MBL

Biological Discovery in Woods Hole

Catalyst

Founded in 1888 as the Marine Biological Laboratory

FALL 2012
VOLUME 7, NUMBER 2

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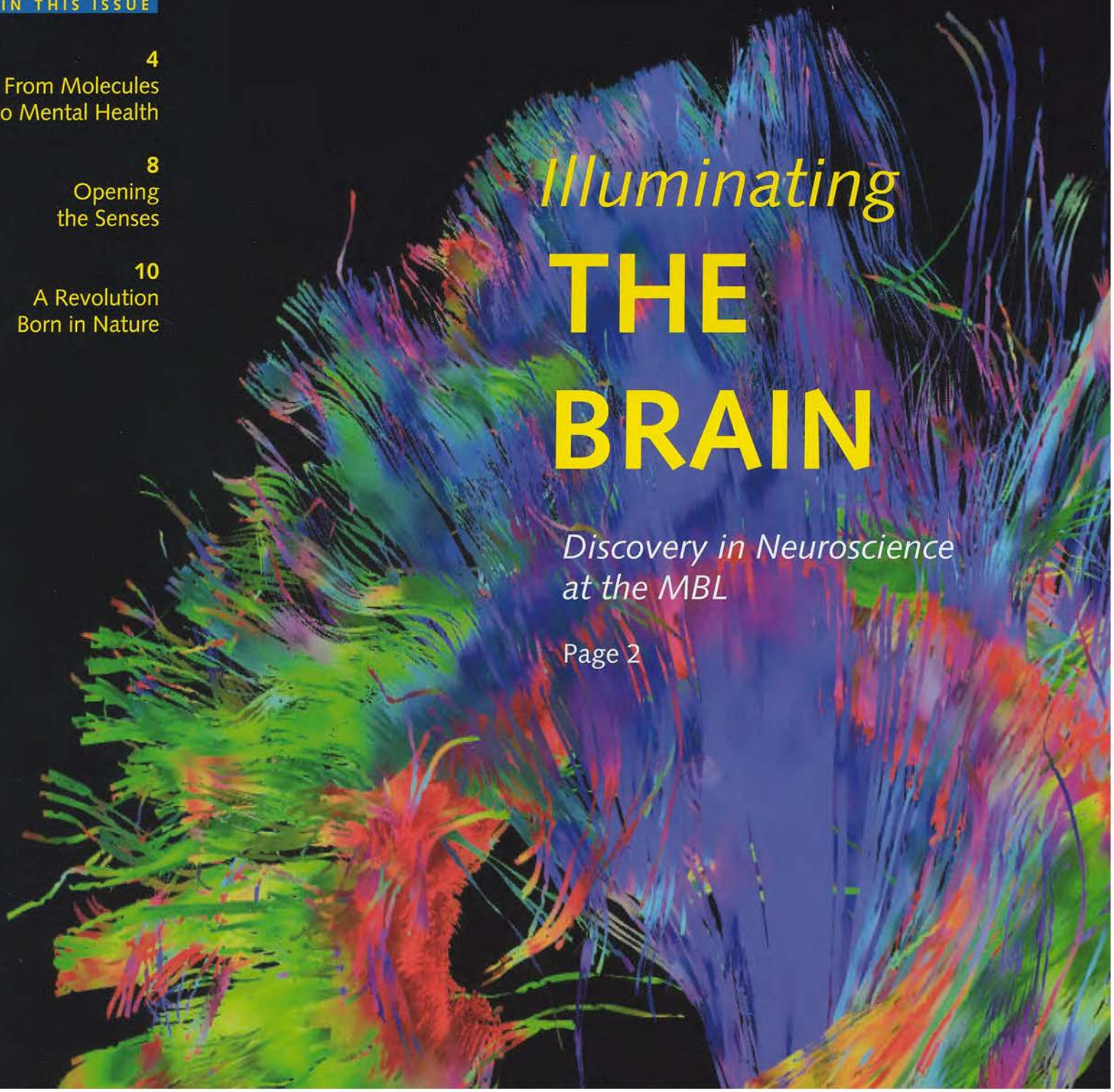

Illuminating THE BRAIN

Discovery in Neuroscience at the MBL

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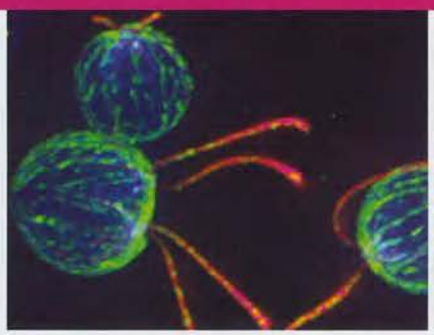
A Revolution

FROM THE MICROBIAL WORLD COME POWERFUL NEW TOOLS TO ILLUMINATE THE HUMAN BRAIN



A familiar furnishing in the MBLWHOI Library is this elegantly penned motto of 19th-century zoologist Louis Agassiz: "Study Nature, Not Books." The wisdom of this phrase is often reproven, as in the serendipitous discovery of a green fluorescent protein (GFP) in jellyfish by Osamu Shimomura, now an MBL Distinguished Scientist, in 1961. Decades later, others turned GFP into a revolutionary tool for illuminating the workings of cells, one that brought Shimomura the Nobel Prize. Agassiz's motto still reverberates today, most recently in the form of a sensational technique that is taking neuroscience by storm: Optogenetics.

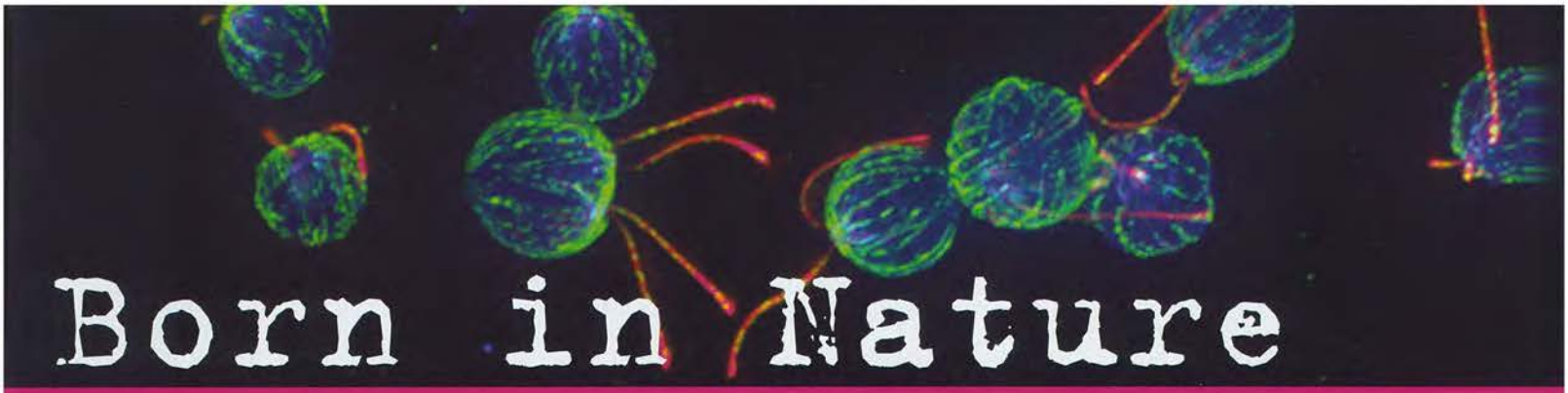
"Optogenetics is a revolution, and the MBL is in the midst of it," says George Augustine, a researcher and frequent course faculty member at the MBL since 1979. Barely ten years old, optogenetics is so promising that its discoverers are widely considered candidates for the Nobel Prize.

With amazing precision, optogenetics allows scientists to control the electrical activity of neurons simply by targeting them with beams of light. Besides being much less invasive than using electrodes—which has been the standard way to study neural activity since the 1930s—optogenetics allows scientists to turn on or off specific types of neurons in the brain (say, only those that produce dopamine), which is a huge advance. It throws open the door to pinpointing exactly which neurons and circuits cause specific human sensations, thoughts, and behaviors—and perhaps one day, to light-based therapies for mental and sensory disorders.

Yet this powerful tool for illuminating the animal brain emerged out of a quite distant realm of curiosity. Since the early 1970s, a small group of scientists had been studying the membrane proteins that some microbes (which, of course, lack eyes) use to respond to light. Called opsins, they help the microbe do a variety of things, such as move toward a light source or hold steady at an ocean depth. Animals, too, have opsins, which they use for vision.

The first microbe with an opsin was discovered in a high-salt environment; others were later found in variety of ecosystems. Although they fascinated those who discovered them, hardly anyone else took notice. When scientists reported in 2002 that an opsin from a green alga, now aptly called Channelrhodopsin, seemed to "open" just like an ion channel when stimulated by light, neuroscientists barely noticed. "It's not something I, or pretty much anyone outside of the aquatic algae field, was paying attention to," says Augustine.

Fortunately, at least two brilliant neuroscientists (both alumni of MBL courses) were paying attention: Ed Boyden, a graduate student and engineering whiz, and Karl Deisseroth, an MD-PhD who was devoted to finding cures for the devastating mental disorders he saw during his psychiatric training. The two met at Stanford and began dreaming about ways to control subsets of neurons in the brain and, ultimately, repair neural circuits that were malfunctioning. When the Channelrhodopsin paper appeared, they and others checked out the far-fetched possibility that this green alga (*Chlamydomonas reinhardtii*) might contain the tool they needed.



Born in Nature

They were not prepared for how spectacularly well it would work. Using standard genetic engineering techniques, they inserted the Channelrhodopsin gene into mammalian neurons in culture, and then pulsed them with blue light. Amazingly, the neurons fired. "It worked right out of the gate," Augustine says, which happens almost never in science. The startling findings were published in 2005. Later, a different opsin (a Halorhodopsin) was shown to inhibit or silence neurons when hit with yellow light.

Augustine, who had been one of Deisseroth's mentors on optics in the 1990s, right away recognized the discovery's power. He and his colleagues at Duke University tried introducing the Channelrhodopsin gene into a live mouse, to see if they could activate subsets of neurons from the millions in the animal's brain. "We turned on the light and, boom, the mouse's neurons fired. It was magical," Augustine recalls.

"Optogenetics is a revolution, and the MBL is in the midst of it."

— George Augustine, MBL Whitman Investigator

A distinct buzz about the new "optogenetics" soon spread through the neuroscience community. "It has absolutely enabled experiments that before were impossible to do," says MBL Neurobiology course co-director Graeme Davis of University of California, San Francisco. And it allows one to dream that cures for long-intractable brain disorders might someday be at hand.

Augustine is excited about the more immediate prospect of using optogenetics to construct a "wiring diagram" of the neural circuits in the brain, a field of research known as connectomics. "In the past, figuring out how a whole brain works would have been just lunacy. But I think with optogenetic approaches, it's within the realm of feasibility," he says.

"The historical way to define a neural circuit is anatomically. You simply look at this neuron and see if it touches the next neuron. If it does, they are probably talking to each other," Augustine says. "But the problem with this method is, it doesn't tell you anything about the functioning of that circuit. Do all of its synapses actually work, or are some of them silent? Before optogenetics, it was well nigh impossible to tell."

Buoyed by the possibilities, Augustine founded the Center for Functional Connectomics in Seoul, South Korea, in 2010. So far, he has used optogenetics to selectively activate about 100 different kinds of neurons in the mouse brain. "The goal is to get them all, by hook or by crook," he says. The big remaining challenge is getting a reliable readout of which neurons are talking, which are listening, and when (see Cool Tool, page 15). Then, Augustine says, all the tools will be in place to map every circuit in the brain.

As for the origin of this revolutionary tool? Deisseroth, for one, hasn't forgotten that it sprang from the study of microbes that may seem just weird. To him, the discovery of optogenetics carries two big lessons: The importance of undirected, basic inquiry into nature and of protecting biodiversity, even in "the harsh, barren and otherwise useless Saharan salt lakes from which some of the most useful opsins originated." Undoubtedly, Agassiz would have agreed. • — DK