic spines on striatal projection cells, and if these early changes persist for many hours, spindling in Stage 2 sleep could exert a powerful, synchronous excitatory drive at cytoskeletally altered dendrites during the period of their modifiability. Thus spindling could work to stabilize – for instance, by stimulating AMPA receptor insertion – the early cytoskeletal changes. Such a role in stabilization would not, of course, exclude a role for spindling in the processes of consolidation-based enhancement.

(3) An excellent fit between corticostriatal anatomy and physiology, on one hand, and the physical properties of the sleep spindle, on the other, furthers the case for both consolidation and consolidation-based enhancement of motor procedures in sleep.

On the corticostriatal side, it is well known that a large number of cortical neurons projects to a much smaller number of striatal projection neurons. A recent estimate based on the arborization of cortical pyramidal neurons axons in striatum has 17 million corticostriatal neurons projecting to 1.7 million striatal projection neurons (Zheng & Wilson 2002). This anatomic convergence has important physiologic correlates. As demonstrated by Wilson (1992), neostriatal projection neurons are strongly hyperpolarized at rest, where potassium currents resist depolarization by weak or desynchronous synaptic excitation. Where excitation is strong, distributed, and synchronous, however – as presumably it is during a sleep spindle – the inwardly rectifying membrane currents are deactivated, and striatal spiny projection neurons are successfully depolarized.

On the spindling side, the elementary physics of the sleep spindle are instructive. Spectral analysis (by FFT) of any epoch of Stage 2 sleep containing spindles produces a Gaussian distribution of peak frequencies in the circa 12–14 Hz bandwidth; this frequency range is narrow, and within it any two spectral peaks will differ relatively little. If the original sleep epoch is then filtered without phase distortion at any two peaks, each of the resultant waveforms will approximate a simple harmonic oscillator. Where two harmonic oscillations are of nearly the same frequency, as in this example, a special case of the physical principle of superposition states that the oscillators will add to produce periodic "beats" that regularly wax and wane in amplitude. At maximal beat amplitude, the oscillators are maximally in phase; at minimal beat amplitude, they are maximally out of phase. In my view, the characteristically waxing and waning EEG sleep spindle similarly records a physically inevitable, repeating phase synchrony among many voltage oscillations.

Spindling differs from "beats," of course: Because a spindle superposes many oscillators at variable frequencies within the circa 12–14Hz band – legible to the scalp electrode via corticostriatal axonal arborization in cortical layer I – phase synchrony is irregularly intermittent, not regularly periodic. Nonetheless, if each "pure" frequency component of a sleep spindle reflects synchronous membrane voltage oscillation in a discrete population of corticostriatal neurons, then spindling may provide a mechanism for coherent activity within the set of motor and sensory corticostriatal cell populations that uniquely represents a given motor procedure. In this view, a sleep spindle is precisely what is needed to depolarize striatal projection cells, at once convergently and selectively, and thus to disinhibit a particular CSTC motor circuit.

The physical properties of the sleep spindle are hospitable not only to motor procedural learning but also to alteration by it. If intensively practicing a motor procedure produces more or larger sleep spindles, that change is consonant with (1) increased amplitude of voltage oscillation in corticostriatal cell populations, (2) a shift in spectral peak distribution, or (3) increased numbers of spectral peaks. Any or all of these physical changes could ensue from the consolidation-based enhancement (or consolidation) of a recently learned motor procedure – as if evolution had adapted the spindle to practice the task again, outside of consciousness and without behavioral consequence.

NOTE

1. Intermittent synchronous activity in neostriatal networks, interrupting relatively long periods of silence, may go unread during neuroimaging studies of the sleeping brain.

REM sleep, dreaming, and procedural memory

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Abstract: In this commentary the "incredibly robust" evidence for the relationship between sleep and procedural memory is questioned; inconsistencies in the existing data are pointed out. In addition, some suggestions about extending research are made, for example, studying REM sleep augmentation or memory consolidation in patients with sleep disorders. Last, the possibility of a relationship between dreaming and memory processes is discussed.

The model proposed by Walker does have a great impact on the current research in the field of sleep and memory. First, it is important to differentiate between procedural memory and declarative memory because research (e.g., Markowitsch 1996) has shown that the different memory systems are located in different brain areas. Evidence that this is also valid for sleep-related learning was provided by Peigneux et al. (2003). Second, the model includes learning processes during wakefulness and during sleep,

which settles the debate about the exclusiveness of memory consolidation during sleep.

In describing the findings regarding procedural memory and sleep in humans, Walker states that the evidence is "incredibly robust." Reviewing the literature, however, one must say that the number of studies is quite small, and direct replication studies carried out in different laboratories are scarce. Often different tasks (e.g., a visual discrimination task [Stickgold et al. 2000b], motor skills like finger tapping [Walker et al. 2003b], acquisition of probabilistic rules [Peigneux et al. 2003], and priming [Plihal & Born 1999a]) as well as different manipulation techniques (e.g., early versus late sleep [Plihal & Born 1997], REM sleep deprivation [Karni et al. 1994], and correlations between sleep parameters and improvement [Stickgold et al. 2000b]) have been used. In our laboratory, we are currently conducting a correlation study applying the mirror trace task used by Plihal and Born (1997). The preliminary findings ($N = 12$) are promising: a significant correlation ($r = .430$, $p < .05$, one-tailed) between percentage of REM sleep and improvement in speed from the evening session to the morning session was found. This is not completely consistent with the finding of Stickgold et al. (2000b) for the visual discrimination task; they reported a much higher correlation ($r = .74$; $N = 14$).

Next, my coworkers (Orla Hornung, Francesca Regen, Heidi Danker-Hopfe, and Isabella Heuser) and I utilized a modified version of the mirror-tracing task in a study of memory in elderly, healthy persons and were also able to demonstrate a correlation between the percentage of REM sleep and performance (this is a preliminary result; the study is still in progress). On the other hand, the insignificant finding regarding non-REM Stage 2 sleep and performance is not in line with the findings of Walker et al. (2003b). In addition to these conflicting results, other inconsistencies between the different studies in the field can be pointed out. Karni et al. (1994), for example, found an effect of REM sleep deprivation on the improvement in the visual discrimination task but not for slow wave sleep deprivation, whereas Stickgold et al. (2000b) reported correlations for slow wave sleep and REM sleep. To summarize, although the amount of evidence supporting a close relationship of procedural memory and sleep is growing, many inconsistencies have to be clarified by futures studies.

If sleep plays a crucial role in memory consolidation, one of the next steps will be to study patients with primary sleep disorders. Although Fulda and Schulz (2001) published a extensive meta-analysis on the cognitive impairment in patients with sleep disorders, detailed studies using paradigms including evening training sessions and morning retest sessions have not yet been carried out in these patient groups. Keeping in mind the reduced daytime vigilance in these patients, it will be interesting to search for correlations between sleep architecture (total sleep time, percentage of REM sleep) and performance improvements in procedural as well as declarative tasks.

Assuming that REM sleep plays a crucial role in consolidation of procedural memory (e.g., Plihal & Born 1997), studying the effects of REM sleep augmentation on learning will be of interest. Schredl et al. (2001) have published the first human study in which donepezil, an acetylcholinesterase inhibitor, was administered to enhance REM sleep. A significant correlation ($r = .669$, $p < .05$, one-tailed) between percentage of REM sleep and the improvement of a task (relearning a word list) that comprises declarative and implicit features was found for the donepezil nights. Although this pilot study leaves many questions unanswered, this research area is of interest because it was found that patients with Alzheimer's disease have reduced REM sleep (Bliwise 1993), and cholinergic agents, which often enhance REM sleep – one of the measurable effects of these agents on the cholinergic system – (see Schredl et al. 2000), are widely used in the treatment of Alzheimer's disease.

The last topic to be addressed here is the possible relationship between dream content and learning. Some preliminary evidence has been reported by De Koninck et al. (1988) for intense language learning, and De Koninck et al. (1996) for adaptation to vertical inversion of the visual field. In the second study, the persons who experienced incorporations of the inverted visual field in their dreams performed better on tasks (reading and writing) measuring adaptation. This relation makes sense since research (Schredl 2000) has shown that dream content is related to specific brain activation patterns and other physiological parameters measured during sleep. Moreover, this is in line with the continuity hypothesis of dreaming (cf. Schredl 2003), which states that waking-life experiences, for example, the evening learning sessions, are probably incorporated into subsequent dreams. An experimental approach to this topic could be the technique of lucid dreaming, since it is possible to carry out assigned tasks during the dream (e.g., LaBerge & Rheingold 1990). For a simple motor activity (hand clenching), Erlacher et al. (2003) were able to demonstrate that the related area of the motor cortex was active during the lucid dream (EEG measure). This approach makes sense in the light of the extensive literature on the effect of mental training on performance (e.g., Driskell et al. 1994). Single cases of successful training of sport skills in lucid dreams have been reported (LaBerge & Rheingold 1990; Tholey 1981). On the other hand, one should consider that dreaming as reportable subjective experiences during sleep is only a small part of the total activity of the sleeping brain (comparable to consciousness during the waking state), so it remains unclear how close the relationship between dream content and learning processes during sleep might be.

To summarize, the model proposed by Walker is a promising starting point for future research investigating, in addition to the time course, influential factors such as task type, experimental difficulty, and performance level in the relationship between sleep and procedural memory.

Memory consolidation during sleep: A form of brain restitution

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Abstract: Does sleep restore brain function or does it consolidate memory? I argue that memory consolidation during sleep is an offshoot of restitution. Continual learning causes local synapse-specific neural fatigue, which then masks expression of that learning, especially on time-limited tests of procedural skills. Sleep serves to restore the fatigued synapses, revealing the consolidation-based enhancement observed as a "latent" overnight improvement in learning.

Evidence for the involvement of sleep in memory consolidation comes in many forms, such as the effects of learning on postlearning sleep and the re-expression of behavior-specific patterns during postlearning sleep. However, a cause-and-effect relationship or even a robust correlation between the effects of learning on sleep or the replay of patterns during sleep, on the one hand, and the magnitude of consolidation, on the other, has yet to be effectively demonstrated. Improved learning following a period with sleep, compared to one without, remains the most consistent evidence to date; I propose an explanation for this.

I begin by noting that there exists emerging evidence for sleep as a localized brain process. While Rechtschaffen (1998) suggests that it is "difficult to arrive at a widely acceptable theory of sleep function because that function is not reflected at the organ or system level," he and others (e.g., Moruzzi 1966) propose that sleep is a localized process that provides basic cellular resources. Indeed, no brain lesion has ever successfully eliminated sleep totally for long periods (Rechtschaffen 1998). In certain marine animals, sleep is sometimes localized to one brain hemisphere at a time (Oleksenko et al. 1992). Continual tactile stimulation of the right hand prior to sleep results in increased spectral power in the delta band during early non-REM sleep in the contralateral somatosensory cortex (Kattler et al. 1994).

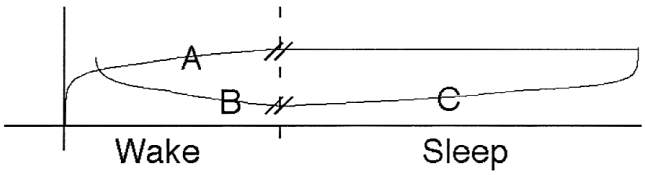

Figure 1 (Sheth). A hypothetical evolution of local brain processes as a function of behavioral state, and the effects on memory performance. Various processes (A, B, and C) combine to affect memory test performance (ordinate). With continual practice while the observer is awake, learning occurs (A), which improves performance. However, neuronal fatigue (B), which occurs hand in hand with the learning, impairs performance. During sleep, neural circuits slowly recover (C), which gives rise to "latent learning." A, B or C are transparent to the experimenter. Observed performance is some (nonlinear) combination of them.

With these ideas as a basis, I propose that two separate local brain processes are involved in the learning of a procedure or skill (see Fig. 1). Over repeated trials, the awake observer practices specifics of the procedure (A). Learning is a multifaceted process, one facet being the progressive restriction in the brain circuits that influence performance (Edelman & Tononi 2000; James 1890). I propose that while this process does not depend on sleep, a second independent process exists that does. With increasing neural specialization during learning, the circuits or synapses repeatedly engaged in the procedure adapt or fatigue (B). Synapse-specific fatigue during procedural learning is unavoidable. Repeated stimulus processing produces decreased responses in brain circuits associated with that processing – a "repetition suppression" effect (Brown & Xiang 1998; Desimone 1996; Wiggs & Martin 1998). The inefficiency in local signal transmission that arises from the synaptic fatigue or adaptation masks expression of the learning. With prolonged training on a task that involves both speed and skill, the net product of these two contravening processes, measured behaviorally, is asymptotic learning (Karni & Sagi 1991). Over still longer training periods, a decline in performance is observed (Mednick et al. 2002). Several studies (e.g., McCollough 1965) have shown that the effects of adaptation can be long lasting, particularly if a select few synapses, specific to certain stimuli or conditions and not others, are adapted.

The recovery of functions related to sensory transmission, such as the restoration of neurotransmitters or the re-formation of receptors, likely involves protein synthesis, which has its own characteristic time course, one that is longer than the time course of resource depletion in the synapse. Thus, sleep-dependent synapse-specific recovery (Fig. 1) is independent of the training in the wake state. It is, however, dependent on sleep; sleep cannot be replaced with awake resting, which fails to control internally generated activity in key brain areas, or by reversible inactivations of brain areas engaged in the consolidation, which only delays the recovery and may even shrink the critical time window during which the learnt information can be actively enhanced (target article, sect. 2.3.2.2).

Sleep is clearly not monolithic. SWS, and non-REM sleep in general, are believed to have a restorative role in brain function (Horne 1988). It is notable that there is correlational evidence for the role of non-REM sleep in memory consolidation in humans (Stage 2 sleep for motor skill learning, Walker et al. 2002; early SWS for visual discrimination skill consolidation, Gais et al. 2000; Stickgold et al. 2000b). This dovetails nicely with the idea of synapse-specific recovery. Replay of behavior-specific patterns during late REM sleep, if short-lived, may reactivate and reinforce the task-related synapses (target article, sect. 2.4.2) with minimal synaptic adaptation or fatigue.

In contrast to procedural memory, evidence that sleep improves declarative memory is inconsistent (sect. 2.2). Perhaps conclusive evidence exists but has eluded researchers, or perhaps procedural and declarative memories differ in the same respects that make the former more susceptible to sleep. Procedural learning is usually dependent on the context and modality in which the material was presented initially (Squire 1986), are "realized as cumulative changes stored within the particular neural systems engaged during learning" (Squire 1986), and typically require training for several minutes to several hours on the procedure. In contrast, declarative learning is flexible, accessible to all modalities and can be "one-shot." The weaker synaptic specificity and quicker learning of declarative as opposed to procedural learning implies less localized declarative storage, which means, by our hypothesis, less synapse specific fatigue, and smaller benefits of sleep.

In sum, two issues are critical in the present account: (1) Synaptic specificity: With greater synaptic specificity, there is greater impact of sleep on local synaptic recovery; and (2) the need for speed: On perceptual as well as motor learning tasks, perception and/or motor action must be conducted within a finite period of time for optimal performance (e.g., Stickgold et al. 2000b; Walker et al. 2002). With time constraints, inefficiency of synaptic transmission takes on even greater significance, and, because speed-accuracy tradeoffs are commonplace, the effects of sleep deprivation are observable on measures of speed as well as accuracy.

By varying each factor, this hypothesis can be experimentally verified. One possibility is to vary the degree of synapse-specific adaptation in two sets of synapses that exhibit learning during training. Visual discrimination skills that transfer to different conditions (Ahissar & Hochstein 1996; 1997) are suitable for this. Synapse-specific sleep dependent recovery will accordingly differ between the two sets. Learning following sleep loss will be impaired following sleep loss in both brain circuits, but less so in the brain circuit that learnt the procedure indirectly via transfer.

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The incredible, shrinking sleep-learning connection

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Abstract: Initial claims that REM sleep is important in the consolidation of all memories have been revised and reduced to the claim that sleep has a role only in the consolidation of procedural learning. Now, Walker hypothesizes that sleep has no role in the "stabilization phase of consolidation" but only in the "enhanced learning" phase of procedural learning. Evidence for this vague, truncated hypothesis remains as inconsistent as that for prior claims.

The idea that REM sleep is important for memory consolidation is attractive, since it would explain the vivid imagery of dreams as a repetition of the events of the prior day to enable the laying down of permanent memory traces. Unfortunately, dream reports do not support this idea. Most dreams concern emotions and activities that did not occur during prior days. Furthermore, most dreams are not subsequently recalled unless they are immediately rehearsed in waking following the dream (Rechtschaffen & Siegel 2000).

Those working on the role of sleep in human learning have modified their hypotheses to include non-REM sleep as well as REM sleep. Many studies of the relationship between human sleep and learning have focused on sleep's role in learning of word recognition and associations between words and events – tasks mimicking most of what goes on in school; this is what learning

and memory researchers call *declarative learning*. Dr. Carlyle Smith, a leader in the sleep-memory consolidation field, after reviewing his own studies and many negative studies in the world literature, recently concluded that sleep is not important in declarative memory. He was quoted as saying "Declarative memory is such a large part of our memory that everybody would like to find [a link]. Yet no matter what I have done – I have deprived people of sleep, I have deprived people of REM sleep, I have deprived them of non-REM sleep – I have never seen any difference between people who got a good night's sleep and those who didn't" (*Los Angeles Times*, Feb. 3, 2003; see Smith 2001). Walker appears to accept this conclusion in his review, stating "a clear understanding of the role of sleep in declarative memory formation remains to be established in humans" (sect. 2.2, para. 6). However, if one accepts this conclusion, the domain of the sleep–learning connection is dramatically reduced.

In addition to redefining the role of sleep in human memory consolidation, this conclusion also has important implications for animal studies that have been used to support a role for sleep in memory consolidation. Several studies have claimed to see evidence of "replay" of neuronal activity during REM sleep or non-REM sleep. Most of these studies have seen this replay in the hippocampus (Lee & Wilson 2002; Louie & Wilson 2001; Pavlides & Winson 1989). However, it is well known that the hippocampus is critical for declarative leaning but of little importance in procedural learning (Eichenbaum 1999). Thus, even if one dismisses the technical problems with these studies (see Siegel 2001), their relevance to procedural learning and hence to the sleep-learning field is questionable.

A hallmark of sleep learning theories is the variability of hypotheses from study to study, even within studies by the same group. For example, studies of the consolidation of human procedural learning make contradictory claims, with some saying that REM but not non-REM sleep is important (De Koninck & Prevost 1991; Pearlman 1971), others stating just the reverse (Gais et al. 2000; Portnoff et al. 1966), others claiming that both sleep states are essential (Stickgold et al. 2000a), and still others making ad hoc claims, such as that "only the amount of stage 2 nonREM sleep obtained during the last quarter of the night" is important (Walker et al. 2002). The statistical reliability of such ad hoc hypotheses is questionable.

The most striking aspect of the current review is the further redefinition of the role of sleep in learning to be so limited and vague as to defy disproof. In earlier formulations, the author's colleagues indicated that memory consolidation occurs in sleep. It was emphasized that "no improvement" occurred in waking, and that therefore sleep is "absolutely required" for performance improvement (Stickgold et al. 2000b). In the current review, Walker subdivides consolidation into a "sleep-independent" process that makes memory "resistant to interference" and a "sleep-dependent" process of "enhancement." The "sleep-independent" process that makes memory "resistant to interference" sounds a lot like what learning theorists refer to simply as "consolidation." The two subdivisions of consolidation created by Walker's reformulation are difficult to separate operationally and this subdivision invites post hoc explanations of any observed effect.

Fatigue, circadian factors, and simply the passage of time have long been known to affect performance. In order to properly control for performance effects, it needs to be shown that sleep disruption produces a long term impairment of consolidation of tasks learned before the interrupted sleep, and that any decrements in performance during retesting were specific for the recently learned task. Similar tasks that had been learned previously should not be comparably affected by deprivation. It also needs to be shown that recovery from the performance decrements during learning that are known to be caused by intense practice were not creating an illusion of consolidation or "enhancement" when retesting after a recovery period. These sorts of controls have not been thoroughly and systematically done in studies claiming a role of sleep in memory consolidation (Siegel 2001; Vertes & Eastman 2000).

The scientific and popular interest in the possibility that sleep is important in memory consolidation does not derive from the hypothesis that sleep is "one of many states" in which memory consolidation occurs. If this were the case, we would be excited over the possibility that consolidation occurs during eating, drinking, and engaging in sexual behavior, and we would be exhorted to increase these activities when learning. Rather, it derives from the idea that sleep has a unique and important role in consolidation. The reformulated sleep–memory consolidation model proposed here advocates a "democratic," equal division of memory consolidation across sleep and waking states, a considerable dilution of the original idea.

Millions of humans have taken MAO inhibitors or tricyclic antidepressants, often for 10–20 years. These drugs profoundly depress or in many cases completely eliminate all detectable aspects of REM sleep. However, there is not a single report of procedural or declarative memory deficits attributable to such treatment. Similarly, well-studied individuals with permanent loss of REM sleep resulting from brain damage show normal learning abilities, including the best studied case of an individual who completed law school after his injury and was the puzzle editor of his city newspaper (Lavie et al. 1984). The "dual process" theories of learning, with both REM and nonREM sleep participating in memory consolidation, as well as REM sleep-based theories, are contradicted by these findings. Yet this literature is ignored in the current review.

It is common knowledge that sleep loss produces sleepiness and impaired concentration. Similarly, it is well established that sleep loss impairs performance of a variety of tasks in subsequent waking. Studies claiming to demonstrate an important role for sleep in memory consolidation have yet to establish that the effects they are observing are independent of these well-known phenomena.

Consolidation enhancement: Which stages of sleep for which tasks?

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Abstract: The Walker model raises a number of questions, particularly about the nature of the sleep states involved in consolidation enhancement. While REM sleep, Stage 2 sleep, and Stage 3/4 sleep have been implicated in procedural learning, we still do not understand which types of learning are involved with specific sleep states. Several possible ideas for future research are suggested.

Walker's article provides an interesting theory about the nature of procedural learning and how it relates to sleep. The theory is based primarily on the author's own work, but there are also data from other sources. The theory also relies heavily on the results of simple motor procedural or skills tasks, and the author's studies have reported on the sequential finger-tapping task. The idea that there are two basic components to motor skill learning is an interesting one. The concept of stabilization clearly seems to fit with the data that have been collected so far and the vulnerability of recently learned motor sequences in the first 6 hours after acquisition is quite interesting. However, of greater interest is the longer term second phase of consolidation enhancement, which appears to require sleep.

Involving sleep with memory systems has brought into focus the possibility that very different subsystems are at work, depending on the nature of the task. While it has been clearly demonstrated that sleep is necessary for consolidation enhancement, the particular state or states of sleep involved remains unclear. At this point, although some studies do not differentiate between sleep states, there is some information from different procedural learn-

ing tasks to implicate some or all of the sleep stages in the consolidation enhancement process. A small, but growing number of reports suggest that Stage 2 is the sleep state involved with further off-line memory processing of simple motor skills (Fogel et al. 2002; Smith & MacNeill 1994; Walker et al. 2002). On the other hand, there are a number of procedural tasks that seem to require REM sleep rather than Stage 2 sleep. They include the Tower of Hanoi (Smith 1995) and the Mirror Trace task (Plihal & Born 1997; Smith & Nixon 2001). The texture discrimination task appears to involve both Stage 3/4 and REM sleep (Stickgold et al. 2000b). Of particular interest is the Mirror Trace task, which requires motor skill learning, but has been implicated with REM sleep rather than Stage 2 sleep, as have other motor procedural tasks. As Walker clearly points out, non-REM (including Stage 2 as well as Stage 3/4) and REM sleep are brain states that are markedly different in terms of electrophysiology and biochemistry. This supports the idea that two different memory-consolidation subsystems could exist. However, why a given task would, for example, require REM sleep rather than Stage 2 or vice versa remains unclear.

There are several possible ways of trying to sort out this sleep state paradox. A "motor" versus "cognitive" learning dichotomy appears to be too simple, and the Mirror Trace task in particular does not conform. An examination of the tasks reveals that it might be possible to separate them into "simple" and "complex" categories, with simple tasks relying on Stage 2 sleep and complex tasks requiring REM sleep for consolidation enhancement. The problem here is deciding which tasks are simple and which are complex, and surely the REM and non-REM sleep-dependent texture-discrimination task would be classed as simple. Perhaps a more useful task dichotomy might be "novelty" versus "familiarity." Tasks already familiar to the subject require less training than tasks that are unfamiliar. For a task such as the sequential finger-tapping task or the rotary-pursuit task, subjects have a high probability of having already performed similar activities in their life history. They are able to draw on these existing strategies and/or motor programs, which they can then improve upon. Thus, they are simply refining existing programs and do not need to devise new strategies. From this point of view, every newborn child initially has to come up with a new cognitive strategy for each problem he or she encounters. This would require a preponderance of REM sleep and, as is well known, fits with the relatively high levels of REM sleep observed in children. In older individuals, the proportion of Stage 2 sleep goes up at the expense of Stage 3/4 sleep, and the amount of REM sleep also declines. Thus, one of the next steps in examining the relationship of procedural memory to sleep states is to closely examine the sleep states involved with the various kinds of tasks presented. It may well be that there is a distinction to be made between novel versus familiar procedural tasks in terms of sleep state that is subsequently involved in the off-line memory processing. Using this model, one might predict that if the task is relatively new and novel to the individual, REM sleep would be important following successful acquisition. On the other hand, if the task is similar to previous experiences encountered by the individual, Stage 2 sleep would be important following successful task improvement. By this theory, one might even imagine that someone could encounter a novel task that would initially require the presence of REM sleep, but as daily trials continue and learning progresses, Stage 2 sleep might become more important. Thus, consolidation enhancement may require REM sleep and/or Stage 2 sleep (or even Stage 3/4) depending on the previous experience of the learner. There is reason to believe that both REM and non-REM sleep are important for synaptic plasticity. Yet, they are very different brain states, and it is tempting to think that they represent two quite different memory consolidation systems or subsystems that could interact. Future research will decide.

The challenge of identifying cellular mechanisms of memory formation during sleep

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Abstract: Cellular mechanisms hypothesized to underlie sleep-dependent memory consolidation are expressed throughout the brain during sleep. Use of sleep deprivation to evaluate the functional importance of these mechanisms is confounded by degradation in waking performance resulting from impaired vigilance. There is a need for methods that will permit disruption of specific mechanisms during sleep only in the neuronal circuits most critically involved in learning. This should be accomplished without global sleep disruption and with preservation of the restorative aspects of sleep.

As expertly summarized by Walker in the target article, there is a large experimental literature implicating a role for sleep in learning and memory. At present, much of this evidence is correlational in nature, including the findings that learning is correlated with changes in subsequent sleep amount and/or composition and that sleep loss is correlated with impaired memory retention. This is not a criticism of the sleep and learning literature. In many areas of behavioral neuroscience, correlational studies are a necessary prerequisite to the search for mechanisms and the determination of the functional significance of identified mechanisms. However, the demonstration that a specific cellular mechanism that operates during sleep is functionally important for memory consolidation presents some unique and difficult experimental challenges.

Sleep is accompanied by global changes in the cellular electrophysiology and neurochemistry of the brain. Several of the mechanisms hypothesized to underlie sleep-dependent learning reviewed in the target article are expressed throughout the brain during sleep. These include increases in intracellular Ca^{2+} that accompany rhythmic hyperpolarization-depolarization sequences in thalamus and cortex and increased synchrony of spike train discharge among neurons in the neocortex and hippocampus. Changes in monoamine levels and/or the ratio of aminergic to cholinergic activity occur throughout the brain during both non-REM and REM sleep.

Evaluation of the functional importance of any proposed synaptic, neurochemical, or molecular mechanism for memory consolidation during sleep will require the demonstration that disruption of that mechanism impairs learning and memory. Current experimental paradigms employ partial or total sleep deprivation to assess the functional role of sleep-dependent processes on memory, typically by assessing performance during retest following the period of sleep loss. This paradigm has some significant shortcomings. While the function(s) of sleep is not known, it is clear that a sleep-deprived brain does not perform as well as a sleep-satiated brain in a variety of ways. Sorting out the effects of sleep loss on synaptic plasticity versus impaired performance due to increased sleepiness/decreased vigilance is a significant problem with many experimental paradigms that employ standard sleep deprivation methods.

A convincing demonstration of the functional importance of potential mechanisms of synaptic plasticity during sleep would seem to require the experimental disruption of a particular mechanism (e.g., increased intracellular Ca^{2+}) in a specific subset of neuronal circuits most critically involved in the type of learning being studied. Ideally, this would be accomplished without causing a global disruption of sleep and with preservation of other sleep functions, most importantly, the ability to restore normal levels of vigilance during subsequent waking. Clearly, studies of this type pose many difficult methodological challenges. Perhaps this is why that in the 50-plus years since the discovery of REM sleep and the subsequent explosive growth in the fields of sleep neurobiology and

sleep medicine, not a single function of sleep has been convincingly identified.

Sleep and synaptic homeostasis

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Abstract: We propose that sleep is linked to synaptic homeostasis. Specifically, we propose that: (1) Wakefulness is associated with synaptic potentiation in cortical circuits; (2) synaptic potentiation is tied to the homeostatic regulation of slow wave activity; (3) slow wave activity is associated with synaptic downscaling; and (4) synaptic downscaling is tied to several beneficial effects of sleep, including performance enhancement.

Walker presents strong evidence that sleep enhances certain memories, although it is not clear how it would do so. We have hypothesized that sleep promotes synaptic homeostasis: the maintenance of a baseline amount of synaptic weight impinging on neurons (Tononi & Cirelli 2003). One of the predictions of the hypothesis is that, under certain circumstances, synaptic homeostasis during sleep should lead to an increased signal-to-noise ratio (SNR) in cortical circuits, which should become apparent as enhanced performance. The hypothesis considers performance enhancing as one among several benefits of sleep and its homeostatic regulation. The hypothesis makes four claims:

1. Wakefulness is associated with synaptic potentiation. During wakefulness many brain circuits undergo LTP, resulting in a net increase in the strength or number of synaptic connections between neurons. Among supporting arguments are: (1) The expression of LTP-related genes, such as *Arc, BDNF, NGFI-A*, and phosphorylated CREB, is high during wakefulness and low during sleep (Cirelli et al. 1996; 2004a). (2) The activity of the noradrenergic system, which is responsible for the induction of LTP-related genes (Cirelli & Tononi 2000a; 2004), is high during wakefulness during salient events but is very low during sleep (Aston-Jones & Bloom 1981). (3) Absolute values of cerebral glucose consumption at rest are 18% higher after having been awake than after a night of sleep (Braun et al. 1997). Assuming that neural activity at rest is similar before and after sleep, such marked increase in baseline energy consumption suggests a diffuse increase in synaptic strength because close to 80% of brain metabolism is due to synaptic activity (Attwell & Laughlin 2001; Rothman et al. 2003). (4) From an evolutionary perspective, it makes sense that the potentiation of neural circuits should occur during wakefulness, when an animal is active and exposed to the environment, and not during sleep, when neural activity is unrelated to external events (Tononi & Cirelli 2001). Note that, according to the hypothesis, LTP-like changes in the brain occur whenever presynaptic firing is accompanied by postsynaptic depolarization in the presence of appropriate neuromodulators, whether or not an animal is engaged in learning paradigms.

2. Synaptic potentiation is tied to the homeostatic regulation of slow wave activity. One of the best-established facts in sleep regulation in mammals is that slow wave activity (SWA) increases in proportion to the duration of wakefulness and decreases progressively during sleep (Borbely 2001). The hypothesis states that increases in sleep SWA are a direct reflection of synaptic potentiation in cortical circuits during wakefulness. Among supporting arguments are: (1) Animals with a lesioned noradrenergic system, which have a greatly reduced expression of LTP-related molecules after wakefulness (Cirelli & Tononi 2000a; 2004), show a corresponding reduction in SWA homeostasis (Cirelli et al. 2004b). (2) Performing a visuomotor learning task produces an increase in SWA during subsequent sleep that is localized to right parietal cortical areas (Huber et al. 2004) presumably modified by learning (Ghilardi et al. 2000). (3) Sleep slow oscillations depend on cortico-cortical connections (Steriade 2003) and, according to computer simulations (Hill & Tononi 2005), their amplitude and synchronization reflects the overall strength of cortico-cortical synapses. Also, after visual deprivation during the critical period, which is associated with synaptic depression (Heynen et al. 2003), slow waves are reduced by 40% (Miyamoto et al. 2003). (4) The increase in power after wakefulness extends to other frequency bands (Cajochen et al. 1995), consistent with a generalized increase in neural synchronization due to increased synaptic strength.

3. Slow wave activity is associated with synaptic downscaling. According to the hypothesis, sleep SWA actively promotes a generalized depression or downscaling of synapses in response to the diffuse potentiation occurring during wakefulness. The progressive decrease of SWA during sleep reflects the progressive return of total synaptic weight to a baseline level. Among supporting arguments are: (1) During non-REM sleep, virtually all cortical neurons undergo a slow oscillation, cycling from a depolarized state of intense firing to a hyperpolarized state of silence at around 1Hz (Steriade 2003). Notably, sequences of spiking-hyperpolarization at around 1Hz are ideal for inducing synaptic depression (Kemp & Bashir 2001). (2) Recent molecular studies have shown that molecules implicated in synaptic depression are selectively upregulated during sleep (Cirelli et al. 2004a). (3) Studies in kittens show that sleep results in ocular dominance changes similar to those induced by monocular visual deprivation (Frank et al. 2001), which is known to act through LTD of cortical connections (Heynen et al. 2003). (4) Synaptic scaling occurs *in vitro* and *in vivo* in neocortical cells (Desai et al. 2002; Turrigiano 1999) and it can serve to preserve a constant level of synaptic input without obliterating memory traces (Miller & MacKay 1994). Note that downscaling is conceptually different from LTD, which affects select groups of synapses, or depotentiation, which affects only recently potentiated ones (Kemp & Bashir 2001). Note also that downscaling during sleep could be self-limiting since, when synaptic weight has returned to a baseline level, the amplitude of slow oscillations would be reduced to the point of preventing further downscaling. Finally, note that this process would be problematic during wakefulness but ideally compatible with sleep, a state during which the brain is both spontaneously active and virtually disconnected from the environment.

4. Synaptic downscaling is tied to the beneficial effects of sleep on performance. The performance-enhancing effect of sleep described by Walker is explained, according to the hypothesis, by an increase in neuronal SNR due to synaptic downscaling. Take the sleep-related enhancement in the visuomotor learning task we studied with high-density EEG (Huber et al. 2004). During wakefulness, synapses contributing to correct movements become progressively more efficacious (signal), but it is likely that potentiation extends to other synapses contributing to erroneous movements (noise). During sleep, assuming a threshold below which synapses become ineffective, downscaling would ensure that synapses contributing to the noise, being on average weaker than those contributing to the signal, cease to interfere in the execution, and SNR would increase. Indeed, we found that performance enhancement after sleep was strongly correlated with the increase in SWA in brain areas involved in the task, and the strongest correlation was with the increase of SNR during learning.

It should be emphasized that, while the synaptic homeostasis hypothesis accounts nicely for sleep-mediated enhancements in the performance of certain learning tasks, this would be only one of the benefits of synaptic downscaling during sleep. For example, downscaling could promote synaptic competition, especially during development, and avoid saturation. Most importantly, it could prevent unwelcome imbalances at the cellular level, including metabolic overload resulting from synaptic overload (Cirelli et al. 2004a). Finally, the hypothesis suggests new roles for REM sleep, as either complementary to non-REM sleep or achieving similar effects with different means (Tononi & Cirelli 2003).

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Sleep is for rest, waking consciousness is for learning and memory – of any kind

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Abstract: Although considerable attention has been paid to the possible involvement of sleep in memory processing, there is no substantial evidence for it. Walker describes a phenomenon of consolidation-based enhancement (CBE), whereby performance on select procedural tasks improves with overnight sleep; that is, without additional practice on the tasks. CBE, however, appears restricted to a few tasks, and even with these tasks CBE is not confined to sleep but also occurs during wakefulness. Sleep serves no unique role in this process. At best, CBE is a slow, time-dependent process of consolidation that begins with task acquisition in waking and can under some circumstances extend to sleep.

Walker presents evidence supporting the view that sleep serves a role in procedural learning/memory. The notion that sleep is involved in the off-line processing of information has recently met with strong criticism (Siegel 2001; Vertes & Eastman 2000a; 2000b). Although Walker offers a new formulation for the manner in which procedural skills could be strengthened in sleep, there are several problems with his scheme and supporting data, as discussed below.

1. Importantly, Walker reaffirms the conclusions reached by others (Smith 2001; Smith & Rose 2000; Stickgold 2000) that sleep is not involved in the processing/consolidation of declarative memories; that is, memory for facts, events, people, places, history, or the type of memory commonly referred to by the terms "memory" or "remembering."

2. Walker discusses a process termed consolidation-based enhancement (CBE), wherein performance on certain perceptual and motor tasks improves with sleep. The notion that skills simply improve over time (in sleep or waking) without additional practice is counterintuitive. That aside, it seems that the critical measure of whether there were improvements on retest after sleep would be to examine performance on the first few sequences of finger movements after sleep – as opposed to averaging performance over blocks of trials after sleep. The post-sleep results shown in Figure 3 of the target article (sect. 2.3.2.2) represent approximately 80 sequences of finger movements, which undoubtedly, when averaged, would give the appearance of enhanced performance. In effect, however, this post-sleep retest serves as an additional training session, with expected improvements with rehearsal. What was the performance of the subjects on the first few sequences of finger movements at the start of post-sleep retest?

3. Walker states that: "this process of CBE develops only during intervening periods of sleep and not during wake" (sect. 2.3.2.2, para. 11). Actually, CBE has been shown to occur in waking as well as during sleep. For instance, Karni and Sagi initially demonstrated that subjects showed improved performance on a perceptual discrimination task over time during waking (Karni & Sagi 1993), and in a subsequent report (Karni et al. 1994) improvement on the task during waking as well as during REM sleep. Karni (1995) clearly indicated that "enhancement" (or CBE) occurs during waking, and, further, that CBE is similar in waking and REM sleep and possibly interchangeable in the two states. Karni (1995) stated:

> Indeed our results suggest that REM sleep is not a unique brain state for memory processing in adults – normal skill (procedural) learning does occur during the waking state. Our somewhat counterintuitive finding was, however, that much of this improvement happens not during or immediately after practice but rather 8–10 hours after a training session has ended, suggesting a slow, latent process of learning.

Further:

> The issue of whether experience-triggered brain changes, presumably occurring during sleep (for which REM sleep is needed) are qualitatively different from the neural mechanisms subserving waking state consolidation remains open. Nevertheless, one would expect that systematic deprivation of REM sleep would not be very detrimental to skill learning in general because normal consolidation should occur during the waking state. (Karni 1995, p. 395)

CBE has also been described during waking for motor learning. Walker et al. (2003b) trained subjects on the finger-tapping task at 10:00 a.m. and demonstrated significant gains in performance at three successive four-hour test intervals during waking (see their Fig. 2A, p. 277) – as well as during overnight sleep. In like manner, Fischer et al. (2002) demonstrated highly statistically significant gains in performance on the same motor task of subjects trained at 10:00 a.m. and tested 8 hours later (their daytime waking group). The foregoing suggests a slow time-dependent process of consolidation (or CBE) that begins with task acquisition during waking and can in some circumstances extend to sleep. Sleep would serve no unique role in this process. Finally, it is important to note, as pointed out by Walker et al. (2003b), that the gains in performance with the mere passage of time (in waking or sleep) are very small compared to improvements with repeated practice on motor tasks.

4. Walker refers to the work of Shadmehr and coworkers (Brashers-Krug et al. 1996; Shadmehr & Brashers-Krug 1997) demonstrating time-dependent stabilization of procedural learning (CBS). He does not, however, discuss an important study by this group that failed to show CBE during sleep on an arm-reaching task. Specifically, Donchin et al. (2002) described a decline rather than an improvement on the arm-reaching task over a normal night of sleep, and, importantly, further reported that sleep deprivation did not alter performance on the task. They addressed discrepancies between their findings and earlier ones, stating: "A number of studies have found a role for sleep in consolidation of certain kinds of perceptual skills. In those studies, sleep, and not simply the passage of time, has been shown to be required for changes in performance between the end of training and test of recall." By contrast, "we found no significant effect of sleep on performance" (Donchin et al. 2002). Finally, Goedert and Willingham (2002) similarly found no evidence for long-term or sleep-dependent consolidation (CBE) for select motor and visuo-motor tasks.

5. Three laboratories (Karni's, Born's, and Stickgold's) have examined the effects of sleep on the perceptual discrimination task of Karni and Sagi (1993), and, surprisingly, all differed with respect to the stage(s) of sleep responsible for improved performance (consolidation) on the task. For instance, it was variously reported that consolidation occurs during REM sleep (Karni et al. 1994), during SWS (early sleep dominated by SWS) (Gais et al. 2000), or both (amount of SWS in the first quartile of the night plus amount of REM sleep in the last quartile of the night) (Stickgold et al. 2000b). Along the same lines, enhancement with sleep on the finger-tapping task has been attributed to Stage 2 SWS (Walker et al. 2002) or to REM sleep (Fischer et al. 2002). These are puzzling inconsistencies, especially considering that identical perceptual or motor tasks were used in the two sets of studies.

6. In the final section, which deals with possible neural substrates for CBE (electrophysiological, neurochemical, and molecular/cellular), Walker describes several general events that could selectively participate in CBE during sleep, such as sleep spindles, PGO waves, transmitter levels, immediate early gene expression, and so forth. Walker then asks the difficult question of how these global changes in sleep could selectively influence very specific networks or circuits responsible for coding experiences. Or in his words, "how do such global phenomena selectively assist a discrete network of neurons crucial to a specific 'memory'"? (sect. 2.4.2, para. 5). The answer was not satisfying. Walker essentially proposed that experience-dependent activity during acquisition may prime specific networks (or tag them), "leaving them in a heightened level of excitability which carries over into sleep" (sect. 2.4.2, para. 5). Hence, the "tagged" networks and not others would undergo further potentiation or consolidation in sleep. Aside from the unlikely possibility that circuits remain in heightened state of

excitability (or self-excitation) during extended periods of waking, there does not appear to be a mechanism for distinguishing between correct and incorrect choices – that is, sequences of movements (and associated neural circuitry) responsible for correct or incorrect choices. It would seem that activity would be as "heightened" in waking (and carrying to sleep) with incorrect as with correct movements, and if so, the net effect of their co-strengthening would be an equivalent potentiation in sleep. Accordingly, based on Walker's scheme, it would be difficult to account for the reduction in errors (i.e., correct choices) during sleep as shown for the finger-tapping task in Figure 3 (B and D) of the target article.

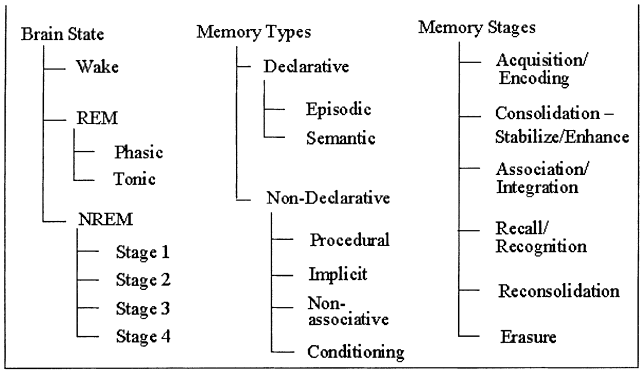

Figure R1. Brain states, memory types, memory stages.

Author's Response

Past, present, and the future: Discussions surrounding a new model of sleep-dependent learning and memory processing

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Abstract: Following on from the target article, which presented a new model of procedural skill memory development, in this response I will reflect on issues raised by invited commentators and further expound attributes of the model. Discussion will focus on: evidence against sleep-dependent memory processing, definitions of memory stages and memory systems, and relationships between memory enhancement, sleep-stages, dreaming, circadian time, and sleep-disorders.

I will start by saying how delighted I am that such a diverse body of commentators took the time to contribute to the discussion of the target article by way of their valuable commentaries in this publication. From reading the commentaries several issues are clear. First, we have yet to arrive at a consensus on what we think *memory consolidation* means – evidently it means different things to different people – as well as how many subcategories there may be. Second, it is striking that some commentators describe definitions of *consolidation* classically in terms of behavioral outcomes, as the target article does, others conceive of consolidation as defined by forms of plasticity; and still others define it in pure physiological measures. On the one hand this indicates the rich diversity of research focusing on memory consolidation, while on the other, it demonstrates the variability with which we conceptualize the term and thus the difficulties in interpretation we may face.

To that end, in writing the original target article I had several goals in mind. Perhaps most grand was an attempt to bring a degree of consensus to the field in terms of brain-state dependent memory stages, specifically the varied forms of memory consolidation that are becoming apparent. My approach was to introduce the concept of consolidation as two forms, either stabilization or enhancement, and describe their relationship to time, wake, sleep, and the physiological characteristics of sleep. Based on the even *more* varied potential forms of consolidation noted by a host of commentators here, I accept that in this endeavor, greater refinement is required. Indeed, the target article may not have gone far enough in its dissection of the term and the necessary role sleep plays. Furthermore, while the current memory-stage model appears to fit a large proportion of the literature, several findings (either noted by commentators or raised by myself in this response) appear not to fit comfortably into the model, indicating areas of future modification.

My second, perhaps more realistic goal, was to trigger a dialogue between researchers in the field of sleep and memory. We need to recognize that the blanket term "consolidation" is not only too broad in our own conceptions, having multiple meanings, but also that this generality results in a confusion of how and when we consider factors such as wake and sleep causal to memory processing. In this respect, I feel the target article has made progress. There seems to be little resistance to the concept of consolidation developing in a variety of ways across a variety of forms of learning during either wake or sleep.

By way of these discussions, I feel we are moving closer to understanding how stabilization, enhancement, and the additional steps of memory, either between or beyond, relate to brain states. It is no longer acceptable to simple state that "sleep" is involved in "memory," or that "REM sleep" is not involved in "consolidation." We must be more specific. To all but a few commentators, this now seems obvious and is embraced. I emphatically state that we do not yet have a complete understanding of how brain states, memory categories, and memory stages are related. But before this statement is used obstinately as a quotation to support a lack of evidence for the role of sleep in memory stage processing, let me explain. To demonstrate the complexity that we face, consider Figure R1. Here we can appreciate, even with the admittedly gross simplification of subcategories, the scope of questions we must ask, and the directions of causality we must test. The model embodied within my current target article represents just one component of this larger framework, as noted in the article's conclusions. Looking beyond the target article and the associated commentaries, it is this level of complexity, and the specificity of terminology, I hope we can keep in mind as we continue exploring memory processing.

From reading the commentaries, several common themes appear, which I will use as a structure to reply to the pertinent aspects of each. These topics are: (1) evidence that sleep does not play a role in memory processing; (2) different systems of memory and different forms of learning; (3) the multiple stages of memory that may or may not exist; (4) definitions surrounding plasticity and sleep characteristics; (5) potential mechanisms of sleep-dependent memory plastic-

Table R1. *Cross-reference guide to commentary responses*

Author / Theme	Is there evidence against sleep-dependent memory processing?	Memory systems and forms of learning	Memory stages	Definitions	Sleep consolidation mechanisms	Memory and dreaming	Circadian time, attention and sleep deprivation	Sleep abnormalities and memory
Atienza & Cantero			X		X			
Bramham					X			
Clarke		X						
Coenen			X		X			
Doyon et al.		X	X					
Dumay & Gaskell		X	X					
Finelli & Sejnowski					X			
Foster & Wilson		X		X				X
Greenberg						X		
Groeger & Dijk		X					X	
Korman et al.					X			
Pagel						X		
Payne et al.				X	X			
Peigneux et al.			X					
Piggott & Perry								X
Porte					X			
Schredl		X						X
Sheth					X			
Siegel	X			X				
Smith		X						
Szymusiak					X			
Tononi & Cirrelli					X			
Vertes	X	X	X					

ity; (6) the relationship between dreaming and memory processing; (7) the influence of circadian test time, attention, and sleep deprivation on memory processing; and (8) sleep abnormalities and alterations of sleep-dependent learning. A cross-reference guide for these topics and their relationship to specific commentaries can be found in Table R1.

R1. Is there evidence against sleep-dependent memory processing?

The commentaries by **Siegel** and **Vertes** both argue against the empirical evidence for sleep-dependent memory processing; I would like to rebut.

Both these authors describe studies of patients treated with monoamine oxidase inhibitors (MAOIs), which alter sleep structure and interfere with REM sleep. They claim that these patients show no signs of impaired memory, even after receiving such medication for years, and believe this is strong evidence against the role of sleep in memory consolidation. First, although MAOIs appear to reduce REM sleep to varying degrees early in medication (Landolt et al. 2001; Monti et al. 1990), REM sleep re-emerges later in course of medication (Landolt & de Boer 2001; Mendelson et al. 1982; Minot et al. 1993), suggesting a strong REM compensatory mechanism. Furthermore, there is a potent REM rebound during the frequent periods when medication is paused (Minot et al. 1993; Steiger et al. 1987; 1994). As such, the claim that patients live for years with no REM sleep is unfounded.

Second, using just a simple one-off test of memory tells us nothing about intact or impaired sleep-dependent learning, or consolidation of any sort, the perils of which are evident in the misgivings of **Vertes** and **Siegel** surrounding MAOIs. For example, Vertes and Eastman (2000) cite 29 articles to argue that such REM suppressants had no deleterious effects on memory. Of these, 19 were available in the Harvard Medical School's electronic and print libraries. An analysis of these (see Table R2) shows that of the 16 primary source articles, 5 reported no memory tests at all. Of the remaining 11, 7 retested memory within minutes of training, and only one had a retest interval of greater than 30 minutes. Most strikingly, none involved retesting following sleep, none tested tasks that have been reported

Table R2. *Analysis of reports studying effects of REM suppressant drugs on memory*

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

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

to undergo sleep-dependent consolidation, and none recorded subjects' sleep to determine the extent of REM suppression. It therefore seems clear that such studies provide no useful information regarding the role of REM sleep in memory consolidation, let alone the role of sleep in general.

In his commentary, **Siegel** does not appear to consider all the evidence for my thesis. For instance, Siegel raises an issue about fatigue during performance/practice preventing the expression of possible waking consolidation. He states

> [I]t also needs to be shown that recovery from the performance decrements during learning that are known to be caused by intense practice were not creating an illusion of consolidation or "enhancement" when retesting after a recovery period. These sorts of controls have not been thoroughly and systematically done in studies claiming a role of sleep in memory consolidation (Siegel 2001; Vertes & Eastman 2000).

However, such studies *have* been systematically and thoroughly carried out to control for this specific objection. For example, my colleagues and I have shown that following extended practice, neither a 10-minute rest period, a 4-hour rest period, an 8–12-hour rest period, nor even a 12-hour period with total hand rest, can trigger significant improvement across waking intervals (Walker et al. 2002). Only during time periods containing sleep does such enhancement occur (Walker et al. 2002). This negates the argument that practice-induced fatigue without enough recovery time falsely inflates, or triggers an illusion of, sleep-dependent memory enhancement.

Then, **Siegel** claims (albeit using a newspaper citation) that researcher Carlyle Smith has previously concluded that sleep has no role in the consolidation of declarative memory. Similarly, **Vertes** attempts to suggest that the target article declares no role for sleep in declarative learning. Both these points are incorrect, as is the assertion that I, too, believe sleep plays no role in declarative memory. On the contrary, I believe sleep does contribute significantly to declarative memory processing (see sect. R2). Smith does not in fact conclude that sleep plays no role in declarative learning in his article, but rather that the evidence for a link between *REM* sleep and consolidation of declarative memory has not been consistently found, while there was evidence for such a link between declarative memory and other sleep stages.

Finally, **Siegel** argues my claims are excessively ad hoc, for example, that only Stage 2 non-REM (NREM) sleep in the last quarter of the night is important. In that report (Walker et al. 2002), all appropriate statistical tests, together with correction for multiple statistical comparisons, highlighted Stage 2 NREM sleep as important in the described overnight improvement (therefore not an "ad hoc" claim). Indeed, the sleep-dependent nature of this motor task has since been replicated by two independent groups (Fischer et al. 2002; Korman et al. 2003).

Vertes raises the issue that practice-dependent learning during the short retest session after sleep (2–3 trials, a total of just 60–90 seconds) may be the true cause of what we claim to be delayed sleep-dependent improvement. However, our experiments have explicitly addressed this issue. First, in our past studies (Walker et al. 2002; 2003b), we have demonstrated that the amount of improvement expressed after sleep (but not wake) is far beyond that which can be predicted based on practice-dependent learning rates alone, modeled specifically on each subject's own practice-dependent learning curve during training. Second, an even more compelling reason to reject Vertes's hypothesis is that the number of retest trials that subjects perform after either wake or sleep are identical, and therefore, subjects have just as many trials to demonstrate improvement at retest following wake or sleep. However, there is a very clear difference between retest performance after wake or sleep, with improvement developing only after sleep and not wake, despite subjects gaining just as much practice (and opportunity to improve) at each time point (Walker et al. 2002; 2003a; 2003b). As such, a practice-dependent explanation for improvement after sleep but not wake is implausible.

Vertes also suggests that I have stated sleep-dependent learning is modest or even small compared to practice-dependent learning during training, stating that "it is important to note, as pointed out by Walker et al. (2003b), that the gains in performance with the mere passage of time (in waking or sleep) are very small compared to improvements with repeated practice on motor tasks." I have never made this claim. To be clear – and to correct this statement: One session of practice on this motor task produces, on average, a 55% improvement in performance speed and approximately a 45% improvement in accuracy (Walker et al. 2002; 2003a; 2003b). Yet, just one night of sleep triggers an average 20% additional improvement in speed and approximately an extra 35% improvement in accuracy (Walker et al. 2002; 2003a; 2003b), which is not "very small" in comparison to training. Furthermore, three nights of sleep, without further training, trigger speed improvements of nearly 30% and accuracy improvements of 50%, almost equivalent to training (Walker et al. 2003b). In addition, if practice- versus sleep-dependent improvement is being compared, it is also pertinent to note that a second training session before sleep offers only a 9% additional improvement in speed and no significant further improvement in accuracy, while the subsequent night of sleep triggers

improvements in both speed and accuracy far in excess of these additional practice-dependent improvements (Walker et al. 2003b). Thus, sleep-dependent learning appears to provide a very large and highly significant amount of the improvement one can develop on this task.

Ultimately, the expanding database of sleep-dependent studies exploring the links between sleep, learning, and plasticity, will resolve these objections even more clearly.

R2. Memory systems and forms of learning

Regarding memory and anatomy, it is tempting to assign an exclusive, one-to-one isomorphic exemplar of a particular memory type (such as declarative memory) with an anatomical structure (such as the hippocampus), as some commentators attempt; but this would be a mistake. It is correct to note that declarative memory has consistently been associated with the medial temporal lobe, particularly the hippocampus. Yet, this does not mean that the medial temporal lobe is only concerned with declarative memory. In fact, semantic memory (another form of declarative memory) is largely considered to be independent of the hippocampus. In contrast, models of associative and also sequential skill learning do implicate involvement of the hippocampus (Poldrack & Packard 2003; Poldrack & Rodriguez 2003). Thus, the question raised by **Foster & Wilson**, about sleep-dependent hippocampal replay in animals (learning spatial navigation tasks and associative learning paradigms) being seemingly at odds with the inconclusive findings of REM sleep-dependent declarative memory formation, is moot (also see commentaries by **Groeger & Dijk**, and **Dumay & Gaskell**). The important issue here is the need to resist trying to fit the properties of a procedural memory model onto declarative memory (and vice versa), and instead accept that complex systems, the brain being the quintessential example, are highly unlikely to be explained by generalized rules. This was part of the target article's direction – to specifically focus on one form of memory and explain the patterns of memory-stage development apparent within that framework, rather than suggest it was a "one model fits all memory domains" theory.

As noted in the target article, the effects of sleep on declarative memory may be very different. **Foster & Wilson** misquote the target article as suggesting that "sleep may be less important in declarative memory than in procedural memory." In fact, **Vertes** misreads (or misinterprets) this point completely, as have other non-memory researchers (**Seigel**), suggesting that the target article concludes sleep plays no role in declarative learning. The target article does nothing of the sort. Instead, the target article simply states that the evidence is currently less resolved than in the procedural domain. It does not mean sleep plays no role in declarative memory. Sleep may very well have important effects on declarative memory processing. First, sleep may prevent the gradual decay of declarative memory over time. Second, sleep may be essential in terms of declarative memory transfer between storage sites (translocation), a theory already put forward by Buzsaki (1998) and Hasselmo (1999). Third, sleep may also be important for improving associative connections between newly learned information and previously retained information, a point discussed further in the commentary and discussion of **Dumay & Gaskell**.

Following on an issue raised by **Groeger & Dijk**, **Smith**, and **Dumay & Gaskell**, I would also note that categorical separations of memory, such as declarative and non-declarative, while useful in their simplicity, may preclude subtle nuances in understanding. I would be more than happy if future models attempted to move away from these theoretical memory categories and their generalized assignment to anatomical structures, and instead, be guided more by specific task characteristics and their relationship to sleep: For example, investigating the question "is there a relationship between NREM sleep and tasks that require sequential ordering" – be it the ordered recall of a specific word list (a "declarative episodic task"), or the ordered retrieval of a specific series of finger movements (a "non-declarative procedural task"). This orthogonal approach to understanding the relationship between sleep and learning may well be a useful exercise as discussed below. Alternative methods of investigating these novel predictions may also be useful, such as modeling the influence of sleep or wake in neural networks (**Clarke**), and artificially testing hypotheses across a variety of altered conditions (Hinton et al. 1995).

Commentaries by **Schredl**, **Smith**, and **Doyon, Carrier**, **Simard**, **Tahar**, **Morin**, **Benali**, **& Ungerleider** (**Doyon et al**.) all address a point of importance often overlooked by those who deny the role of sleep in memory processing. Although delayed overnight improvement appears to occur robustly and consistently across a wide variety of procedural tasks in the motor (Fischer et al. 2002; Maquet et al. 2003; Robertson et al. 2004; Smith & MacNeill 1994; Walker et al. 2002; 2003a; 2003b), visual (Gais et al. 2000; Karni et al. 1994; Mednick et al. 2002; 2003; Stickgold et al. 2000a; 2000b), and auditory (Gaab et al. 2004) domains, they do not all show a relationship with the same stage of sleep. For the naysayer, this has been taken as evidence against the role of sleep in memory processing stages. Why? As the above commentators and the target article note, these tasks, despite being grouped under the rubric of "procedural skill learning," undoubtedly rely on vastly different neural systems. Moreover, the functional changes occurring within these networks to produce behavioral improvement are also likely to be equally diverse.

The fact that, for example, a motor skill task shows a different sleep-stage correlation to a visual discrimination task surely does not represent inconsistency within a theory. Such a claim would be an oversight of brain mechanistic complexity. Even within the seemingly uniform domain of "motor skill learning," all things are not equal. Take for example the task of learning to use a computer mouse, and compare that to learning of a piano scale. Both are motor skill tasks, but while the effector limb may be the same, this is where many similarities end. Mouse skills require adaptation to environmental forces (e.g., the mouse mat texture), the software settings (e.g., fast or slow acceleration), and the quality of on-line feedback one receives (e.g., can you see the mouse arrow on the screen and use it as visual feedback to correct erroroneous movements?). In contrast, learning a piano scale requires the formation of a different and very specific program of motor sequence units (e.g., a series of unique finger flexions and extensions), the execution of which must be timed in a temporally specific manner (not depressing the third piano key position before the second), and a tactile or even auditory (rather than visual) feedback system for error monitoring.

Without laboring the point, this example illustrates how

vastly different two apparently similar "procedural motor skill memory tasks" can be, and presumably how different the governing mechanisms of learning may be; something Doyon and colleagues have recently discussed (Doyon et al. 2003). In this respect, it seems very unsurprising that different neural processes relating to different tasks would be dependent on different brain states (sleep stages in this case). The distinction of different forms of learning may already be helpful in explaining differences in sleep-stage dependence. **Smith** notes that while many sequential motor skill tasks appear to correlate with Stage 2 NREM sleep, a mirror tracing task, a form of visuo-motor adaptation, has been associated with REM sleep. Appreciation of such subtle but important differences in task characteristics within the same memory category (procedural motor skill learning) thus offers more refined interpretations of the above correlations, rather than reflecting inconsistency. It also supports the sentiments of Smith in his commentary that a "'motor' versus 'cognitive'" learning taxonomy is overly simplistic.

Smith also remarks that sleep-stage correlation diversity may arise for other possible reasons across a range of experimental axes – for example, task complexity (simple or easy), sensory or motor characteristics, novelty or familiarity, and degree of training duration, to name but a few. Though it may be easy to trivialize these factors as the cause of differences in sleep-stage correlation, this would be unwise. However, we, the memory researchers, could aid our own cause in this respect. Even when using the same task in independent studies, we sometimes use slightly modified task versions, together with different testing regimens, be it the number of training trials during acquisition, the number of retest trials before or after sleep, or the number of those respective trials at training and at retest that we compare. Based on the variability this may cause, I would urge those in the field to communicate more readily and find ways in which we can standardize our methods, an act I'm sure will only produce even greater degrees of successful replication than those we have already achieved.

So, before we simply dismiss findings that different sleep-stages correlate with different memory tasks, effectively throwing the baby out with the bath water, it maybe a wiser tactic to look a little deeper into the task characteristics and ask what differences and similarities can help explain these varied correlations.

R3. Memory stages

Atienza & Cantero and **Peigneux**, **Destrebecqz**, **Hotermans**, **& Cleeremans** (**Peigneux et al.**) correctly point out that it remains unknown whether consolidation-based stabilization (CBS) occurs for procedural sensory memory representations, as it does for certain motor memories. They discuss the results of Mednick et al. (2002; 2003), which demonstrate that repeated practice on a visual skill task causes deterioration in performance through the course of the day, but that short episodes of sleep enhance learning – either to initial baseline levels following a 60-minute sleep epoch, or beyond these baseline levels after a 90-minute sleep period. However, such a result can be interpreted in at least two possible ways. First is that the return of performance to baseline levels following a 60-minute sleep period constitutes a process of stabilization, relieving the deficit induced by training, while any additional learning beyond this point reflects a different mechanistic process of enhancement. However, a second alternative interpretation – not noted – is that the improved performance following any period of sleep, be it returning performance levels to baseline following practice-induced impairment or enhancing it beyond baseline levels, simply reflects the same process at work, that of consolidation-based enhancement (CBE) all along. That is to say, sleep episodes always trigger a process of enhanced learning from whichever end point has been achieved following practice, whether it is one of a deficit following prolonged or repeated practice, or an initial baseline following just one training session. Unfortunately, the claim that two discrete processes exist can only be defined using an interference paradigm, which has yet to be carried out using such sensory tasks. Without such an experimental challenge, we are not able to differentiate between these alternative interpretations, rendering modification of the current model premature.

Atienza & Cantero also point out that on an auditory discrimination task, some aspects of behavior do not show the expected deficits in learning following sleep deprivation, deficits that have been seen using visual and motor skill tasks (Fischer et al. 2002; Maquet et al. 2003; Stickgold et al. 2000a). This echoes the commentaries by **Smith** and **Korman**, **Flash**, **& Karni** (**Korman et al.**), as well as the point at the beginning of this response, that even sensory and motor categories of procedural memory may be too broad. Instead, more subtle classifications could increase our understanding regarding different behavioral outcomes following sleep and wake. Interesting, the studies of Atienza and colleagues did demonstrate that although certain behavioral measures on this task showed no change with sleep deprivation, neurophysiological measures of automaticity (a specific waveform peak in the event-related brain potential) demonstrated severe impairments following sleep deprivation. It would therefore be interesting to find a behavioral measure of automaticity to complement these electophysiological measures of sleep-dependent consolidation. For example, if a secondary concurrent task were introduced, presumably the automaticity that developed on the first task following sleep would effectively prevent a large proportion of impairment by the second concurrent task. Yet, subjects who had not slept and not gained the benefit of automaticity would presumably show profoundly impaired performance in the presence of a concurrent interfering task. By investigating alternate behavioral measures of consolidation, the distinction of sleep-dependent enhancement may still exist in this case.

On a related issue, **Vertes** describes work by Donchin et al. (2002) using a motor skill adaptation task. This is the same task that has previously shown evidence of both consolidation-based stabilization across wake, and subsequent delayed consolidation-based enhancement across 24 hours following a night of sleep (Brashers-Krug et al. 1996). But, Donchin and colleagues reported no change in performance at a later 24-hour retest, either with or without sleep. However, a closer examination of these reports reveals that different performance variables are reported as the measure of learning – a correlation coefficient in the earlier study Brashers-Krug et al. describing both CBS and CBE, and a "learning index" in the report by Donchin et al. showing no delayed performance changes. Which of these mea-

sures represents consolidation is unresolved, and the utility of this description by Vertes is uncertain.

Dumay & Gaskell offer important suggestions regarding the potential role of sleep beyond stages of memory consolidation and propose that sleep may facilitate a process of integration, in addition to the enhancement of newly formed memory representations. They build on this interesting idea using data from a lexicalization task, describing a delayed learning effect over 24 hours, following a night of sleep, which persists for at least one week. A related study by Fenn et al. (2003) adds to these ideas and may expound on the time course of the effects in even more detail. Using a naturalistic spoken-language task (learning synthetic speech), Fenn and colleagues investigated the generalization of phonological categories across different acoustic patterns, and observed how this learning changed over practice and time. The task required forming new mappings from complex acoustical patterns to pre-existing linguistic categories, which then generalized to new stimuli. As such, it involved both a declarative process of forming specific memories associated with the learned words, together with a procedural component involving mapping across the set of learned words that supports generalization to novel stimuli. During the initial training session there was a significant improvement in recognition performance on the task. However, when retested after a 12-hour waking interval, performance decreased – either due to waking interference (although see discussion on **Coenen**, below) or a process of memory decay. Yet, if subjects were retested following a night of sleep, the recognition performance was completely restored. Furthermore, this effect was present irrespective of whether the post-sleep retest occurred in the morning or later in the evening, illustrating that these performance changes could not be explained by different circadian test times.

These data would indeed fit with the notion that sleep can enhance performance, effectively recovering representations and mappings associated with generalization of previously learned phonological memories. Moreover, such findings suggest a sleep-dependent effect beyond enhancement, potentially offering a generalization of learning to other newly encountered stimuli. However, this sleep-facilitated generalization may not be evident in all tasks, since sleep-dependent learning of certain visual and motor skills is specific to the characteristics of the original task stimuli (i.e., retinotopic visual stimulus location, or the specific motor sequence), and does not transfer to similar stimuli in different configurations (i.e., switched retinotopic location or a new motor sequence pattern).

Coenen raises the issue of consolidation-based enhancement and its dependence on sleep. Coenen questions whether sleep itself plays a proactive role in memory consolidation, or whether the behavioral state of sleep (lacking external sensory perception and outward motor action) simply offers a permissive time for memory consolidation. In this sense, there is nothing unique to the biology of the sleeping brain that triggers memory consolidation. Instead, it is simply an offshoot of the sleeping state itself (devoid of interaction with the external world, preventing sensory and motor activity), which allows the brain to consolidate memories; something the brain may not be able to do during wake.

First, the notion of the sleep brain as simply quiescent (thus passively offering "downtime" for consolidation) is somewhat outmoded. While clearly the visual external environment is not perceived during sleep, nor is there considerable motor output, this by no means suggests that visual and motor regions of the brain are not highly active. In fact, animal and more recent human neuroimaging studies demonstrate that sensory and motor regions are particularly active during sleep, especially REM sleep (for reviews see Hobson et al. 2000). Therefore, if the presence of sensory and motor activity during time awake is the argument to explain a lack of consolidation, this reasoning must also be applied to the sleeping brain as well, since here too we find prolific sensory and motor activation, equally capable of blocking consolidation. However, the fact that delayed performance enhancements only occur during sleep and not wake, even though sensory and motor activity prevails during both states, makes a classical interference explanation untenable.

Second, the possibility that waking activity prevents consolidation has been specifically tested in several sleep-dependent visual and motor learning studies, the results of which are difficult to reconcile with the reasoning put forth by **Coenen**. These reports have used control experiments to demonstrate that periods of quiet rest without motor or visual activity during the day (mimicking the behavioral features during sleep) are still not able to produce consolidation-based enhancements during these waking intervals. For example, after having learnt a finger-tapping motor skill task in the morning, subjects in one such study had enforced total hand rest for an 11-hour waking interval – far in excess of the average 8-hour sleeping period (Walker et al. 2002). Nevertheless, subjects still expressed no behavioral improvement across the waking interval with total hand rest, yet they went on to demonstrate improvement after a night of sleep. In a similar experiment, following training on a visual skill task, a control group of subjects were required to lie supine, in a dark quiet room, without any visual stimulation, and were blindfolded for a 90-minute period (although they remained awake, as verified by full polysomnography recordings), while an experimental group of subjects were allowed to sleep during the 90-minute period (Mednick et al. 2002). When retested, only the group that had slept showed consolidation-based enhancements in performance, whereas subjects who spent this time awake, but without visual stimulation or interference, showed no improvement. Such studies therefore do not support a classical theory of simple passive rest (either during sleep or during wake), promoting consolidation. Instead, the only viable explanation given these data is that sleep itself, and not the lack of interference during this state, is responsible for the consolidation-based enhancement triggered by sleep.

Some tasks have been reported to show delayed improvement across time intervals without the need for sleep, and would therefore not fit easily into the sleep-dependent, consolidation-based enhancement framework of the target article – findings that can help refine the current model.

The first result, reported in the commentary of **Doyon et al.**, describes evidence that learning of a motor adaptation task shows improved performance as a function of time and not necessarily sleep. Several observations may be of interest. One is that the data comparison involved the last 32 trials at testing relative to the first 32 trials of retesting, within which there may be significant practice-dependent learning, perhaps making it more difficult to conclude

whether these differences reported between each time point are truly time-dependent rather than practice-dependent. For example, our previous motor studies investigating delayed learning used just the last 2–3 trials on day 1, relative to the first 2–3 trials on day 2 (only 60–90 seconds of performance measure at each retest), removing a practice-dependent learning contribution to the comparison (**Vertes**). It would therefore be interesting to change the former comparison from Doyon et al. to, say, the last 2–5 trials at testing relative to the first 2–5 trials at retesting, effectively removing a practice-dependent influence. If the performance differences remained across the 8-hour period, it would indeed indicate that this form of delayed enhancement was sleep-independent.

Also, the 5-hour and 8-hour delay periods without intervening sleep (groups 1 and 2) appear to show quite similar amounts of percentage improvement (about 9% and 10%, respectively, calculated from the figure provided), while the 24-hour delay period (group 3), containing a night of intervening sleep, express greater improvement (about 14%), although this difference is noted as not significant. It is interesting to speculate that this variation may also be related to intervening sleep. Regardless, **Doyon et al**. make an important separation between forms of motor skill learning, and highlight the possibility that these forms of learning may follow different courses of delayed learning over time and brain state, notions that hold important implications for refining the CBS-CBE model.

The second report is an ingenious study by Robertson et al. (2004), which demonstrates that explicit procedural learning of a motor sequence, but *not* an implicitly learned version of the task, requires sleep for delayed consolidation-based enhancement. Performance on the implicit version of the task demonstrated delayed learning across 12 hours irrespective of whether it contained sleep or not. This also raises two interesting possibilities. One is that the comparable behavioral improvement in delayed implicit procedural learning occurs by way of a similar process of CBE to that observed with explicit skill learning (such as a systems level plastic change; **Korman et al**.), but without the need for intervening sleep. An alternative possibility is that while behavioral improvement on both forms of the task appear similar (albeit developing across different brain states), the underlying mechanisms of this improvement are different. In either case, it would seem that the current model put forth in the target article can be modified. The former possibility suggests an exception to the exclusivity of CBE to sleep, occurring when awareness of learning is absent. The latter suggests a fundamentally different mechanistic form of CBE may exist which does not rely on the physiological specificities of the sleeping brain. With continued research on delayed learning in explicit and implicit task paradigms, these issues will become clearer.

R4. Definitions

Several issues were raised in the commentaries regarding definitions concerning memory stages, systems, and sleep stages.

With respect to defining the sleep characteristics we choose to correlate with learning, I too sympathize with **Payne**, **Britton**, **Bootzin**, **& Nadel** (**Payne et al**.) in the hope of supplementing classical Rechtschaffen and Kales sleep scoring with more independent physiological variables in attempting to understand the basis of sleep-dependent memory processing. For example, rather than correlating word-pair retention or visual skill improvement with slow wave sleep (SWS), we should instead investigate relationships between these learning measures and EEG delta power (Huber at al. 2004), or investigate overnight enhancement of motor skill learning with sleep spindles (number, frequency, or amplitude), rather than just Stage 2 NREM sleep. While it would be unwise to abandon the classical Rechtschaffen & Kales scoring method completely, it is surely as dangerous not to co-investigate these alternative sleep characteristics as explanatory variables.

Foster & Wilson question the use of the term *consolidation* across memory categories. I agree with Foster & Wilson that declarative memory has received greater research attention, and thus the term consolidation is similarly more strongly associated with this form of memory. However, it has never prohibited the association of procedural memory with the term consolidation, and nor should it. Consolidation refers to a process, and does not belong to one memory category. But such a debate of semantic origin serves little benefit for the current framework, other than perhaps a historical reference. It has not precluded the utility of the term throughout the neuroscience community, applied across most all memory domains (see McGaugh 2000). If we are to continue using the term *consolidation* in a meaningful way, which I think we still can, we must accept that it requires subdivisions, each of which may be applied and modified to different memory systems (a point discussed further below).

As an aside, in perhaps a misreading, **Foster & Wilson** suggests that the word "passive" was used in the target article to define procedural learning. However, *passive* was used in reference to implicit learning, not procedural learning. To clarify, I specifically cast procedural learning in proactive terms, noting that it often requires subjects to undergo a "training interval involving repeated engagement with the procedure being learned."

Finally, I feel that the subdivisions of consolidation are clearly described using operational definitions (**Siegel**, **Coenen**). Indeed, rather than accepting this more refined level of definition of different stages of memory development, **Siegel** propounds a less differentiated framework that does not appear to fit a vast majority of the empirical data. My position, however, remains that the careful separation of different consolidation forms will help resolve areas of perceived conflict in the sleep and memory field.

R5. Sleep consolidation mechanisms

A host of commentaries offer important mechanistic information corresponding to unique stages of consolidation and how sleep may be important. In addition, **Szymusiak** notably provides a careful consideration of issues surrounding sleep-dependent plasticity, and how to test these ideas empirically.

In his commentary, **Bramham** focuses on brain-derived nerve growth factor (BDNF), which may participate in the regulation of the sleep-wake cycle, and is also reported to trigger protein synthesis essential to plasticity. It is possible that increased release of BDNF during synchronous activity in NREM sleep may play a role in sleep-dependent con-

solidation. Here too, terminology becomes different, with the contribution of protein synthesis to plasticity discussed as *stabilizing* synapses that have undergone learning-dependent changes, which is different compared with the *stabilization* of behavioral performance suggested to occur with wake, as put forth in the target article. This aside, Bramham builds a very attractive model, recognizing that the combined processes of synaptic potentiation and depotentiation together may lead to the behavioral effect of improved task performance after sleep. To interpret this theory in terms of the current framework, it may be that without synaptic stabilization during wake (occurring via early neural changes [(Lamprecht & LeDoux 2004)], or following a first wave of protein synthesis which protects newly formed synaptic connections), subsequent overnight enhancement may not occur, and instead may actually lead to weakened synaptic strength.

Tononi & Cirelli add a valuable contribution in proposing possible molecular mechanisms of CBE during sleep. Their commentary is a tour de force indicating why we can no longer consider neural activity in wake and sleep as active or restful respectively. Indeed, as they point out, absolute levels of cerebral metabolism are in fact *higher* after having been awake than after a night of sleep (Braun et al. 1997), a finding which would work against a theory of neural fatigue progressing across waking hours, preventing expression of consolidation that may have occurred. In light of such evidence, theories that suggest a passive repletion process occurring during sleep, whereby neural function is restored and masquerades as overnight improvement, become harder to accept. **Tononi & Cirelli**'s sophisticated level of description goes far beyond the sleep-associated neuronal rest theory for memory networks, and describes a more complex series of *active* events which could trigger true post-sleep memory enhancements, evidence that is also difficult to reconcile with more restitutive theories that have been proposed (see **Sheth** and **Coenen**). Indeed, several factors run counter to the argument that simple rest triggers learning rather than sleep itself, or that fatigue impairs expression of learning during wake (**Siegel**). First, human studies of sleep-dependent learning have provided several control conditions that mimic the behavioral rest characteristics of sleep, but during periods of wake, and still result in no significant evidence of consolidation-based enhancement (see detailed response to Siegel and Coenen above). Additional evidence has been offered by Frank et al. (2001), who have described cellular level sleep-dependent plasticity using a monocular deprivation paradigm. They reported a considerable enhancement of synaptic plasticity following 6 hours of sleep, while an equivalent period of wake caused a *reduction* in the size of this plasticity measure. Most telling, however, Frank et al. note that these effects were not just an offshoot of a non-waking brain (i.e., a time during which transmitter concentrations could be restored, or a time without external competing sensory stimuli, which normally block consolidation), since the state of anesthesia actually impairs this form of ocular column plasticity, rather than enhancing it, as sleep does. Again, this appears to contradict the predictions of a restitutive model.

Supporting the active, sleep-dependent model of memory processing, and slightly different to the mechanism proposed by **Bramham**, **Tononi & Cirelli** suggest that SWS dynamically promotes the depression of synaptic strengths, effectively reducing synaptic connections, improving efficiency. These claims are supported by empirical data suggesting that molecules associated with synaptic depression are indeed up-regulated in a sleep-dependent manner. Given these findings, they propose a SWS model whereby an active process of balancing synaptic efficiency, in the endeavor to create a refined memory representation, takes place during sleep. As a consequence, neuronal networks benefit from improved signal-to-noise ratio within the system, a process that may not be possible during the time of initial memory acquisition or across waking hours which confer stabilization.

It may be that both processes – of synaptic potentiation and synaptic depression – occur during the different stages of sleep and both are essential requisites for memory enhancement, as the theories of **Porte** and **Finelli & Sejnowski** describe. They suggest that sleep spindles, another property of NREM sleep, may have a role to play in synaptic potentiation, leading to consolidation-based enhancement by cellular mechanisms discussed in the target article. Porte specifically notes the intriguing anatomical expression of sleep spindles in "(cortico)striatothalamocortical (CSTC) loops," a location that is likely to play a role in certain forms of procedural motor representations (see **Doyon et al**.). Moreover, it is just such procedural memory representations, among others, that have previously expressed CBE overnight, pertaining to NREM sleep (Robertson et al. 2004; Smith & MacNeill 1994; Walker et al. 2002; although see Fischer et al. 2002). If NREM sleep and particularly sleep spindles are crucial to certain types of sleep-dependent motor learning, we can invert this equation and ask the reverse question: Does increased daytime motor learning alter the physiological characteristics of NREM sleep or sleep spindles? One would predict that practice-dependent alterations of these circuits would, in turn, reciprocally modify the homeostatic expression of sleep spindles in the subsequent night(s). Interestingly, just such a modification has been reported by Fogel et al. (2001), who demonstrated that in humans, relative to a night of sleep without motor learning, intensive motor skill practice triggers a significant, 40% increase in the number of spindles during the post-training sleep night.

Taken together, the neurophysiological properties of NREM sleep could act in two different but mutually beneficial ways in terms of enhancing certain forms of memory. Slow wave oscillations may provide a form of synaptic downscaling of initially over-potentiated networks, which are formed (and stabilized) across waking episodes, while spindle events are able to selectively strengthen these refined representations by triggering intracellular cascade events important for synaptic potentiation. It is also intriguing to note the similar possibility that pontine-geniculate-occipital (PGO) burst activity may offer potentiation of synapses. This notion is supported by work from Datta and colleagues demonstrating enhanced avoidance learning which is dependent specifically on PGO activity in rats, and can even be dissociated from the process of REM sleep itself (Datta 2000; Datta et al. 2004).

Payne et al. make an important contribution by highlighting the potential influence of several neurochemicals known to fluctuate across brain states – chemicals that are intricately linked to mechanisms of learning and plasticity. Advancing the target article's statement describing the influence of molecules ranging from hormonal substances, to

cytokines and even gaseous substances, Payne et al. focus on cortisol, noting the dramatic nocturnal concentration swings from early to late in the night. They build on seminal work by Born and colleagues, along with work outside the field of sleep, which demonstrates mediation of learning and plasticity by cortisol. In doing so, they convincingly remind us that a sole focus on classical neuromodulators may obscure other/complementary mechanisms at work during sleep; mechanisms that may also help in clarifying sleep-dependent findings in the field.

Korman et al. and **Atienza & Cantero** both discuss the possibility that plasticity can occur in a variety of alternate forms, across different brain states. Specifically, Korman et al. skillfully build on the concept of different forms of consolidation as determined by behavioral performance (similar to the stages of consolidation put forth in the target article), and introduce the concept that different types of plasticity may underlie these different forms of consolidation. They introduce the notion that plasticity can be extended beyond the local, Hebbian synaptic level of description, into what has been termed "systems level plasticity." While this concept may be operationally difficult to define (how "far" does the locus of a memory representation have to travel before it can be deemed different from the original memory representation and thus be termed a "systems level" plastic change?), it could hold utility in understanding the stages of learning and their brain-state dependency.

There is already evidence that sleep induces both local level plasticity as well as systems plasticity. For example, the monocular deprivation study by Frank et al., (2001) described in the target article, is indicative of a local synaptic plastic change. Yet, Ribeiro and colleagues have also described plasticity-related gene expression across large-scale anatomical areas during successive REM cycles (Ribeiro et al. 2002) consonant with the idea of systems-level plasticity. In addition, using the sleep-dependent visual and motor skill tasks separately, my colleagues and I have recently described fMRI data (Walker et al. 2005; in press) indicating that, following equivalent amounts of task training, a subsequent night of sleep produces a form of systems-level plasticity throughout several cortical and subcortical areas.

On a cautionary note, it must be considered that defining different forms of plasticity may be a derivative of experimental technique. For example, whole brain fMRI presumably offers the ability to investigate systems-level plasticity, while single-unit recordings in the CA3 region of the hippocampus, or even focused fMRI on one cortical region, precludes knowledge of systems-level plasticity. But neither technique tailored to investigate one form of plasticity should prevent consideration that the other is co-occurring, or that this unmeasured plasticity forms the basis of behavioral change. Contentions aside, the concept that different forms of plasticity may be related to different brain-state dependent stages of consolidation is both an appealing and insightful one, requiring further consideration.

R6. Memory and dreaming

The eloquent and detailed psychophysiological discourse described in the commentaries of **Pagel** and **Greenberg**, as well as **Schredl**, are most encouraging. I too agree that we, as a field, are fast approaching a time when we have consistently and confidently explicated inimitable evidence of sleep-dependent learning and plasticity, and with this solid foundation in place, are ready to add new layers of experimental complexity which include a triangulation of behavior (performance), brain (sleep physiology and plasticity) and mind (dreaming). Early signs are already emerging (Cipolli et al. 2001; 2003). But we must proceed with rigor, and not fall into interpretive trappings. We must clearly demonstrate that any relationships between dreaming and memory development are functionally related and not simply epiphenomenal. For example, incorporation of newly learned words into sleep mentation does not alone indicate a functional role of dreaming in memory processing. Instead, demonstrating a link between the degree of next-day retention, improved memory recall, or even the degree of plasticity, and the frequency or intensity of prior nocturnal mentation is required to entertain a learning-related function of dreaming. As poignantly noted by Greenberg, triangulated research such as this offers a much richer appreciation of the entire process being studied, leading eventually to a complete understanding of all known sleep characteristics and how they contribute to different memory systems and stages.

R7. Circadian time, attention, and sleep deprivation

When investigating potential sleep-dependent learning, several other factors, such as circadian test time (which may result in attentional differences) and testing in a sleep-deprived state, must also be excluded and controlled for. As described in the target article, while some earlier studies did not adequately control for this, many recent studies have effectively done so.

Several careful explications of the detrimental effects of total sleep deprivation have been carried out which circumvent the rote arguments around sleep deprivation. For example, several groups have investigated, in a thorough and systematic manner, how sleep deprivation interferes with memory consolidation (Fischer et al. 2002; Maquet et al. 2003; Stickgold et al. 2000a). In these investigations, subjects first trained on the task (day 1), and across the following evening were deprived of sleep. However, rather than being retested the following morning in a sleep-deprived state (day 2), subjects were instead allowed either one or two subsequent nights of recovery sleep; thus being retested on day 3 or day 4 in a fully alert state. Results demonstrate that following first-night sleep deprivation, subjects still showed no significant improvement on the task at the later retest many days later, despite being evaluated in a fully recuperated state following ample recovery sleep (Fischer et al. 2002; Maquet et al. 2003; Stickgold et al. 2000a). It is not then possible to dismiss these results on the grounds of fatigue, deficits in basic attention, or stress. Instead, the conclusion that sleep, and specifically sleep in the first 24 hours after training, is crucial to the enhancement of procedural motor and visual skills becomes self-evident.

Groeger & Dijk provide several important issues for consideration. First, they remind us about the concern regarding interactions between sleep-dependent learning and where across the day or night that sleep arrives in the

circadian cycle. This is a relatively uninvestigated factor in studies of sleep-dependent memory process, and I agree that it should receive greater attention. Some data are relevant to this issue. For example, using a sleep-dependent motor skill task, Fischer et al. (2002) have demonstrated that nocturnal sleep triggers delayed improvements in task performance, as previously reported (Walker et al. 2002). In addition, they also reversed subjects' sleep phase, and had participants sleep during the day instead of at night. Despite sleeping at this reversed circadian phase, subjects expressed a near-identical amount of improvement across the sleep period during the day. Thus, improvement critically depended on sleep itself, rather than on where sleep occurred in the circadian cycle. Yet this is not a thorough examination of a completely desynchronized circadian phase, and it would be interesting to test the hypothesis that sleep at one particular time of the night (or day) is more efficacious for learning than another.

Further, **Groeger & Dijk** also note the possibility that simple sleep completion, rather than a specific sleep stage, may be a contributing factor to overnight learning. Interestingly, on a visual skill task that has been shown to correlate with the combined product of SWS early and REM sleep late (Stickgold et al. 2000b), the authors also reported evidence to suggest that subjects who slept less than 6 hours would potentially show no overnight improvement. This would lend support to the theory of Groeger & Dijk that sleep completion may not have been achieved at 6 hours, thus preventing the development of delayed learning. However, it has also been reported that short daytime sleep epochs of 90 minutes are sufficient to trigger delayed improvement on this task, a time period that would represent a curtailed sleep amount in the context of normal overnight durations, presumably being less supportive of a sleep completion theory. A recent study of avoidance learning in rats has also suggested that physiological sleep phenomena (in this case PGO waves), rather than sleep completion, or even the behavioral state of sleep itself, are the true causal trigger of this form of sleep-dependent learning (Datta et al. 2004). In summary, the idea of sleep completion is an interesting one but appears to require considerably more supportive evidence.

R8. Sleep abnormalities and memory

Foster & Wilson, **Piggott & Perry**, and **Schredl** all raise the important issue of testing this model using clinical cohorts with sleep abnormalities, and also to evaluate the relationship between sleep and memory across the life span, since both these factors change as a consequence.

We have begun testing this memory model using a sleep-dependent motor skill task in schizophrenic patients (Stickgold et al. 2003), a disease with known sleep abnormalities expressing both insomnia and especially disrupted NREM sleep (Monti & Monti 2004). In a recent collaboration, Dara Manoach and colleagues trained schizophrenic patients and age match control subjects on a motor skill task and retested them following a night of sleep (Stickgold et al. 2003). As predicted by this model, across initial acquisition during training (claimed not to rely on sleep), schizophrenic subjects showed near-identical amounts of practice-dependent improvement on the task relative to age-matched controls. However, a clear dissociation became evident at retesting following a night of sleep. Control subjects showed normal overnight improvement on the task, yet schizophrenic subjects showed a complete absence of sleep-dependent learning. Indeed, even if schizophrenic subjects were allowed additional retest trials to display overnight learning, no such improvement could be expressed. Note that if the overnight retest session had not been conducted, one might be deceived into thinking that "procedural motor skill memory" is intact in schizophrenics. But clearly this is not the case, with an obvious impairment in delayed sleep-dependent learning. Therefore, similar encompassing studies testing both practice-dependent learning, and delayed overnight sleep-dependent learning must be carried out across the host of clinical disorders expressing sleep abnormalities, before any broad conclusions about sleep and memory processing are made.

An alternative way to test the model, albeit less directly, is to make predictions about sleep based on the intensity of prior learning. For example, if Stage 2 NREM, or specifically sleep spindles, are essential for sleep-dependent motor skill learning, then increased daytime motor learning should subsequently modify these sleep phenomena. Early evidence is also supportive of the model. As described above (see discussion of **Porte** and **Finelli & Sejnowski**), Fogel and colleagues (Fogel et al. 2001) have shown that intense motor skill learning in humans induces a significant increase in the number of sleep spindles across the proceeding night, relative to a night of sleep without prior motor skill learning.

Additional support for this argument comes from literature focusing on ontogenesis and development. Young human infants begin learning to coordinate their limbs and digits in skilled sequential programs around 12 months of age (Frankenburg & Dodds 1992). Therefore, if Stage 2 NREM sleep is important for consolidating these experiences, then Stage 2 NREM amounts should be correspondingly high at these times. Indeed, this is the case – while SWS and REM sleep show a continuing decrease across the first 2 years of life, Stage 2 NREM shows a very different profile. Instead, Stage 2 NREM increases and peaks at this 12-month mark (Louis et al. 1997), precisely at the time of intensive motor skill learning. These data are suggestive of a learning-related, homeostatic Stage 2 NREM sleep response to the ongoing intensity of motor skill learning.

Thus, with careful consideration and experimental design, together with instructive trends in the literature, support for sleep-dependent memory processing is evident in clinical and experimental data.

R9. Conclusions

From both the target article and the associated commentaries, the question appears to be not *whether* sleep mediates specific forms of memory consolidation, but instead, *how* it does so. Our challenge will be, first, to uncover the mechanisms of brain plasticity that underlie both wake/time-dependent stabilization and sleep-dependent enhancement; and second, to expand our understanding of sleep's role in the constellation of different processing stages which are critical for efficient memory development. Work across the neurosciences will be necessary to answer these questions, but with the current rate of growth, the

next decade should provide important advances in our understanding of this critical function of sleep.

Finally, with regard to memory processing and the terminology we choose, I would be happy to embrace a new vernacular for the ever-increasing dissociable stages of memory formation – be it an expansion of the terms put forward here, or even a reconstitution of the terms. Indeed, this paper was written, in part, to demonstrate the current restrictive nature of the term *consolidation*. Even the refined theory presented here is undoubtedly oversimplistic, and the true spectrum of different memory stages will, I'm sure, be amplified many times. I look forward to the community entering into continued and constructive discussion regarding the creation and use of new terms, defined by experimental data, with the hope of developing an expanded vocabulary for memory, agreed by consensus. This can only help further clarify, in more exacting terms, the factors that influence memory development, be they practice, time, wake, or sleep.

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Letters "a" and "r" appearing before authors' initials refer to target article and response respectively.

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