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Technology & Engineering,Brain & Behavior

# New light on brain science

*What scientists have been learning by using light to turn brain cells on or off*

By Kathiann Kowalski 7:15am, October 23, 2015

Researchers used flashes of blue light to trigger neurons to fire off electrical impulses in genetically modified in mice. This — an example of optogenetics — produced different rhythms of brainwaves and made the mice more sensitive to touch.

Michael Cohea, Brown University

Flip a switch and you can turn on or off lights, fans and all sorts of other things. Individual nerve cells in the brain are now the latest addition to this list. Over the past decade, scientists have found a way to use light to control the brain's nerve cells, or neurons.

This new field is called optogenetics (OP-toh-jeh-NEH-tix). *Opto-* is a prefix that refers to light. Genetics deals with the biological instructions encoded in our genes. As its name suggests, this new technology uses light to either turn on or shut down genetically programmed actions in brain cells.

Keith Bonin calls this technology "revolutionary." He says it "is going to allow us to much better understand how the brain works." A physicist, Bonin works at Wake Forest University in Winston-Salem, N.C.

The brain acts as command central for everything we do. It's a hive of neurons — an estimated 86 billion of them. The brain also contains many different types of neurons. As many as 100,000 of the very smallest would fit on the head of a pin.

To understand how animals move, learn or behave, scientists used to have to wait and watch, hoping they would be there when an anticipated event or behavior might occur. No longer. With optogenetics, scientists now can turn on these tasks or behaviors with the flip of a switch. A light switch.

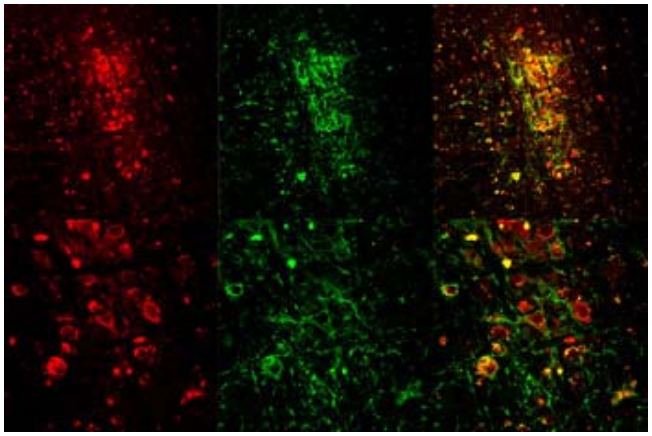
This new technology is opening up new pathways for research. For instance, scientists are learning more about what goes right in healthy brains — and wrong when brains are afflicted by various disorders.

**Finding the right chemical switches**

In many ways, the brain is a living computer. It receives data, processes them into information and then generates a response. And the brain does these things with electricity, just as computers do.

With a computer, however, you can easily enter data and then run a program to see what happens. Researchers have long wanted to do that with the brain. But it hasn't been easy.

"There's no keyboard for the brain," notes Ed Boyden. He's a neuroscientist at the Massachusetts Institute of Technology (MIT) in Cambridge. He was on the research team in 2004 that first got optogenetics to work.



Researchers at the Massachusetts Institute of Technology made these images when they used optogenetics to trigger Rapid Eye Movement, or REM, sleep in mice. The left image shows a signaling chemical called acetylcholine. The middle shows light-sensitive ion gates. The far right image merges the two.
Christa J. Van Dort et al., MIT

Proteins are molecules that form the basis of living cells and other tissues. Many also serve as molecules that perform actions in and around cells. Boyden's group identified proteins that were sensitive to light. They became the key to optogenetics.

Your eye contains opsin (OP-sin), one of these proteins. When light reaches cells of the retina at the back of the eyes, opsin triggers electrical signals. Immediately, those signals shoot to the brain. The brain then translates those signals into sight.

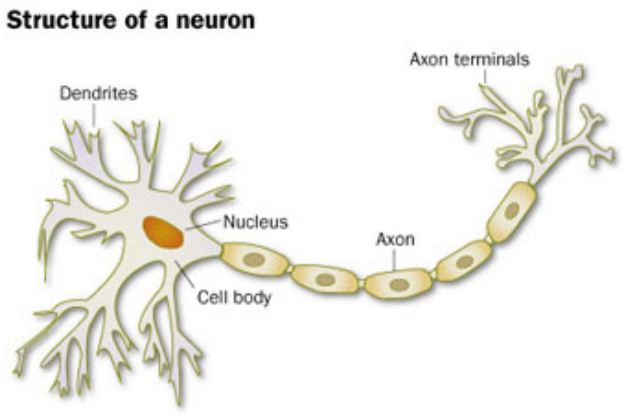
Lots of bacteria, fungi, algae and plants have opsins too. Many opsins work like gatekeepers. Think of the gate as a one-way turnstile, says Bonin. When light hits the turnstile, the opsin allows an *ion* — an atom or molecule with an electric charge — to pass through. Depending on the gate, an opsin can either turn a neuron's action on or off.

Some gates let in positively charged sodium or hydrogen ions. That action produces an electric current. If the current reaches a certain level, the neuron turns on, firing off an electrical impulse. Other gates release negatively charged chloride ions. These can turn a neuron off. That stops its firing.

Both types of gates interest researchers. "We want to do different things to a neuron," Boyden explains. "Sometimes we want to turn it on. And sometimes we want to turn it off."

## Designing switches

The brains of animals generally don't have opsins. But scientists can engineer cells in an animal's brain to make them. They do this by inserting genes from other organisms. Through this *genetic engineering*, the added genes instruct their new host cells to make opsins.

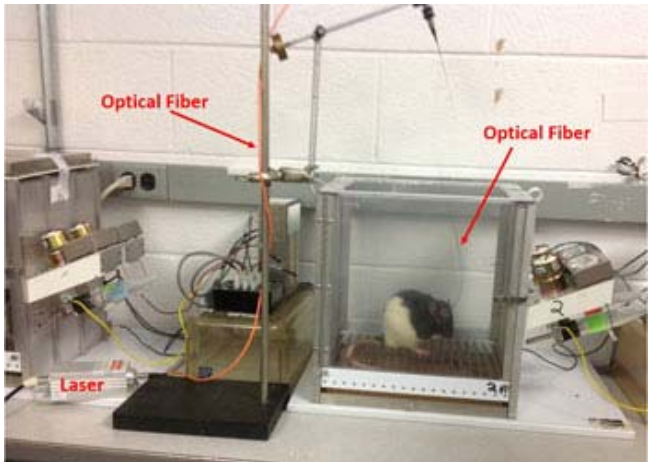



A neuron's axon and dendrites help it to transmit electrical signals. Dendrites bring information to the body of the neuron, and axons take information away from the cell body.
National Cancer Institute

To get light to those cells, researchers implant tiny fiber-optic probes — essentially plastic wires — into the brains of lab animals, such as mice or rats. "When we shine light through this probe, the light goes directly into the brain," Zayra Millan explains. She's a neuroscientist at Johns Hopkins University in Baltimore, Md. As light reaches a neuron, its new opsin starts to work as a gatekeeper. For instance, if the gates open and the current reaches a threshold level, the neuron will fire off an electrical impulse.

This electrical impulse travels down the cell to its end point, or *terminal*. There the impulse triggers the release of some chemical (a neurotransmitter) across a small gap. That gap, called a synapse (SIH-napz), separates the chemical's transmitter from its receiver on some neighboring neuron. This process, Millan explains, is how one brain cell talks to its neighbor.

"This is really the heart of how the brain works — synaptic transmission," says Carl Petersen. He and Aurélie Pala are neuroscientists at the Swiss Federal Institute of Technology in Lausanne. They have used optogenetics to measure communication between individual nerve cells in a live mouse.

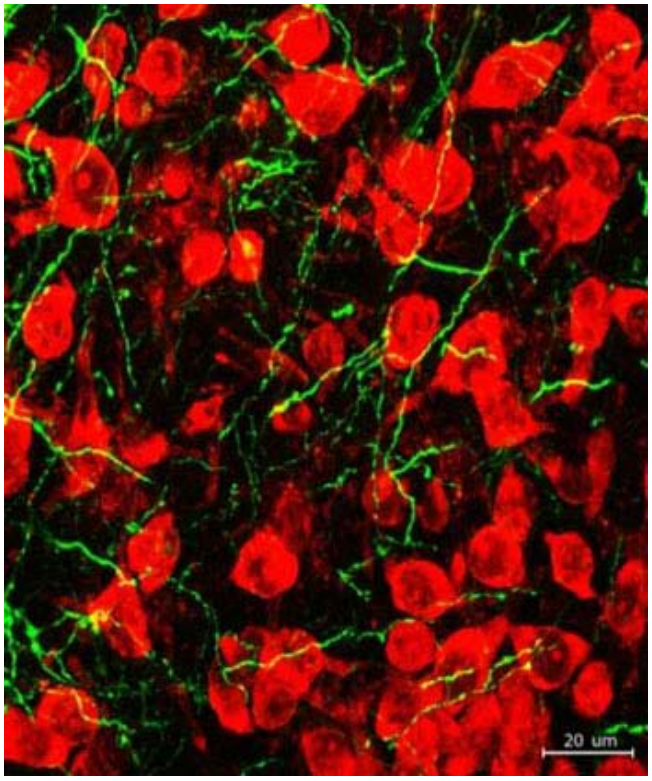


This image shows how researchers at Wake Forest University used lasers and fiber-optic cables to deliver light to genetically modified neurons in a targeted part of a rat's brain. That light then triggered actions that caused neurons to fire.
Evgeny Budygin, Wake Forest School of Medicine
By adding opsin genes to certain lab animals, "we can genetically target specific cells," Peterson explains. "And just by shining light on [those cells], we can activate them and see what types of signals are driven by the cells." Just a millisecond of light may be all it takes to make a neuron fire, he notes.

He and Pala focused on a chemical messenger called glutamate (GLU-tah-mate). How much of it a cell sends across the synapse varies with the type of neuron on the receiving end, they found. Knowing that can help scientists explore further how different types of connections work. Their findings appeared in the January 7 issue of *Neuron*.

Dopamine (DOH-puh-meen) is another chemical used to relay messages around the brain. Brain neurons naturally release this chemical in a wide range of situations. Some neurons release dopamine to make the body move in certain ways. Others release it when an animal receives something or does something it finds pleasing or rewarding. Exercising and achieving a goal are healthy examples.

Neurons also can release dopamine in response to unhealthy behaviors, such as abusing alcohol or other drugs. Now, with optogenetics, researchers can test whether treatments that boost dopamine in the brains of lab animals will cut their desire for alcohol or drugs.



The red shows nerve cells in part of the brain called the nucleus accumbens. Green shows fibers from neurons in the amygdala that send signals to the nucleus accumbens.
Stuber lab/UNC-Chapel Hill
Two years ago, Bonin at Wake Forest University and his team used optogenetics to trigger the release of dopamine in a brain area called the nucleus accumbens (NU-klee-us Uh-KUM-benz). And sure enough, rats cut their alcohol consumption after 250 light pulses at the rate of 5 per second. A shorter period of flashes with more light pulses per second light did not have that effect. The scientists published their finding in *Frontiers in Behavioral Neuroscience*.

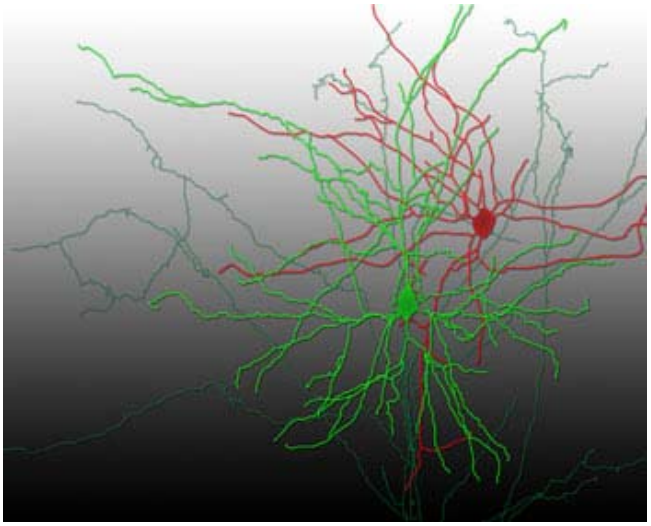
One recent study by Millan at Johns Hopkins also looked at alcohol consumption. It delivered five seconds of flashing light. The light stimulated a brain circuit that starts at the amygdala (Ah-MIG-duh-lah). This structure sits deep inside the brain. The circuit connects the amygdala to the nucleus accumbens. That structure also lies deep in the brain but nearer to the face.

“When we stimulated or turned on this circuit, we were able to stop our animals from drinking alcohol,” Millan says. She presented her findings in November 2014 at the annual meeting of the Society for Neuroscience.

Both studies are helping scientists better understand how brain circuits work. They also might suggest ways to treat addiction. For example, researchers might now identify which cells to target with drugs or other techniques.

**Choosing colors**

In optogenetics, the color of light that a neuron “sees” also matters. The cells "respond to very specific frequencies,” explains Millan. (The color of light is typically measured in *frequencies* — or the number of wavelengths per second for this type of electromagnetic radiation.) In her rat studies, opsins in their brains cause certain neurons to fire only in response to blue light.



The brain contains many different types of neurons. These brain cells are separated by small gaps, called synapses.
A. Pala and C. Petersen, EPFL, Swiss Fed. Inst. of Tech.

Green light, by contrast, was used in a recent study by Joaquim Alves da Silva. He’s a neuroscientist at the Champalimaud Center for the Unknown in Lisbon, Portugal. His team used this light to inhibit, or turn off, certain neurons that release dopamine in mice. The goal was to better understand the role that dopamine plays in movement. Such knowledge might lead to better treatments for people with disorders, such as Parkinson’s disease. Its characteristic tremors are triggered by a shortage of dopamine. Alves da Silva presented his team’s green-light data, too, at the 2014 Society for Neuroscience meeting.

Some opsins even respond to red light. In 2014, Boyden’s group found an opsin in algae that they called Chrimson. Red light makes this protein excite, or turn on, neurons. The team published its findings in the March 2014 issue of *Nature Methods*.

A second red-sensitive opsin can turn off firing in these neurons, Boyden’s group reported in the August 2014 *Nature Neuroscience*. They found this opsin, called Jaws, in a type of single-celled marine organism called an archaeon (Ar-KEE-on).

Finding such opsins expands the types of research scientists can do. For example, Bonin explains, a study might test whether turning on two types of nerve cells — each with a different opsin — gives different results from switching on just one.

Red light also has a longer wavelength than other colors. “If you aimed red light at the brain, it could go very deep,” Boyden notes. That means researchers might not even need a fiber optic probe to deliver this light to its target.

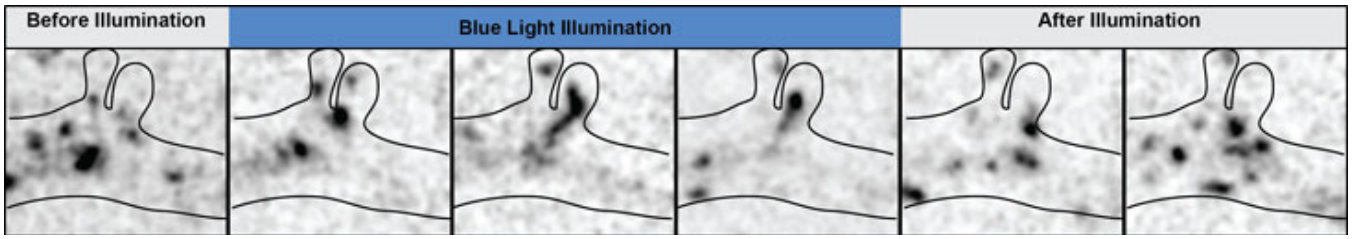
**More possibilities**

Turning neuron signaling on and off is not the only trick optogenetics can perform. Proteins besides opsins might let scientists affect other processes in cells.

Recently, scientists found a way to use light to control motor proteins in cells. “These are molecules that can literally walk and take steps of 8 to 30 nanometers along protein fibers that are present in the cells,” explains Lukas Kapitein. He’s a cell biologist at Utrecht University in the Netherlands. (A nanometer is one-billionth of a meter.)

Motor proteins move materials within a cell. But the proteins only do this when they are connected to their cargo. Think of how a trailer won’t haul goods until it is hitched to a truck that can tow it.

Kapitein and his colleagues found a way to use light to trigger that connection and get things moving. Now, he says, “We can really control transport action within the cell.” His team described how the process works, earlier this year, in the January 8 issue of *Nature*. The method can help researchers learn more about the shape, organization and function of cells in the brain and elsewhere.




Researchers at Utrecht University used blue light to get proteins to move special structures (organelles) inside nerve cells to their outermost branches. That’s where those cells receive signals from neighboring cells. Such movement may play a role in how neurons grow or form connections. Petra van Bergeijk et al., Utrecht University

Boyden’s group published the first study on optogenetics just 10 years ago this past summer. Since then, this field has opened new ways to explore how neurons work. The next 10 years will teach researchers even more.

For instance, optogenetics “will help us improve our understanding of how to treat different psychiatric and neurological disorders,” Bonin predicts. This knowledge could lead to new medicines and therapies for a wide range of medical conditions.

One day, optogenetics might itself become a treatment. That’s even more likely if red light can reach cells without the need to implant probes. “One of the dreams is that you could do this noninvasively,” Boyden says — meaning without having to physically open the body or send a tool into it.

Imagine treating addiction, Alzheimer’s disease, Parkinson’s disease and other disorders with pulses of light. It all starts with shining more light on understanding how our brain works.

## Power Words

**(for more about Power Words, click here)**

**addiction** The uncontrolled use of a habit-forming drug or uncontrolled and unhealthy habit (such as video game playing or phone texting). It results from an illness triggered by brain changes that occur after using some drugs or engaging in some extremely pleasurable activities. People with an addiction will feel a compelling need to use a drug (which can be alcohol, the nicotine in tobacco, a prescription drug or an illegal chemical such as cocaine or heroin), even when the user knows that doing so risks severe health or legal consequences. (For instance, even though 35 million Americans try to quit smoking each year, fewer than 15 out of 100 succeed. Most begin smoking again within a week, according to the National Institute on Drug Abuse.)

**algae** Single-celled organisms, once considered plants (they aren't). As aquatic organisms, they grow in water. Like green plants, they depend on sunlight to make their food.

**Alzheimer's disease** An incurable brain disease that can cause confusion, mood changes and problems with memory, language, behavior and problem solving. No cause or cure is known.

**amygdala** Area deep within the brain and near the temporal lobe. Among other things, the amygdala plays a role in emotions. The term comes from the Greek word for an almond, which its shape resembles.

**atom** The basic unit of a chemical element. Atoms are made up of a dense nucleus that contains positively charged protons and neutrally charged neutrons. The nucleus is orbited by a cloud of negatively charged electrons.

**biology** The study of living things. The scientists who study them are known as biologists.

**data** Facts and statistics collected together for analysis but not necessarily organized in a way that give them meaning. For digital information (the type stored by computers), those data typically are numbers stored in a binary code, portrayed as strings of zeros and ones.

**DNA** (short for **deoxyribonucleic acid**) A long, double-stranded and spiral-shaped molecule inside most living cells that carries genetic instructions. In all living things, from plants and animals to microbes, these instructions tell cells which molecules to make.

**dopamine** A neurotransmitter, this chemical helps transmit signals in the brain.

**electric charge** The physical property responsible for electric force; it can be negative or positive.

**electromagnetic radiation** Energy that travels as a wave, including forms of light. Electromagnetic radiation is typically classified by its wavelength. The spectrum of electromagnetic radiation ranges from radio waves to gamma rays. It also includes microwaves and visible light.

**fiber optics** The use of thin, flexible fibers of glass (known as optical fibers) or other transparent solids to transmit light signals, chiefly for telecommunications.

**frequency** (In physics) The number of wavelengths that occurs over a particular interval of time.

**gene** (adj. **genetic**) A segment of DNA that codes, or holds instructions, for producing a protein. Offspring inherit genes from their parents. Genes influence how an organism looks and behaves.

**genetic engineering** (or **genetic modification**) The direct manipulation of an organism's genome. In this process, genes can be removed, disabled so that they no longer function, or added after being

taken from other organisms. Genetic engineering can be used to create organisms that produce medicines, or crops that grow better under challenging conditions such as dry weather, hot temperatures or salty soils.

**hydrogen** The lightest element in the universe. As a gas, it is colorless, odorless and highly flammable. It's an integral part of many fuels, fats and chemicals that make up living tissues.

**information** (as opposed to **data**) Facts provided or trends learned about something or someone, often as a result of studying data.

**ion** An atom or molecule with an electric charge due to the loss or gain of one or more electrons.

**microscope** An instrument used to view objects, like bacteria, or the single cells of plants or animals, that are too small to be visible to the unaided eye. Microscopy is the field of technology devoted to using microscopes.

**molecule** An electrically neutral group of atoms that represents the smallest possible amount of a chemical compound. Molecules can be made of single types of atoms or of different types. For example, the oxygen in the air is made of two oxygen atoms ($O_2$), but water is made of two hydrogen atoms and one oxygen atom ($H_2O$).

**nano-** A prefix indicating a billionth. In the metric system of measurements, it's often used as an abbreviation to refer to objects that are a billionth of a meter long or in diameter.

**neuron** or **nerve cell** Any of the impulse-conducting cells that make up the brain, spinal column and nervous system. These specialized cells transmit information to other neurons in the form of electrical signals.

**neuroscience** Science that deals with the structure or function of the brain and other parts of the nervous system. Researchers in this field are known as **neuroscientists**.

**noninvasive** Not requiring surgery or other procedures to see or affect something inside an organism.

**nucleus accumbens** An area deep within the front part of the brain that is linked to pleasure and motivation.

**opsin** A light-sensing protein such as that found in a part of the eye called the retina.

**optogenetics** A technique that uses light to better understand genes and cells in the nervous system, especially the brain.

**Parkinson's disease** A disease of the brain and nervous system that causes tremors and affects movement, memory and mood.

**physicist** A scientist who studies the nature and properties of matter and energy.

**proteins** Compounds made from one or more long chains of amino acids. Proteins are an essential part of all living organisms. They form the basis of living cells, muscle and tissues; they also do the work inside of cells. The hemoglobin in blood and the antibodies that attempt to fight infections are among the better known, stand-alone proteins. Medicines frequently work by latching onto proteins.

**psychiatry** (adj. **psychiatric**) A field of medicine where doctors study and treat diseases of the human mind. Treatments may consist of talking therapies, prescription drugs or both.

**retina** A layer at the back of the eyeball containing cells that are sensitive to light and that trigger nerve impulses that travel along the optic nerve to the brain, where a visual image is formed.

**sodium** A soft, silvery metallic element that will interact explosively when added to water. It is also a basic building block of table salt (a molecule of which consists of one atom of sodium and two atoms of chlorine: $H_2O$).

**synapse** The junction between neurons that transmits chemical and electrical signals.

**terminal** The end point or last station in some system, network or process. The end of the line.

**wavelength** The distance between one peak and the next in a series of waves, or the distance between one trough and the next. Visible light — which, like all electromagnetic radiation, travels in waves — includes wavelengths between about 380 nanometers (violet) and about 740 nanometers (red). Radiation with wavelengths shorter than visible light includes gamma rays, X-rays and ultraviolet light. Longer-wavelength radiation includes infrared light, microwaves and radio waves.

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# Further Reading


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Questions for 'New light on brain science.'

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