

there before - I just knew
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*memories
are made
like this*



By Tom Siegfried

Photograph by Fredrik Brodén

*Researchers
believe they are deciphering some of
the mysteries of sleep, particularly
its role in forging new memories.*

Editor's note: The computer-based system for analyzing electrical activity in the cerebral cortex during sleep that is used in Terrence Sejnowski's studies at the Salk Institute of Biological Studies and is discussed in this article was developed by Sejnowski and Philip Low, a doctoral student in his laboratory.

Perhaps,
as Homer wrote in The Iliad, sleep is “the twin
of death.” But to many modern neurobiologists,
sleep is more like the mother of memory.

Sleep provides downtime for processing the previous day's events. Free from the rush of messages bombarding the waking senses, the brain can converse with itself. Just as your computer warns you to close all running programs before installing a new one, the brain closes your eyes each night to install memories from the day before, numerous researchers believe.

In fact, its role in making memories may explain why sleep is so popular—a necessity really—throughout the animal kingdom. Nearly all creatures great and small sleep to some extent, suggesting that evolution found it valuable for survival—despite the apparent risk of spending so much time in a defenseless and vulnerable condition.

But that doesn't mean memory was sleep's original purpose, says HHMI investigator Terrence J. Sejnowski.

“Asking what sleep is for is a little bit like asking what blood is for,” he says. “Maybe blood originally was there to get oxygen to different parts of the body, but once you have this big conduit running through your body you can put all kinds of things in it.” From delivering drugs to disposing of waste, blood performs dozens of valuable tasks.

“Same thing with sleep,” Sejnowski says. “It may be that it started out as some sort of way to recharge your energy supplies.” But during the time that nerve cells don't have to worry about their day job, they can engage in other interesting biochemistry, free from the interference of wakeful activity.

Pursuing the secrets of that nighttime biochemistry has led Sejnowski and other

scientists to a new and deeper understanding of sleep, which ultimately could benefit the many victims of sleep-related disorders.

A New View of Sleep

More than 50 million Americans suffer from conditions ranging from insomnia to restless legs syndrome to narcolepsy. In some people, sleep apnea interrupts breathing and deprives the body of oxygen, fueling metabolic problems that contribute to obesity and diabetes.

“That translates into an enormous impact on quality of life,” Sejnowski says.

Work in his lab, at the Salk Institute for Biological Studies in La Jolla, California, has produced a computer-based system for analyzing sleeptime electrical activity in the cerebral cortex, the brain's wrinkled outer layer. That activity is recorded via a single pair of electrodes attached to the scalp to produce electroencephalogram (EEG) readouts.

Similar analyses for assessing sleep problems are performed at sleep clinics, where patients snooze while wearing a cap covered by a dozen or more electrodes. Human experts then study the EEG graphs to identify how long the sleeper has spent in sleep's various stages. But these analysts typically take hours or days to decipher the EEG recordings. By contrast, Sejnowski's computer system can report on sleep state in real time, with an accuracy rate that is as good as or better than the humans' analyses. (Sejnowski is on the scientific advisory board of a new company, NeuroVigil, that

will use the system to offer sleep EEG analysis over the Internet to the nation's 2,000 or so sleep clinics.)

Furthermore, the computer can tease out other details from the data, identifying previously undetected features in the electrical activity underlying sleep's stages. “Some of the work we're doing in my lab has actually overturned a lot of the beliefs in the textbooks about the different sleep states,” Sejnowski says.

For one thing, his computer analysis shows that the rapid eye movement (or REM) sleep associated with dreaming does not, in fact, show basically the same electrical activity as an awake brain, as textbooks assert.

Besides REM, sleepers cycle through several other phases, including an intermediate state of sleep (with a mix of slow and fast electrical activity) and deeper, “slow-wave” sleep. Some studies have identified slow-wave sleep as important for firming up memories, but Sejnowski's work suggests that intermediate sleep may play a more significant role in memory formation. His analyses have detected new patterns of activity within that state.

At times during intermediate sleep, the research indicates, cortex electrical activity rapidly alternates between high frequencies and low frequencies every few seconds. “We think that's going to be the best place to look for the biochemical changes that are occurring [during sleep]. In some cases you can spend half your sleeping hours in intermediate sleep,” says Sejnowski, “and I think that's where the key to understanding the true function of sleep is going to be found.”

Intermediate sleep is marked by brief bursts, or “spindles,” of electrical signaling produced by the thalamus, an important relay station for transmitting information between the cortex and various other parts of the brain. Those spindles recur every few seconds, setting up synchronized electrical oscillations throughout the cortex. Sejnowski hypothesizes that the spindle activity puts the brain into a state conducive to storing new memories without interference from other activity.

Nighttime Replay

New details about sleep’s role in memory also come from HHMI’s Janelia Farm Research Campus in Ashburn, Virginia, where Jeffrey C. Magee and his team seek help from rats to decipher sleep’s mysterious methods. Magee and collaborators perform experiments impossible in live animals by extracting slices of living neurons from a rat brain and recording their electrical activity.

Memory storage is believed to involve the strengthening of synapses, the junctions connecting neurons. To build stronger synapses, the neuron must be studded with abundant quantities of protein molecules that sense the neural messenger molecule glutamate. When deprived of sleep, the neurons display fewer of those sensor proteins, and the ability to make permanent memories diminishes, Magee’s research shows.

“If you don’t get enough sleep, you mess up this whole process of keeping the right amounts of membrane proteins at their right locations inside the cell,” he says.

Magee and his colleagues study slices of rat neurons taken from the hippocampus, the brain region that plays a prominent role in forming long-term memories. Those neurons retain their

connections and signaling patterns, responding to the stimulus of messenger molecules just as neurons in a living animal do. Magee and colleagues have developed techniques to deliver those messenger chemicals to specific neurons, thereby stimulating the slices into states similar to those found in either the awake or sleeping animal. In the “awake” neurons, input from other cells flows in haphazardly, and a neuron fires its electrical signals based on the summed-up influences of all those inputs.

“In the sleep state, we see a very different kind of output pattern,” says Magee, who reported on his work in the February 2006 issue of *The Journal of Neuroscience*. The

same information is processed, but much more rapidly and precisely. The signaling speed is accelerated to 20 times the original rate. So it seems that during sleep, the cells from the hippocampus may be replaying the day’s activity.

“In fact, the networks that are involved in the replay are the exact same sets of cells that actually process that information to begin with,” he says.

This work supports the developing view that memory formation depends on cross talk between hippocampus and cortex, where memories are ultimately stored. The hypothesis is that daytime memories held temporarily in the hippocampus are rebroadcast during sleep from the hippo-



Ramped up information processing in the hippocampus during sleep suggests to Jeff Magee that the brain uses this “downtime” to replay the day’s events.



There are dozens of different memory systems, says Terry Sejnowski, that use different mechanisms and different parts of the brain.

campus to the cortex, which then replays the signals itself, strengthening the synapses to imprint the new memories. “The hippocampus can learn very, very rapidly, but it doesn’t have a very high capacity,” says Sejnowski. “The big knowledge storage is in the cortex.”

Knowledge in the cortex changes more slowly, though. It has to rehearse many times to learn a new memory. “Through the replaying of the hippocampus, the cortex will gradually figure out which of the new items coming in are the most important ones and how to fit them into existing knowledge,” says Sejnowski. “That’s the story that’s emerging from all the electrical recordings.”

Still, many issues about sleep and memory remain to be resolved, such as the relative importance of slow-wave sleep and

WHEN THE CLOCK RUNS FAST

Some of us may decide to live by an “early to bed and early to rise” routine, but certain people—those with a particular genetic mutation—have no choice. Individuals with familial advanced sleep-phase syndrome (FASPS) are the ultimate early birds, awakening in the wee hours of the morning (by 4 a.m. or so), then turning desperately tired just as prime-time TV is about to begin. ¶ FASPS occurs in people with a rare variant in a gene implicated in regulating the body’s internal clock. That gene, called human *Period 2* (*Per2*), is one of a small number of genes that influence the length of the circadian rhythm cycle governing sleep. Ordinarily, the body’s clock runs on a timetable that nearly matches the 24-hour day, sounding a biochemical alarm in the morning that calls the slumbering brain to action. But a variant in the *Per2* gene can shorten and displace the ordinary circadian cycle, causing

those possessing it to wake up extra early, according to HHMI investigator Louis J. Ptáček of the University of California, San Francisco. ¶ *Per2*’s machinations have recently been rendered less mysterious by work in Ptáček’s lab, in collaboration with the UCSF lab of Ying-Hui Fu, using mice implanted with human versions of the gene. Their insights are helping to explain the genetics and biochemistry of sleep in normal people as well. Ultimately, the research could lead to new drugs for sleeping disorders or for coping with jet lag and shift work. ¶ In a normal sleep cycle, *Per2* codes for a protein that builds up during sleep time until it surpasses a threshold level, thereby triggering biochemical signals to inactivate the gene. The PER2 protein then gradually decomposes until its levels drop so low that the gene is reactivated, restarting the wake-sleep cycle. ¶ A key chemical governing production and destruction of this protein is the enzyme casein kinase I (CKI), which attaches

Tim Mantooth

Asking

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asking what blood is for.* —Terrence Sejnowski

intermediate sleep. And questions linger about which types of memory are actually stored during sleep. Evidence is strong that memory for procedures and skills is improved by sleep, Sejnowski says. But whether factual (declarative) memories are consolidated by sleep as well has been more controversial.

“Memory is not a monolithic single thing,” says Sejnowski. “One of the major discoveries we’ve made is that there are dozens of different memory systems . . . that use different mechanisms and different parts of our brain.”

Unquestioned Importance

Other researchers point out that much of this story, while plausible, awaits rigorous

confirmation. For one thing, whether the information in the sleeping brain really flows from hippocampus to cortex needs to be established more definitively, says Giulio Tononi, winner of an NIH Director’s Pioneer Award in 2005 for his studies of sleep and consciousness.

“I don’t suspect that the hippocampus cannot talk back to the cortex, it just needs to be proven better,” says Tononi, a neuroscientist at the University of Wisconsin—Madison who is studying other synapse mechanisms during sleep. He suggests that more work is needed to show whether the replay activity is faithful enough to the original input for strengthening long-term memories effectively.

Tononi also notes that some studies find similar replay signaling during quiet wakefulness, suggesting that sleep itself may not

really be needed for memory storage. If that is so, the mystery of why evolution has made sleep so ubiquitous resurfaces.

There is no disagreement, though, about sleep’s importance and the need to understand it better. This is a message that today’s society seems to be neglecting, according to Magee, and we are paying a price in the reduced productivity and degraded learning capacity that come from sleep deprivation.

Sleep is not simply a time for storing memories, he points out. It’s also a time for tune-up and repair to keep the brain in peak operating order. “There is a housekeeping function going on,” he says. If you don’t get enough sleep tonight, it’s not just today’s memories that will be less likely to be permanently stored. Your brain won’t be working so well tomorrow, either. ■

phosphate groups to it. Depending on where the phosphate is attached, the result is either increased production or faster destruction of the protein. “We believe this is a way the clock is really fine-tuning the system,” says Ptáček. ¶ CKI cannot enhance PER2 protein production, though, unless a phosphate has already been attached at link 662 in the protein’s chain of amino acids. That phosphate is installed with the help of an as-yet-unidentified “priming” enzyme. ¶ In a normal PER2 protein, position 662 is occupied by the amino acid serine, which is happy to accept the phosphate provided by the mystery enzyme. But in people with FASPS, position 662 is occupied by glycine, an amino acid that refuses to have anything to do with phosphate. Thus, the mystery enzyme is powerless to attach the phosphate, which in turn means that CKI can no longer stimulate PER2-protein production. But CKI continues to facilitate protein destruction, the transgenic mouse studies show. Thus, protein levels fall faster,

making the circadian period shorter and causing early awakening, just as in humans with FASPS. ¶ The latest work, published in the January 12, 2007, issue of *Cell* by Ptáček and Fu with collaborators from China, Singapore, and the University of Utah, has gone a long way toward teasing out the molecular intricacies underlying *Per2*’s function. Now someone needs to identify the mystery priming enzyme. “I think it will be an outstanding candidate for drugs to modulate the circadian period,” Ptáček says. ¶ That will be good news to some people with FASPS, at least those bothered by their condition. “I don’t call this a disease,” he says. “It’s a behavioral trait, a behavioral variant. Some people do not like it—they think it’s a disease and would do anything possible to fix it if we could do that.” Yet others, he says, find early rising an advantage that actually does pave the way to health, wealth, and wisdom. ¶ “Whether it’s a good or bad thing,” says Ptáček, “really depends on the person’s perspective.” —T.S.