Optogenetics

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A story spanning four decades that began with one the most basic of science questions—how microscopic organisms sense light—has changed the way researchers approach brain science. Turning on and off neurons in the brains of mice, by coopting the microbial sensors, has become almost as easy as flicking a light switch.

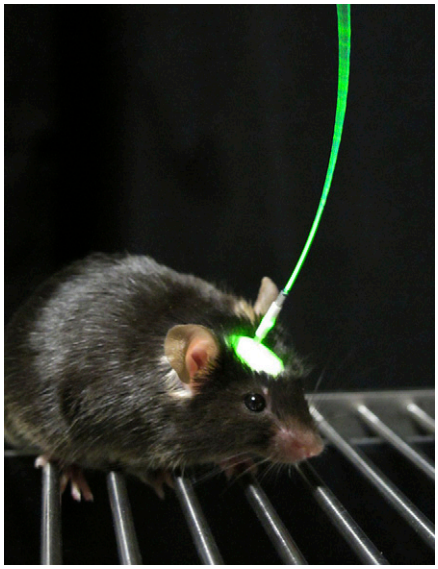
In the past, determining which collections of neurons in the brain carry out which functions—mediating behaviors, storing memories, controlling movement, or relaying sensory input—had often meant waiting until something went wrong with those neurons and taking note of the effect, or altering neurons with low-resolution methods using electrodes or drugs. Now, researchers can use light to achieve precise control of neurons to study their effects (1).

From the 1970s through the 2000s, biophysical laboratories around the globe identified, one-by-one, a diverse family of proteins called microbial opsins, which react to light by shuttling charged ions through membranes (2–5). The resulting change in charge across the membrane is similar to what happens when a neuron fires, although single-celled microbes use the protein for other purposes, such as guiding their movement relative to light sources, not transmitting brain signals. However, in 2005 researchers found that by integrating one of these opsins into brain cells extracted from mice, they could force the cells to fire with precise timing when exposed to light (6). By 2007, the technology had been adapted to achieve precise control of the behavior of mice (7, 8). Since then, many related proteins—including members of the bacteriorhodopsin, halorhopsin, and channelrhodopsin gene families—have been engineered and demonstrated to be useful for turning neurons either on or off with millisecond timing (9–11).

The power of this technique, dubbed "optogenetics," is that by using genetic engineering techniques, opsins can be selectively inserted into any chosen subpopulation of neurons in the brain. Then, when light shines on the brain through fiberoptics or other light-guiding tools (7, 11), only those neurons will be activated or inactivated. Optogenetics is a research tool; the main goal of those in the field isn't to genetically engineer humans to have opsins in their brains and control people's behaviors with light, but rather to use the optical control of neurons in model organisms to reveal how the brain works.

Early behavioral applications of the technique induced mice to act in certain, easily observable ways: to awaken (8), or to turn in a circle when the light shone (12), for example. In the past decade, however, optogenetics has helped answer many clinically relevant questions about what causes neuropsychiatric disorders and how brain diseases can be treated. When researchers turned on or off one set of neurons in the brains of mice using optogenetics, the animals' anxiety levels changed, revealing the importance of those cells in mediating anxiety (13). In other studies, activating different kinds of neurons either created or eased the symptoms of Parkinson disease in rodents (14, 15). Furthermore, when certain neurons known to be involved with addiction were turned off using optogenetics, rodents could be prevented from responding positively to cocaine, or—if already addicted to cocaine—stopped from seeking the drug (16, 17). That's only a sampling of the kinds of studies that can now be performed through the control of neurons with light.

Optogenetics is still rapidly growing as a method, and those in the field expect that the use of light to control cellular processes will continue to be applied to new problems over the coming years. This year, for the first time, researchers used a light-sensitive protein not to strictly turn on and off neurons but to turn on and off genes (18); this method can be applied to any cell in an animal's body, on which light can be shone, to control its physiology. With that kind of creativity in using optogenetics, there's no shortage of research problems on which it can help shine light.



By selectively inserting opsins—which react to light—into them, neurons can be activated or inactivated for research purposes. Image courtesy of Inbal Goshen and Karl Deisseroth.

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