

The science of slumber

Despite its utter mundanity, sleep resists simple scientific explanation. It appears to recuperate the body and refresh the mind, but exactly how isn't at all clear. The brain appears to be as active in some of the throes of somnolence as it is in sustaining wakefulness.

By inquiring into all that happens in the brain and body during sleep, researchers aim to paint a more complete picture of why people sleep—and why sleep sometimes goes awry, as *Science News* staff writers Tina Hesman Saey and Laura Sanders report in this special section.

Scientists seeking the reasons for sleep hope to discover some evolutionary insight: Mammals sleep presumably because it offers some survival advantage. But recent work suggests that explaining sleep as an adaptation for saving energy doesn't add up. Scientists are skeptical that saving energy is the only (or even the main) reason that sleep has evolved, as described in the article “The why of sleep.”

Extreme fatigue is the closest humans ever come to sleep while still aware enough to ponder its mysteries. At those times, sleep pulls hard, like a current sweeping up a tired mind, carrying consciousness away. How the brain controls this transition between wake and sleep lies at the heart of disorders such as insomnia and narcolepsy, as discussed in “Sleep gone awry.” The third article, “Dying to sleep,” documents what happens when people go without enough sleep. Chronic sleep deprivation poses more serious health risks than many had thought, research shows.

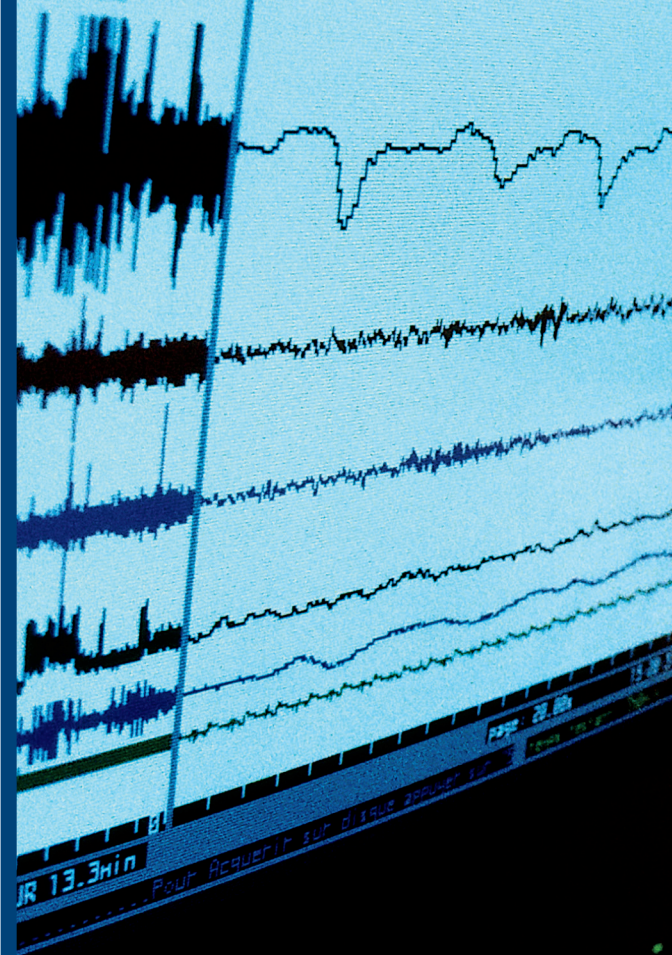
In sleep, the very tool humans use to explore and analyze the world seems to go blank—or, in some dreamy interludes, apparently haywire. No wonder then that scientists, and especially those who study the brain, urgently want to fill in that blank and explain the still largely veiled experience into which most fall thankfully every night. —*Eva Emerson*

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Web edition

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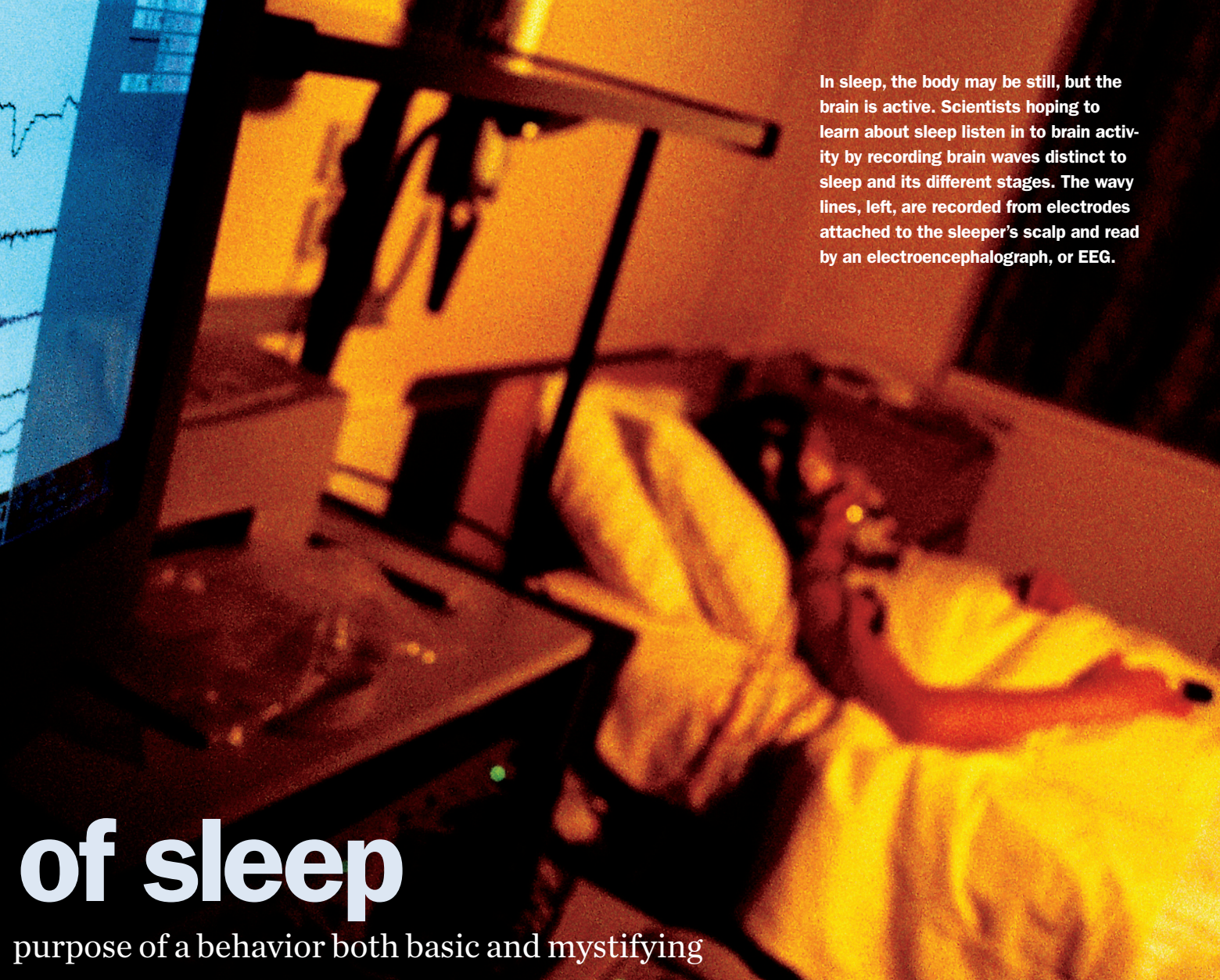
The why

Brain studies may reveal the

By Tina Hesman Saey

In a lab at MIT, a small black mouse named Buddy sleeps alone inside a box. A cone resembling a satellite dish sits atop his head. But the dish doesn't receive signals from outer space. Instead it sends transmissions from deep inside Buddy's brain to a bank of computers across the room.

Scientists like Jennie Young eavesdrop on the transmissions, essentially reading Buddy's mind, or at least that part of his mind occupied with a recent trip along a Plexiglas track littered with chocolate sprinkles. Young and her colleagues in Susumu Tonegawa's laboratory are monitoring nerve cells inside



In sleep, the body may be still, but the brain is active. Scientists hoping to learn about sleep listen in to brain activity by recording brain waves distinct to sleep and its different stages. The wavy lines, left, are recorded from electrodes attached to the sleeper's scalp and read by an electroencephalograph, or EEG.

of sleep

purpose of a behavior both basic and mystifying

the hippocampus, one of the brain's most important learning and memory centers. Some of the cells in the sea horse-shaped hippocampus fired bursts of electrical energy as Buddy moved along the track. As he sleeps in his black box, those same cells spark to life again, replaying progress along the track in fast-forward or rapid reverse.

By recording the slumbering Buddy's brain cell activity, the scientists hope to glean clues to one of biology's greatest mysteries: the reason for sleep. Although sleep is among the most basic of behaviors, its function has proved elusive. Scientists say sleep's job is to save energy,

or to build up substances needed during waking or to tear down unneeded connections between brain cells. Some emphasize sleep's special role in learning and memory. Others suggest that sleep regulates emotions. Or strengthens the immune system. And some scientists believe sleep is simply something that emerges naturally from having networks of neurons wired together.

"There are as many theories of sleep's functions as there are sleep researchers," says Mehdi Tafti, a geneticist at the University of Lausanne in Switzerland.

None of the many models for why people (and other animals) sleep can explain

all of its complexity, says Robert Stickgold of Harvard Medical School in Boston. He equates proponents of the different sleep theories to blind men describing an elephant. It's a snake, or a tree or a wall, depending on which part of the elephant the men touch. Similarly, the answer to sleep's function seems to depend on what approach a given researcher takes. And each proposed idea contains inconsistencies that keep other sleep researchers from embracing it.

"There's no one theory that has enough unified evidence for it to be widely accepted," says Paul Shaw of Washington University in St. Louis.

LAURENT/LAE/AMERICAN HOSPITAL OF PARIS/PHOTO RESEARCHERS, INC.

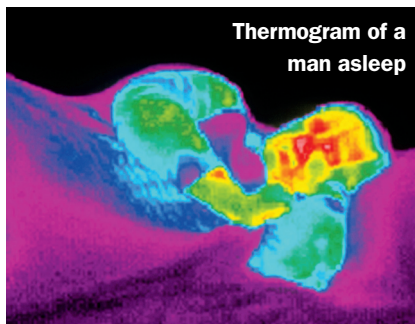
Many sleep theories have been widely tested, though. Using brain wave recordings, genetic analyses, word tests, video games and various other methods, researchers have uncovered many of the pieces to the puzzle of sleep, even if they don't yet all fit together.

Asleep and fired up

Not knowing why humans spend a third of their lives unconscious hasn't prevented scientists from describing five different stages of sleep from recordings of brain waves. Stage one, marking the transition between awake and asleep, is shallow. Stage two, which lasts the longest, features two forms of brain waves known as spindles and K-complexes (*SN Online*: 5/21/09). Stages three and four are the deepest, often referred to collectively as slow-wave sleep. Fifth is REM, the stage accompanied by rapid, jerky eye movements.

REM is the stage most often associated with dreaming, but plenty of dreaming occurs in the other sleep stages, too. These stages are repeated in roughly 90-minute cycles throughout the night, with more slow-wave sleep early on and more REM toward morning.

In the first four stages of sleep, heart rate, body temperature and brain activity drop, supporting the view that sleep serves to save energy. But then REM comes along. During REM sleep, the body becomes paralyzed, which keeps people from acting out their dreams.



In REM sleep, “the brain is on fire. The brain is cooking, but the body is a cold fish.”

MICHAEL PERLIS

Although the body is still as stone, the flight-or-fight response system is in overdrive, says Michael Perlis of the University of Pennsylvania in Philadelphia. Brain activity is as high or sometimes even higher than during wakefulness. "The brain is on fire," during REM, Perlis says. "The brain is cooking, but the body is a cold fish."

Since the brain burns up to 20 percent of the calories used by the body, REM may consume many of the calories saved during other stages of sleep.

Still, because morning brings renewed vigor, many people believe that sleep must save energy. And sleep certainly feels restorative. Recent genetic work suggests a molecular basis for that refreshment.

Allan Pack, a geneticist at the University of Pennsylvania, and his colleagues

have been keeping mice up for hours after their normal bedtime. Activity of 2,000 to 3,000 genes differs in the sleep-deprived mice compared with mice that slumber undisturbed. None of the changes are dramatic, Pack says; they just nudge gene activity up or down a bit. Activity of genes involved in making large molecules consistently goes up during sleep. Examples include genes needed to build cholesterol and the oxygen-carrying substance, called heme, in red blood cells. Genes for molecules that help remodel neural connections are also revved up in sleep.

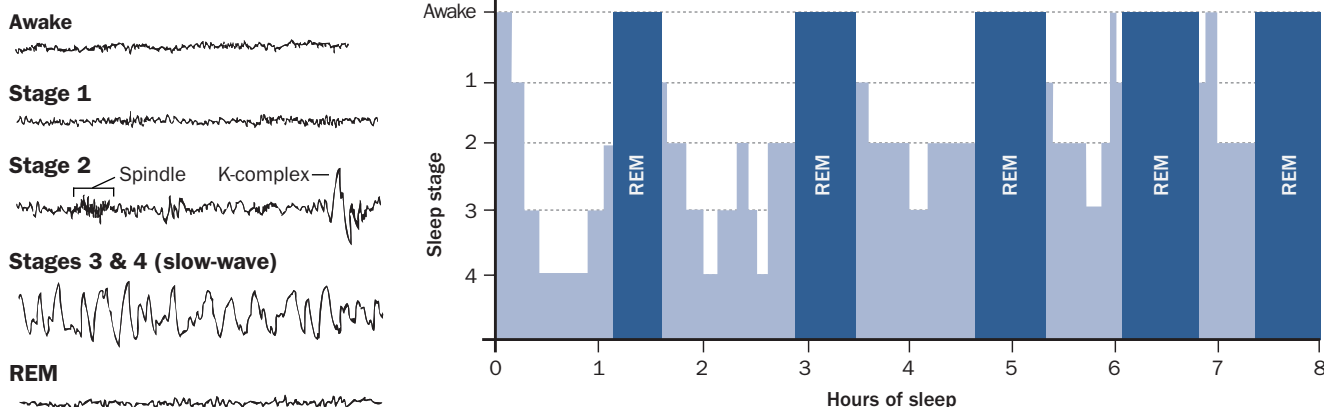
Studies in mice, rats, fruit flies and white-crowned sparrows have found similar patterns of gene activity, Pack and colleagues noted in a review in the February *Trends in Molecular Medicine*.

Sleep and wake are part of the metabolic cycle in the brain, Pack says. In this view, sleep is a time for replenishment and construction of cellular parts. "So when wakefulness comes along, you have the building blocks to make synapses," the junctures between neurons through which signals flow.

From calories to connections

To test the hypothesis that sleep alters metabolism, Amita Sehgal and Susan Harbison of the University of Pennsylvania left the lights on for some fruit flies. Each night for a week, the light deprived the flies of about two hours of sleep. Males made up for the loss by

Sleep waves People oscillate between two types of sleep each night, REM (short for rapid eye movement) and non-REM. Non-REM sleep occupies about 80 percent of sleep time and consists of ever-deepening stages (shown in EEGs below left). Most sleep time is spent in stage 2, which has two signature brain wave signals. About 20 percent of the night is spent in REM sleep, with REM bouts growing longer as the night progresses.



sleeping far more than usual the next day. Most females, though, just lost sleep and didn't make up the difference. The researchers also perturbed the flies' sleep by mechanical stimulation, which involved randomly jerking the flies' test tubes. Other flies were bumped while awake during the day, but their sleep was not disturbed.

Whether applied during day or night, mechanical stimulation resulted in decreased stores of glycogen, a starch, and increased triglycerides, a type of fat, the researchers reported in July in *PLoS One*. Light didn't affect stores of either substance much.

The stress of being jostled, rather than losing sleep, is probably what alters metabolism, at least in these fruit flies, Sehgal says. The study represents a growing trend in sleep science — the idea that sleep offers some advantage besides altering metabolism and saving energy.

"We're moving away from historical ideas of sleep saving calories," says James Krueger, a sleep researcher at Washington State University in Pullman. "It does do that, no question. But that's probably not why sleep evolved."

Sleep saves about 110 calories — about a cookie's worth — each night, Krueger says. That's not enough to make up for missing out on eating, mating or any of the other waking activities an animal does to survive. "It's a few more nuts. It's not worth it. You'd rather be awake avoiding predators," he says.

But sleep must provide some benefit that outweighs waking activities, Krueger says — such as, perhaps, forging connections between neurons.

Krueger, in fact, suggests that sleep itself is an unavoidable result of having neurons wired together in networks. Nerve cells that work hard, electrochemically signaling neighbors, eventually need to rest and recharge. Neural quiet can spread through the brain as neurons pull their wired partners along with them over the brink into sleep, Krueger argues in a December 2008 paper in *Nature Reviews Neuroscience*. The quiet time may allow neurons to strengthen or weaken connections with partners.

Of course, neural remodeling is also important for learning and memory — processes often suggested as sleep's *raison d'être* (*SN*: 4/28/07, p. 260).

Breaking bonds

But even sleep's role in learning and remembering evokes much dispute. One controversial theory, for instance, suggests that sleep, especially the powerful slow-wave variety, weakens synapses. That keeps the brain from filling up with useless connections, say sleep researchers Giulio Tononi and Chiara Cirelli of the University of Wisconsin–Madison. Their theory, known as synaptic homeostasis, is a sort of neuronal version of survival of the fittest. As an animal or person learns things throughout the day, connections between neurons get strengthened. All synapses are weakened during sleep, so tenuous connections are severed altogether and only the strongest bonds between neurons remain. This erasing of the blackboard makes room and preserves resources for the next day's learning, Cirelli and Tononi contend.

Some experiments seem to support the theory. While awake, rats build up levels of the protein GluR1, which helps increase the strength of synapses, the team reported in the February 2008 *Nature Neuroscience*. Levels of that protein drop when the animals sleep.

Studies in fruit flies show that snoozing leads to losing synapses. Cirelli and Tononi's group reported in the April 3 *Science* that proteins that help determine the strength of synapses build up while flies are awake and during sleep deprivation. Protein levels drop as flies slumber.

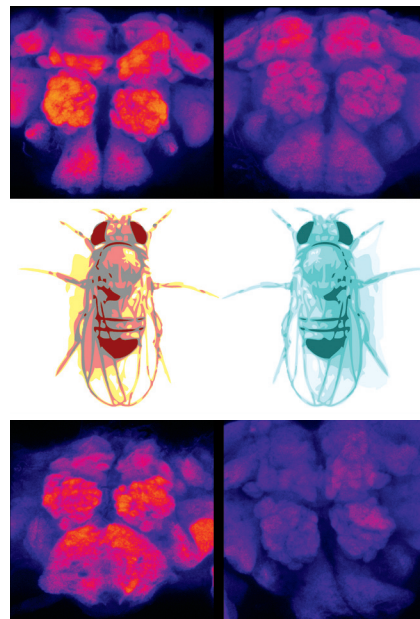
And while fruit flies sleep, they also lose synapses formed during social interactions, another study in the same issue of *Science* reported. When flies socialized, synaptic connections formed between neurons. Flies allowed to sleep after the exhausting social encounters pruned away some of the connections, but flies forced to stay awake retained the connections, researchers in Shaw's lab at Washington University found. Downsizing the number of neuronal connections could keep

brain circuits from being overwhelmed by all the exciting information gathered from social interactions, Shaw says.

On the other hand, experiments with kittens suggest the opposite. In kittens with one eye sewed shut, connections between the closed eye and the brain's visual centers weakened while the kitten was awake, Marcos Frank of the University of Pennsylvania and colleagues reported in the Feb. 12 *Neuron*. The open eye showed stronger connections to the visual center, but only after the kitten slept. Frank says his data show that sleep strengthens connections between brain cells rather than weakening them.

Studies of Buddy and other mice, using electrodes implanted in their brains, tend to support the results from kittens. Recordings of the activity of brain cells sensitive to the mice's location, called "place" neurons, show that sleep allows the brain to replay events, strengthening connections between neurons and preserving long-term memories.

When Young records the firing of Buddy's neurons, a speaker crackles with what sounds to the untrained listener like radio static. To Young's ear the static



Brain reset? Proteins (orange) that help forge connections between neurons build up in the brain while a fly is awake (left) but are depleted after sleep (right), suggesting sleep prunes neural connections, perhaps ensuring only the day's strongest memories remain.

Your brain on sleep

The brain orchestrates the daily sleep-wake cycle by responding to external cues, such as sunlight, and the body's own rhythms. Levels of chemical messengers, hormones and proteins rise and fall in key parts of the brain to generate wakefulness and sleepiness. Tracking brain activity during sleep, scientists have also revealed regions important for other putative functions of sleep, such as memory storage and information processing.

Hippocampus

The hippocampus is active during some stages of sleep. Scientists think that memories may be transferred from short-term storage in the hippocampus to long-term storage in the cortex during sleep.

Eye

Specialized cells in the eyes sense daylight, sending a signal to the brain. These cells help set the body's daily biological clock.

Prefrontal cortex

Activity of neurons rises and falls during different stages of sleep in this area, which may have a role in dreaming and is particularly sensitive to sleep deprivation.

Hypothalamus

An important sleep and regulatory area, the hypothalamus contains the suprachiasmatic nucleus (SCN), the master biological clock that controls the body's circadian rhythms, and other clusters of neurons that trigger sleepiness and wakefulness. Some clusters inhibit arousal systems, promoting sleepiness. Groups of histamine-making neurons and orexin-producing neurons stimulate arousal by producing wake-inducing chemical signals.

Brainstem

A major arousal center that responds to wake-inducing signals from other brain regions and stimulates wakefulness.

Daily dose of zzz The circadian system that regulates many of the body's daily rhythms (including blood pressure, temperature and hunger) also plays an important role in determining bedtimes.

Sunlight helps set the master clock in the brain. In the **eye**, intrinsically photosen-

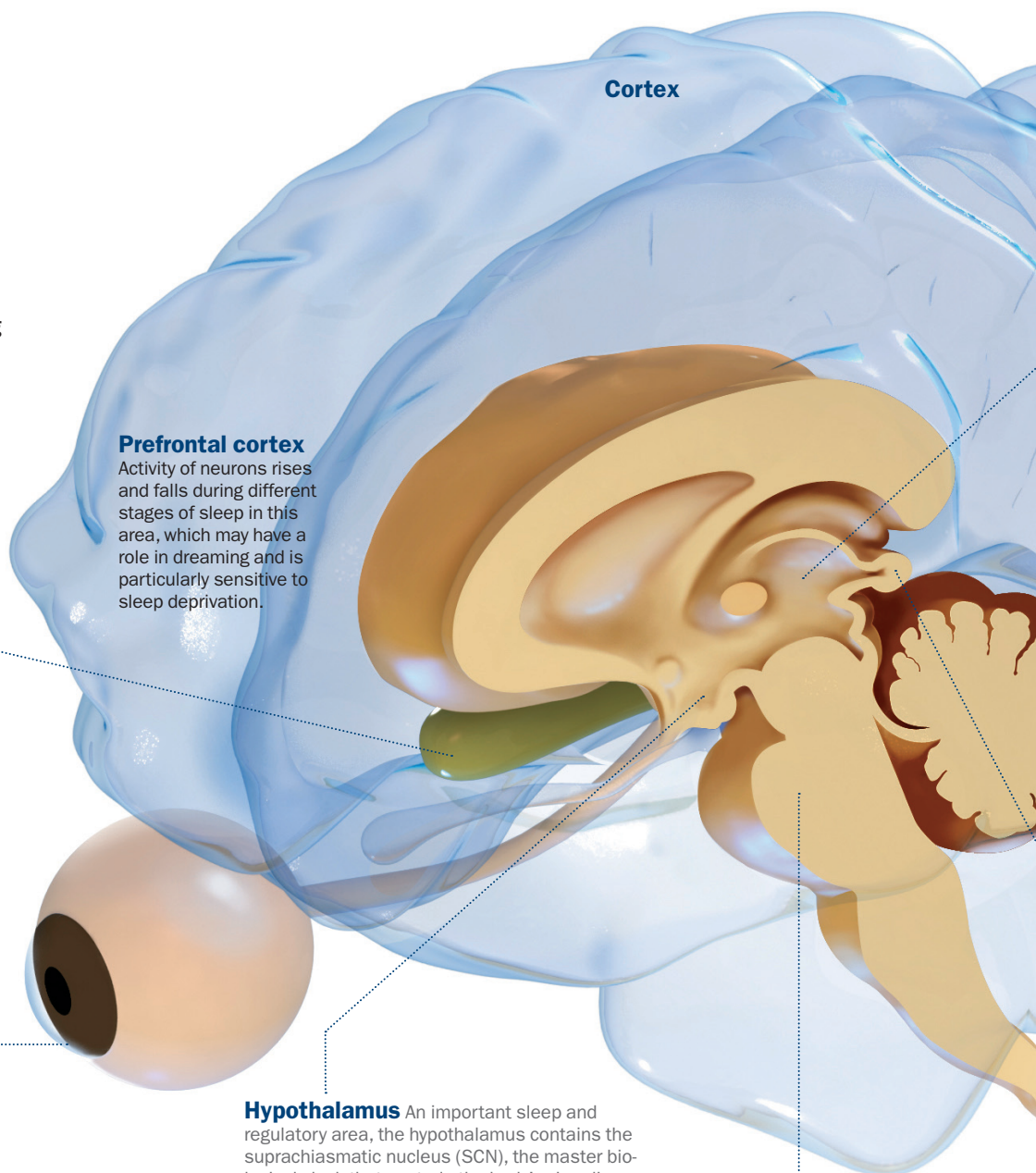
sitive retinal ganglion cells sense bright blue and green wavelengths of light and send a daylight signal to the brain.

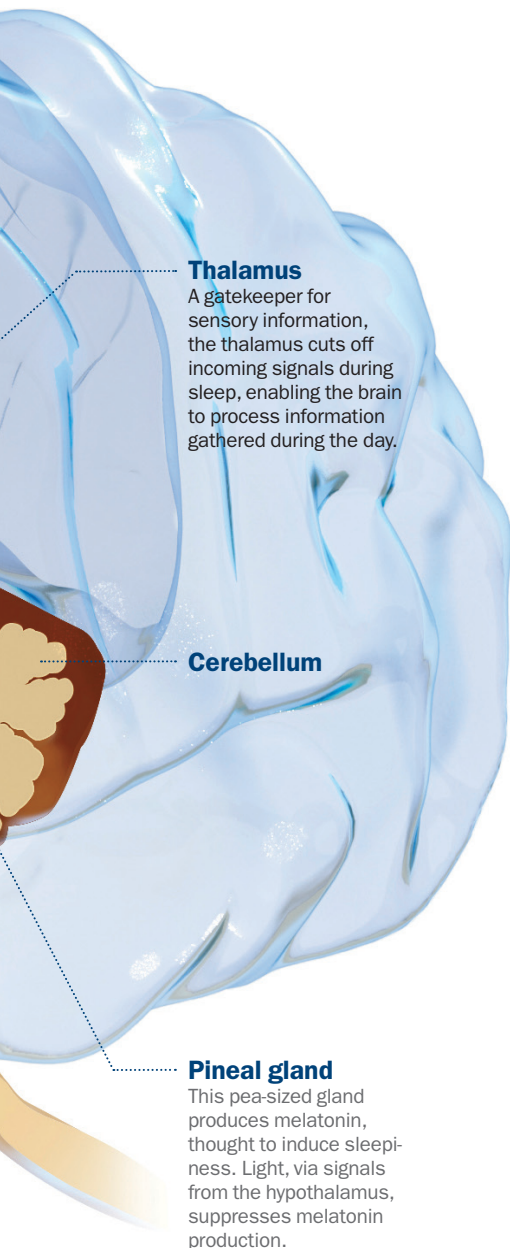
Located within the hypothalamus, the **suprachiasmatic nucleus**, or **SCN**, is made up of a cluster of about 50,000 brain cells. The SCN is the master clock that helps

regulate the time of sleeping and waking as well as the rise and fall of body temperature and other body processes.

The **pineal gland**, located above the cerebellum, produces melatonin, one of the chemicals that helps regulate sleep.

The circadian system balances out the





drive to sleep—known as sleep pressure—with other signals to keep people alert throughout the day. Although scientists suspect that sleep pressure results from the buildup of some substance in the brain, no one knows for sure what that substance is.

is the sound of memories being made. Each time an electrode detects electrical activity in one of the neurons, it translates the activity to those audible crackles and to tracings on a computer screen.

While Buddy is awake and moving around in his box, running a maze or exploring new objects, his brain cells fire in a rhythmic pattern. As he sleeps, his brain waves slow down. But small, rapid spurts of brain cell activity, called ripples, interrupt the slow-rolling waves of sleep and burst above the background static. During those ripples, which last a fraction of a second, the place-denoting neurons fire in the same order as when the mouse was awake and exploring.

MIT's Matthew Wilson was among the first to discover these ripples. Ripples during slow-wave sleep replay the day's events, but the timing is compressed. During REM sleep, he says, rats and mice also replay events, but in real time, and not always in the same order or way they actually happened.

Cells in the hippocampus fire off a burst of ripple waves first. Then, 100 milliseconds later, cells in the prefrontal cortex, commonly considered to be the seat of the brain's "executive centers," take up the refrain, Caltech researchers reported in the Feb. 26 *Neuron*. Such bursts of activity could represent transfer of information from temporary memory storage in the hippocampus to long-term storage in the cortex, Wilson says. In REM sleep, the timing of the firing between the hippocampus and the cortex is not as tightly coordinated as it is in slow-wave sleep.

Rats relive memories while awake, too, and that replay can help the animals plan their next move, Wilson and colleagues show in the Aug. 27 *Neuron*.

Scientists have speculated that such replay is also important for forming long-term memories. Researchers in Tonegawa's lab tested this theory directly: They blocked ripples by essentially paralyzing part of the hippocampus with tetanus toxin. Apart from diminished ripples, the mice slept normally and could remember tracks they had run for a short time. But the mice were unable to form long-term memories, the team reported in the June

25 *Neuron*. When researchers reversed the effect of the toxin, the ripples returned, along with the ability to form long-term memories, indicating that replaying and rehearsing memories during slow-wave sleep is a key step in solidifying them.

Across the Charles River in Boston, Harvard Medical School researchers have some evidence that replay may also be important for humans. Stickgold and Erin Wamsley have recruited volunteers to play a maze video game. After playing the game, some volunteers take a nap and some stay awake watching videos. The participants are awakened at the first sign that they are about to enter REM sleep, but some still report vivid dreams—some tangentially related to the game, such as hearing the music or exploring bat caves reminiscent of the maze. Preliminary results indicate that people who report game-related dreams improve their performance more when tested again. The dreamers improve more than either people who remained awake and thought about the game or people who slept, but didn't remember dreaming about the game.

"To us it's an indication that some of the networks related to that learning are active" during sleep, Wamsley says.

Its importance for memory is the only proposed explanation for sleep that contains a clear reason why consciousness must be shut down, says Stickgold. Human brains don't have TiVo, with the ability to record one thing while watching another. People use the same brain areas to perceive the world and then process what is happening. To fully digest information gathered throughout the day, at some point the brain has to block more input, he speculates.

In slow-wave sleep, the hippocampus shows home movies of the day's events to the cortex. During REM sleep, the hippocampus is issued a gag order, leaving the cortex to freely associate different pieces of information without the detail-oriented hippocampus stepping in to say, "no, this is what really happened." That free association may allow the brain to tie disparate experiences and facts together, making them easier to remem-

ber, or prompting new solutions to problems encountered during the day.

Learning and memory studies also suggest that sleep helps extract the gist of memories, enabling them to be filed under the correct headings, Stickgold says. How the brain does this is illustrated by studies in which participants “remember” that they learned a word such as *hospital* when actually the list of words they memorized contained *doctor*, *nurse*, *stethoscope*, *bed* and *patient*, but not *hospital*. Such associations give memories context and meaning.

“What your brain is leaving you with in the morning is a memory that is less accurate, but more useful,” Stickgold says.

Sleep researchers still don’t know how the brain decides which memories to review, edit and save, and which are junk, says Matthew Walker of the University of California, Berkeley. Emotion-associated chemicals may mark memories as important and worth saving, or send up a red flag to the brain that the memory is problematic. Over time, as sleep extracts the informational core of memories, it

may also strip away the emotional blanket surrounding them, so that a person learns the lesson of the memory without all the drama of emotion. REM sleep in particular “is like group therapy for memories,” he says.

Walker theorizes that this process may go awry in post-traumatic stress disorder. He lays out his case for sleep’s role in processing emotional memories in the *Annals of the New York Academy of Science’s Year in Cognitive Neuroscience 2009*. Removing the emotional blanket from memories is probably possible only during sleep, when outside stimulus is shut off, he says.

Wilson agrees that sleep can be an unfettered time to come up with new solutions. “The ‘problem’ with the awake state is that it is being influenced by the outside world,” he says. “It is constrained by what you’re currently experiencing. During sleep you can explore. The breadth of experience one has access to is much greater. I think it’s very likely that during sleep you have the flexibility to evaluate and solve problems in novel ways.”

REM sleep may be just what is needed to get creative juices flowing, suggests a study in the June 23 *Proceedings of the National Academy of Sciences*. People who had a nap with REM sleep performed almost 40 percent better on a word test requiring a creative solution than people who didn’t nap or had only non-REM naps, researchers led by psychologist Sara Mednick of the University of California, San Diego show. The improvement happened only when participants drew information from a seemingly unrelated word test administered earlier in the day to solve the new problems. REM sleep seemed to help make that otherwise unrecognized connection.

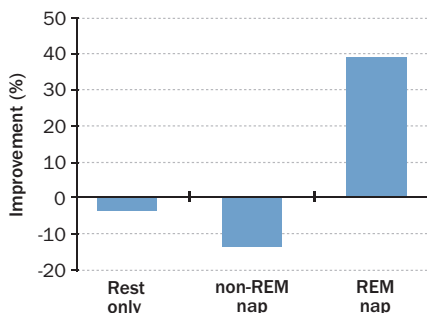
“People in the REM group were able to use information they didn’t know they had in their brains,” Mednick says. Still, she doesn’t believe all dreams mean something or that “sleeping on it” will solve every problem.

“Some dreams are going to be very, very meaningful, and some dreams are just your brain rooting through things that don’t mean anything,” she says.

Multitasking while you sleep

A lot appears to be going on behind all that shut-eye: Studies show sleep probably serves many different functions, including enhancing learning and memory, regulating emotions, stimulating creativity and boosting the immune system.

REM sleep and problem solving

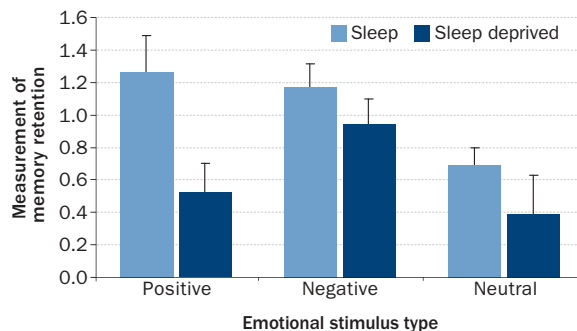


SOURCE: CAI ET AL./PNAS 2009

Creative sleep

A nap that included REM sleep improved volunteers’ ability to solve a word problem requiring a creative approach. Volunteers whose naps included only non-REM sleep and those who rested but stayed awake didn’t improve on the word test. The result could be evidence that REM sleep boosts creativity.

Sleep and memory formation

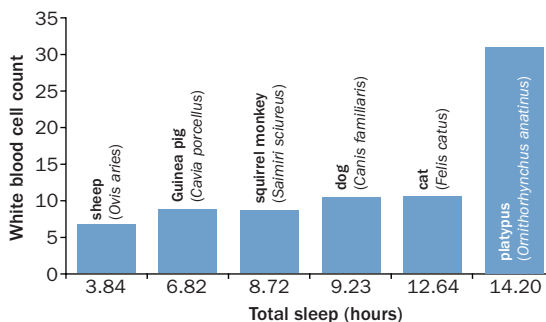


SOURCE: WALKER/NYAS 2009

Emotional recharging

Sleep is known to enhance memory and seems to play a special role in creating emotional memories. Sleep-deprived volunteers had trouble remembering positive and neutral words in one test, but remembered negative words about as well as rested people did. The result could help explain why things that seem so bad at night look better in the morning.

Sleep and immune cell count



SOURCE: PRESTON ET AL./BMC EVOL. BIO. 2009

Sleep's immune boost

Sleep and the immune system are intimately acquainted—immune chemicals that fight off infection also increase sleepiness. One study found that animals that sleep more have higher white blood cell counts and tend to have fewer parasites, perhaps indicating that sleep and immune function coevolved.



Despite the evidence of sleep's role in brain performance, not all researchers believe that aspect to be the end of the sleep story.

"The notion that sleep is by the brain, for the brain — which is a motto in the field — is outdated," says Eve Van Cauter of the University of Chicago. "Sleep affects everything in the body and everything in the body affects sleep."

Short-term studies show that cognitive problems follow sleep deprivation, but scientists have no idea whether those problems relate to longer-term decline in memory or degenerative brain disorders, Van Cauter says.

Nearly 100 studies link sleep loss to cardiovascular disease, she says. "But we don't even have 10 studies on whether short sleep contributes to cognitive decline or dementia." (See Page 11.)

Others agree that sleep plays an important role in regulating the immune system. In fact, sleep may have evolved to improve the immune system's ability to fight off parasites, argue Patrick McNamara of Boston University and his colleagues in the Jan. 9 *BMC Evolutionary Biology*.

Species of animals that spend more time sleeping each day tend to have higher counts of infection-fighting white blood cells, a database analysis revealed. The more sleep on average a species gets, the fewer parasites plague its members, and the parasites that do infect longer-sleeping species are not as prevalent in their populations as parasites that sicken shorter-sleeping species.

Still, whether sleep's purpose is fighting parasites, making memories or modifying metabolism remains as much a matter of dispute as the blind men's competing images of the elephant. But perhaps that parable suggests a strategy for progress.

"The only mistake the blind men made is that they argued with each other," says Stickgold. If sleep researchers are willing to take a step back, confer and concede that others may have a point, perhaps one day the mystery of sleep will be solved. ■

Explore more

- Read Harvard Medical School's sleep guide at www.understandingsleep.org

All kinds of tired

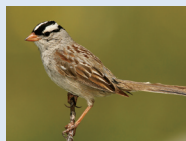
Donkeys sleep about three out of each 24 hours.

Certain reef fish spend the night moving their fins as if swimming in their sleep. Some biologists argue that all animals sleep in some form or another. But identifying sleep can get complicated. Insects have brain architecture so different from humans', for example, that electrophysiological recordings during "sleep" won't match human patterns. The real problem may be that researchers haven't agreed on what sleep does for people, so it's hard to agree on the animal equivalent. Studying animal sleep, though, offers the prospect of discerning evolutionary patterns in sleep pointing to some ancient function. —Susan Milius



Fruit fly 8–10 hours of inactivity each day

Lab fruit flies droop into less-responsive, sleeplike periods mostly at night. If deprived of these quiet bouts, flies spend extra time stationary later, as if catching up. Caffeine keeps them awake, and antihistamines increase downtime. Studies haven't found REM patterns, but brain activity does shift during the droops.



White-crowned sparrow 3–8 hours (depends on season)

During migration season, white-crowned sparrows perplex researchers with the birds' apparent power to cheat on sleep. Birds get not quite 40 percent as much sleep as usual, with drops in both slow-wave and REM sleep. Yet the birds don't get stupid in performance tests.



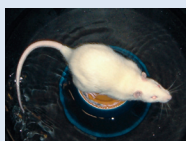
Platypus 14 hours

From an ancient mammal lineage, the platypus shows REM activity in its brainstem but not simultaneously in its forebrain, as many other mammals do. The platypus forebrain shows non-REM sleeplike activity during this time, though, and the REM session lasts long relative to other mammals.



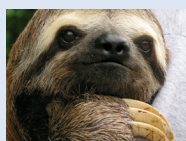
Armadillo 17–20 hours

Armadillos appear to be prodigious sleepers. The nine-banded armadillo has been clocked sleeping more than 17 hours, and the giant South American armadillo 20 hours, among the longest stretches recorded.



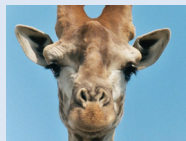
Lab rat 11–14 hours

A lab rat perishes when marooned for weeks on a disk that tips it into water when the rat dozes off. Rats survive other kinds of sleep-deprivation tests, though, inspiring a debate on whether it's sleep loss or a side effect that is fatal.



Three-toed sloth 9.6 hours (measured in the wild)

Brown-throated three-toed sloths wearing portable recorders became the first free-living animals to have their electroencephalograms studied. Out in the forest, the adult female sloths slept some six hours less in a 24-hour period than captive sloths did. The wild animals' EEGs showed about two hours in REM sleep.



Giraffe 4–5 hours

Giraffes sleep only a few hours out of 24, but lions, which prey on giraffes, have been clocked snoozing around 13 hours a day. Some researchers have noted a trend toward less sleep in species that, like giraffes, rest in more exposed situations in which they might be more vulnerable to predators.



Bottlenosed dolphin 4 hours (in each brain half)

Bottlenosed dolphins and other cetaceans studied so far show typical mammalian slow-wave brain activity during sleep but in only one brain hemisphere at a time. Researchers have documented little, if any, REM sleep in cetaceans.



More than a third of U.S. adults suffer occasional bouts of insomnia, with 10 to 15 percent experiencing a long-term, chronic form of the sleep disorder.

Sleep gone awry

Researchers inch closer to causes, cures for insomnia, narcolepsy

By Laura Sanders

If Ben Franklin had been able to live by his own advice, he might have been even healthier, wealthier and wiser. But he was a notorious insomniac, rumored to have been such a poor sleeper that he required two beds so he could always crawl into one with cool sheets when he couldn't sleep. Getting a

good night's sleep turned out to be more difficult than taming lightning, heating houses or designing bifocal specs.

Today millions of people afflicted by sleep disorders know how Franklin felt. Some people can't fall asleep even when they're exhausted. Yet other people fall asleep when they should be wide awake.

Although sleep disorders take many different forms, they do have one thing in common: The more researchers learn, the more they have left to figure out. Sleep problems present a constellation of symptoms, trigger overlapping diagnoses and divulge no clear causes.

"We always feel like we're one step

away from getting all of the answers,” says Adi Aran of Stanford University, “but I really believe that in the next decade we will understand much more about sleep disorders.”

Already, some recent advances have brought scientists closer to discerning the ultimate causes of such disorders, even suggesting possible treatments. Masashi Yanagisawa of the University of Texas Southwestern Medical Center at Dallas believes researchers are poised to “crack open the black box of sleep regulation.”

Glimpses into that black box suggest that insomnia stems from overactive body systems that conspire to overtake a perfectly functional sleep system. Two reports find that one measure of arousal, blood pressure, is elevated in people with insomnia even while they are asleep.

Other glimpses come from studies of narcolepsy. Scientists have known for almost a decade that narcolepsy is caused by a dearth of a brain communication chemical called orexin. But researchers are still struggling to explain why the neurons that produce orexin are lost in the brains of people with narcolepsy. New evidence implicates a malfunction of the immune system as a likely culprit.

Understanding what goes wrong in sleep disorders such as narcolepsy and insomnia may lead to more targeted treatments. Instead of flooding an insomniac’s brain with a general depressant, clinicians may one day specifically target particular overactive brain regions. Rather than giving people with narcolepsy stimulants that rev up the entire body, preventive measures may halt neuron death before narcolepsy sets in. More generally, understanding these disorders may help researchers create a more complete picture of normal sleep and normal wakefulness, and how bodies and brains transition between the two.

Sleepless nights

For some people, the Franklinesque advice to go to bed early is impossible. Trouble falling asleep or staying asleep (or waking up still tired) is loosely defined as insomnia. It’s a big problem:

The National Center on Sleep Disorders Research reports that 30 to 40 percent of Americans say they suffer insomnia symptoms at least once over the course of a year.

“Almost everybody has insomnia at some point in their life,” says Michael Bonnet of Wright State University’s Boonshoft School of Medicine in Dayton, Ohio.

Sleeplessness may be brought on by traumatic events such as a death in the family, an illness such as cancer or anything else distressing, causing a person to lie awake at night with a racing mind. For a subset of people, though, insomnia has no prompting signal — a condition called primary insomnia.

Regardless of the trigger (or lack thereof), temporary insomnia has a nasty way of becoming a habit. Poor sleep habits can become ingrained. When trouble sleeping persists for three or four nights a week over several months, insomnia is considered chronic.

It may turn out that untangling the prompting signals of insomnia, as many sleep researchers attempt, is a fool’s errand, says Michael Perlis, director of the University of Pennsylvania’s Behavioral Sleep Medicine Program in Philadelphia. “The whole zeitgeist has changed,” he says. Most sleep researchers now agree that “once insomnia goes chronic, it stays that way,” regardless of the prompting signal, Perlis says. So rather than focusing on the immediate trigger for insom-

nia, many scientists are trying to figure out why it becomes chronic and how to prevent that from happening.

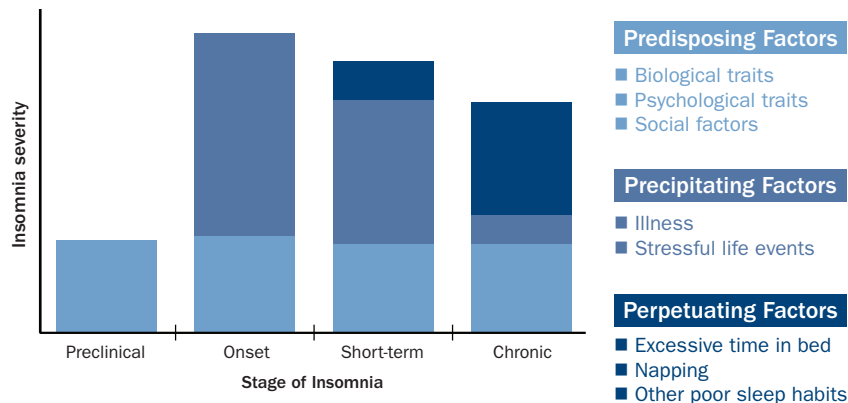
A growing body of evidence supports a hyperarousal explanation of chronic insomnia, in which the sleep centers in the brain are overwhelmed by amped-up “awake” signals.

For instance, people with primary insomnia have higher hormone secretions, higher body metabolism, heightened activity in certain brain regions and elevated heart rates, studies show. Even body temperatures may be raised in people with primary insomnia. This heightened activation is present in the day and remains through the night.

After a traumatic event or a fright, the body and brain are in an aroused state. Heartbeat increases, blood flows faster and stress hormones flood the body, putting the muscles and the brain on high alert, ready to quickly deal with whatever comes next. A meeker version of this excited state might be what keeps people with insomnia awake, Perlis says. People with insomnia don’t constantly have the extreme palpitations that come from an encounter with Freddy Krueger, he says. “We’re hardly talking about panting and heart thumping.”

But the heightened alertness is just enough to interfere with sleeping, making insomnia more of a disorder of wakefulness than of sleep. “Patients with insomnia in general could have a fairly decent sleep system,” Bonnet says. “And

Can’t sleep Certain traits make a person more susceptible to insomnia, which can be initiated by illness, other stresses or distressing events. As short-term insomnia becomes chronic, perpetuating factors, such as napping, play a greater role in insomnia’s severity than the initial triggers.



SOURCE: ERMAN/PRIMARY PSYCHIATRY 2007

that's kind of hard for a sleep researcher like myself to say."

Two reports make the case that people with insomnia are hyperaroused, Bonnet says. A case-controlled study conducted in a Canadian sleep lab found that 13 patients with primary insomnia had higher systolic blood pressure than people in a comparison group. What's more, those people with insomnia failed to show the characteristic dip in systolic blood pressure when day turns to night. Heightened brain activity at night correlated with higher blood pressure, researchers led by Paola Lanfranchi at the Hôpital du Sacré-Coeur de Montréal reported June 1 in *Sleep*.

A larger study of 1,741 people from central Pennsylvania found that people with chronic insomnia and short sleep duration (as measured in a sleep lab) were more likely to have high blood pressure. Cardiovascular diseases including strokes and heart attacks may go hand in hand with chronic insomnia, Alexandros Vgontzas of Pennsylvania State University College of Medicine in Hershey and colleagues suggest in their paper in the April 1 *Sleep*.

Other reports show that regions of the

brain remain unduly active in people with insomnia, including the hypothalamus, a brain center important for sleep and arousal. In the not-too-distant future, Bonnet says, scientists may identify the precise brain regions where activity is too high at night, and the regions that tell the body to rev up. "Obviously once you've found specific brain areas where you have activation, you can find ways to direct drugs to those areas," he says.

Treating a disorder before it is fully understood is hard, but researchers are developing some new therapies that seem to work. Several reports over the last few years have explored a treatment called cognitive behavioral therapy for insomnia, or CBTi. The method works by training people to change behaviors that interfere with sleep. Participants are instructed to avoid naps, get out of bed if they're not sleeping and stop stressing over lost z's, all steps that can boost sleep. Continued practice of CBTi may reprogram the parts of the brain that control the sleep-wake cycles. "Even though we know not what we deal with, CBTi is highly effective," says Perlis, a strong proponent of such behavioral interventions.

While peeking into the black box of insomnia reveals an array of overactive body and brain offenders, the black box of another sleep disorder — sleep-inducing narcolepsy — holds just one culprit: a small group of specialized neurons that make a chemical with two names.

Narcobiochemistry

About a decade ago, experiments by Yanagisawa with mice and by other researchers with dogs found that narcolepsy is almost certainly caused by the absence of a single chemical messenger in the brain. This chemical, called orexin by some scientists and hypocretin by others, is produced by a small pocket of neurons in the hypothalamus.

"Narcolepsy is very special in the whole variety of sleep disorders," Yanagisawa says. "So far, narcolepsy is the only sleep disorder that has been reduced to the biochemical level."

People lacking orexin-producing neurons fall asleep uncontrollably. In extreme forms of narcolepsy, this happens every one to three hours. Narcoleptic attacks can also be accompanied by a loss of muscle tone, called cataplexy. Severe cataplexy can leave the entire body as limp as a rag doll.

Examining brains from people who had narcolepsy, researchers found that the neurons in the hypothalamus that secrete orexin are almost completely absent. Narcoleptic brains had an 85 to 95 percent reduction in orexin neurons, Jerome Siegel, of the University of California, Los Angeles and his colleagues found. Since that study, published in 2000, scientists have been intent on figuring out how these neurons die, in order to find a way to prevent narcolepsy by helping the cells survive.

One possible suspect is the immune system, which ordinarily protects the body from harmful outside threats. Genetic studies in the 1990s provided a strong hint for the immune system's role: About 90 percent of people with narcolepsy have the immune gene variant *HLA-DQB1*0602*, whereas only about 25 percent of the normal population carries that variant. HLA genes encode

Missing neurons A small group of neurons nestled in the hypothalamus die in people with narcolepsy. These neurons usually produce orexin, a chemical that carries wakefulness-promoting signals to other nearby neurons and to other brain regions, such as the brainstem and cortex.

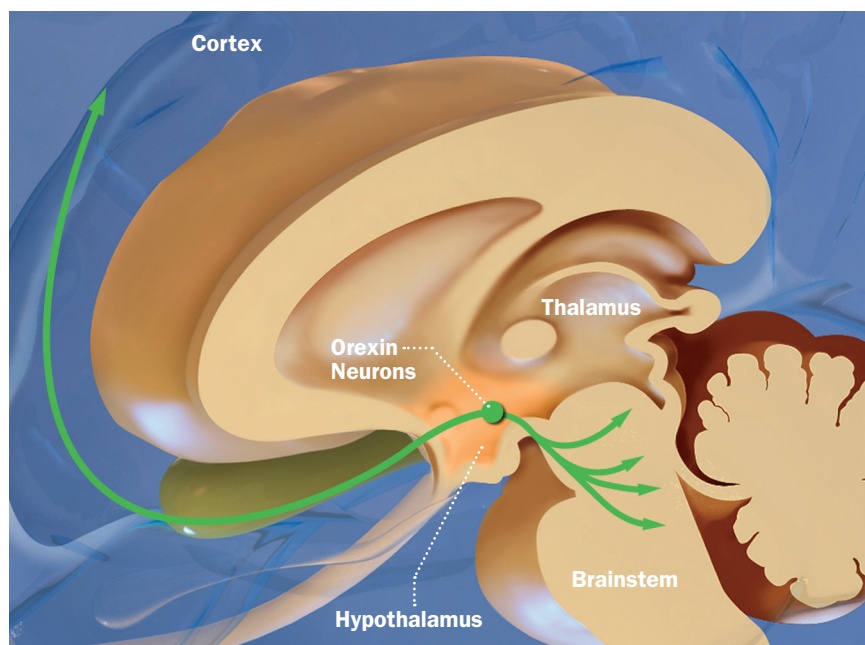


ILLUSTRATION BY CHARLES FLOYD

proteins that sit on the outside of cells and help the immune system recognize the body's own cells. In people with this variant, the reasoning goes, self-recognition may be more likely to go awry, causing the immune system to attack this small, important population of neurons in the hypothalamus.

Recent work from Emmanuel Mignot, a sleep researcher at Stanford University, and his colleagues uncovered another immune system link. A study of over 4,000 people found that those with narcolepsy were more likely than others to have a certain DNA letter in part of a gene called the T-cell receptor alpha locus. This gene codes for a protein that recognizes the HLA pattern on the outside of cells. Erroneous readings of the HLA pattern might cause an immune cell to mount an attack on the body's own orexin-producing neurons, the authors hypothesize in a report published in *Nature Genetics* in June.

Another recent study found that certain bacterial infections might spur the destruction of these neurons. In some diseases, streptococcus infection has been shown to trigger autoimmune attacks. It may signal the body to mistakenly kill orexin neurons too. "It makes sense that these cells die due to some kind of inflammation," says Aran, who collaborated with Mignot on the research, which appeared August 1 in *Sleep*.

In the study, people with newly diagnosed narcolepsy had higher blood levels of strep antibodies than did controls, suggesting the patients' immune systems were geared up to fight off an infection. What's more, this antibody response lingered for up to three years in people with narcolepsy, whereas the antibody levels go down in just months in most healthy people. "We believe that strep infection might be one of the triggers for narcolepsy," says Aran. "We don't know exactly

how, but we believe streptococcus does something."

Identifying the autoimmune response trigger (or triggers) would still not answer the greater mystery, though. Scientists remain baffled by how the immune sys-



Studies on narcoleptic animals (such as the dog shown here awake, left, and asleep, right) led to the discovery that a lack of the neurons that produce the brain chemical orexin causes the disorder.

tem conducts such a targeted kill-off of orexin neurons. Almost all of the orexin neurons are destroyed, while other kinds of neurons — even those nearby — remain untouched. Presumably, orexin neurons have some identifying mark that the immune system specifically detects, but so far, that mark

is a mystery. "Despite over 15 years of research, no one knows," says Aran.

Current treatments for narcolepsy, while somewhat effective, address only the symptoms, not the underlying loss of neurons. In most cases, once the symptoms show up, the neurons are already gone, says Aran. "If we know the exact pathogen, it might prevent some of the cases," he says. If strep is verified as a trigger, preventing such infections in people — especially those with the particular HLA variant that makes them susceptible — might thwart narcolepsy.

Uncovering the root causes of sleep disorders will undoubtedly lead to better therapies, and maybe even preventions. More than that, though, scientists may have a better chance of learning what happens when sleep goes right — a question that remains largely unanswered — by understanding how sleep goes wrong. "One of the very satisfying things," Siegel says, "is that it gives you insight into how sleep and wake are controlled." ■

Explore more

- M. Bonnet and D. Arand. "Hyperarousal and insomnia: State of the science." *Sleep Medicine Reviews*. 2009.
- The National Sleep Foundation website www.sleepfoundation.org

Sleep gone bad

Besides insomnia and narcolepsy, various other disorders can impair sleep. Among them:

Restless legs syndrome

People with restless legs syndrome experience tingling or prickling sensations during periods of stillness, often before falling asleep. This disorder often prevents restful sleep by causing disruptive limb movements.

REM behavior disorder

People with this disorder physically act out their dreams, which are typically frightening or aggressive. It predominantly affects males over age 50 and is usually noticed when a person screams, punches or thrashes violently while asleep.

Circadian rhythm sleep disorders

Caused by extreme mismatches between the normal sleep-wake cycles dictated by a person's environment and the body's natural biological clock, circadian rhythm disorders often lead to excessive sleepiness.

Sleep paralysis

In sleep paralysis, a person is unable to move for a time just before falling asleep or after waking up. Paralysis can be partial or complete and may be accompanied by hallucinations.

Sleep apnea

Sleep apnea occurs when breathing is repeatedly halted during sleep, interrupting both sleep and oxygen flow. The most common form, obstructive sleep apnea, occurs when throat muscles fail to keep the airway open. A rarer form, known as central sleep apnea, occurs when brain signals fail to control breathing. —L.S.

Dying to sleep

Getting too little sleep can impair body and brain, and could even be deadly **By Tina Hesman Saey**

For many people, days just don't seem long enough. In order to cram everything into one 24-hour period, something has to give. Judging by many surveys of Americans, it's sleep.

Sleep is regarded by some as unproductive, wasteful downtime. People who would rather hit the hay than the dance floor are told that only losers snooze and that they can sleep when they're dead.

But new data about sleep's benefits suggest that losing sleep might speed up death's arrival. Recent research also shows that people who don't snooze enough face a higher risk of losing their health than those who regularly get a good night's sleep.

"What is certain is that we can't do without sleep," says Peter Meerlo, a neuroscientist at the University of Groningen in the Netherlands.

Some of the consequences of lost sleep are immediate, obvious and unpleasant, such as a toddler's crabbiness after missing a nap. Older children and adults get irritable when tired, too. Sleepy students don't learn or perform as well as their well-rested peers (*SN: 09/09/06, p. 174*). And nodding off at work probably won't help anyone get a promotion.

Other penalties for staying up too late can be far more serious, even deadly. Studies have linked chronic sleep loss to obesity (*SN: 11/17/07, p. 318; SN: 4/1/06, p. 195*), heart disease, high blood pressure, diabetes (*SN: 1/3/09, p. 5; SN: 1/19/08, p. 46*) and shorter lives (*SN: 2/8/03, p. 85*) in people and laboratory animals. And now, a new study links sleep loss in mice to Alzheimer's disease plaques (*SN: 10/24/09, p. 11*). And some evidence suggests that stinting on sleep night after

night may cause long-term — maybe even permanent — changes in the brain, some of which may predispose people to mental disorders such as depression.

Just one night of short sleep has been shown to increase levels of inflammatory chemicals in the blood (*SN: 10/11/08, p. 14*) and increase hunger-promoting hormones. A week of getting just two hours less sleep per night than usual changed the way people in one study responded to glucose, mirroring a change seen in people who develop diabetes.

And lack of sleep can also have immediate injurious or fatal consequences: The National Highway Transportation Safety Administration estimates that drowsy-driving crashes result in about 40,000 nonfatal injuries and 1,550 deaths each year, probably a conservative estimate. Now, scientists are trying to understand not only how sleep deprivation affects driving performance, but also why one sleepy person might drive fine while another becomes a road menace.

Too tired to function

Nodding off behind the wheel is a common occurrence in David Dinges' lab at the University of Pennsylvania School of Medicine in Philadelphia.

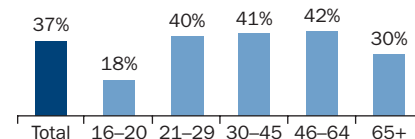
Dinges and his colleagues limit volunteers' time in bed to four hours a night for five nights, then let the volunteers sleep up to 10 hours for two days. The aim of the experiments is to learn more about how the brain responds to the kind of chronic sleep deprivation people experience in real life, and to find out how much sleep is needed to repay the debt.

In the dimly lit laboratory, a volunteer named Heather sits behind the wheel of

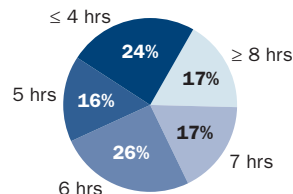
a driving simulator with electrodes taped to her head. She pushes the accelerator so that her virtual car buzzes along at just over 60 miles per hour on a dark road illuminated only by her headlights. White poles flash by. Suddenly, around a bend, the back of a large cargo truck looms in the darkness. Heather quickly brakes to avoid colliding with the slow-moving truck.

Drowsy driving More than one-third of U.S. drivers have fallen asleep behind the wheel. While most of those surveyed were startled awake, some crashed.

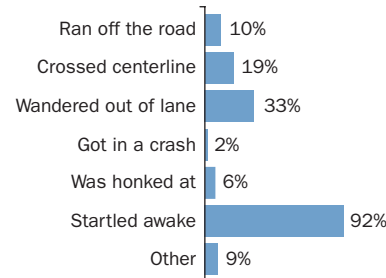
Percentage of people who have nodded off while driving, by age



Hours slept the night before driving drowsy



Outcome of nodding off while driving



SOURCE: 2002 SURVEY OF DISTRACTED AND DROWSY DRIVING/ NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION



Sleepy volunteers put pedal to the metal in a University of Pennsylvania driving simulator. Lab technician Christopher Jones demonstrates: electrodes on his head register brain waves on an EEG and the simulator measures his driving performance.

For each of the past four nights, Heather has gotten just four hours of sleep. “My limbs feel heavy,” she reports. She isn’t used to this curtailed sleep schedule. “I never stay up all night,” she says. “I always get my sleep.” She is forgoing shut-eye for a study of genetic differences that may affect people’s responses to sleep deprivation.

The electrodes on Heather’s head are monitoring her brain waves and eye movements so that researchers can detect even brief bouts of sleep. But despite feeling tired, “a little light-headed and dizzy,” Heather hasn’t nodded off when she’s not supposed to, and her performance on the driving simulator and other tests hasn’t deteriorated from her well-rested showing.

The tests in Dinges’ lab have shown just how severely most people’s performance of daily activities can deteriorate with sleep loss. But Heather may be one of a few rare people whose brains don’t become mush when deprived of sleep. By figuring out which genes keep Heather’s brain functioning despite so little sleep, researchers may be able to develop drugs that affect those genes and help ordinary people resist making sleepy mistakes.

James, an architecture student, routinely pulls all-nighters, especially at the end of a semester. He expected to feel horrible after missing out on four hours of sleep each night for several days. “I thought I was going to be like a zombie, not able to process things and short-tempered,” he says. But despite the lab’s dim lighting, “I’m functioning,” he says.

Functioning perhaps, but not as well as he does when well-rested. On this day, he fell asleep while driving the simulator. He woke up to find that he’d smashed into the back of a truck.

James is certainly not alone in misjudging his ability to function while sleepy. Despite evidence to the contrary, many short-sleepers are convinced that they function well on less sleep, Dinges says. One constant is that people are generally not good at predicting how well they will perform when deprived of sleep.

Driving while drowsy was a contributing factor in more than 20 percent of the

crashes and near-crashes recorded in a study by researchers at Virginia Tech in Blacksburg. The team fitted 100 cars with cameras and sensors and then recorded drivers’ actions for about a year. A drowsy driver was four to six times more likely to have a crash or near-crash. In contrast, reading, putting on makeup and dialing a cell phone increased crash risks threefold, the researchers found.

No one could have predicted Heather’s and James’ individual responses to sleep deprivation, Dinges says. In his studies, he has found that some people fall apart after missing just a few hours of sleep. Others, like James, show a slow, steady decline in their ability to remain vigilant and sharp on tests as their sleep is cut short over the course of five days. Then there are the people Dinges refers to as “type 1s,” like Heather. Those people’s performance on a variety of attention and response-time tests doesn’t change with five days of restricted sleep. “People are walking around with grossly different brain activity profiles,” Dinges says.

How much is enough

No magic number exists for the amount of sleep people need each night. The “normal” range includes as little as six hours (*SN: 9/12/09, p. 11*) and as much as 10 hours of sleep per night, depending on the person. But studies of various diseases show that sleeping about seven to eight hours each night carries the least risk of obesity, diabetes, heart disease and other illnesses.

Whatever the need for sleep is, many people don’t get enough. In fact, Americans are sleeping less than ever before, according to the National Sleep Foundation, which conducts periodic surveys of sleep habits. In 2009, 20 percent of survey participants said that they slept less than six hours on weeknights, compared with 12 percent in 1998. That lost sleep isn’t being recovered on weekends, either. On average, respondents in 2009 reported sleeping 7.1 hours on weekend nights, down from an average of 7.8 hours in 1998.

Humans are the only animals that

willingly deprive themselves of sleep, says Eve Van Cauter, a sleep researcher at the University of Chicago. “You can’t put a rat in front of the television, give him the remote and tell him, ‘you have to stay awake,’” she says.

People think that they are just too busy to bother with sleep. “We are ignoring that sleep, like exercise and proper feeding, is crucial for health,” Van Cauter says.

Those respondents who slept less than six hours a night were also less likely than people who slept eight hours or more to say that they work well and efficiently, eat healthy diets, engage in leisure activities, exercise or have sex. Short-sleepers also were more likely to smoke, drink caffeinated beverages and eat high-sugar or high-carbohydrate foods.

An analysis of several population studies worldwide showed that children who sleep less than 10 hours a night are nearly twice as likely to be obese compared with children who slept more than 10 hours. The study, published last year in *Sleep*, also showed that short-sleeping adults (those who got less than five hours of sleep per night) were more likely to be obese, with body mass index increasing with each hour of lost sleep.

Some data suggest that people who sleep far more than average are also at risk for health problems. Both short- and long-sleepers were more likely to have symptoms of “the metabolic syndrome,” a cluster of conditions — including high blood pressure, high cholesterol levels and reduced sensitivity to insulin — that presage diabetes and heart disease.

Among people who get seven to eight hours of sleep each night, only 17 percent had such symptoms, researchers from the University of Pittsburgh and collaborators reported last year in *Sleep*. But almost a quarter of people regularly sleeping more than eight hours a night had the symptoms, and nearly a third of those getting less than six hours of sleep nightly did too, the researchers reported.

Both short- and long-sleepers were also at higher risk for diabetes than people who sleep seven hours on average, shows another study led by researchers

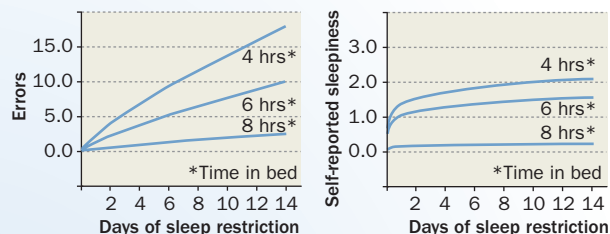
Effects of sleep deprivation

Losing sleep, even for one night, can trigger a flood of changes throughout the body. Scientists don't fully understand how the sleep-starved body goes awry, but many studies find clear relationships between sleep and the health and function of body systems.

Brain

Cognitive impairment, declines in memory and judgment, and brain chemical changes that can lead to depression

Attention and sleep



People's performance on an attention test declines with sleep loss (left), even though they don't feel much sleepier (right). SOURCE: VAN DONGEN ET AL./SLEEP 2003

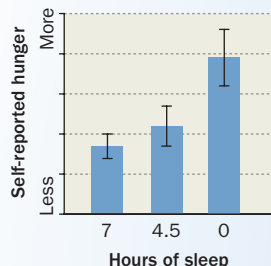
Thymus

Immune system impairment

Stomach

Increased hunger

Hunger and sleep



SOURCE: SCHMID ET AL./J. SLEEP RESEARCH 2008

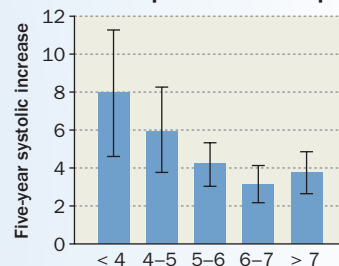
Pancreas

Insulin resistance and higher risk of type 2 diabetes

Heart

Higher disease risk, irregular heart beat

Blood pressure and sleep

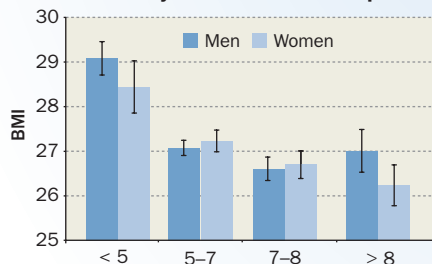


SOURCE: KNUTSON ET AL./ARCHIVES OF INTERNAL MEDICINE 2009

Fat layer

Increased risk of obesity

Body mass index and sleep



SOURCE: PATEL ET AL./INTERNATIONAL JOURNAL OF OBESITY 2009

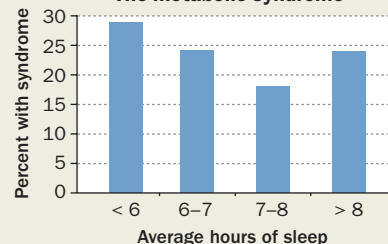
Joints

Increased inflammation, which can lead to atherosclerosis (artery hardening) and rheumatoid arthritis

Metabolism

Higher risk of "the metabolic syndrome," which includes high blood pressure and cholesterol and reduced insulin sensitivity, sometimes leading to diabetes and heart disease

The metabolic syndrome



SOURCE: HALL ET AL./SLEEP 2008

Muscle

Decreased reaction time and accuracy

at Columbia University and published in *Sleep* in 2007.

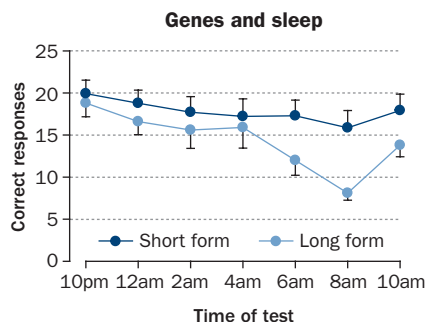
Most people are fooling themselves if they think they need less sleep than average, Van Cauter says. A study of healthy young adults, published in 2005 in *Sleep*, seems to back her up. Volunteers were given the opportunity to get some extra shut-eye for three days in a study conducted by researchers at Harvard Medical School in Boston and the University of Surrey in Guildford, England. Everybody slept more the first day of the study, but by day three, people who normally sleep more than nine hours a day had maxed out their sleep. People who normally slept less continued to catch extra z's. The researchers concluded that people with shorter sleep times probably carry a bigger sleep debt than others, one that couldn't be paid back in three days.

Sleeping in your genes

Researchers would dearly love to know what makes people like Heather resistant to the attention-degrading effects of sleep loss. (Though scientists don't know whether these people's bodies hold up against sleep deprivation as well as their brains do.) Studies of twins suggest that a large part of the resistance is genetic: Identical twins' responses to sleep deprivation are as similar to each other as an individual's results in repeated tests.

Previously, researchers reported that a gene called PERIOD3, or *PER3*, might be involved in the response to sleep deprivation.

Wake up, sleepy gene Despite being "morning people," those with a long form of the *PER3* gene perform worse on memory tasks when sleepy than people with the short form.



SOURCE: J.A. GROEGER ET AL./SLEEP 2008

Sleeping about seven to eight hours per night carries the least risk of obesity, diabetes, heart disease and other illnesses. Whatever the need for sleep is, many people are not getting enough.

variation (*SN*: 3/24/2007, p. 190). *PER3*, a cousin of genes involved in the circadian clock, which governs daily body rhythms including meal times and bedtimes, comes in two common forms. The more common form contains four repeats of a segment of the gene, and a less-common variant contains five repeats of that segment. People who have inherited two copies of the longer form tend to be morning people, while people with two copies of the shorter form tend to be night owls.

When their circadian alertness level was at its lowest daily point, sleep-deprived people with the long form performed worse on some tasks than people with the short gene, researchers led by Derk-Jan Dijk at the University of Surrey reported in 2008 in *Sleep*. Many researchers interpret that result to mean that the long form of the gene makes people more vulnerable to sleep deprivation.

But people with different forms of the *PER3* gene didn't show any differences in responses to partial sleep deprivation over five nights in a study by Dinges and colleagues published online June 11 in *PLoS ONE*. The two results can't be directly compared, because the volunteers in Dinges' study were asleep during the time of day that the Surrey group found differences in performance. So the jury is still out on whether *PER3* protects some people against the effects of sleep deprivation, and researchers are hunting for other genes that may contribute to differences in sensitivity to sleep loss.

No snooze, you lose

All the consequences for chronically missing out on slumber aren't yet known, but some studies suggest sleeping too little for too long can change the brain. In a study in rats, Meerlo examined serotonin — a brain chemical thought to be important in sleep, depression and

many brain functions. The researchers didn't find any changes in the rats' brains after a single night of sleep loss, but after a week of getting shortchanged, the rats' brains became less sensitive to serotonin. Such changes could make rats, and people, more prone to developing depression, Meerlo says.

As bad as that news potentially is, Meerlo has worse news. Even after he let the rats sleep in on the weekend, their brains still didn't respond to serotonin as effectively as before sleep deprivation, Meerlo and his colleagues reported last year in *Sleep*.

Even more disturbing is the finding from a study of sleep deprivation in rats conducted by researchers at Northwestern University in Evanston, Ill. The researchers found that rats deprived of about 35 hours of sleep over five days — an extreme sleep loss — didn't make up that lost sleep when given three days to do nothing but sleep. The result, reported in the *Proceedings of the National Academy of Sciences* in 2007, suggests that chronic sleep loss may actually prevent the body from sleeping more to recover.

"That would limit your ability to make up your sleep debt," Van Cauter says.

And sleep deficit is a debt you can't afford, Meerlo says. "One night of missed sleep isn't going to kill you," he says, "but the danger is that if you're not getting enough sleep night after night, small cumulative effects could add up."

So while you may be dying to stay up one more hour to finish reading that chapter or reach one more level on that video game, researchers say that in the long run, you could be inching closer to a state of permanent rest. ■

Explore more

■ The National Sleep Foundation's 2009 Sleep in America Poll: <http://bit.ly/18Wpld>