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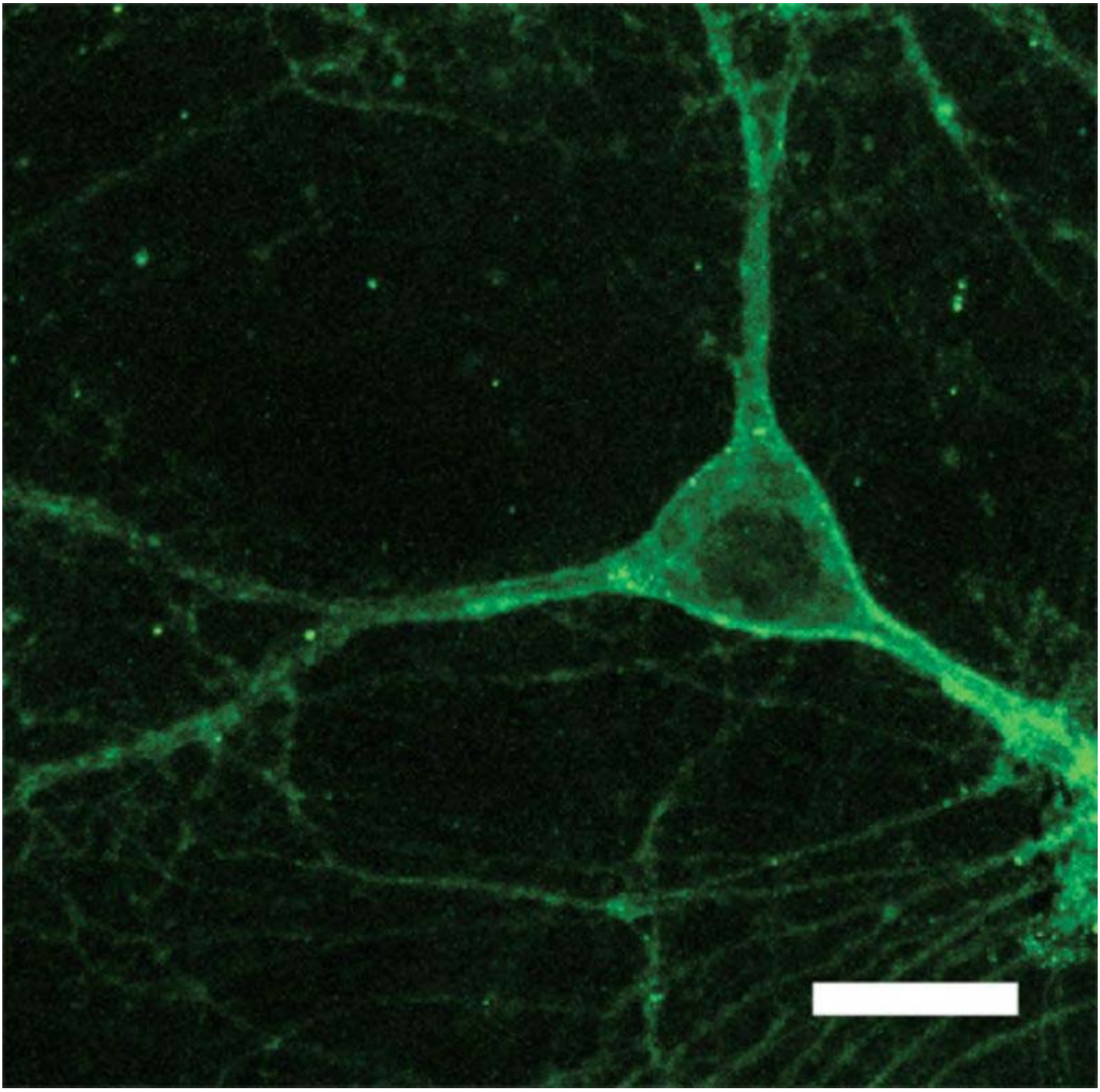
Lights on, brain off

If you're a night owl like me, then those first rays of sunshine in the morning often seem to make you feel even groggier than you did when you went to bed. But scientists have found a new, efficient way to use simple beams of light to literally—not just metaphorically—shut down the brain.

Ed Boyden, a research professor at the Massachusetts Institute of Technology, and his colleagues have discovered two new light-sensitive proteins that, when implanted into neurons, prevent those cells from activating in the presence of certain wavelengths of light. Arch, found in a species of bacteria, is sensitive to yellow light, whereas Mac is of fungal origin and responds to blue light, the scientists report in the Jan. 7 issue of Nature.



A mouse neuron expressing Arch

These proteins, Boyden says, will not only provide scientists with a powerful but reversible way to study specific brain regions, but may also provide promising new gene therapy treatments for diseases caused by overactive brain cells. One of the most drastic examples of such a disorder is epilepsy, in which spontaneous activity by neurons can sometimes spread throughout the entire brain, causing violent seizures and occasionally death.

These aren't the first light-sensitive proteins, or opsins, that neuroscientists have adapted to their purposes. For some time, researchers have been using opsins to both selectively activate and inhibit brain cells, a field known as optogenetics. As we reported last month, such techniques allow scientists to study the function of specific brain cells, such as those involved in memory or disease, with greater detail and precision than previously possible.

Opsins work because they are ion channels; when activated, they allow charged particles into a cell. In the case of ChR2, blue light causes an influx of charged particles that mimic what naturally occurs when a neuron is told to fire. Halorhodopsin, on the other hand, adds chloride ions to a cell's interior that make it unable to send a signal. Halorhodopsin, however, quickly becomes inactive in the presence of light, whereas the new proteins, which allow protons into cells, "reset" themselves and can shut off cells for very long

periods of time. “These are an order of magnitude better,” Boyden says. “They allow for near-digital turning off of neurons in awake animal cortexes.”

In the Nature paper, Boyden and his colleagues demonstrate the use of Arch and Mac in awake mice, but he says that the team has also conducted tests in nonhuman primates with no apparent side effects yet. They are also “very eager” to begin studying prototype therapies in mouse models for epilepsy, chronic pain, brain injuries, and other brain diseases, he adds. Opsins are normally implanted using gene therapy, in which a retrovirus is used to insert the opsin-producing gene into the relevant brain cells. In recent years, scientists have significantly improved their gene therapy techniques—for instance, they can now target the right cells by altering the protein coat of the virus or by adding different DNA promoter regions to the implanted gene—Boyden says, and thus the risk of side effects such as cancer has dropped dramatically.

Another benefit of the new long-lasting proteins, he adds, is that scientists can now precisely and reversibly shut off small regions of the brain to study their roles in activities like cognition and attention—essentially, a “high-throughput scan for the brain.” Previously, scientists have obtained this information largely by looking at lesions, but these are relatively large and haphazard and provide no information about timing. “It’s like pulling the power cord of a laptop. You don’t know if it’s the lack of a power or the processing input causing the problem,” Boyden says. “We believe this will have a significant effect on neuroscience.”

—Aalok Mehta

Image courtesy of Brian Chow, Xue Han and Ed Boyden / MIT

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