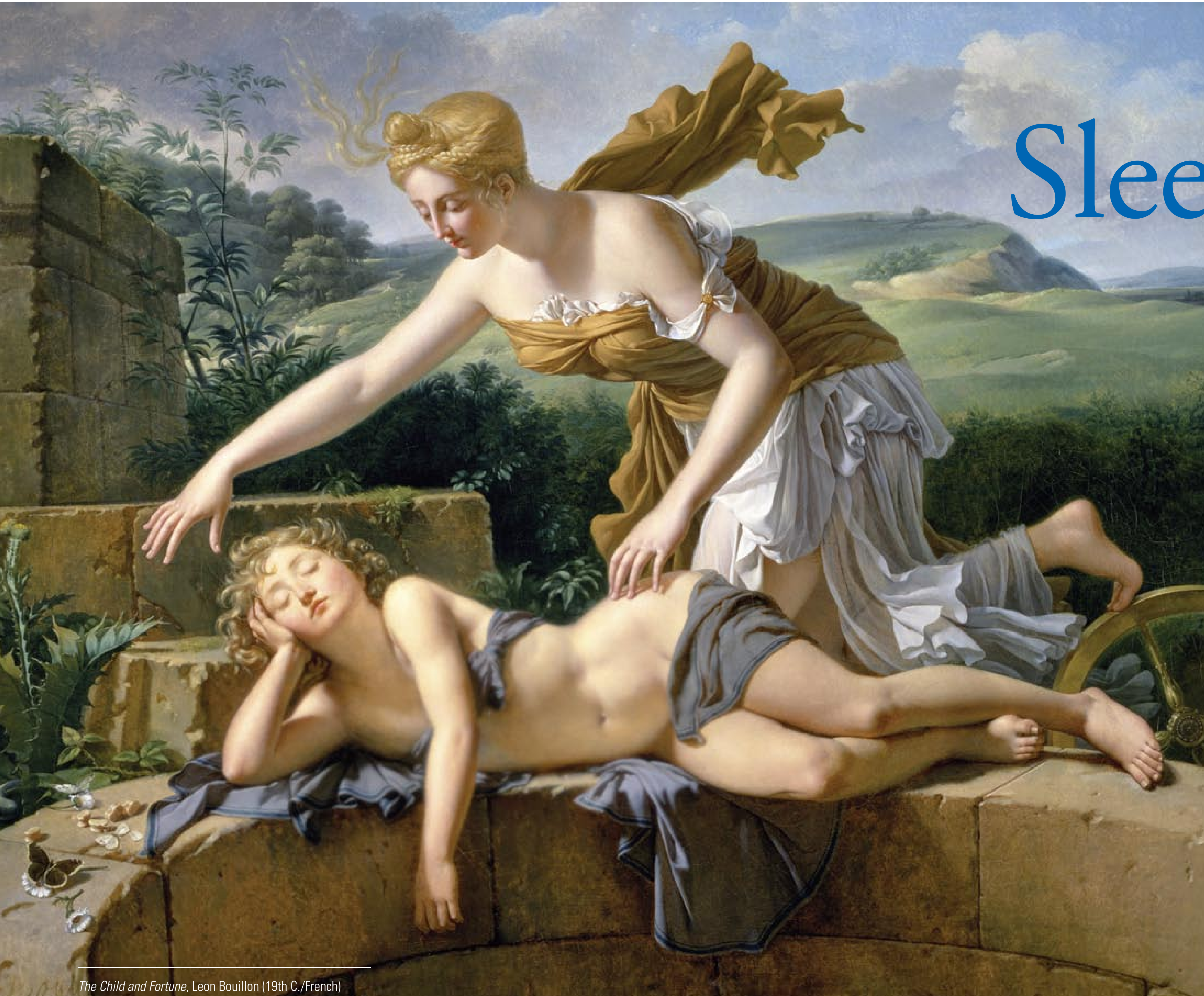
research report



The Child and Fortune, Leon Bouillon (19th C./French)

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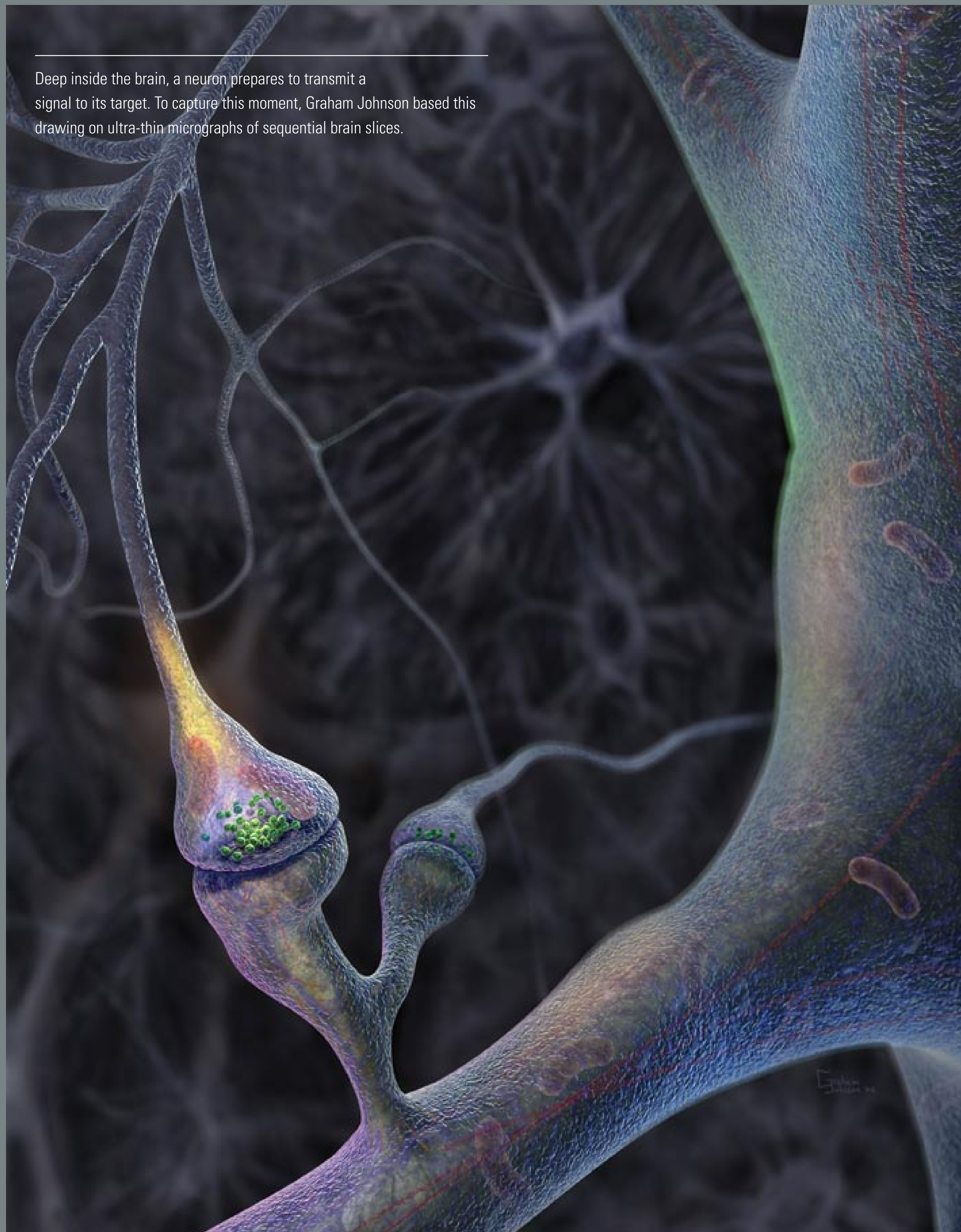
Sleep to Repair

"What probing deep Has ever solved the mystery of sleep?"
—Thomas Bailey Aldrich, *Human Ignorance*

The poet and novelist Thomas Bailey Aldrich died in 1907, just before the birth of modern sleep research. Since then, researchers have advanced the study of sleep with instruments such as electroencephalograms (EEGs), computerized axial tomography (CAT scans), and magnetic resonance imaging (MRI). Some have even begun to identify the molecular signals that accompany sleep and wakefulness. But Aldrich's words still ring true, and the basic question of why we sleep remains a mystery. There are many hypotheses that offer explanations for the purpose of sleep, but in the absence of a convincing way to test and compare them, no consensus has emerged.

SFI researchers Van Savage and Geoffrey West have narrowed down the quest for a sleep theory by extending their gaze beyond human beings or any single species. In a study published in the January 2007 issue of the *Proceedings of the National Academy of Sciences USA,* the researchers examined sleep times across 96 different mammals. They were able to test various hypotheses that connected sleep to functions in the body and/or brain, ruling out several with a thoughtful examination of sleep times, animal size, and metabolic rates. Having honed in on a quantitative connection between sleep times and the brain's metabolic rate, the pair put forth a theory that suggests sleep's primary function is to repair and reorganize the brain. The theory explains why a mouse sleeps 14 hours a day, an elephant sleeps less than four, and a human being falls in the middle with eight. It also provides a basis for further research into the nature of REM sleep, sleep and aging, and sleep times during development.



Deep inside the brain, a neuron prepares to transmit a signal to its target. To capture this moment, Graham Johnson based this drawing on ultra-thin micrographs of sequential brain slices.

GRAHAM JOHNSON MEDICAL MEDIA / WWW.FIVTH.COM

The idea for a cross-species sleep study came about when Van Savage was pondering biological time scales for animals of different sizes. He knew that most biological times, such as gestation and lifespan, increase in length for organisms of increasing size. Just to be sure, he went to check the data and found that sleep times didn't fit the pattern: they actually decrease for larger animals. "Sleep scales the opposite of everything else—it was a completely different pattern than you see for other biological times," Savage says. "So that made me fascinated from the perspective that it's different. It was really weird, and the more I got into it, the more I realized that sleep is a fascinating subject." Savage asked Geoffrey West, an expert in biological scaling and his advisor, to join the investigation, and they began to read up on sleep literature.

One of the better-known sleep hypotheses they encountered holds that sleep gives rest to the body and brain. This idea has been met with skepticism because sleeping doesn't conserve much energy. The metabolism only slows 10 to 15 percent during sleep, and for humans, the energy saved from eight hours of sleep versus eight hours of sedentary wakefulness is roughly equivalent to the number of calories in a dinner roll.

Another hypothesis says that sleep protects the brain from overheating. The idea was first propounded by Hippocrates around 400 BC, and while thermoregulatory theories have few living advocates of note, they still crop up in lists of potential explanations for sleep. Savage and West elegantly debunked the heating and cooling theory on the grounds that it didn't account for the drastically different sleep times observed in different animals. They speculated that if the theory were true, heating and cooling rates would depend on metabolism (which heats the brain) and brain size (the amount of brain being heated). Because both bear the same relation to body mass, then the ratio between them remains constant for all animals. The thermoregulatory theory would predict that the amount of waking time, in which the metabolism would heat the brain, and sleeping time, in which the brain would cool, would remain constant for all mammals. Since the prediction flatly contradicted the observed differences in sleep times across species, Savage and West crossed the thermoregulatory sleep theory off their list.

Yet another sleep hypothesis holds that sleep's function is to repair damage in the body and/or brain. Cellular damage is a secondary effect of metabolism, which slowly harms the very cells it keeps alive. When a cell produces energy, it also releases free radicals—the infamous molecules that age cells and damage DNA. To find out whether sleep might serve to repair the damage wrought by metabolism, Savage and West looked at metabolic rates across species. According to Savage, one of the well-known facts of biological scaling is that "smaller and hotter" animals generally live life at a faster pace than "larger and colder" ones. Rodents have quicker metabolisms than primates, which have quicker metabolisms than pachyderms. And since sleep times scale in reverse (pachyderms sleep less than primates, etc.), the researchers surmised that the amount of sleep an animal requires might well be dictated by some secondary effect of metabolism, such as the need for repair.

> "O peaceful Sleep! until from pain released
> I breathe again uninterrupted breath!
> Ah, with what subtile meaning did the Greek
> Call thee the lesser mystery at the feast
> Whereof the greater mystery is death!"
> —*Henry Wadsworth Longfellow*

But how to tell if the repair occurs at the level of the body or the brain? The brain seemed a likelier candidate than the body because neurons, unlike other cells, are not replaced when they die. It seemed reasonable, then, that the body would

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Hibernating dormouse (*Muscardinus avellanarius*) curled up asleep in nest, Sussex, UK.

quickly and have more sensory input in a given period of time than do large and slow ones. Because processing this sensory input might require sleep, neural reorganization fits the metabolic sleep theory just as well as neural repair. In the end, Savage and West did not choose between repair and reorganization. They suspect that sleep may serve a dual function. "A certain amount of your metabolic energy goes into repair, a certain amount goes into reorganization," West says. "At the level at which the theory was developed, it does not distinguish the proportion."

Yet another intriguing finding that fell out of the research was that the fraction of time spent in rapid eye movement (REM) sleep is independent of body mass. Elephants sleep less than mice, but devote the same percentage of their total sleep time to REM sleep. "We argue that total sleep time is this effect of metabolism that you have to respond to in some way," Savage says. "But then there's REM sleep and it's not clear if it's repair and reorganization or something else." Savage is now looking for clues about the function of REM by studying sleep times in babies, who sleep more than adults and spend a greater proportion of their sleep time in REM.

West points out that the study could also provide a framework for further research into the connection between sleep and aging, both of which tie into metabolism. "People my age seem to sleep less and I don't know why that is," West says. "I'm sure there are people studying it, but I'm not sure anyone understands why that should be. Now when you get really old, you do sleep more like cats, for 15 hours a day. There are a million reasons people sleep for longer times and there are all sorts of factors that are neglected, so this study forms a baseline for trying to discover what those factors are."—*Jenna Beck* ◀

invest in a daily repair process for the precious cells, and that such a brain-level process might require unconsciousness. The researchers' quantitative tip-off to the connection between sleep and the brain was that sleep times, which generally decrease as body size increases, tended to scale to brain size rather than body size. A horse is 10,000 times larger than a mouse, but its brain is only 1,000 times larger. And while a horse sleeps less than a mouse, its nightly sleep time is not 10,000 times shorter. Savage and West calculated a mass-specific brain metabolic rate: a rate that, when coupled with an animal's brain size, would predict the amount of time the animal devoted to sleep. The rate they calculated fit with rough empirical measurements of brain metabolic rates, so the brain-level repair hypothesis was still in the running.

Though the researchers had traced sleep's primary function to the brain, they didn't have evidence that the process was repair per se. Another of sleep's functions could be processing memories of the waking day. This cortical reorganization might also be governed by metabolism, because small animals with fast metabolisms move more

A History of Sleep Research

Ca 350 BC—Aristotle wrote that sleep results from warm vapors rising from the digestive tract.

Ca 400 BC—In the *Corpus Hippocratum,* Hippocrates hypothesized that sleep protects the brain from overheating.

1907—French scientists Rene Legendre and Henri Pieron kept dogs awake for several days and extracted a toxin from their blood serum. When they injected the toxin of the sleep-deprived dogs into healthy dogs, the recipients were induced to sleep. The book that the researchers published in the wake of the experiment laid out a scientific approach to the study of sleep, and is generally thought to be the foundational text of modern sleep research.

1929—Constantin Von Economo, a doctor who treated encephalitis lethargica patients in the wake of the 1918 flu, observed that patients who suffered brain damage in the hypothalamus and preoptic area, succumbed to long periods of sleep and unconsciousness. He posited that sleep is regulated by a specific location in the brain.

1929—Hans Berger, a German professor of neurology and psychiatry, recorded his son's brain waves by attaching wires to the boy's scalp. He published a report on the "Elektrenkephalogramm," or "electroencephalogram" (EEG) in English.

1935—Alfred Loomis used the electroencephalogram to detect different patterns in the brain activity of sleeping persons, hypothesizing that the various EEG patterns corresponded to various states of consciousness.

1953—The "Father of American Sleep Research," Nathaniel Kleitman, and his student Eugene Aserinsky reported in the journal *Science* that rapid eye movement (REM) occurs during sleep. To accompany their EEG measurements, the researchers devised an electro-oculogram (EOG) to record changes in electrical activity, hence, in movement, around the eyes.

1958—William C. Dement, another of Kleitman's students, connected REM sleep to dreaming and found that both cats and humans sleep in REM and non-rapid eye movement (NREM) stages. Scientists would later discover that almost all mammals have REM sleep. (It was once thought that platypuses and dolphins did not have REM sleep. The notion was contradicted for platypuses in 1999, when a group of researchers constructed an elaborate platypusarium and discovered that platypuses actually have more REM sleep than any other mammals. It is now thought that dolphins may spend a very small fraction of their sleep time in REM.)

1967—Michel Jouvet advanced the modern biochemistry of sleep with the observation that the sleep stages in cats depend on the presence of a neurotransmitter. Jouvet also located the area in the brainstem wherein neurons regulate REM and NREM sleep stages.

1968—Allan Rechtschaffen and Anthony Kales published a standardized method for interpreting EEG recordings.

1974—Harold Zepelin and Rechtschaffen published sleep times in different mammalian species, mostly observed in zoos and laboratories.

1979—An analysis of data from the American Cancer Society found that people who slept less than four, or more than ten hours per night had shorter life expectancies. The results were confirmed with a follow-up study between 1982 and 1988.

1989—By experimenting on rats, Rechtschaffen and colleagues concluded that sleep deprivation leads to death in two to three weeks. Deprivation of either REM or NREM sleep killed the rodents over a slightly longer time span. Today there are over 200 sleep centers and laboratories in the United States. A mass of experimental evidence documents the cognitive and physiological effects of sleep deprivation, and there is a widespread effort to research sleep disorders such as narcolepsy, insomnia, and sleep apnea. Researchers have shown that sleep is essential for some forms of learning and processing memories, and they continue to explore the nature of dreams and cognition during sleep.—*Jenna Beck*