NEUROSCIENCE

To Sleep, Perchance to... Learn? New Studies Say Yes

"Learn while you sleep" has long been a popular advertising slogan for subliminal tapes that promise to teach you anything from memory improvement to how to play the piano as you dream the night away. Whether those tapes live up to their advertising claims remains unclear, but even without such aids, your sleeping hours may indeed be devoted to honing your memory and even to improving certain skills you practiced during the day. That, at least, is the conclusion of studies reported in this issue of *Science* by two independent research teams, one in Israel, the other in Arizona.

Although both studies deal with the role of sleep in memory, their experimental approaches were quite different, and they focused on two distinctly different types of memory. Avi Karni and Dov Sagi of the Weizmann Institute in Rehovot, Israel, and their colleagues, whose results appear on page 679, have shown for the first time that during sleep human subjects improve at skills learned by repetition, and that the improvement depends on brain activity of the type that occurs during the rapid eye movement (REM) phase of sleep. Matthew Wilson and Bruce McNaughton of the University of Arizona in Tucson have found neuronal activity in the brains of sleeping rats that may help strengthen the animals' spatial memories (p. 676).

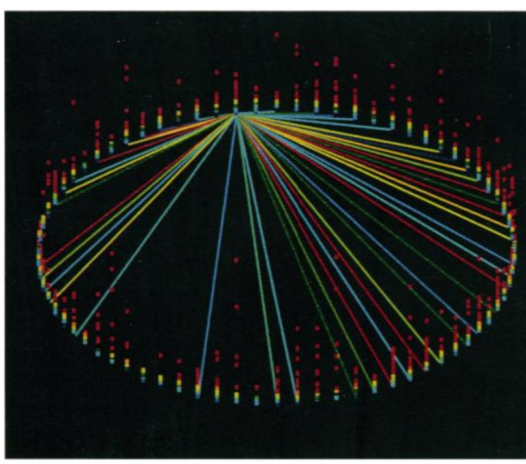
Despite having used such different experimental systems, both groups' conclusions support the notion that consolidation or strengthening of memories occurs during sleep. Together, the findings provide "evidence that something important is happening [during sleep] with regard to learning and memory," says Salk Institute neuroscientist Terrence Sejnowski. In addition, both studies shed light on how memories are consolidated in the waking brain. They may lead to a better understanding not only of how memories are saved, but also of how they are lost in diseases such as Alzheimer's.

Researchers have suspected for decades that something that goes on during sleep, and in particular, during REM sleep, may play a role in the strengthening of memories. In the early 1970s, Vincent Bloch of the University of Paris showed that during periods when rats were being trained in a maze-learning task, the amount of time they spent in REM sleep increased. And several studies in both rats and humans, also dating back to the early 1970s, have shown that REM-sleep deprivation has a negative effect on the recall of events from the previous day.

Even so, Karni and Sagi's finding that REM sleep is needed to form memories of a simple repetitive task came as a surprise to memory researchers because most REM-sleep studies have focused on declarative memory, which is recollection of one-time events, such as where you were yesterday or what you did. The Weizmann team, however, is studying an entirely different type of memory known as procedural memory, which stems from repeated practicing of a task, such as learning to type, play the piano, or ride a bicycle.

Most researchers had assumed that during procedural learning, memories were etched permanently into the cerebral cortex purely by repetition of the task, without requiring consolidation during sleep. "The very concept of consolidation has been most often linked with declarative memory," says Larry Squire, a neurobiologist at the University of California, San Diego, who studies the distinction between declarative and procedural memory.

Now, says Squire, Karni and Sagi have broadened the definition of memory consolidation to include procedural memory as well. Subjects in their study were trained in a simple visual task: describing the orientation of an object that appeared briefly in their peripheral vision. With repeated practice sessions over the course of days, subjects are able to make the identification more quickly. Last year, the Weizmann researchers reported that once subjects have learned the skill, they retain it for years.



MATTHEW WILSON/UNIV. OF ARIZONA

Ring of fire. The diagram shows the firing pattern of 74 rat hippocampal cells recorded during sleep after a behavioral experience. The colored lines indicate how the firing of one cell *(upper left center)* correlates with that of others; the strongest correlations are in red and the weakest in blue.

But the subjects learned in a surprising way, says Karni, who is now at the National Institute of Mental Health. If the memory were fixed in the brain purely by repetition of the task, skill improvement ought to occur immediately. But in fact the subjects improved during the 8-hour period following a training session. "When they returned and were remeasured," Karni says, "the surprise was that they were much better than they had been at the end of the training session."

The subjects improved whether they were trained in the evening and then went to sleep or trained in the morning and then went about their day. But Sagi and Karni decided they could learn more about whatever was causing the improvement by focusing on sleep. Sleep comes in several discrete stages, each of which is dominated by certain types of neural activity. So, Karni explains, "If we could come up with a specific sleep stage that is important for the learning effect, this might be a clue" to what types of neural activity account for the learning.

To find out whether memory consolidation occurs during a specific sleep stage, the researchers trained subjects in the evening before they went to sleep. Then they awakened the subjects with a bell every time brain waves showed they were entering REM sleep—about 60 times a night. Other subjects had their sleep interrupted comparable numbers of times, but during a non-REM form of sleep, called slow-wave (SW) sleep. The results were clear-cut, Karni says: "With REM deprivation, the subjects had no learning at all. They were the same as on the night before." On the other hand, subjects who were awakened during SW sleep improved over the night.

Exactly what happens during REM sleep to improve performance on the procedural memory task remains unclear. But Karni hopes the characteristics of REM sleep will provide clues. One hallmark, discerned from studies of sleeping animals, is a flow of the neurotransmitter acetylcholine into the cerebral cortex from subcortical neurons. Activity of these neurons may be important for memory consolidation, Karni suggests. One indication that they are comes from studies showing that acetylcholine-producing neurons are among the brain cells that degenerate in Alzheimer's disease. It should be easy to test the cells' importance, Karni suggests, by seeing if drugs that block acetylcholine interfere with procedural memory.

While Karni and Sagi's finding may have broadened the notion of memory consolidation to include procedural memory, Wilson and McNaughton's work focuses on the type of memory that has always been associated with consolidation: declarative memory. Declarative memories require a brain structure called the hippocampus for their formation; over time they are consolidated, becoming long-term memories that can be retrieved from the other areas of the cerebral cortex without hippocampal involvement. Researchers have hypothesized that during consolidation the hippocampal neurons must do something that strengthens links between the neurons in other cortical areas that carry different parts of the memory, thus binding parts of the memory together into a coherent whole that can later be retrieved. No one knows how the strengthening occurs, and that's what the Arizona team set out to investigate by studying how the hippocampus records memories of places a rat has explored.


MATTHEW WILSON/UNIV. OF ARIZONA

Wired. The rat is fitted with a device for recording from many brain neurons at once.

They already knew that hippocampal neurons were likely to be involved in place recognition. John O'Keefe of University College, London, discovered in the late 1970s that many hippocampal cells fire specifically when the rat is in a certain part of its environment and stop firing when the rat leaves that place. But recording from only one neuron at time, O'Keefe couldn't get the whole picture of how these "place neurons" encode a rat's location.

McNaughton, working with O'Keefe as a postdoc in the early 1980s, took a step toward solving this problem by developing a specialized multichannel electrode that detects and separately identifies signals from many neurons at once. For the past decade he has been perfecting a system that uses 12 of these electrodes to record activity from up to 150 neurons at a time. Using this system, McNaughton and postdoc Wilson last year extended O'Keefe's findings, showing that each place the rat visits triggers firing in a unique set of hippocampal place cells. Within a visit or two to a new place, a new firing pattern representing that place would develop, and would continue to represent that location in future visits. "If you put the animal back the next day and the next day, you will see the same general pattern of activity," says Wilson, who is now at the Massachusetts Institute of Technology.

That work identified the hippocampal code for the spatial memory, but didn't answer the next question: How would the pattern be committed to long-term memory? McNaughton, as well as Rutgers University neuroscientist Gyorgy Buzsaki, had independently hypothesized that the hippocampus might do this by using "off-line" time—during sleep—to replay neural patterns encoded during the previous waking period. During non-REM, slow-wave sleep, hippocampal neurons fire off signals to other cortical areas in "sharp wave bursts," which are well suited to strengthening the synapses that link cortical neurons. If the sharp wave bursts carried information that had been gathered earlier by the hippocampus, they could help transfer that information to other neurons of the cortex.

There was already a precedent suggesting that the firing of hippocampal place neurons during sleep may reflect information picked up earlier. In 1989, Rockefeller University neuroscientist Jonathan Winson, along with graduate student Constantine Pavlides, reported that individual place cells in the hippocampus that had fired while a rat was exploring new surroundings were more likely to fire during the sleep following that exploration than they had been during sleep prior to the exploration. "This could be a consequence of patterns being reactivated," says Wilson.

With the multichannel electrodes, Wilson and McNaughton were equipped to see whether that was the case. They implanted electrodes in the brains of test rats and recorded from a set of hippocampal neurons while the rats slept to provide a pre-exploration base line. Then they allowed the rats to explore a new environment while they continued to record from the same neurons. After exploration, when the rats slept, more recordings were taken.

COMPARISON OF MEMORY TYPES

Memory	Example	Features
Procedural	Repetitive skills (typing, bicycling)	Does not require hippocampus
Declarative (episodic)	One-time memories (place or event)	Requires hippocampus

Wilson and McNaughton found they could gather the most data during SW sleep, because it is the most common sleep period and is also a time when hippocampal neurons are very active. Slow-wave sleep was also of special interest, says McNaughton, because of his suspicion that the sharp wave bursts may be key for memory consolidation. And what they saw during SW sleep "was exactly what we expected," says McNaughton. "Those groups of cells that were active at the same time during the behavior became active at the same time during the sleep that followed the exploration."

As the firing of the hippocampal place cells during SW sleep is usually compressed into a much shorter period than the firing during the actual learning task, Wilson likens the sleep pattern to the "playback mode" on tape recorders, in which a recorded voice is condensed and played back at high speed. That may be the key to memory consolidation for several reasons, says McNaughton. "In order for memory consolidation to take place, there must have to be multiple reactivations of the same memory trace. If you played it back in real time, you would have to spend all your time asleep." In addition, he adds, the bursts of activity are likely to be the most effective way of modifying connections in the cortex. Buzsaki, who first analyzed the sharp wave bursts in SW sleep, agrees. "The sharp wave bursts can compress time," he says, reviewing the high points of hours of behavior in less than a second.

Buzsaki welcomes Wilson and McNaughton's finding as "the most beautiful confirmation so far" of the relation of these bursts of activity to memory. "What was missing from this theory was the demonstration that indeed the structure of the sharp wave bursts is regulated by experience. What Matt Wilson has shown is that it *is* specifically tied to the previous experience."

What is still lacking from the work, says Wilson, is evidence linking long-term memory to these playback sessions. But experiments can be designed to test that link, such as giving rats a drug that impairs spatial learning and checking to see whether it influences playback patterns during sleep.

This new emphasis on SW sleep doesn't mean that REM sleep doesn't also have a role in memory consolidation. REM sleep has been shown to be important in declarative learning, and Karni and Sagi have just shown that it seems to be necessary for procedural learning as well. Indeed, it may be alternation of the two states that is key to memory consolidation, says Salk's Sejnowski. Some recent neural-network models suggest that is the case; they show that alternation of states that resemble SW and REM sleep helps adjust the strength of neural connections in a way that would allow memories to be stored and retrieved. With the recent revelations about both REM and SW sleep, researchers are one step closer to understanding why our memories improve during sleep, even without subliminal tapes.

–Marcia Barinaga