

NEUROSCIENCE

SLEEP ON IT!

Your nightly rest turns out to affect your mind and health more than anyone suspected

By Robert Stickgold

“Do I really need to sleep?” As I travel around the world talking about sleep, I am asked this question over and over. The answer has always been clear—yes, everyone needs to do it. Just like hunger, thirst and sexual desire, the urge to sleep is a physiological drive. Exactly what spending a third of our lives unconscious gets us, however, has long mystified scientists.

In acknowledging our lack of an answer, Allan Rechtschaffen, one of the world’s foremost sleep researchers, said in 1978, “If sleep does not serve an absolutely vital function, then it is the *biggest mistake* the evolutionary process has ever made” (emphasis mine). In the 1990s J. Allan Hobson, another leading sleep researcher, quipped that the only known function of sleep was to cure sleepiness.

Research over the past 20 years has finally begun to provide at least a partial explanation for why we must sleep. The clearest finding is that sleep does not serve just a single purpose. Instead it appears to be needed for the optimal functioning of a multitude of biological processes—from the inner workings of the immune system to proper hormonal balance, to emotional and psychiatric health, to learning and memory, to the clearance of toxins from the brain. At the same time, none of these functions fails completely in the absence of sleep. In general, sleep seems to *enhance* the performance of these systems instead of being absolutely necessary. And yet anyone who lives for months without sleep will die.

Even this imperfect understanding has taken decades to develop. By the end of the 20th century researchers had replaced ancient notions about sleep—that it was caused by blood retreating from the surface of the skin or by the buildup of warm vapors from the stomach—with detailed measurements of brain-wave activity, breathing patterns, and daily oscillations in the amount of hormones and other molecules in the blood. More recently, investigators have begun identifying the exact aspects of sleep that are important for each of its benefits. Ironically, though, the more researchers uncover about the unconditional necessity of a good night's sleep for the proper functioning of mind and body, the less time 21st-century citizens spend in the soothing arms of Morpheus, the Greek god of dreams.

FATAL INSOMNIA

THE clearest evidence of our absolute need for sleep comes from a study published in 1989 by Carol Everson when she was working in Rechtschaffen's laboratory. Everson, now at the Medical College of Wisconsin, found that rats totally deprived of sleep all died within a month. In actuality, all she had to do to achieve this fatal result was to prevent the animals from entering the stage of sleep characterized by rapid eye movement (REM). But a quarter of a century later researchers still cannot explain *why* the rats died. A series of experiments in the intervening years has only served to eliminate possible causes; it is not caused by, for example, increased stress, excessive energy consumption, or failure of the body's internal heat regulators or the immune system.

Death by sleep deprivation is not unique to rats. Fatal familial insomnia, first described about 30 years ago, is, as the name suggests, a heritable human disorder that leads first to unremitting insomnia and thence to death. A team of Italian researchers, then at the University of Bologna's medical school, reported it in 1986. The group, led by Elio Lugaresi and Rossella Medori, told the story of a 53-year-old man who died within months of developing intractable insomnia—as had many of his relatives over two generations. Postmortem analysis of his brain showed massive loss of nerve cells in two regions of the thalamus, a structure about the size of a walnut that is found in the midbrain and generally acts as a way station for incoming sensory input. The two particular regions in question, however, are known more for their role in regulating emotional memory and producing so-called sleep spindles, a key pattern of waves found in electroencephalograms of the sleeping brain.

How this deterioration in the thalamus might lead either to insomnia or to death is unclear. But the immediate cause of the damage itself is now known. In the early 1990s Medori, by then at Case Western Reserve University, and her colleagues determined that a malformed protein, called a prion, was responsible for the destruction. Prions are also known to cause scrapie in sheep and bovine spongiform encephalopathy (“mad cow disease”) in hu-

Robert Stickgold is director of the Center for Sleep and Cognition at Beth Israel Deaconess Medical Center and an associate professor at Harvard Medical School.



mans—though in the case of fatal familial insomnia, the prion is inherited from one generation to the next rather than being ingested from the environment, as in the other two ailments.

Fortunately, there are no other reported instances of human death caused by sleep deprivation (aside from accidental deaths when, for example, a sleepless driver falls asleep at the wheel). But there are also no other reports of people going several months without sleep. We are thus left with two examples of prolonged and total sleep deprivation leading to death—experimentally induced sleep deprivation in rats and a heritable prion disease in humans—and with no understanding of the exact cause of death in either case.

ANTIBODIES AND HORMONES

MEANWHILE WE DO KNOW that as little as one night of complete or even partial sleep loss can interfere with various bodily functions, such as hormonal activity and protection against infections. Two studies looking at the body's response to immunization with hepatitis vaccines show how dramatic the effects of sleep deprivation can be on the immune system. In the first experiment, from 2003, a small group of college students received a standard hepatitis A vaccination consisting of inactivated virus in the morning, after which investigators permitted half of them to sleep normally; the other half were kept awake all night.

The sleep-deprived subjects were not allowed any sleep until the following night. Four weeks later researchers took blood samples from the students and measured the amount of protective antibodies that their immune system had produced in response to the virus in the vaccine. Higher levels of antibodies would indicate a better response to the vaccine and thus likely greater protection against future infection with disease-causing versions of the virus. After the four weeks, the group that had enjoyed a normal night's sleep had 97 percent higher antibody levels than the one that had been sleep-deprived.

Negative effects are measurable with less than a full night's sleep as well. In the second study, adults received the standard three doses of hepatitis B vaccine over the course of six months. (Repeat vaccination is required to build up full immune protection.) Researchers gave each participant a motion detector similar to a watch, which monitored their sleep at home. By com-

IN BRIEF

Many studies—not to mention common experience—support the link between a good night's sleep and improved mood, memory and learning.

A growing number of experiments carried out over the past two decades have also found that the mechanism of sleep directly affects other workings

of the body, from hormonal balance to immune protection.

Despite these findings, researchers still do not understand exactly why we

need our daily visit to the land of Nod, but they are learning a great deal about what precisely happens when we sleep.

paring the subjects' average amount of sleep during the week of their first shot to the level of antibody protection they displayed after the second shot, investigators determined that antibody levels increased 56 percent for every additional hour of sleep. Six months after the final vaccination, those who had averaged less than six hours of sleep a night during the week around the first vaccination were seven times more likely to have such low amounts of antibodies in their blood that they were considered unprotected against future infection with the hepatitis B virus.

Impressive evidence for impaired hormonal function came from a series of studies performed by Karine Spiegel, who was at that time working with Eve Van Cauter of the University of Chicago. In one of these experiments, researchers allowed 11 healthy young men to get just four hours of sleep a night. After five nights of restricted sleep, the men's ability to clear glucose from the blood—a process that the hormone insulin manages—was reduced by 40 percent. In a separate study, Spiegel and her colleagues similarly limited the amount of sleep of 12 men for two nights. The scientists measured the amount of ghrelin, an appetite-stimulating hormone, found in the volunteers' blood and found it had jumped by 28 percent. At the same time, amounts of a different hormone, known as leptin, decreased by 18 percent; leptin inhibits hunger by signaling the brain that there is no need to eat. Not surprisingly, the sleep-deprived men reported an average 23 percent increase in their hunger levels.

Taken as a whole, these studies of human physiology suggest that reduced sleep could lead to increased weight gain—a hypothesis that is now supported by at least 50 other studies. In several of the investigations, children from six to nine years of age who got fewer than 10 hours of sleep were one and a half to two and a half times more likely to be obese, and studies in adults suggest a 50 percent increase in obesity among participants with fewer than six hours of sleep. Research also shows an association between sleep restriction and the development of type 2 diabetes.

NEGATIVITY BOMB

DESPITE THE REMARKABLE EFFECTS of restricted sleep on immune and hormonal function, its greatest impact probably occurs in the brain. In a 2006 study I conducted with Matthew P. Walker, now at the University of California, Berkeley, we looked at how a single night of sleep deprivation affected the emotional memories that people laid down. Twenty-six subjects—half of whom had been sleep-deprived the night before—were shown positive, negative and neutral words (for example, “calm,” “grief” or “willow”) and asked to rate their emotionality. Then, after two nights of recovery sleep, they were given a surprise memory test.

Compared with the subjects who had slept normally, those who were sleep-deprived before

seeing the words for the first time showed a 40 percent deterioration in their ability to recognize them. But more striking was the relative impact of sleep deprivation on the three categories of words. When subjects were sleep-deprived, their recognition of positive and neutral words both deteriorated by 50 percent. Their ability to recognize words with negative connotations, however, deteriorated only 20 percent. In contrast, the memory formed after normal sleep for positive and negative words differed little, with neutral words being less memorable than either positive or negative words. In other words, the memory of negative words appeared to be at least twice as strong as positive or neutral words after study volunteers were forced to cut back on their sleep.

FINDINGS

Don't Skimp on Sleep

Research has uncovered many ways that sleep deprivation impairs mental and physical health. Some of the best-studied and most significant impacts are highlighted below.

Central Nervous System

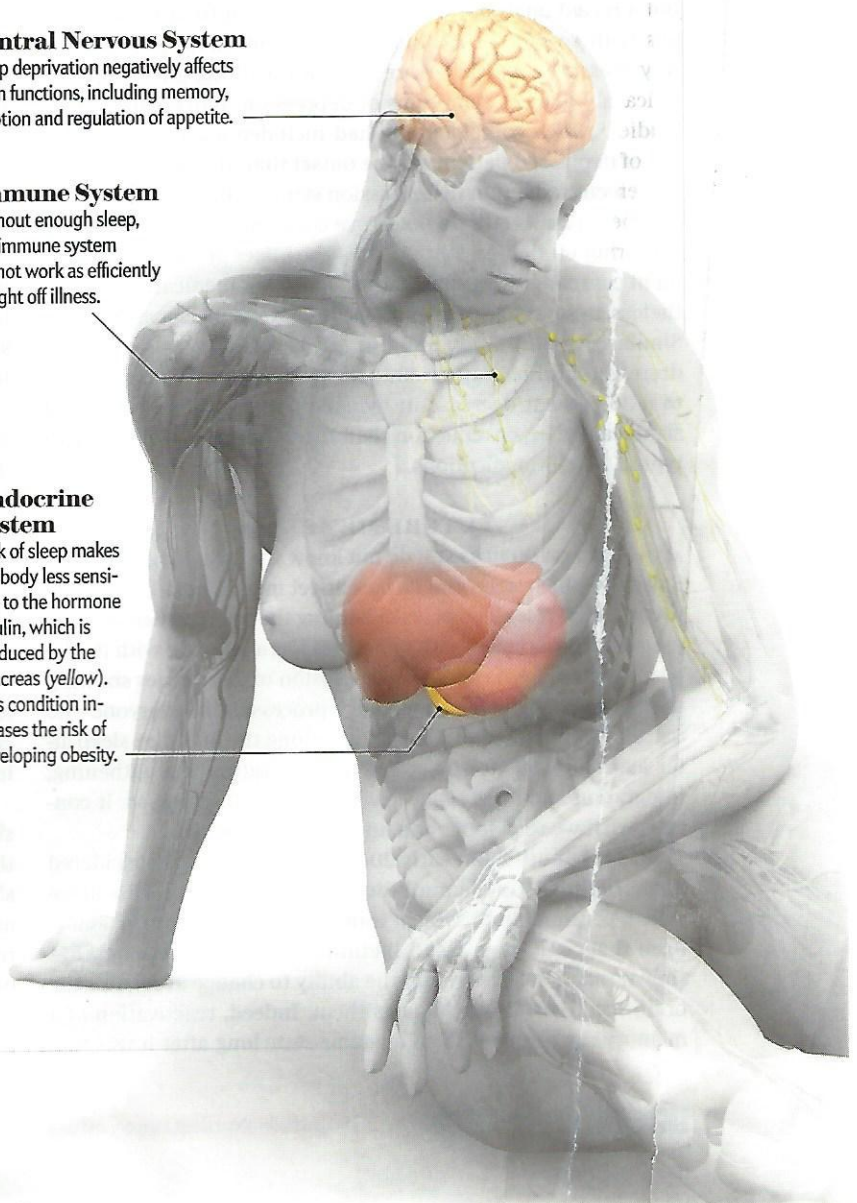
Sleep deprivation negatively affects brain functions, including memory, emotion and regulation of appetite.

Immune System

Without enough sleep, the immune system cannot work as efficiently to fight off illness.

Endocrine System

Lack of sleep makes the body less sensitive to the hormone insulin, which is produced by the pancreas (yellow). This condition increases the risk of developing obesity.



This result suggests the rather horrifying possibility that when you are sleep-deprived, you effectively form twice as many memories of negative events in your life as of positive events, producing a biased—and potentially depressing—memory of your day. Indeed, several studies over the past 25 years have now concluded that poor sleep can, under certain circumstances, lead to depression severe enough to be diagnosed as major depression and may contribute to other psychiatric disorders as well.

The evidence of a causal link with depression in particular has grown significantly in recent years and comes to a large extent from studies of sleep apnea, a disorder in which the flow of air into the lungs becomes interrupted during sleep. It may lead to snoring, gasping and other disruptions of respiration. Each time individuals with sleep apnea briefly stop breathing, they awaken momentarily to start breathing again. As a result, sufferers of severe apnea might wake up every minute or two throughout the night. A 2012 study by the U.S. Centers for Disease Control and Prevention found that men and women with a diagnosis of sleep apnea are, respectively, 2.4 and 5.2 times more likely to have major depression compared with their better-rested counterparts.

Of course, finding a correlation between these two conditions is not the same thing as proving that one causes the other. But a recent analysis of 19 studies found that treating sleep apnea with so-called CPAP devices (for *continuous positive airway pressure*), which restore normal breathing and sleep, significantly reduces symptoms of depression. Indeed, one of the studies, which coincidentally had included a greater percentage of depressed patients at the outset than the others, found a 26 percent reduction in depression symptoms in CPAP users.

These results still do not prove conclusively that fitful sleep can bring on depression, nor was the effect of the CPAP treatment compared with that of antidepressant medication. Nevertheless, these suggestive findings deserve further investigation. Similarly, a 2007 study found that treatment of apnea in children who also had attention-deficit/hyperactivity disorder led to a 36 percent decrease in hyperactivity symptom ratings—a significantly larger reduction than the 24 percent achieved with typical ADHD medications.

FUTURE MEMORIES

ALTHOUGH RESEARCHERS still do not know the physiological mechanism by which sleep and its lack affect mental health, they suspect that the role sleep plays in helping the brain transform people's daily experiences into memories has a lot to do with it. The past two decades have seen an explosion of discoveries showing that sleep participates in memory processing in everyone—no matter what their emotional state. Among the findings: sleep after learning leads to the selective stabilization, strengthening, integration and analysis of new memories. In doing so, it controls what we remember and how we remember it.

In the late 19th and early 20th century scientists considered memories to be fragile until they went through a process of so-called consolidation, which transformed them into a stable form that could then last a lifetime. More recent research has shown that memories retain the ability to change even after the brain records and consolidates them. Indeed, reactivation of a memory can return it to an unstable state long after it was first

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formed, requiring reconsolidation; while in this labile form, it can be changed or lost altogether. This finding is both a curse and a blessing—a curse because originally accurate information can be corrupted and a blessing because inaccurate information can be corrected. Researchers have thus begun to talk about memory *evolution* instead of memory consolidation, especially when discussing sleep-dependent memory processing.

The modern era of research into sleep and memory began just over 20 years ago, when Avi Karni and his colleagues in Israel demonstrated that subjects trained on a visual discrimination task actually improved over a night of sleep but only if they were allowed to enter REM sleep. (As an aside, most dreams take place during REM sleep.) Their experiment showed that sleep does more than just stabilize memories, keeping them from deteriorating over time; it actually improves them.

In 2000 Walker came into my office waving a journal article and predicting, “This one is sleep-dependent, too!” The paper described a task in which subjects learned to tap out a particular sequence of finger movements, which became easier for them to do over time, even without additional practice. Still, the authors had not looked at how sleep might contribute to this improvement. Within two weeks Walker had the answer. He found that sleep had indeed improved their performance, and he later determined that the benefit depended on experiencing a light stage of non-REM sleep rather than on REM sleep, as in the Karni vision experiments. The inescapable conclusion: the brain strengthens different types of memories during different stages of sleep.

Further research showed that not all memories undergo this sleep-dependent stabilization. In 2008 Jessica Payne, now at the University of Notre Dame, conducted a study in which she showed volunteers various scenes with aversive objects—such as a dead cat in the middle of a road. She found that after a night of sleep the subjects could accurately recognize the image of the dead cat, but they had forgotten the background street scene. What was most impressive was that this selective forgetting of the background details did not happen when she trained

subjects in the morning and then tested them in the evening after a day spent awake. And it did not happen if the central image was nonaversive—for example, if it was just a cat crossing the road. Thus, sleep, but not wakefulness, caused the brains of the study participants to retain the highly emotional central images in preference to either the neutral images (cat crossing the road) or their background scenes.

But it is not just emotional memories that are preferentially enhanced during sleep. It appears that anything you think is important will be selectively retained while you are asleep. Two groups in Europe have shown that telling subjects who have been trained on a particular task that they will or will not be tested on that information after they sleep affects what happens during that sleep. As you might expect, only the information that subjects are told they will be retested on shows improvement the next day. In contrast, when subjects are trained in the morning, informing them that they will or will not be tested that evening does not seem to make any difference. Sleep, then, and not wakefulness, selectively strengthens memories that our brain deems valuable.

These findings provide elegant support for the arguments of Daniel Schacter of Harvard University that memory is about the future, not about the past. He has argued that we have evolved memory systems not so we can reminisce about the past but so we can use prior experience to enhance our future performance. In this context, it is not surprising that sleep seems to care most about information that is likely to be of future relevance. When we talk about sleeping on a problem, we are not merely asking the sleeping brain to remember something. We want our brain to take the information that is already stored there and do some kind of calculation, to juxtapose different possibilities, to find the best solution to a problem. Lucky for us, it can!

An example of this analytic ability is highlighted in a weather-prediction experiment developed by Barbara J. Knowlton and her colleagues at the University of California, Los Angeles. Knowlton showed subjects one or more cards from a set of four—each of which displayed a particular geometric design (circles, diamonds, squares or triangles). Before the subjects began the task, the researchers assigned each card to a particular imaginary weather outcome—rainy or sunny—without sharing the information with the participants. Then, based on the cards shown, investigators asked those participants to predict whether the cards indicated the weather would be rainy or sunny. Over time subjects got a sense of how the cards related to the weather. For example, the first trial might show the diamonds card, and the weather, the subjects are told, turns out to be sunny. Then, on the second trial, the circles and triangles cards are both displayed, and the weather turns out to be rainy. Even after just these two trials, subjects inevitably would begin to construct hypotheses about the relations, such as that diamonds mean sunshine. But then, on the third trial, the diamonds card might appear again, only to be followed by rain.

The trick here is that the cards are only *probabilistically* related to the weather. Thus, the diamonds card predicts sun 80 percent of the time, but for the other 20 percent, it is followed by rain. Other cards end up predicting sun just 20 to 60 percent of the time. In Knowlton's study, even after 200 trials, subjects still had not mastered the task, guessing the most likely outcome only about 75 percent of the time.

Use of such tasks has allowed researchers to discriminate between different memory systems within the brain—those involved in remembering facts (the “what” system) and those involved in learning skills (the “how” system). As subjects train on the weather-prediction task, they slowly shift from using the *what* system to the *how* system. When Ina Djonlagic in my lab asked what happens to this information with sleep, she obtained an amazing result. When volunteers who had trained in the morning were retested the same evening, they also performed at around 75 percent, apparently fully retaining the information they had learned that morning. But when other subjects were trained in the evening and tested after a night of sleep, they were 10 percent better at predicting the outcome than they had been the evening before. Somehow the sleeping brain was actually able to improve participants' understanding of the relation between the cards and the subsequent weather. They had gained a better model of how the world worked.

The more researchers explore what happens while we sleep, the more they discover new benefits to a good night's sleep. The most recent possible addition to the list is the clearance of waste products from the brain. In 2013 Lulu Xie and her colleagues at the University of Rochester Medical Center reported that the space between cells in the brain increases during sleep, allowing for better flow of cerebrospinal fluid between the brain and the spine. When the investigators injected beta-amyloid (the precursor of the amyloid plaques found between neurons in Alzheimer's disease) into mice, they found that it was cleared from the brain during sleep at twice the rate seen in awake animals. Presumably the increased flow of cerebrospinal fluid helped to move the potentially toxic molecule out of the brain, away from the areas where it could cause the most damage. Now researchers would like to find out whether the increased flow normally seen during sleep is impaired in people who have Alzheimer's.

Given all the latest research on the many functions of sleep and the likelihood that yet more will be discovered, skimping on sleep is looking like a worse and worse strategy for dealing with the demands of daily life. Taken together, the results of studies looking at the role of sleep in hormonal, immunological and memory functions suggest that if you do not get enough, you could—besides being very tired—wind up sick, overweight, forgetful and very blue. ■

MORE TO EXPLORE

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