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Optogenetics: Not a flash in the pan for neuroscience



Mark Wanner Sep 26, 2013 1:28 PM

A flash of light can do the most amazing things.

First came films of mice changing behaviors on cue, literally in a flash. Recent news stories have covered how light flashes can be used to **implant false memories**. In another study they were used to stimulate neurons in specific regions of the brain to turn on—and off--behaviors related with **obsessive-compulsive disorder**. Light is also being used at the single-gene level to rapidly **start and stop the expression of a targeted gene**. It essentially creates an on-off switch that can make it much easier to perform research.



What sounds like science fiction is actually some of the progress being made using an exciting new technology in neuroscience called optogenetics. Don't reach for the dark sunglasses and aluminum foil just yet, however. The research is still being done largely in mice at this time.

Room for debate

In fact, the whole field came under fire recently for amping up the wow factor without clear and practical clinical connections. John Horgan sparked a spirited discussion via a blog post in *Scientific American* that argued optogenetics **has been vastly oversold** regarding its clinical impact. Horgan argues his case within a larger framework—namely that he “can't get excited about an extremely high-tech, blue-sky, biomedical 'breakthrough'—involving complex and hence costly gene therapy and brain surgery—when tens of millions of people in this country still can't afford decent health care.”—but his is **not the only cautionary perspective**.

Others, including fellow *Scientific American* blogger Scicurious, disagree, **pointing out the real research utility of optogenetics** and that often “you need a technique that will allow you to find out more about neurons, circuits, and systems in models. That knowledge of those systems can then be applied to how we treat and understand human conditions.”

So which is it? Have neuroscientists been seduced by a fancy but hollow technology, or is optogenetics a boon to understanding how the heck our brains actually work?

From far-fetched to practical

First, what exactly is optogenetics? The technique is barely a decade old, born of the seemingly far-fetched notion of using light to selectively control neural activity that was originally proposed in the late 1990s. Less than a decade later, in 2005, a group at Stanford University led by Karl Deisseroth

published a practical way to actually accomplish the feat.

The key components for the technique come from unlikely sources—algae and bacteria—but optogenetics is allowing researchers to study mammalian neuron function with far more precision than previously possible. In basic terms, optogenetics uses a family of proteins called opsins, which have light-sensitive regions connected with regions that act as tiny ion pumps across cell membranes. Why is marrying light sensitivity with ion flow important? An [overview from Michael Mohammadi](#) provides an excellent summary (and do read the entire post if interested in more detail and to see a video of how a mouse's behavior can be changed with light):

“ . . . the foundation of neurotransmission rely on the movement of positively charged ions (anions) and negatively charged ions (cations) across the cellular membrane. The balance of these ions inside and outside of a cell, and the potential of the membrane, contribute greatly to whether or not the neuron fires an action potential. Action potentials are central to communication between neurons. Therefore, if we can control the movement of those ions, we can control the cells excitability and how and when it communicates (fires action potentials) with other cells in a network.”

In this manner, it's possible to use opsins to control neurons and turn them “on” or “off”—activate or inhibit them—with light. And with advanced genetics techniques, it's currently possible to make the opsins functional only in a very specific region of the brain in mice.

“Researchers are able to turn up or turn down certain parts of the brain and see what happens,” says Michael Sasner, Ph.D., who works with optogenetic mouse models in his role as the associate director, bioinformatics & model development in Genetic Resource Science at The Jackson Laboratory (JAX). “You can induce or repress defined behaviors just by shining light. Being able to manipulate the system in such precise ways—you can turn off a specific neural circuit for 10 milliseconds, for example—provides a very sophisticated, non-invasive way to look at neural function.”

Putting the pieces together

As a research technique, optogenetics is undeniably cool and, pardon me, flashy. It's not surprising that it's captured a lot of attention and, on the heels of the acclaim, some backlash. But what is its real utility, and is it really a non-starter on the human side?

Up front, I must say that it's almost reassuring that it's still far, far from something that can be used in human medicine, given the relative ease with which it is used for behavior manipulation in research animals. The ethics tangle that would ensue in humans boggles the mind. But as a research tool, optogenetics illustrates a very real philosophical struggle of our time—is research worth anything if it's not readily translatable? The answer here is yes.

One element of its value is that it showcases how work can progress more rapidly with a commitment to data sharing and open access. Innovators Karl Deisseroth, Ed Boyden (now at MIT) and Feng Zhang (now at the Broad Institute) set the tone from the beginning, freely providing resources and expertise. Others have continued the culture of open access, and Sasner and JAX now maintain a crucial mouse model resource hub as the field progresses and expands. The openness has helped accelerate the adoption and usefulness of the technique, which in turn has somewhat ironically fueled much of the backlash.

Second, there's so much still to learn about normal brain function that you must have tools for the most basic of neurological research. “Optogenetics is one of the most powerful research tools available to illustrate the mechanisms of brain function and the composition of brain circuitry,” says Hongkui Zeng, Ph.D., of the Allen Institute for Brain Science (AIBS), a current leader in developing and expanding the use of optogenetic techniques. “It isn't directly translatable to humans yet, but understanding the mechanisms will provide insight into how brains work and how to treat human diseases. It is a key first step to developing therapies.”

Thinking BRAIN and beyond

Another initiative that has brought its share of discussion is the federal BRAIN (**Brain Research through Advancing Innovative Neurotechnologies**) effort. BRAIN's mission is to "accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought." Debates over its feasibility and funding priorities aside, optogenetics clearly has a role to play here.

Indeed, the advisory committee for the BRAIN initiative's interim report included a summary of nine priorities for the project moving forward in 2014. The first six involve basic science in model organisms, and it doesn't take a scientist to see how at least four in particular—create structural maps of the brain; develop new large-scale network recording capabilities; develop a suite of tools for circuit manipulation; and link neuronal activity to behavior—will benefit from the new optogenetic tools and techniques.

One of the arguments against BRAIN is the sheer scale of the effort involved. Neuroscience is still a young science, and our brains—with their almost unimaginably dense collections of circuits and connections and biochemistry and electricity—are a largely unexplored frontier. But we have to start somewhere, and optogenetics, applied with care and precision, provides an intriguing and potentially better way to explore what's going on inside our own heads. Sasner sums up the situation well: "Simply put, optogenetics is a technological leap that provides tools that allow a much greater understanding of biology than was previously possible."

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