

“It was literally true: I was going through life asleep. My body had no more feeling than a drowned corpse. My very existence, my life in the world, seemed like a hallucination. A strong wind would make me think my body was about to be blown to the end of the earth, to some land I had never seen or heard of, where my mind and body would separate forever.”

—From *Sleep*, by Haruki Murakami, 1989



PHYSIOLOGY

Sleeping While Awake

During microsleep, the entire brain nods off so briefly that we often don't notice it. Now research shows that individual neurons in the brain can slumber, too, especially when we are sleep-deprived



BY CHRISTOF KOCH

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We've all been there. You go to bed, close your eyes, blanket your mind and wait for consciousness to fade. A timeless interval later, you wake up, refreshed and ready to face the challenges of a new day (note how you can never catch yourself in the act of losing consciousness!). But sometimes your inner world does not

turn off—your mind remains hypervigilant. You toss and turn but can't find the blessed relief of sleep. The reasons for sleeplessness may be many, but the consequences are always the same: You are fatigued the following day, you feel sleepy, you nap. Attention wanders, your reaction time slows, you have less cognitive-emotional control. Fortunately, fatigue is reversible and disappears after a night or two of solid sleep.

We spend about one third of our lives in a state of repose, defined by relative behavioral immobility and reduced responsiveness to external stimuli. Cumu-

JON HAN (Illustration); SEAN McCABE (Koch)

lately, this amounts to several decades' worth of sleep over the lifetime of an average person. Ah, I know you're thinking, Wouldn't it be great if we cut down on this "wasted" time to be able to do more! When I was younger, I, too, lived by the motto "You can sleep when you're dead." But I've woken up to the fact that for optimal, long-term physical and mental health, we need sleep.

Humans share this need for daily sleep with all multicellular creatures, as anybody growing up with dogs, cats or other pets knows.

An understanding of sleep's importance can be observed by contemplating the biological process itself. Sleep is homeostatically regulated with exquisite precision: pressure to go to sleep builds up during the day until we feel sleepy in the evening, yawn continuously and nod off. If deprived of sleep, humans experience an ultimately irresistible need to seek repose—they, in fact, become "sleep drunk." An older, 19th-century term, closer to the truth, is "cerebral exhaustion," the brain demanding its rest.

In my last *Consciousness Redux* column, I described how clinicians define sleep by recording brain waves from a net of electroencephalogram (EEG) sensors placed on the scalp of the sleeper [see *photograph on next page*]. Like the surface of the sea, the electrical brain is ceaselessly in commotion, reflecting the unseen, tiny tremors in the cerebral cortex underneath the skull that are picked up by the EEG electrodes. Rapid eye movement (REM) sleep is characterized by low-voltage, choppy, swiftly changing brain waves (paradoxically, also typical of relaxed wakefulness), whereas non-REM sleep is marked by slowly rising and falling waves of larger amplitude. Indeed, the deeper and more restful the sleep, the slower and larger the waves that reflect the brain's idling, restorative activity. These voltage oscillations, referred to as delta waves, can be as slow as once every four seconds and

as fast as four times a second (that is, in the 0.25- to four-hertz frequency range). Tuning into the discharge of individual neurons during deep sleep reveals discrete off periods, when nerve cells cease generating any electrical activity for 300 to 400 milliseconds. Such recurring silent periods, synchronized across large

pants had 79 microsleep episodes per hour, lasting between 1.1 and 6.3 seconds apiece, with an attendant drop in performance. Microsleep shows up in the EEG record by a downward shift from activity dominated by the alpha band (8 to 13 Hz range) to oscillations in the theta band (4 to 7 Hz).

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parts of the cortex, are the cellular hallmark of deep sleep.

Microsleep

My last column, "To Sleep with Half a Brain," highlighted the growing realization of sleep researchers that being awake and asleep are not all-or-none phenomena. Just because you're asleep doesn't necessarily imply that your entire brain is asleep. Conversely, as I will describe now, we have also learned that even when you're awake, your entire brain may not be awake.

A case in point for sleep intruding into wakefulness involves brief episodes of sleep known as microsleep. These intervals can occur during any monotonous task, whether driving long distances across the country, listening to a speaker droning on or attending yet another never-ending departmental meeting. You're drowsy, your eyes get droopy, the eyelids close, your head repeatedly nods up and down and then snaps up: your consciousness lapses.

In one experiment attempting to explore this condition, participants had to track a randomly moving target on a computer monitor with a joystick for 50 minutes. While straightforward, this visuomotor task demands nonstop attention that becomes difficult to sustain after a while. Indeed, on average, partici-

Perniciously, subjects typically believe themselves to be alert all the time during microsleep without recalling any period of unconsciousness. This misapprehension can be perilous to someone in the driver's seat. Microsleep can be fatal when driving or operating machinery such as trains or airplanes, hour after tedious hour. During a microsleep episode, the entire brain briefly falls asleep, raising the question of whether bits and pieces of the brain can go to sleep by themselves, without the entire organ succumbing to slumber.

Indeed, Italian-born neuroscientists Chiara Cirelli and Giulio Tononi, who study sleep and consciousness at the University of Wisconsin–Madison, discovered "sleepy neurons" in experimental animals that showed no behavioral manifestation of sleep. In this research, 11 adult rats had microwires implanted into their frontal motor cortex, which controls movement. Inserted into the cortical tissue, the sensors picked up both the voltage called the local field potential (LFP), akin to the EEG, in addition to the spiking activity of nearby nerve cells. As expected, when awake, the LFP was dominated by low-amplitude, fast waves readily distinguishable from the larger and slower waves characteristic of non-REM deep sleep [see *box on page 23*].



The author, his head clad in a dense net of EEG sensors, participates in a sleep study in the laboratory of Chiara Cirelli and Giulio Tononi at the University of Wisconsin–Madison.

At the level of individual neurons, the awake animals' cortical cells chatted away in an irregular, staccato manner over an extended period. Conversely, during deep sleep, cortical neurons experienced pronounced “on” periods of neural activity and “off” times during which they are silent. This neuronal reticence occurs simultaneously all over the cortex. It alternates with regular on periods, leading to the rising and falling brain waves that are the hallmark of deep sleep.

Knowing all this, the researchers decided to probe further. Instead of letting the rats go to sleep at their usual bedtime, the experimentalists engaged the animals in a rodent version of late-night video gaming, continuously exposing them to toys and other objects to sniff, explore and play with. They tapped on the cage and otherwise prevented them from assuming a sleep posture or becoming drowsy. After four hours of such excitement, the rats could finally slumber.

As expected from previous animal and human studies, by the end of the sleep deprivation phase, the LFP began to shift to lower frequencies, compatible with the idea that the pressure for the animals to sleep steadily built up. Closer inspection of the electrical signatures, however, revealed something unexpected: occasional, sporadic, silent periods of all or most of the neurons in the recorded brain region [see box on opposite page] without the animals showing either behavioral or EEG manifestations of micro-sleep. These short, off-like episodes were often associated with slow waves in the LFP. The opposite happened during

recovery sleep, toward the end of this six-hour period, when the pressure to sleep had presumably abated. At this point, large and slow waves in the LFP became more infrequent, and neuronal activity turned more irregular, as it did during wakefulness.

It appears that when awake but sleep-deprived, neurons show signs of sleepi-

One question was whether any one neuron fell asleep independent of any other neuron. Or was this occurrence more of a global phenomenon, whereby all neurons simultaneously transition to an off period? The answer, obtained by implanting a second array of micro-wires into a second cortical region—the parietal cortex, a quite distinct region from the motor cortex—was “yes” to both questions.

That is, sometimes neurons in both regions went off together, whereas at other times they did so independently. Yet as the sleep pressure built up, after several hours of being kept awake, neuronal activity during sleep deprivation did become more globally synchronized (as it does in deep sleep). Likewise, the longer the animal slept during the recovery period, the less likely slow waves were simultaneously detected at both cortical sites. Groups of neurons can be more easily recruited to produce the slow oscillations that constitute deep sleep when sleep pressure is high.

These results paint a more nuanced view of wakefulness and sleep than the prevailing one, in which both conditions were considered to be global, all-or-none states of consciousness. Instead these data, buttressed by single-neuron recordings from patients with implanted microelectrodes, as used occasionally in epilepsy treatment, suggest that even

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ness, whereas after hours of solid sleep, individual neurons start waking up. Careful statistical analysis confirmed these trends: the number of off periods increased during the four hours the rats were forced to stay awake, and the opposite dynamic occurred during recovery sleep.

when the subject is awake, the individual's neurons can become tired and occasionally check out. The heavier the sleep pressure, the more likely this will happen simultaneously at many places in cortex. Conversely, after many hours of restful sleep, some of these neurons become de-

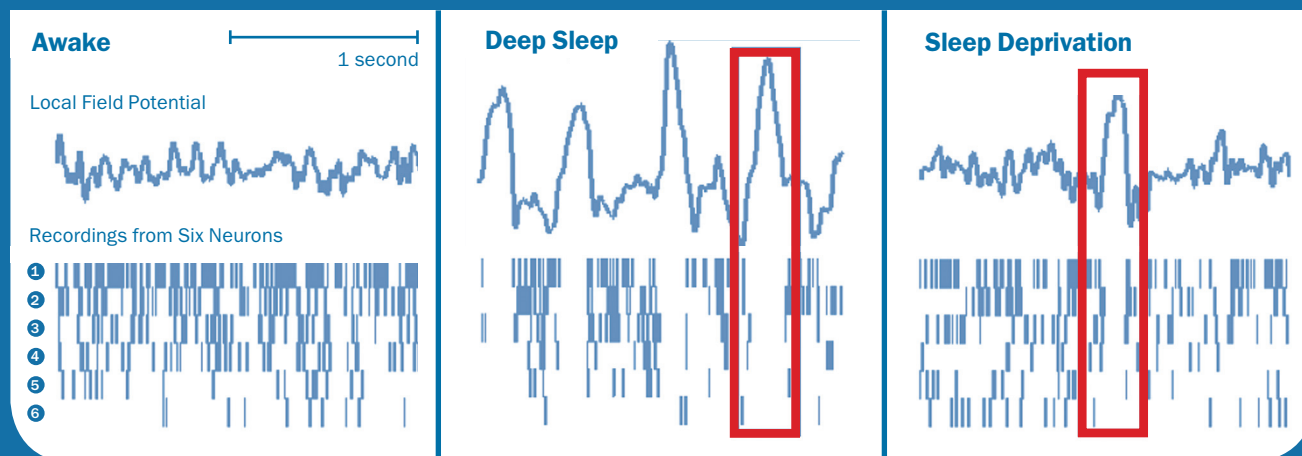
Partially Asleep

Brain studies in animals back the notion that a person could be partially asleep on the job after a late night, with no outward signs of weariness. Local field potential measurements—summed electrical activity of large populations

of nerve cells—show fast, low peaks present when an animal is awake (*left panel*) and slower, wider waves (*center*) during deep non-REM sleep (also called slow-wave sleep). But when an animal is coaxed to stay awake past its bedtime, parts of its brain can go to sleep (local sleep), with occasional sharp peaks in neural

activity akin to those registered during deep sleep (*right panel*).

The tick marks at the bottom show the activity of six closely spaced neurons—all of which periodically switch off during slow-wave sleep. The red boxes highlight the similarity between non-REM and local sleep.



coupled from these brain-wide oscillations and begin to wake up.

But with neurons going off-line during sleep deprivation, shouldn't there be some deterioration in performance? After all, these neurons must serve some purpose, and if they drowse, something ought to suffer. To investigate this question, Cirelli, Tononi and their collaborators trained the rats to reach with one of their front paws through a narrow opening to grasp a sugar pellet on a shelf. If done clumsily, the pellet falls off and cannot be retrieved anymore.

Learning this task engages a particular sector of the motor cortex that undergoes change as a consequence of training. Trawling for off periods while the animal reaches out for the sweets, the investigators found these gaps in neuronal firing are more likely to occur in the motor cortex a fraction of a second before a failed attempt to grab the pellet as compared with when the rat successfully picked up a sweet treat. Indeed, the occurrence of a single off period lowered the odds of a successful trial by more than a third. These effects were restrict-

ed to the motor cortex and were not seen in the parietal cortex, which is not engaged by the reaching task. As the animals became more sleep-deprived, their overall performance suffered, as is typical for sleep-deprived humans.

Local Slumber

What this study discovered is the existence of local sleep during sleep deprivation: isolated cortical groups of neurons that briefly go off-line while the animal, to all outward appearances, continues to move about and do what it does. Local shut-eye is more likely to occur if those neurons are actively engaged, as they are when learning to grab a sugar pellet. Neurons, too, become tired and disengaged, a microcosm of what happens to the whole organism.

Extrapolating from these data, it seems plausible that as the pressure for sleep increases, the frequency of these off events and their preponderance in the cortex increase until activity in the entire brain becomes suddenly but briefly synchronized and the brain falls into deep sleep—the eyes close, and the

head nods. The subject enters microsleep.

Sleep is a fascinating subject, even though we cannot knowingly experience deep sleep, because our consciousness is switched off. Sleep is a finely regulated aspect of our brain's daily cycle as the sun rises and sets, a state whose function remains controversial.

Over the past century clinicians and neuroscientists have discovered different sleep phases (rapid eye and nonrapid eye movements) and the distinct regions of the midbrain and brain stem involved in controlling them. What is more, these researchers have demystified narcolepsy, when patients abruptly and irresistibly fall asleep, microsleep and now local sleep. What will come next? **M**

MORE TO EXPLORE

- **Local Sleep in Awake Rats.** Vladyslav V. Vyazovskiy et al. in *Nature*, Vol. 472, pages 443–447; April 28, 2011.
- **Losing the Struggle to Stay Awake: Divergent Thalamic and Cortical Activity during Microsleeps.** Govinda R. Poudel, Carrie R. H. Innes, Philip J. Bones, Richard Watts and Richard D. Jones in *Human Brain Mapping*, Vol. 35, No. 1, pages 257–269; January 2014.