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
Find a list of scientific references or download a PDF of the entire special section at www.sciencenews.org/sleep
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.
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 junctions 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

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**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,
Schgal says. The study represents a grow-
ing 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 Washing-
ton 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 ben-
efit 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, electrochem-
ically signaling neighbors, eventually
need to rest and recharge. Neural quiet
can spread through the brain as neu-
rons 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

**Breaking bonds**

But even sleep’s role in learning and
remembering evokes much dispute.
One controversial theory, for instance,
suggests that sleep, especially the pow-
erful slow-wave variety, weakens syn-
apses. 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 syn-
aptic homeostasis, is a sort of neuronal
version of survival of the fittest. As an
animal or person learns things through-
out the day, connections between neu-
rons get strengthened. All synapses are
weakened during sleep, so tenuous connec-
tions 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 pro-
tein drop when the animals sleep.

Studies in fruit flies show that snooz-
ing 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 depriva-
tion. Protein levels drop as flies slumber.

And while fruit flies sleep, they also lose
synapses formed during social interac-
tions, 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 num-
ber 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
tillens suggest the opposite. In kittens
with one eye sewed shut, connections
between the closed eye and the brain’s
visual centers weakened while the kitted
was awake, Marcos Frank of the Uni-
versity 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 pre-
serving 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.](https://www.sciencenews.org/biology/brain-reset-proteins-orange-help-forging-connections-between-neurons-build-up-brain-while-fly-is-awake-left-but-depleted-after-sleep-right-suggesting-sleep-prunes-neural-connections-perhaps-ensuring-only-day 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.

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 photosensitive 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
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 rememb-
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 stimuli 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.

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**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**

![Graph showing improvement in problem-solving skills after REM sleep and non-REM sleep.](source: ON ET AL./NHS 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.

**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’s immune boost**
Sleep and the immune system are intimately acquainted—immure 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 everywhere 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 long-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 evolve 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

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**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" don'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 Millus

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**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 3-5 hours (depends on season)**

During migration season, white-crowned sparrows perpex 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 mammalian 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.