To sleep, perchance to integrate

Howard Eichenbaum*

Center for Memory and Brain, Boston University, Boston, MA 02215

One of the most intriguing and lasting proposals in psychological and neuroscience research is that sleep plays an important role in the consolidation of memories from a labile state into a permanent state. In recent years, there has been considerable research on this issue, and the findings have generated both supporters and skeptics locked in heated debate (1–3). A new study by Ellenbogen *et al*. (4) in this issue of PNAS contributes to this debate and may help us get past the superficial question of whether sleep plays a role by beginning to inform us on how sleep might contribute to information-processing that ultimately underlies memory consolidation.

In this study (4), subjects learned a series of "premises" composed as choices between pairs of visual patterns that contained overlapping elements. Thus, subjects were initially taught to choose stimulus A over stimulus B, then B over C, then C over D, then D over E, and then E over F. These pairs can be integrated to form the relational hierarchy A>B>C>D>E>F (where ">" stands for "should be selected over"). The existence of the hierarchical representation is reflected in the capacity for transitive inferences about the relationships between items that are indirectly connected by a single intermediate item (B>D and C>E; a 1° transitive judgment) and by two intermediate items (B>E; 2° judgment). Immediately after learning all of the premise pairs, subjects could not make either the 1° or 2° transitive judgments, indicating that initial learning had not formed the relational hierarchy but had generated only a distinct representation for each premise pair (Fig. 1 *Top*). However, after a 12-h active day, subjects could make 1° relational judgments, indicating partial success in the integration of the premises without sleep (Fig. 1 *Middle*). Moreover, if the subjects had instead slept during the 12-h delay period, they could perform 2° and 1° relational judgments (Fig. 1 *Bottom*). This finding suggests that sleep contributes to memory consolidation by facilitating a process of integrating memory representations.

How do these findings address the debate about sleep and memory? At a National Institute of Mental Health conference on this topic some years ago[†], I began the meeting by suggesting four comments my mother would offer about sleep and memory. I used the metaphor of my mom's critiques to point out that there are issues in the neuroscientific study of this problem that are clarified by a common-sense perspective.

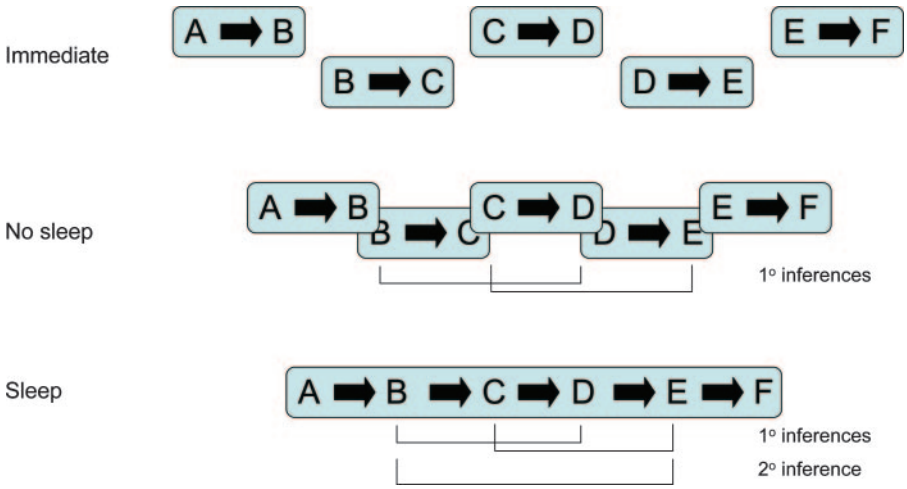

Fig. 1. The effect of sleep on the organization of memory representations suggested by the findings of Ellenbogen *et al*. (4). Immediately after learning, the representation of each premise is constituted as the choice of one item over another (A>B, etc.), and these premises are isolated from one another despite having overlapping elements. After a 12-h period with no sleep, the premise representations are partially integrated by their overlapping elements, sufficient to support first-order transitive inferences. If the subjects sleep during the 12-h period, then the premise representations are fully interleaved, supporting both first- and second-order transitive inferences.

Many studies have documented that sleep deprivation negatively influences subsequent memory performance, suggesting that sleep is needed to consolidate memories. Mom would say, "When I don't sleep, my memory is lousy the next day, but then, most everything else goes to pot, too." My mother is concerned that these effects may not identify a fundamental role for sleep in memory *per se* but instead reflect a general deterioration of cognitive function. It is entirely possible that sleep deprivation constitutes a stress state that results in a general metabolic or physiologic dysfunction and that memory performance is simply a very sensitive test of mild cerebral malaise. In the Ellenbogen *et al*. (4) study, the sleepless subjects were not explicitly deprived of sleep but rather learned the premises in the morning; the subjects were then tested in the evening after a normal 12-h active day. In contrast, the subjects who slept were trained in the evening and then tested in the morning after a normal night's sleep. (There was another sleep group whose members were tested the next evening to ensure that the time of testing was not the critical parameter.) Furthermore, performance on the premise pairs and 1° transitive judgments did not differ between those who slept and those who did not. So the advantage of sleep was not generalized to all aspects of task performance but rather was specific to the most demanding relational component.

Major evidence in favor of an association between sleep and memory involves observations during sleep of the replay of neural activity patterns that occurred in a preceding learning experience, suggesting to some that replayed activity patterns reflect the ongoing consolidation process during which memories are being fixed (5). However, Mom would say, "When something really big happens, I think about it a lot, even when I go to bed that night." My mom is concerned that the replay of neural patterns during sleep after learning instead merely reflects the natural persistence of memory traces. In other words, Are

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*E-mail: hbe@bu.edu.

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these brain activity patterns a consequence, rather than a cause, of memory? It is possible that subjects replayed or ruminated about the premises and how they might be linked during the 12-h delay period, but it is not clear why this would be more likely to occur in the group who slept. Indeed one might expect more rumination during a waking daytime period than during sleep. If there was replay that enhanced the links between the premises, it must have been a form of processing specific to sleep.

Several studies have suggested that dreaming that occurs during sleep involves the replay or integration of new information into memories. "I remember my memories, not my dreams," Mom would say. Her problem is that the contents of dreams, especially those that occur during the deepest stage of sleep, are unlike that of the contents of real experiences. She wonders why the contents of our dreams aren't the best remembered events? The investigators did not determine whether the subjects had dreams during the sleep period (4), so we do not know about the contents of mental activity that led to the improvement in transitive performance. This is a challenge for future studies.

Finally, Mom recalls, "When you came home from school and had a big examination the next day, I told you to study and not to got to bed." Although my mother wondered about the function of sleep, as we all do, she couldn't imagine that sleep would be the best way to consolidate memories. Rather, she insisted that the way to improve memory is to study, to think over the material, and to consciously integrate new material with old material during wakefulness. It's not that memory consolidation can't occur during sleep, but it may be no more than quiet time for consolidation processes that have already been set in motion during wakefulness. Nobody gave the subjects my mom's advice. The results of the current study suggest that integration occurs during wakefulness and during sleep and that it is better to sleep than to stay awake and not study.

There is an additional and potentially quite important question that my mother did not envision: What kind of memories are processed during sleep? Several lines of evidence clearly suggest a connection between sleep and neural plasticity associated with the experience-related changes in behavioral performance that we call memory. However, consider the kinds of memory for which this relationship is most evident. It is now well established that there are multiple forms of memory mediated by distinct memory systems (6). Consistent with the multiple memory systems notion, there is growing evidence that particular types of memory may be associated with sleep and that other types of memory are unrelated to sleep. The best evidence for the involvement of sleep in memory consolidation comes from studies of perceptual and motor learning. In contrast, there is scant evidence that declarative memory, our memory for everyday facts and events that is subject to conscious recollection, depends on sleep (3, 7). This evidence does not detract from the potential importance of sleep in memory consolidation, but it may limit its scope considerably.

Integration occurs during wakefulness and during sleep.

My mom turned me into a skeptic about the research on sleep and memory. However, the report by Ellenbogen *et al.* (4) has caused me to reconsider my position and to take a deeper look at what might be going on during sleep. I should be impressed by this study as a breakthrough example of sleep-dependent declarative memory because I have vigorously argued that the ability to integrate memories in the service of transitive inference is a hallmark of declarative memory (8). There is, however, a caveat. There is now evidence both for a declarative, hippocampal-dependent form of relational learning and for a nondeclarative form that also can support inferential judgments (9). In the present study (4), the sleep boost was not associated with an increase in subjective confidence judgments that reflect an explicit awareness of memories, typically concomitant with declarative memory. Thus, it is entirely possible that the sleep enhancement observed here involves nondeclarative memory, consistent with previous reports on sleep and perceptual and motor learning.

Yet, the kind of information-processing that underlies the integration of premises may be more revealing than whether we label the form of memory studied here as declarative or nondeclarative. In a highly influential model, McClelland *et al.* (10) characterized the key to networking memories in the cerebral cortex as an interleaving of information from related experiences, usually assisted by the hippocampus replaying new memories into an existing knowledge organization. Notably, the integration of the overlapping of premise pairs in the transitive inference task is a prototypical example of this kind of interleaving. Therefore, an interesting possibility emerges. Perhaps sleep influences the integration of the premises in this paradigm at the level of the cerebral cortex, as it surely does in the examples of perceptual and motor learning. Thus, sleep offers a "bypass" to the normal contribution of the hippocampus in the model of McClelland *et al*., directly assisting the cortical integration that supplements what the hippocampus otherwise would do on its own. Furthermore, the mixture of data on sleep and declarative memory may be explained by differences in the demand for the integration of memories rather than merely the ability to recall a recent event.

This speculation serves to say that my (and my mother's) concerns should be taken not as doom and gloom for sleep and memory research. The study by Ellenbogen *et al*. (4) suggests a way to get "underneath" simple characterizations of success and failure in memory and beyond declarative and nondeclarative memory, reaching toward the underlying information-processing that is facilitated during sleep.

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