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

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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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