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NEUROSCIENCE

Controlling the Brain with Light

With a technique called optogenetics, researchers can probe how the nervous system works in unprecedented detail. Their findings could lead to better treatments for psychiatric problems

By Karl Deisseroth

EVERY DAY AS A PRACTICING PSYCHIATRIST, I confront my field's limitations. Despite the noble efforts of clinicians and researchers, our limited insight into the roots of psychiatric disease hinders the search for cures and contributes to the stigmatization of this enormous problem, the leading cause worldwide of years lost to death or disability. Clearly, we need new answers in psychiatry. But as philosopher of science Karl Popper might have said, before we can find the answers, we need the power to ask new questions. In other words, we need new technology.

Developing appropriate techniques is difficult, however, because the mammalian brain is beyond compare in its complexity. It is an intricate system in which tens of billions of intertwined neurons—with multitudinous distinct characteristics and wiring patterns—exchange precisely timed, millisecond-scale electrical signals and a rich diversity of biochemical messengers. Because of that complexity, neuroscientists lack a deep grasp of what the brain is really doing—of how specific activity patterns within specific brain cells ultimately give rise to thoughts,

IN BRIEF

Neuroscientists have long been frustrated by their inability to study how the brain works in sufficiently precise detail. Unexpectedly, a solution has emerged from basic genetic research on microorganisms that rely on light-responsive "opsin" proteins to survive.

By inserting opsin genes into the cells of the brain, scientists can now use flashes of light to trigger firing by specific neurons on command. This technology, optogenetics, permits researchers to conduct extremely precise, cell type–targeted experiments in the brains of living, freely moving animals—which electrodes and other traditional methods do not allow.

Although optogenetics is still in its infancy, it is already yielding potentially useful insights into the neuroscience underlying some psychiatric conditions.

Photograph by Darren Braun

memories, sensations and feelings. By extension, we also do not know how the brain's physical failures produce distinct psychiatric disorders such as depression or schizophrenia. The ruling paradigm of psychiatric disorders—casting them in terms of chemical imbalances and altered levels of neurotransmitters—does not do justice to the brain's high-speed electrical neural circuitry. Psychiatric treatments are thus essentially serendipitous: helpful for many but rarely illuminating.

Little wonder, then, that in a 1979 *Scientific American* article, Nobel laureate Francis Crick suggested that the major challenge facing neuroscience was the need to control one type of cell in the brain while leaving others unaltered. Electrical stimuli cannot meet this challenge, because electrodes are too crude a tool: they stimulate all the cells at their insertion site without distinguishing between different cell types, and their signals also cannot turn neurons off with precision. Crick later speculated in lectures that light could serve as a control tool because it could be delivered in precisely timed pulses in a range of colors and locations, but at the time no one had any idea about how specific cells could be made to respond to light.

Meanwhile, in a realm of biology as distant from the study of the mammalian brain as might seem possible, researchers were working on microorganisms that would only much later turn out to be relevant. At least 40 years ago biologists knew that some microorganisms produce proteins that directly regulate the flow of electric charge across their membranes in response to visible light. These proteins, which are produced by a characteristic set of "opsin" genes, help to extract energy and information from the light in the microbes' environments. In 1971 Walther Stoeckenius and Dieter Oesterhelt, both then at the University of California, San Francisco, discovered that one of these proteins, bacteriorhodopsin, acts as a single-component ion pump that can be briefly activated by photons of green light—a remarkable all-in-one molecular machine. Later identification of other members of this family of proteins—the halorhodopsins in 1977 and the channelrhodopsins in 2002—continued this original theme from 1971 of single-gene, all-in-one control.

What excites neuroscientists about optogenetics is that it provides control over defined events within defined cell types at defined times.

In 20/20 hindsight, the solution to Crick's challenge—a strategy to dramatically advance brain research—was therefore available in principle even before he articulated it. Yet it took more than 30 years for the concepts to come together in the new technology of optogenetics.

Optogenetics is the combination of genetics and optics to control well-defined events within any specific cells of living tissue (not just those of the nervous system). It includes the discovery and insertion into cells of genes that confer light responsiveness; it also includes the associated technologies for delivering light into the brain, directing the light's effect to genes and cells of interest, and assessing readouts, or effects of this optical control. What excites neuroscientists about optogenetics is that it provides control over defined events within defined cell types at defined times—a level of precision that is not only fundamentally new but most likely crucial to biological understanding.

The significance of any event in a cell is understandable only in the context of the other events occurring around it in the rest of the tissue, the whole organism or even the larger environment. Even a shift of a few milliseconds in the timing of a neuron's firing, for example, can sometimes completely reverse the effect of its signal on the rest of the nervous system. Thousands of scientists are now wielding optogenetics to learn how specific activity patterns within select sets of neurons lead to complex physiology and behavior in worms, flies, fish, birds, mice, rats and monkeys. The work has already yielded important insights into human problems, including depression, disordered sleep, Parkinson's disease and schizophrenia.

CASTING LIGHT ON LIFE

Biology has a tradition of using light to intervene in living systems. Researchers have long employed a light-based method called CALI to destroy, and thus inhibit, selected proteins; lasers have also been used to destroy specific cells, for example, in the worm *Caenorhabditis elegans*. Conversely, Richard L. Fork of Bell Laboratories (in the 1970s) and Rafael Yuste of Columbia University (in 2002) reported ways to stimulate neurons with lasers that partially disrupted cell membranes. In the past decade the laboratories of Gero Miesenböck, while at Memorial Sloan-Kettering Cancer Center, and of Ehud Isacoff, Richard H. Kramer and Dirk Trauner, then all at the University of California, Berkeley, have employed multicomponent systems for modulating targeted cells with light. They introduced, for example, both a protein that regulates neurons and a chemical that would spur the protein into action when triggered by ultraviolet light.

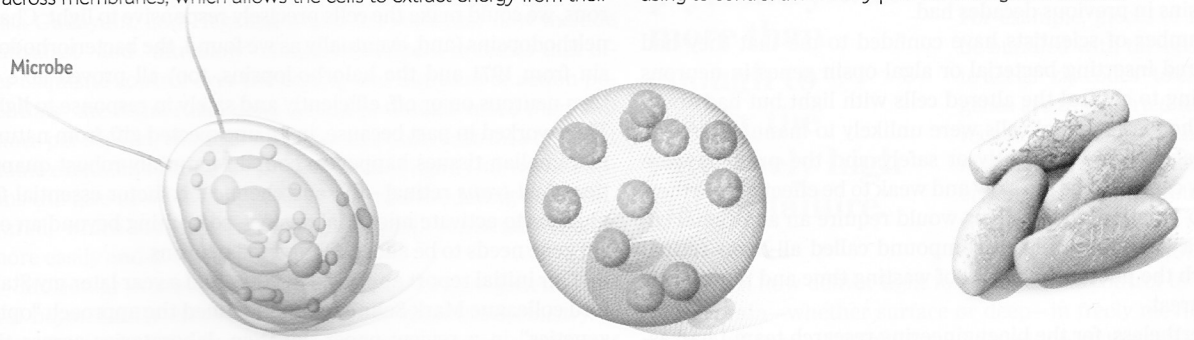
Yet destroying proteins or cells of interest obviously limits one's experimental options, and methods that depend on multiple components, though elegant and useful, entail practical challenges and have not had broad applicability or utility in mammals. A fundamental shift to a single-component strategy was necessary. As it turned out, this single-component strategy was not able to build on any of the parts or methods from earlier approaches but instead employed the remarkable all-in-one light-activated proteins from microbes: bacteriorhodopsins, halorhodopsins and channelrhodopsins.

In 2000, well after bacteriorhodopsin and halorhodopsin had become known to science, the Kazusa DNA Research Institute in Japan posted online thousands of new gene sequences from the green algae *Chlamydomonas reinhardtii*. While reviewing them, Peter Hegemann, then at Regensburg University in Berlin, who had predicted that *Chlamydomonas* would have a light-activated ion channel, noticed two long sequences similar to those for bacteriorhodopsin, obtained copies of them from Kazusa and asked Georg Nagel (then a principal investigator in Frankfurt) to test if they indeed coded for ion channels. In 2002 Hegemann and Nagel described their finding that one of these sequences encoded a single-protein membrane channel responsive to blue light: when hit by blue photons, it regulated the flow of positively charged ions. The protein was consequently dubbed channelrhodopsin-1, or ChR1. The following year Nagel and Hegemann (along with their colleagues, including Ernst Bamberg in Frankfurt) explored the other sequence and named the encoded protein channelrhodopsin-2, or ChR2. Almost simulta-

SOURCE: "OPTOGENETIC INTERROGATION OF NEURAL CIRCUITS: TECHNOLOGY FOR PROBING MAMMALIAN BRAIN

The Humble Origins of Light-Sensitive Proteins

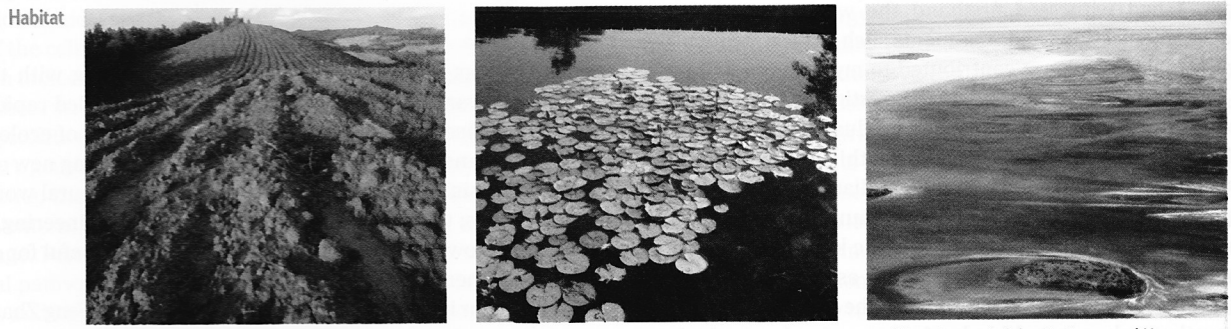
Some types of algae and other microbes depend for their survival on so-called opsin proteins that respond to visible light. When illuminated, these protein channels regulate the flow of electrically charged ions across membranes, which allows the cells to extract energy from their environments. Opsins of different types can vary in their light sensitivity and behavior. The opsin genes that make these proteins are the foundation for the optogenetic technology that neuroscientists are now using to control the activity patterns in targeted neurons.



Chlamydomonas reinhardtii is a single-cell, motile alga equipped with a pair of flagella that allow it to swim through freshwater.

Volvox carteri is an alga closely related to *Chlamydomonas* that consists of hundreds of cells living together as a globular colony.

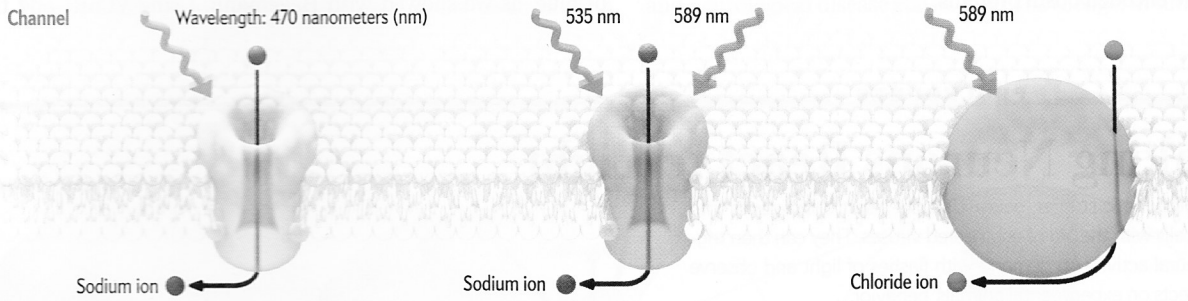
Natronomonas pharaonis is an archaebacterium that can live only in waters with extremely high salt concentrations.



Soil and bodies of freshwater worldwide

Ponds, lakes, pools and water-filled ditches

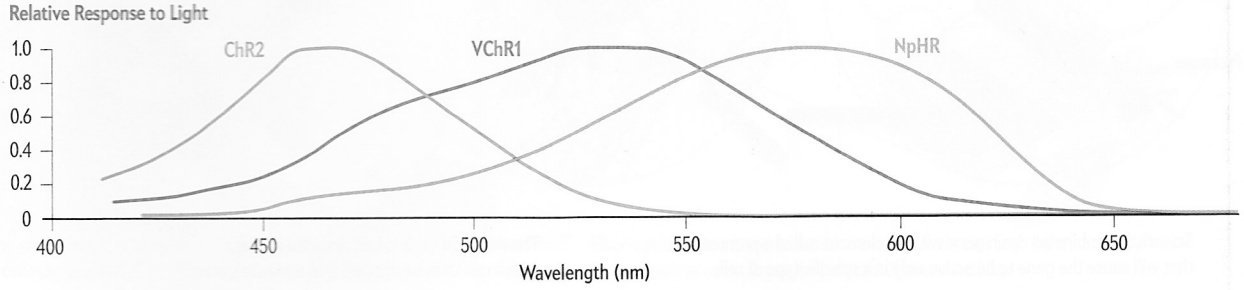
Highly saline soda lakes in Egypt and Kenya



ChR2 channelrhodopsin allows positive sodium ions to pass in response to blue light.

VChR1 channelrhodopsin responds to some wavelengths of green and yellow light.

NpHR halorhodopsin regulates the flow of negative chloride ions in response to yellow light.



SOURCES: "OPTOGENETIC INTERROGATION OF NEURAL CIRCUITS: TECHNOLOGY FOR PROBING MAMMALIAN BRAIN STRUCTURES," BY F. ZHANG ET AL., IN *NATURE PROTOCOLS*, VOL. 5 NO. 3, FEBRUARY 18, 2010 (*channels and light sensitivity curves*)

Illustrations by Bryan Christie

neously, John L. Spudich of University of Texas Medical School at Houston separately provided evidence that those genes were important to the light-dependent responses of *Chlamydomonas*. Yet the discovery of these channelrhodopsins—a third type of single-component light-activated ion-conductance protein—did not immediately translate into an advance in neuroscience any more than the discoveries of bacteriorhodopsins and halorhodopsins in previous decades had.

A number of scientists have confided to me that they had considered inserting bacterial or algal opsin genes in neurons and trying to control the altered cells with light but had abandoned the idea. Animal cells were unlikely to manufacture the microbial proteins efficiently or safely, and the proteins were virtually certain to be too slow and weak to be effective. Furthermore, to function, the proteins would require an additional cofactor—a vitamin A–related compound called all-*trans* retinal to absorb the photons. The risk of wasting time and money was far too great.

Nevertheless, for the bioengineering research team I had assembled at Stanford University, the motivation to improve understanding in clinical psychiatry was more than enough to justify the extremely high risk of failure. During my psychiatric residency, I had witnessed firsthand the weaknesses and side effects of medications and treatments such as electroconvulsive therapy. This experience contributed to my willingness to take the plunge, and so as a principal investigator at Stanford in 2004 I formed a team that included graduate students Edward S. Boyden and Feng Zhang to address this challenge. I introduced channelrhodopsin-2 into mammalian neurons in culture by the well-established techniques of transfection—that is, by splicing the gene for ChR2 and a specific kind of on switch, or promoter, into the genes of a vector (such as a benign virus) that ferried the added genetic material into the cells. Promoters can ensure that only selected kinds of neurons (such as only those able to secrete the neurotransmitter glutamate) will express, or make, the encoded opsin proteins.

Against all odds, the experiment worked—and worked surprisingly well. Using nothing more than safe pulses of visible light, we attained reliable, millisecond-precision control over the cells' patterns of firing of action potentials—the voltage blips, or impulses, that enable one neuron to convey information to another. In August 2005 my team published the first report that by introducing a single microbial opsin gene into mammalian neurons, we could make the cells precisely responsive to light. Channelrhodopsins (and, eventually as we found, the bacteriorhodopsin from 1971 and the halorhodopsins, too) all proved able to turn neurons on or off, efficiently and safely in response to light. They worked in part because, in an unexpected gift from nature, mammalian tissues happen to contain naturally robust quantities of all-*trans* retinal—the one chemical cofactor essential for photons to activate microbial opsins—so nothing beyond an opsin gene needs to be added to targeted neurons.

Our initial report appeared in 2005, and a year later my Stanford colleague Mark Schnitzer and I named the approach "optogenetics" in a review paper. By then, laboratories across the world were employing it, using versions of these genes that my team had synthesized to work optimally in mammalian cells. As of today, we have sent those genes to around 700 labs.

IMPROVING ON NATURE

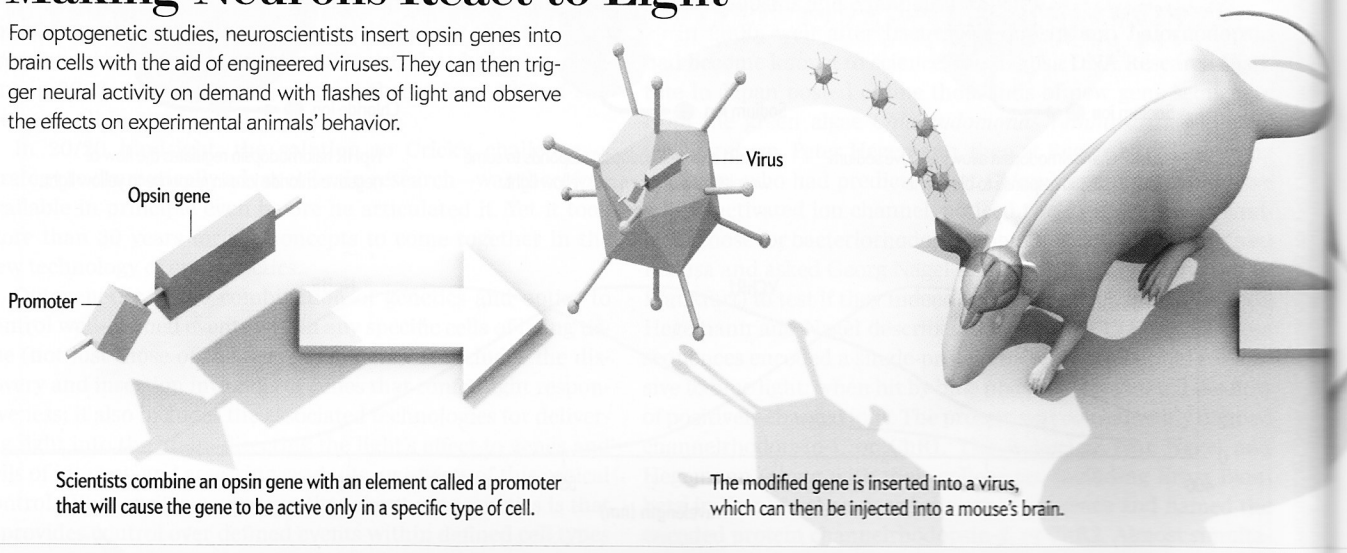
THE NUMBER OF OPTOGENETIC TOOLS, along with the variety of their capabilities, has expanded rapidly because of an astonishing convergence of ecology and engineering. Investigators are adding new opsins to their tool kit by scouring the natural world for novel ones; they are also applying molecular engineering to tweak the known opsins to make them even more useful for diverse experiments in a wider range of organisms.

In 2008, for instance, our genome searches led by Feng Zhang on a different algal species, *Volvox carteri,* revealed a third channelrhodopsin (VChR1), which responds to yellow light instead of blue, as we showed with Hegemann. Using VChR1 and the

PROCEDURES

Making Neurons React to Light

For optogenetic studies, neuroscientists insert opsin genes into brain cells with the aid of engineered viruses. They can then trigger neural activity on demand with flashes of light and observe the effects on experimental animals' behavior.



Scientists combine an opsin gene with an element called a promoter that will cause the gene to be active only in a specific type of cell.

The modified gene is inserted into a virus, which can then be injected into a mouse's brain.

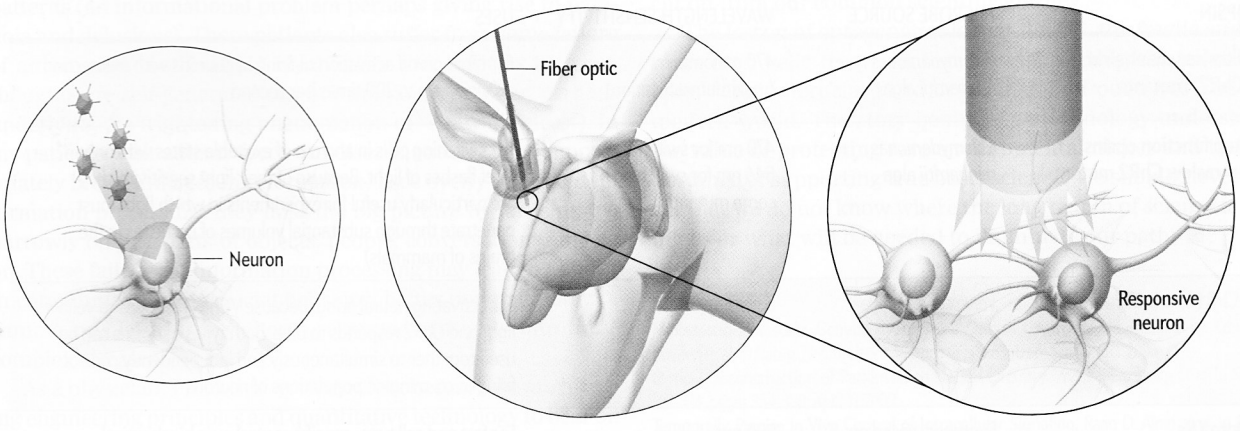
other channelrhodopsins together, we can simultaneously control mixed populations of cells, with yellow light exerting one type of control over some of them and blue light sending a different command to others. And we now have found that the most potent channelrhodopsin of all is actually a hybrid of VChR1 and ChR1 (with no contribution at all from ChR2). Our other modified opsins (created with Ofer Yizhar, Lief Fenno, Lisa Gunaydin, and Hegemann and his students) now include "ultrafast" and "ultraslow" channelrhodopsin mutants that offer exquisite control over the timing and duration of action potentials: the former can drive action potentials more than 200 times per second, whereas the latter can push cells into or out of stable excitable states with single pulses of light. Our newest opsins can also now respond to deep red light bordering on the infrared, which stays more sharply focused, penetrates tissues more easily and is very well tolerated.

Molecular engineering has also extended optogenetic control beyond cells' electrical behaviors to their biochemistry. A large fraction of all approved medical drugs act on a family of membrane proteins called G-protein-coupled receptors. These proteins sense extracellular signaling chemicals, such as epinephrine, and respond by changing the levels of intracellular biochemical signals, such as calcium ions, and thus the activity of the cells. By adding the light-sensing domain from a rhodopsin molecule to G-protein-coupled receptors, Raag D. Airan and others in my laboratory developed a set of receptors called optoXRs that respond rapidly to green light. When viruses insert genetic constructs for optoXRs into the brains of lab rodents, the optoXRs provide us with control over biochemical events in the animals while they are moving freely within a cage. Fast and cell type–specific optical control over biochemical pathways is now therefore possible, both in laboratory dishes and in untethered mammals; this control over biochemistry opens the door to optogenetics in essentially every cell and tissue in biology.

Many of the natural opsin genes now being discovered in various microbes' genomes encode proteins that mammalian cells do not make well. But Viviana Gradinaru in my group has developed a number of general-purpose strategies for improving their delivery and expression. For example, pieces of DNA can be bundled with the opsin genes to act as "zip codes" to ensure the genes are transported to the correct compartments within mammalian cells and translated properly into functional proteins. And with fiber-optic tools we developed in 2006 and 2007, investigators can now deliver light for optogenetic control to any area of the brain—whether surface or deep—in freely moving mammals. And to enable simultaneous readouts of the dynamic electrical signals elicited by optogenetic control, we have developed millisecond-scale instruments that are integrated hybrids of fiber optics and electrodes (which we call "optrodes").

The motivation to improve understanding in clinical psychiatry was more than enough to justify the extremely high risk of failure.

A beautiful synergy can emerge between optical stimulation and electrical recording because the two can be set up to not interfere with each other. We can now, for instance, directly observe the changing electrical activity in the neural circuits involved in motor control at the same time as we are optically controlling those circuits with microbial opsins. The more rich and complex the optogenetic inputs and electrical outputs of neural circuits become, the more we will be able to move toward a form of reverse engineering for neural circuitry: we will be able to infer the computational and informational roles of neural circuits from how they transform our signals. Reverse-engineering healthy neural circuits will offer wonderful opportunities for determining which properties and activities differ in psychiatric and neurological disease states. That knowledge, in turn, should



The virus infects many nerve cells, but because of the promoter only one type of neuron makes the opsin protein.

Fiber-optic probes inserted into the animal's brain can flash light on the brain to control specific patterns of neural activity.

help guide efforts to find interventions able to restore normalcy in those circuits.

REVERSE-ENGINEERING THE MIND

THE IMPORTANCE OF OPTOGENETICS as a research tool, particularly in conjunction with other technologies, continues to grow rapidly. In recent years neuroscience has made many advances based on the brain-scanning technique called functional magnetic resonance imaging (fMRI). These scans are usually billed as providing detailed maps of neural activity in response to various stimuli. Yet strictly speaking, fMRI only shows changes in blood-oxygen levels in different areas of the brain, and those changes are just a proxy for actual neural activity.

Some nagging uncertainty has therefore always surrounded the question of whether these complex signals can be triggered by increases in local excitatory neural activity. This past May, however, my laboratory used a combination of optogenetics and fMRI (ofMRI) to verify that the firing of local excitatory neurons is fully sufficient to trigger the complex signals detected by fMRI scanners. In addition, the pairing of optogenetics and fMRI can map functional neural circuits with an exactness and completeness not previously possible with electrodes or drugs. Optogenetics is thereby helping to validate and advance a wealth of scientific literature in neuroscience and psychiatry.

Indeed, the impact of optogenetics has already been felt directly on some questions of human disease. In animals, we have employed optogenetics on a kind of neuron (hypocretin cells) deep in a part of the brain previously implicated in the sleep disorder narcolepsy. Specific types of electrical activity in those neurons, we have found, set off awakening. Finding a way to induce that neural activity clinically might therefore offer a treatment someday, but most important is the scientific insight that specific kinds of activity in specific cells can produce complex behaviors.

Optogenetics is also helping to determine how dopamine-making neurons may give rise to feelings of reward and pleasure. My team optogenetically induced differently timed bursts of activity in well-defined sets of dopamine neurons in freely moving mice. We identified the stimulus patterns that appeared to drive a sense of reward for the animals. In the absence of any other cue or reward, mice chose to spend more time in places where they had received particular kinds of bursts of activity in their dopamine neurons. This information is useful for teasing out the cellular activity underlying both the normal reward process and the pleasure-system pathologies involved in depression and substance abuse.

The optogenetic approach has also improved our understanding of Parkinson's, which involves a disturbance of information processing in certain motor-control circuits of the brain. Since the 1990s some Parkinson's patients have received a measure of relief from a therapy called deep-brain stimulation, in which an implanted device similar to a pacemaker applies carefully timed oscillating electric stimuli to certain areas far inside the brain, such as the subthalamic nucleus.

Yet the promise of this technique for Parkinson's (and indeed for a variety of other conditions) is partially limited because electrodes stimulate nearby brain cells unselectively and medical understanding of what stimuli to apply is woefully incomplete. Recently, however, we have used optogenetics to study animal models of Parkinson's and gained fundamental insight into the nature of the diseased circuitry and the mechanisms of action of therapeutic interventions.

We have found, for example, that deep-brain stimulation may be most effective when it targets not cells but rather the

MOLECULAR ASSETS

An Expanding Tool Kit of Useful Genes

Scientists continue to expand the capabilities of optogenetics by tinkering with the genes of known opsins and by searching for those of additional light-responsive proteins in nature. New opsins with desirable characteristics, used alone or in combination, enable researchers to solve biological mysteries through once impossible experiments. Below are some valued categories of opsins and their uses.

OPSIN	MICROBE SOURCE	WAVELENGTH SENSITIVITY	USES
Ultrafast channelrhodopsin (ChR2) mutants	*Chlamydomonas reinhardtii* alga	470 nanometers (maximum activation)	For rapid on/off activation of firing in neurons with millisecond precision, up to 200 times per second
Step function opsins (ultraslow ChR2 mutants)	*Chlamydomonas reinhardtii* alga	470 nm for switching on; 546 nm for switching off some mutants	For switching cells in and out of excitable states with only brief flashes of light. Because of their light sensitivity, they are particularly useful for experiments in which light must penetrate through substantial volumes of tissue (as in the brains of mammals)
VChR1 channelrhodopsin	*Volvox carteri* alga	535 and 589 nm	For activating neural firing. Because VChR1 responds to yellow light and ChR2 responds to blue, both types of opsins can be used together to simultaneously and independently control firing in co-mingled populations of neurons
OptoXRs	Synthetic, based on rhodopsin and G-protein-coupled receptors	500 nm	For fast and cell type–specific control over biochemical pathways, rather than electrical signals, in targeted cells. Can be used in free-roaming experimental animals

Does Optogenetics Challenge Ethics?

Optogenetics now joins the ranks of brain-modulation technologies, such as psychoactive drugs and surgical interventions, that are strong enough to raise ethical and philosophical questions. Yet if we look at it one way, optogenetics is actually safer and less fraught with ethical considerations than those older strategies. The increased power and specificity of optogenetics are coupled to its technological complexity: it would be virtually impossible to use optogenetics on an unwitting or unwilling patient.

More subtle (and perhaps more interesting) new issues arise from the precision of optogenetics, however. At some level, all aspects of our personalities, priorities, capabilities, emotions and memories arise from electrical and biochemical events within particular sets of neurons in particular temporal patterns. Controlling those key components of the mind would raise challenging philosophical questions, ranging from when it is appropriate or justifiable to make such modifications to more abstract questions about the very nature and modifiability of the self and the will.

Neural interventions based on surgery, drugs or electrodes have historically been so coarse that those important philosophical issues have been more theoretical than practical; ethicists and the law have only partially addressed them. The psychiatrist is no stranger to this type of question, given even our current medical capabilities to influence human emotions and the psychological construction of reality.

But times change, as the stunning rapidity of developments in optogenetics over the past few years exemplifies. Quantum leaps in the temporal and cellular precision of our interventions require ongoing and thoughtful consideration by society, as all advanced technologies do. Neuroscientists must therefore be prepared to explain carefully to the interested layperson what optogenetics experiments mean (and do not mean) for our understanding and treatment of the human mind. —*K.D.*

connections between cells—affecting the flow of activity between brain regions. And with our colleague Anatol Kreitzer of U.C.S.F., we functionally mapped two pathways in brain movement circuitry: one that slows movements and one that speeds them up and can counteract the parkinsonian state.

We have also learned how to prod one kind of cell, neocortical parvalbumin neurons, to modulate 40-cycles-per-second rhythms in brain activity called gamma oscillations. Science has known for some time that schizophrenic patients have altered parvalbumin cells and that gamma oscillations are abnormal in both schizophrenia and autism—but the causal meaning of these correlations (if any) was not known. Using optogenetics, we showed that parvalbumin cells serve to enhance gamma waves and that those waves in turn enhance the flow of information through cortical circuits.

In my patients with schizophrenia, I see what clearly appear to be information-processing problems, in which mundane random events are incorrectly viewed as parts of larger themes or patterns (an informational problem perhaps giving rise to paranoia and delusions). These patients also suffer from some failure of an internal "notification" mechanism that informs us when thoughts are self-generated (an informational problem perhaps underlying the frightening phenomenon of "hearing voices"). In my patients with autism spectrum disease, rather than inappropriately broad linkages in information, I see overly restricted information processing: they miss the big picture by focusing too narrowly on just parts of objects, people, conversations, and so on. These failures of information processing may lead to failures in communication and social behavior; better understanding of gamma oscillations may therefore provide insights into these complex diseases.

As a physician, I find this work thrilling because we are bringing engineering principles and quantitative technology to bear on devastating, seemingly "fuzzy" and intractable psychiatric diseases. Optogenetics is thus helping to move psychiatry toward a network-engineering approach, in which the complex functions of the brain (and the behaviors it produces) are interpreted as properties of the neural system that emerge from the electrochemical dynamics of the component cells and circuits. It thus fundamentally changes our understanding of how electrically excitable tissues function in health and disease. It has indeed been a long (and unpredictable) journey from marveling at the way a strange bacterial protein—bacteriorhodopsin—reacts to light.

BOUNTY OF THE UNEXPECTED

At meetings of the Society for Neuroscience and some other very large conferences, I have occasionally heard colleagues suggest that it would be more efficient to focus tens of thousands of scientists on one massive and urgent project at a time—for example, Alzheimer's disease—rather than pursue more diverse explorations. Yet the more directed and targeted research becomes, the more likely we are to slow overall progress, and the more certain it is that the distant and untraveled realms of nature, where truly disruptive ideas can arise, will be utterly cut off from our common scientific journey.

The lesson of optogenetics is that the old, the fragile and the rare—even cells from pond scum or from harsh Saharan salt lakes—can be crucial to comprehension of ourselves and our modern world. The story behind this technology underscores the value of protecting rare environmental niches and the importance of supporting true basic science. We should never forget that we do not know where the long march of science is taking us or what will be needed to illuminate our path. SA

MORE TO EXPLORE

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Optical Deconstruction of Parkinsonian Neural Circuitry. Viviana Gradinaru et al. in *Science*, Vol. 324, pages 354–359; April 17, 2009.

Temporally Precise in Vivo Control of Intracellular Signaling. Raag D. Airan et al. in *Nature*, Vol. 458, pages 1025–1029; April 23, 2009.

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