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Hunting for Meaning after Midnight

Author(s): Greg Miller
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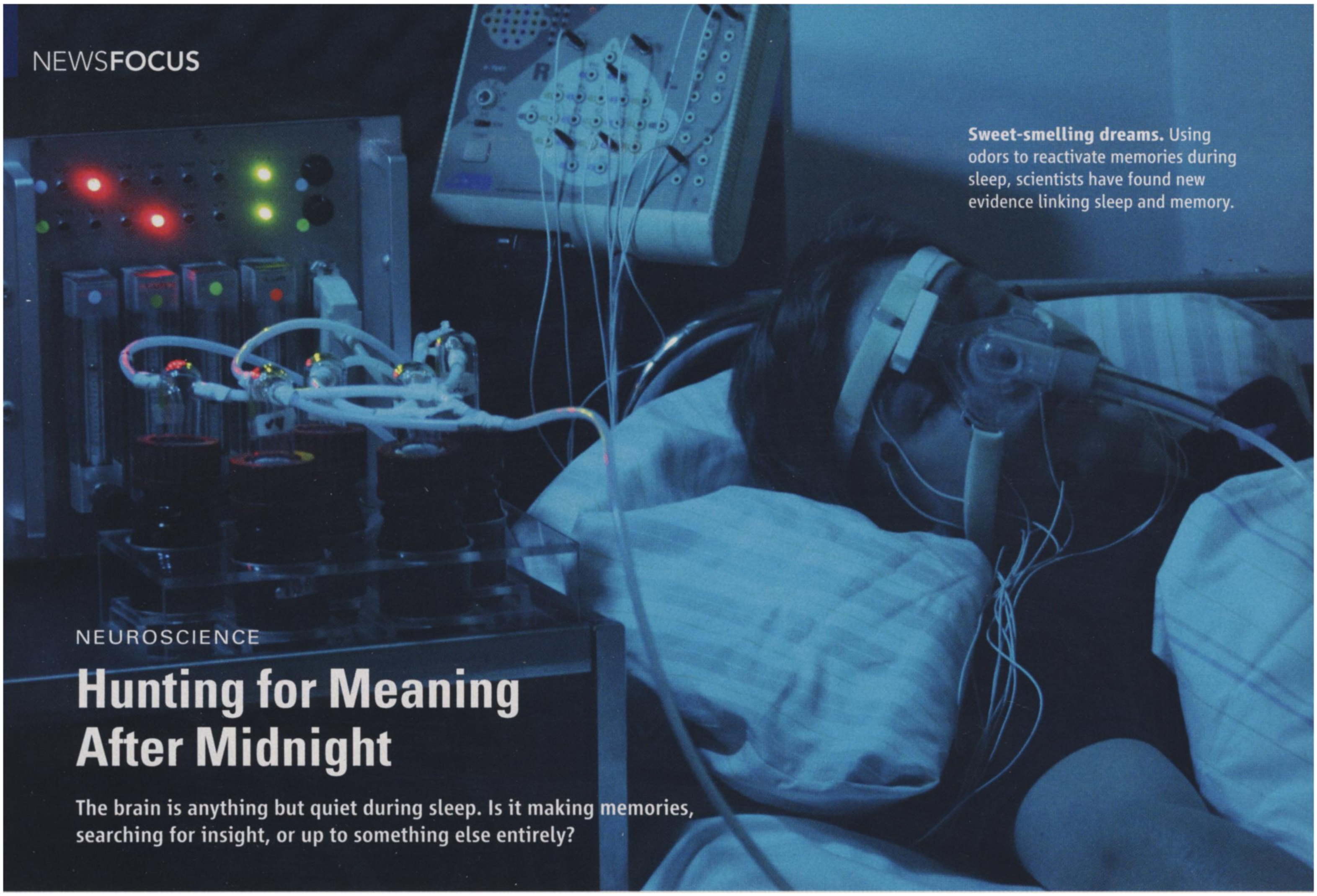

Sweet-smelling dreams. Using odors to reactivate memories during sleep, scientists have found new evidence linking sleep and memory.

NEUROSCIENCE

Hunting for Meaning After Midnight

The brain is anything but quiet during sleep. Is it making memories, searching for insight, or up to something else entirely?

Even sound sleepers have restless brains. Your body may be largely motionless once your head hits the pillow, but inside your skull, millions of neurons are busily firing away, often in synchronized bursts that send waves of electricity sweeping across the surface of your brain.

What all this neural activity accomplishes, if anything, is a mystery, and part of the even larger puzzle of why we sleep. One idea that has gained favor in recent years is that during certain stages of sleep, the brain replays experiences from the day to strengthen the memory of what happened. Support for this notion comes from a variety of experiments with rodents and people, including a new study in this issue suggesting that boosting such memory-related activity in the sleeping brain can improve memory performance in humans.

Some researchers suspect that replaying the recent past during sleep is more than a memory aid. This review may also give the brain a chance to catch important information it missed the first time around. "There's more and more evidence accruing that what we're seeing during sleep is not just a strengthening of memories," says Robert Stickgold, a neuroscientist at Harvard Medical School in Boston. "What the brain is really trying to do is extract meaning."

Such ideas aren't universally accepted, however. One new and controversial hypothesis suggests that memory and other cognitive benefits are merely side effects of the true function of sleep: dialing down synapses that have gotten overexcited by daytime activity. And some skeptics aren't convinced that sleep has anything to do with memory at all. Given all the uncertainties, researchers say the quest to understand the sleeping brain is just beginning. But they're already finding fascinating clues about what happens when we're off in the Land of Nod.

Let me see that again

The first experimental evidence that the brain replays recent experiences during sleep came from experiments with rats begun in the 1990s by neuroscientist Bruce McNaughton of the University of Arizona, Tucson, and his graduate student Matthew Wilson. McNaughton and Wilson recorded the electrical activity of neurons called "place cells" in the rat hippocampus. These neurons have an affinity for particular locations, so that as a rat runs around its enclosure, a given place cell fires each time the rodent passes through that cell's favorite spot. Because individual place cells respond only to a specific location, each time a rat takes a different route, a different sequence of place cells fires. Subsequent studies found that sequences of place-cell firing that occur as a rat explores a new environment are replayed the next time the rat dozes, as if the animal retraces its steps during sleep.

Humans may do something similar. In 2004, a research team led by Pierre Maquet of the University of Liège, Belgium, used positron emission tomography (PET) to monitor brain activity in men playing a virtual-reality game in which they learned to navigate through a virtual town (actually a scene from the shoot-'em-up video game Duke Nukem). The same regions of the hippocampus that revved up when the subjects explored the virtual environment also became active when the men slipped into slow-wave sleep that night. This sleep stage is often considered the deepest: Slow-wave sleepers are hard to rouse. During this sleep stage, electroencephalogram (EEG) traces show waves of electrical activity throughout the brain that peak about once a second. PET scans revealed that the more intense hippocampal activity a volunteer had during slow-wave sleep, the better he performed the next day

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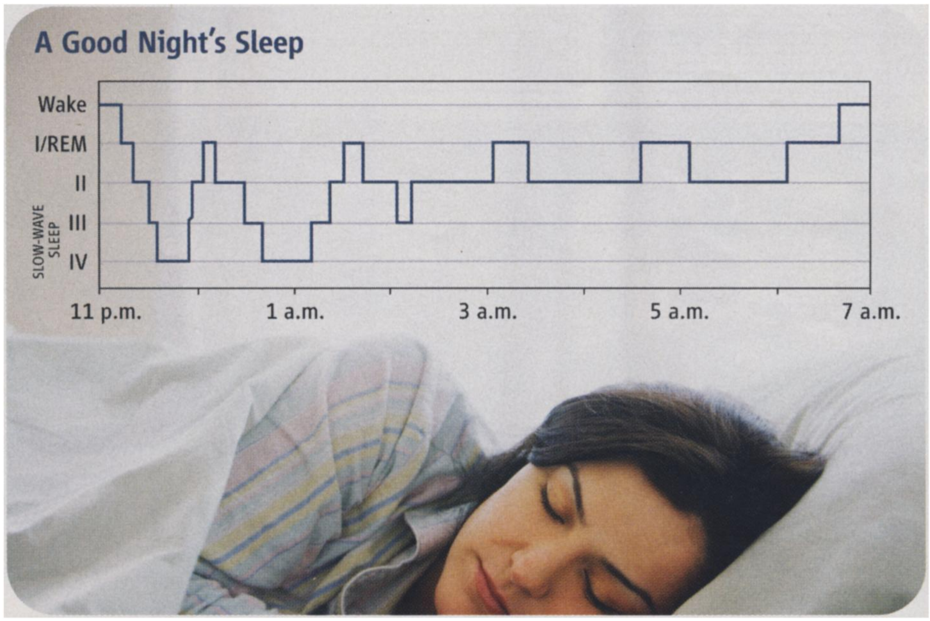
when he sprinted through the virtual town to find certain objects as quickly as possible, Maquet and colleagues reported in the 28 October 2004 issue of *Neuron*.

Maquet's findings showed a nice correlation between neural activity during sleep and subsequent memory performance, says Jan Born, a neuroscientist at the University of Lübeck in Germany. The natural next step, Born says, was to see whether artificially boosting memory-related neural activity during sleep could improve memory performance. On page 1426, Born's team describes an attempt to do just that.

The researchers had volunteers play a video version of the card game Memory (also known as Concentration), in which they had to learn and remember the locations of pairs of cards bearing the same image in a group of 30 cards. Each matched pair flashed on the screen for a few seconds, one at a time, with all the other cards facing down. After the volunteers had seen the locations of all the pairs, the researchers tested the subjects' recall by turning one of the 30 cards face up and asking them to find its match. The researchers then used EEG electrodes to monitor the volunteers' brain activity while they slept.

Once the volunteers entered slow-wave sleep, the researchers gave some of them a puff of rose-scented air. They'd previously given some of the subjects a whiff of rose during their initial training session with the cards, reasoning that the odor would reactivate memories of the training session in these subjects without waking them. Indeed, functional magnetic resonance imaging (fMRI) scans in sleeping subjects revealed that the odor activated the hippocampus in those who had experienced it previously, even though the EEG showed no disruptions in the subjects' slumber. Although they didn't remember smelling roses in their sleep, the subjects who got the fragrant prompt remembered the matched pairs better the next day, getting 97% correct compared to 86% for subjects who'd received no odor while sleeping. Subjects who got the rose odor either while awake or while in REM sleep, on the other hand, showed no memory boost; nor did presenting the odor during slow-wave sleep help subjects who hadn't been exposed to rose during the training session. "It's the first study to really demonstrate that one can influence memory with stimuli that explicitly activate the hippocampus during sleep," says Wilson, now an associate professor at the Massachusetts Institute of Technology in Cambridge.

Born's findings fit with a popular view of how the brain files memories away for long-term storage, a process neuroscientists call memory consolidation. According to this hypothesis, memories are first encoded by the hippocampus and later—perhaps in a matter of hours or days—transferred for long-term storage to the cerebral cortex, or neocortex. Several lines of evidence support this scenario, among them the observation that many people who suffer amnesia following damage to the hippocampus can still recall events and facts learned prior to their injury even though they're unable to form new memories. In such patients, old memories must reside somewhere other than the hippocampus. How the brain might transfer memories from the hippocampus to the neocortex isn't known, but it's assumed to require some kind of back-and-forth communication between the two structures.



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A study by Wilson and postdoctoral fellow Daoyun Ji published in the January issue of *Nature Neuroscience* supports this idea. Wilson and Ji found that, much like hippocampal place cells, neurons in the visual cortex of rats replay firing sequences during slow-wave sleep that match their activity during the rats' daytime maze running. Moreover, the scientists found that the replay in the visual cortex happens in lockstep with replay in the hippocampus. "It's the first time we see sequences both in the hippocampus and the neocortex and their coordination in time," says Maquet.

More than memory

Beyond simply fortifying memories, the brain may be sifting through recent experiences during sleep to identify rules about cause and effect or other useful patterns, some researchers suspect. One of the first hints of this phenomenon came from a 2004 *Nature* paper by Born's group. They reported that people playing a game that required manipulating strings of numbers were more than twice as likely to have a flash of insight that enabled them to solve the problem more quickly after a night of sleep than after a similar time of wakefulness.

More recently, at a sleep research meeting last month at the Salk Institute for Biological Studies, Stickgold presented findings suggesting that people find missing connections while they sleep. His group had volunteers play a card game in which they attempted to predict whether it would "rain" based on cards the researchers had shown them. The game was rigged so that the card with the diamonds, for instance, was followed by sunny weather 80% of the time. Each card had its own rule, but the volunteers did not know the rules even existed. As expected, they did no better than chance at first. But after 200 predictions, their success rates improved. When the subjects came back 12 hours later to try again, they had improved even more—but those who'd slept improved about 10% more than those who hadn't. Although it's a modest improvement, "there's a growing sense that there's active learning during sleep," says Wilson.

There's also increasing evidence that different stages of sleep are involved in consolidating different kinds of memory, says Matthew Walker, a neuroscientist at Harvard Medical School. Spatial memories, like those formed by playing Memory or by navigating through a maze or virtual town, seem to be consolidated during slow-wave sleep. The same appears to be true for declarative memories, which involve remembering facts—but not necessarily other kinds of memory. Some studies have found that the brain processes memories with a

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strong emotional component during rapid-eye-movement (REM) sleep and processes memory for motor skills, such as tapping out a difficult sequence on a keyboard, during stage 2 and REM sleep (see diagram, p. 1361). Why this division of labor exists is a puzzle, but Walker and others speculate that the different physiological and neurochemical milieus associated with different sleep stages may favor certain kinds of neural plasticity.

Some researchers point out, however, that the literature on which sleep stages relate to which types of memory is peppered with contradictions. "There is inconsistency here, and someone has to be wrong," says Jerome Siegel, a neuroscientist at the University of California, Los Angeles. Stickgold and other proponents of a sleep-memory link acknowledge that they face many unresolved issues about the role of sleep in memory consolidation. "There are massive questions remaining about how extensive it is, how important it is, exactly which stages of sleep affect which types of memory," Stickgold says.

Another wide-open issue is whether there's a link between dreaming and memory-related neural activity during sleep. The kind of direct replay of recent experience suggested by Wilson's work, for example, doesn't seem to be the stuff of dreams. Stickgold's group has found that only 1% to 2% of episodes from dreams reflect events from the previous day. If dreams don't directly reflect the memory-consolidation process, what do they reflect? "We're in no man's land," says Walker.

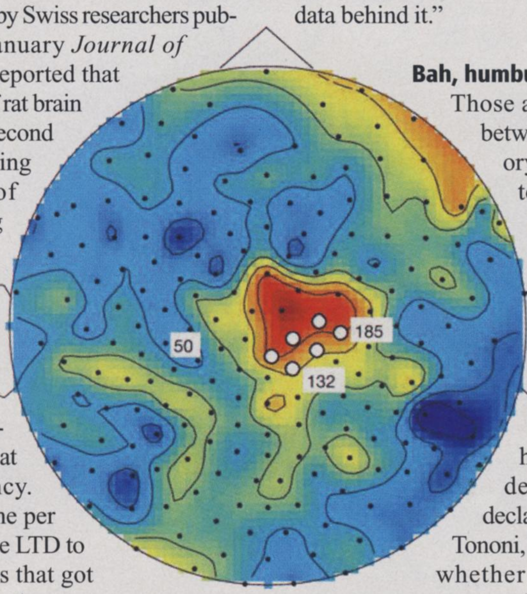
Another hypothesis

Not everyone is onboard with the idea that brain activity during sleep is primarily about replaying recent experiences. Giulio Tononi, a neuroscientist at the University of Wisconsin, Madison, has recently advanced a very different hypothesis. He proposes that the purpose of sleep, at least as far as the brain is concerned, is to weaken neural connections throughout the brain.

In Tononi's view, the synaptic connections between neurons get progressively stronger during the day as a result of long-term potentiation (LTP), a physiological process by which neurons that fire at the same time strengthen their connections with each other. Most neuroscientists consider LTP a major mechanism of neural plasticity—and therefore of learning and memory (*Science*, 22 December 2006, p. 1854). Yet a day's worth of LTP can be too much of a good thing, Tononi contends. Stronger synapses increase the brain's energy needs—a serious concern for an energy-hogging organ that already accounts for 20% of a person's metabolism. Stronger synapses are also bigger, taking up precious space. And finally, too much LTP may saturate synapses, leaving them unable to get any stronger when the brain needs to learn something new.

Sleep restores homeostasis by ratcheting down synaptic strengths, Tononi argues. It's a far more important service than providing a modest boost in memory performance, he says. "Sleep is too high a price to pay for the 15% improvement we see in some things," Tononi says. "I think it does something much more fundamental to the neuron: It's the price we pay for plasticity." How might sleep reset synaptic strengths? One clue, Tononi says, comes from a study by Swiss researchers published in the 15 January *Journal of Physiology*. They reported that stimulating slices of rat brain to cause once-per-second bursts of neural firing induces a type of synaptic weakening called long-term depression (LTD). Tononi thinks it's no coincidence that the coordinated neural firing during slow-wave sleep happens at this same frequency. The slow waves, one per second, could induce LTD to dial down synapses that got too strong during the day.

Other evidence comes from human studies, including one from Tononi's group that found that slow waves measured by EEG in sleeping subjects were most intense in brain regions involved in learning an arm-movement task the previous day. That's consistent with the idea that the slow waves happen where they're needed most to restore synaptic homeostasis. Conversely, immobilizing a person's arm in a sling decreases slow-wave intensity in arm-related areas of neocortex the following night, Tononi and colleagues reported in the September 2006 issue of *Nature Neuroscience*.



Hot spot. EEG recordings during sleep indicate peak slow-wave activity (red) in brain regions involved in daytime learning.

Tononi also points to a paper Walker's group published in *Nature Neuroscience* in January. Those researchers found that undergraduate volunteers deprived of a night's sleep were less able than well-rested peers to learn new word pairs the next day. (fMRI scans suggested that the deficit was specifically related to memory—brain regions that modify attention and alertness functioned normally in the sleep-deprived undergrads.) With no slow-wave sleep to dampen their synapses, the subjects were unable to learn as well the next day, Tononi says.

Tononi's view of the role of sleep is "an interesting and intuitive idea," Walker says. He also thinks it's not necessarily incompatible with the notion that sleep enhances memory by strengthening the underlying synapses, as proponents of the memory-replay scenario have generally assumed. "I think they could act not just independently but synergistically."

But not everyone is ready to embrace Tononi's proposal. Says Stickgold: "It's an elegant hypothesis that doesn't have a lot of data behind it."

Bah, humbug

Those advancing the links between sleep and memory have other hurdles to overcome. One of the most disconcerting inconsistencies in the sleep-memory literature, Siegel explains, is that studies of total sleep deprivation have failed to find a deleterious effect on declarative memory. Like Tononi, Siegel also questions whether relatively modest memory benefits offer enough of an adaptive advantage to compensate for being unresponsive for hours a day. "I'm just not convinced that there is any connection at all" between sleep and memory, Siegel says. He favors the idea that sleep evolved to help animals conserve energy for their entire bodies and to prevent them from being active at times when they're less likely to find food and more likely to be eaten.

To be sure, memory is not the only function of sleep, counters Stickgold, but the evidence that it is one function of sleep, at least in mammals, is too great to ignore. Once sleep evolved, he says, evolution figured out how to make that downtime as productive as possible. Stickgold also argues that the modest improvements typically seen in sleep-memory studies are nothing to yawn at. He is fond of pointing out that a 15% gap in performance is the difference between winning the Boston Marathon and coming in 3000th. In competitive circumstances, small advantages can make a big difference. But whatever you do, try not to lose any sleep over it.

–GREG MILLER

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