NEUROSCIENCE

Sleeping to Reset Overstimulated Synapses

The purpose of sleep is one of the toughest puzzles in biology. Some scientists think animals slumber primarily to save energy. Others have proposed that sleep has special relevance for learning and memory. A newer hypothesis borrows from both ideas, suggesting that sleep dials down synapses that have been cranked up by a day's worth of neural activity. Because stronger synapses use more energy and take up more space, the thinking goes, this synaptic cooldown helps conserve both energy and precious real estate in the brain. It also ensures that synapses don't max out and lose the ability to grow stronger if they're called upon to encode some new experience into memory the next day.

In this week's issue, two studies with fruit flies provide what some researchers say is the most compelling evidence to date for this provocative hypothesis. One finds that levels of several synaptic proteins increase during wakefulness and decline during sleep; the other finds a similar rise and fall in synapse number. "Together, these findings very clearly demonstrate that one major function of sleep is to reduce, on a structural level, synaptic connectivity in the brain," says Jan Born, a neuroscientist who studies sleep at the University of Lübeck in Germany and was not involved with either study.

The so-called synaptic homeostasis hypothesis was first proposed about 5 years ago by neuroscientists Giulio Tononi and Chiara Cirelli at the University of Wisconsin, Madison. The idea had intuitive appeal and elegant simplicity but sparse experimental evidence. Since then, support has come from studies with rodents and people—and now, flies.

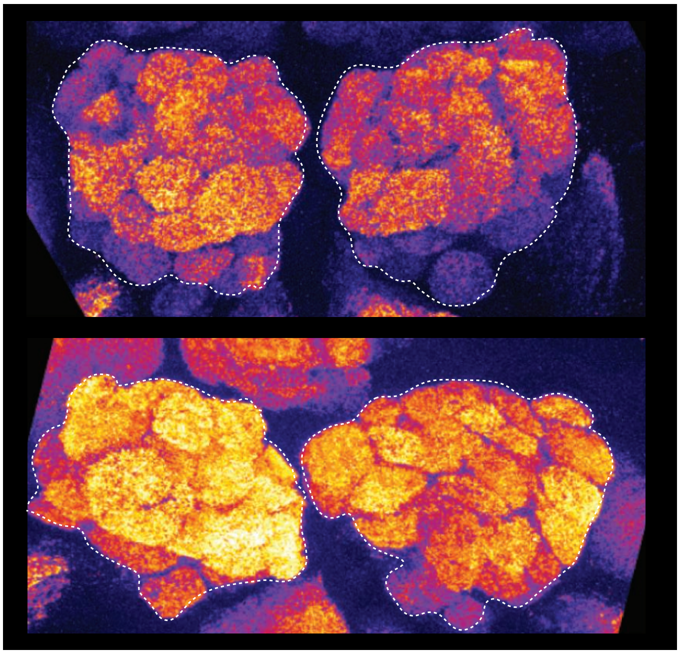
On page 109, Cirelli, Tononi, and postdoc Giorgio Gilestro report that depriving flies of sleep, either by periodically shaking the vials they call home or by forcing individual male flies to cohabitate with an unwelcome stranger (a male from another fly strain), resulted in higher levels of several synaptic proteins throughout the brain. Levels of these proteins, which included components of the transmitting and receiving sides of the synapse as well as proteins involved in neurotransmitter release, declined after flies had a chance to sleep. This pattern held up even when flies slept at odd hours, confirming that the proteins fluctuate with the sleep-wake cycle, not the time of day.

The second paper, on page 105, describes changes in synapse number during sleep. But the experiments weren't conceived as a direct test of the synaptic homeostasis hypothesis, says senior author Paul Shaw of Washington University in St. Louis, Missouri. Instead, the goal was to investigate how daytime activities influence subsequent sleep. Shaw's lab had previously found that flies sleep longer after social stimulation—either a fruit fly party in a vial or "courtship conditioning," in which a male fly learns the futility of trying to mate with another male doused with female pheromones (*Science*, 22 September 2006, p. 1775).

The main goal of the new study, led by Shaw's graduate student Jeffrey Donlea, was to investigate how these daytime experiences affect the sleep of mutant flies. The researchers found that disrupting any one of three genes, including *period*, an integral component of the circadian clock, prevented flies from sleeping longer after a socially stimulating day. Restoring the genes in just 16 so-called ventral lateral neurons—out of some 200,000 neurons in the fly brain—was enough to restore increased sleep after social enrichment.

These findings provide an intriguing link between two major regulators of sleep, Cirelli says. The circadian clock tells animals when to sleep, she explains, but the duration of sleep depends on how long they've been awake and what they've done during that time. The new findings suggest that some of the same cells and genes involved in regulating the circadian clock may also be involved in sensing sleep need.

In the same paper, Donlea and colleagues also report findings that seem to support the synaptic homeostasis hypothesis: They found that the same social experiences that increase the need for sleep also increase the number of synapses between lateral ventral neurons and their partners in the brainstem. After sleep, synapse numbers had declined.



Sleepless synapses. After 16 hours without sleep (bottom panel), synaptic protein levels increase (indicated by warm colors) in the fruit fly brain.

Together, the two papers provide compelling evidence for synaptic downscaling during sleep, says Robert Stickgold, a neuroscientist at Harvard University who was initially skeptical of Tononi and Cirelli's hypothesis. Even so, Stickgold thinks it's unlikely that downscaling happens only during sleep or that synaptic strengthening is limited to waking hours. Human and rodent studies have suggested, for example, that sleep may be important for consolidating newly formed memories (*Science*, 9 March 2007, p. 1360), a process that's widely assumed to depend on strengthening synapses.

And in a 12 February *Neuron* paper, neuroscientist Marcos Frank and colleagues at the University of Pennsylvania reported that synaptic communication between neurons in the visual cortex of cats can grow stronger during sleep. Such findings "raise the question of whether downscaling is *all* that sleep can do to synapses," Frank says.

The apparently contradictory findings may just mean that the sleeping brain is multitasking, says Born. He suggests that an overall decrease in synaptic strength could help conserve space and energy in the brain, while at the same time synapses in specific neural circuits could be strengthened to reinforce newly encoded memories. –**GREG MILLER**

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