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-

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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-

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