Core Concept Neuroscience and Psychology Collection Article

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Shedding Light on How the Brain Works Using Optogenetics

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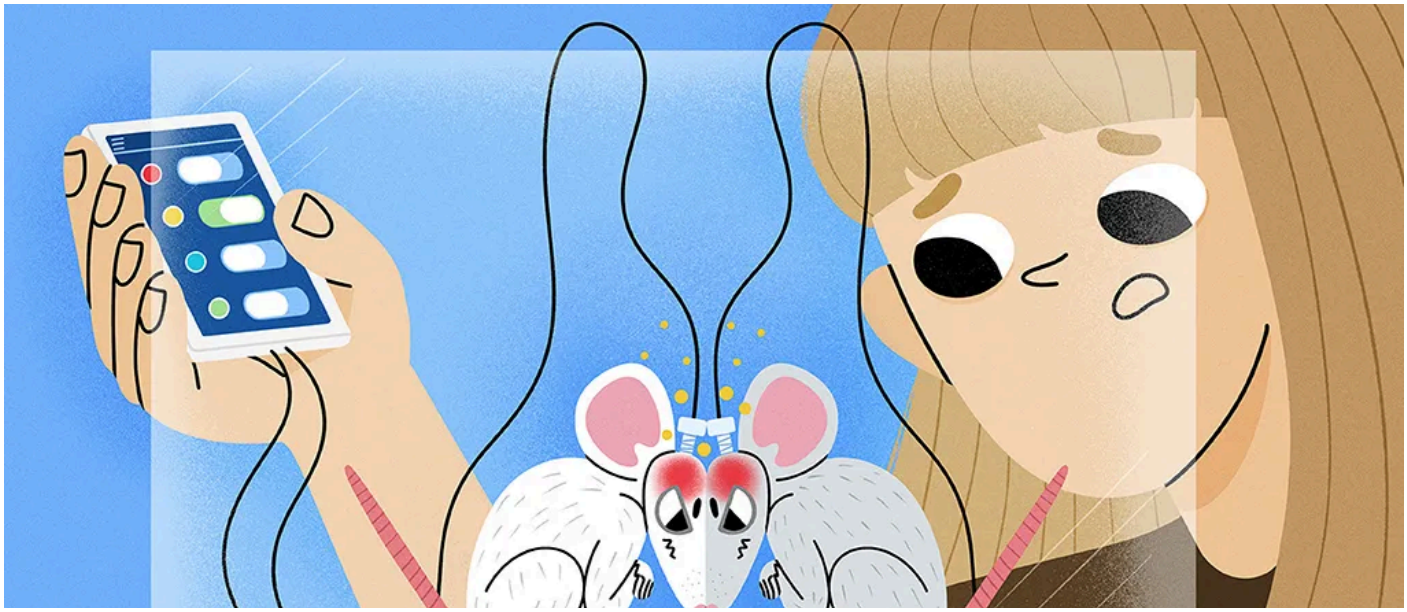

Abstract

what it means to be human, help "fix" the brain when diseases cause it to malfunction, and inspire better artificial intelligence. To gain this understanding, we need tools that let us break the brain down into its building blocks, see how they work, and control their activity. In this article, I describe optogenetics—a method for controlling brain activity with light—and how combining optogenetics with other tools may bring us closer to truly understanding the brain—and what it means to be human.

Professor Edward Boyden won the Brain Prize in 2013, together with Ernst Bamberg, Karl Deisseroth, Peter Hegemann, Gero Miesenböck, and Georg Nagel "for their invention and refinement of optogenetics. This revolutionary technique allows genetically specified populations of neurons to be turned on or off with light, offering not only the ability to elucidate (understand) the characteristics of normal and abnormal neural circuitry but also new approaches to treatment of brain disorders".

The Brain Prize is an international award that recognizes and celebrates highly original and groundbreaking advances in any area of brain research, from basic neuroscience to applied clinical research. Since it was founded in 2011 and up until 2025, The Brain Prize has been awarded to 49 scientists from 11 countries.

Engineering Brain Cells to Respond to Light

As a physicist and engineer, I like to think of the brain as a kind of computer that runs on chemistry. We understand human-made computers so well because we know all their parts and how they work together (in large part because humans designed them). I try to apply the same idea to the brain: break it d into parts and figure out how each one works with the others (you can lear

called neurons. That is why my lab focuses on inventing such tools.

One of the tools we have developed is called optogenetics (Figure 1) [1]. Optogenetics lets us turn the electrical activity of brain cells "on" and "off" using light. We do this by borrowing the DNA instructions for natural light-sensitive proteins found in organisms like bacteria and algae. We deliver these instructions into brain cells, and the cells then make the light-sensitive proteins themselves and place them in their outer membrane.

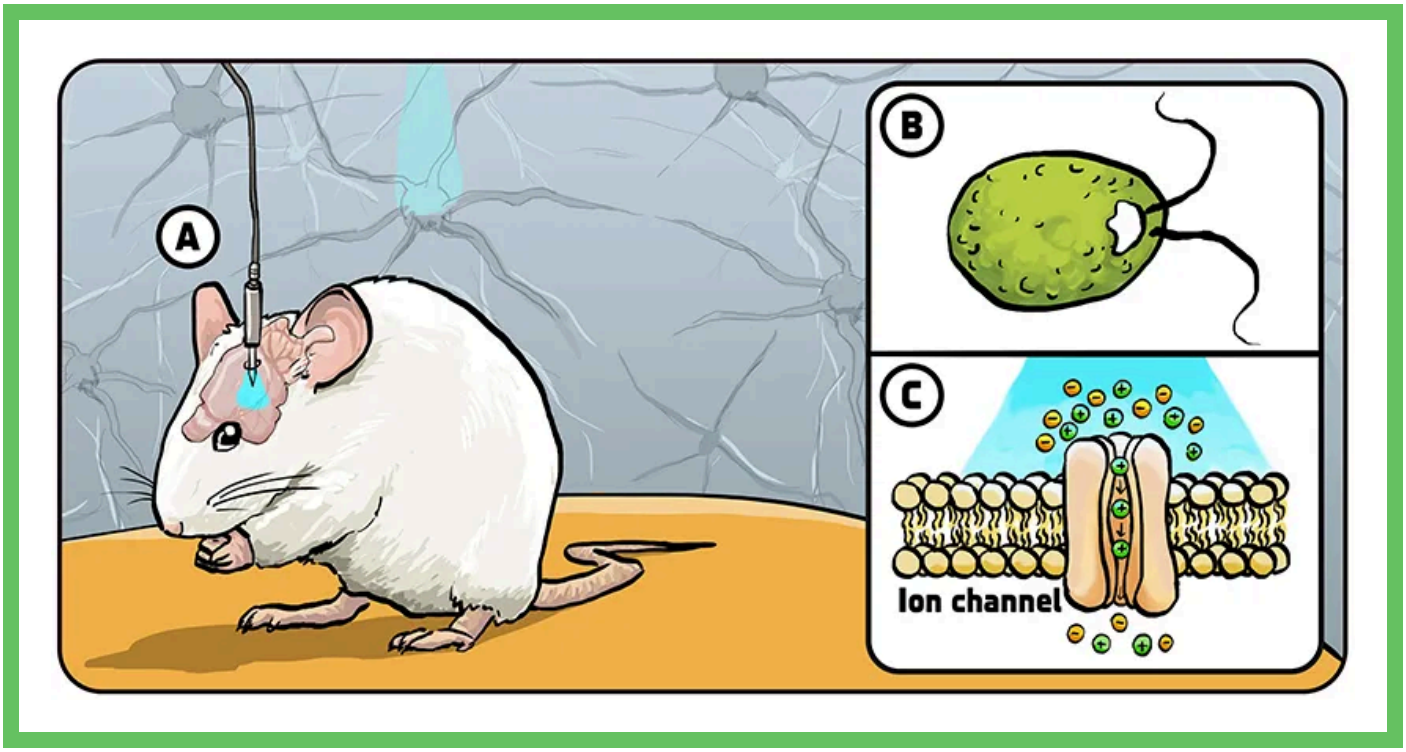

Figure 1 - Switching brain cells "on" and "off".
(A) In optogenetics, scientists provide brain cells with instructions to build light-sensitive proteins that are used to turn those cells "on" or "off" using light. **(B)** These light-sensitive proteins originally came from natural organisms like bacteria and algae, which use them to respond to sunlight. **(C)** Some of these proteins act as ion channels: when light hits them, they open like small tunnels in the cell membrane, letting positive ions flow through and changing the cell's electrical activity. Other proteins act as ion pumps and push negative ions across the membrane, influencing whether the brain cell is active or quiet.

We use two main kinds of light-controlled proteins. The first kind is ion channels, which sit in the cell membrane. When you shine light on light-

actively "pump" ions from one side of the cell membrane to the other. Together, these channels and pumps let us electrically activate or silence brain cells. This technique is so precise that we can target individual cells or specific types of cells.

Before optogenetics, a common way to change the activity of brain cells was by using electrodes—small metal wires that carry electricity. But, when using electrodes, it is almost impossible to focus the control on specific cells, or specific types of cells – instead, electricity goes in all directions, non-specifically engaging cells in the vicinity of the electrode. Optogenetics overcomes this limit by letting us control the activity of specific cells, or types of cells, and not their neighbors, simply by expressing the light-driven ion channel or pump in the targeted cells, and not their undesired neighbors (to learn more about optogenetics and its advantages over electrodes, read this article).

Writing Brain Activity With Optogenetics

The great strength of optogenetics is that it lets scientists test causality—how the electrical activity of brain cells creates behaviors and healthy or unhealthy brain states. By activating a cell, or a group of cells of a specific kind (the cells of the brain come in thousands of kinds, which differ in their shapes, molecular composition, etc.), we can see whether their activity is sufficient to initiate a certain behavior. By silencing the same cells, we can see whether they are necessary for that behavior to occur. For example, a group at the California Institute of Technology activated a set of cells in the brains of male mice using optogenetics, and the mice became violent—even attacking a rubber glove. This experiment showed that this specific set of cells was sufficient to trigger violent behavior. When they silenced those cells with drugs, the violent behavior stopped—revealing a clear causal link between those neurons and aggressive behaviors (Figure 2) [2].

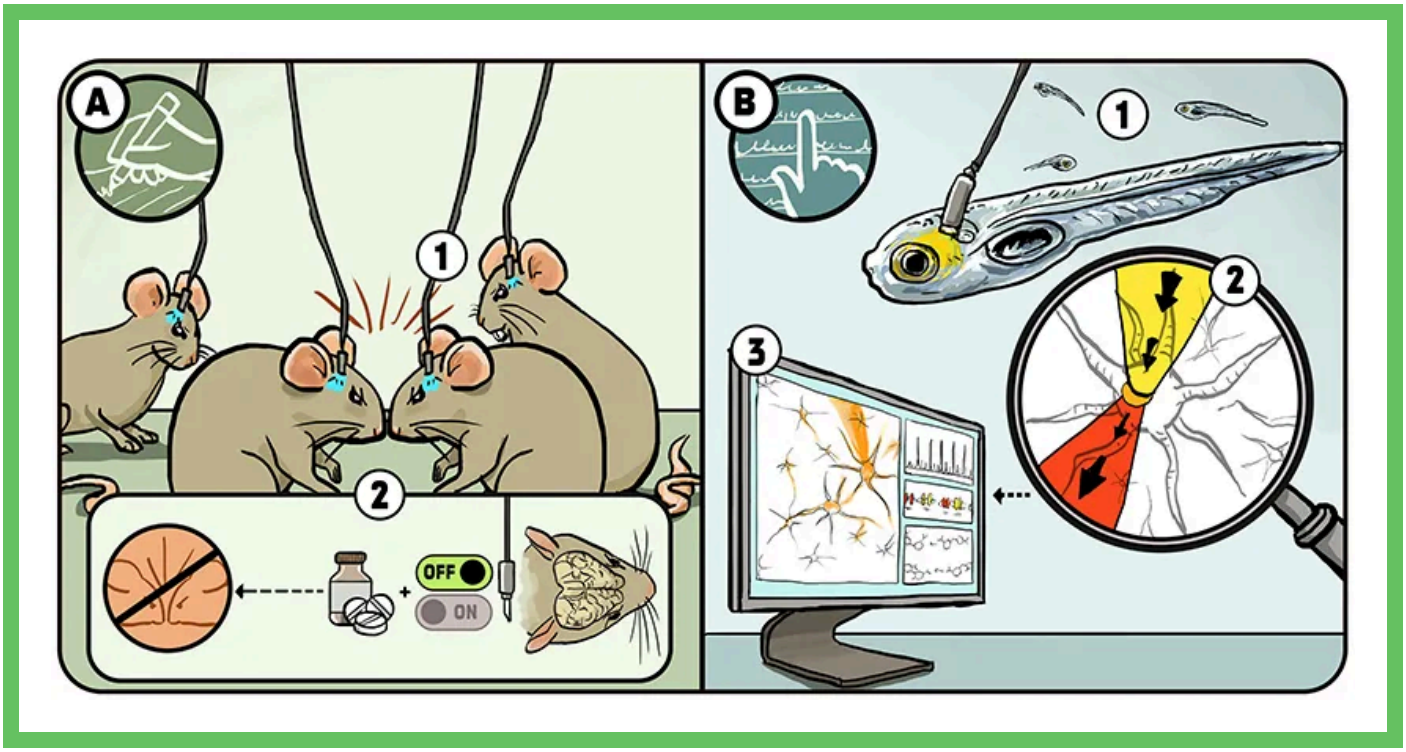

Figure 2 - Writing and reading brain activity with light.
(A) Using optogenetics in male mice, scientists showed that turning on certain brain cells with light caused the mice to behave aggressively (1). When they silenced these cells with a drug, the aggressive behavior disappeared (2), showing that this group of brain cells triggers aggression.
(B) In my lab, we use light-based "reading" tools in larval zebrafish (1). When we shine yellow light on modified optogenetic proteins in their brain cells, the cells emit red light (2). We record this glow with a camera to see which cells are active, and to watch activity patterns across nearly the entire brain (3).

So far, we have focused on the "writing" capabilities opened up by optogenetics—controlling brain activity by turning neurons on or off with light. But we can also modify optogenetic tools to "read" the brain and watch neurons work in real time. This is done by modifying light-sensitive proteins so that, instead of changing the cell's activity, the proteins glow when the cell's electrical activity changes. When we shine light of one color, like yellow, these proteins emit light of another color, like red—this is called fluorescence (to learn more about the discovery of fluorescent molecules read this article; to see how they are used in brain science, see this article).

us see the electrical activity of brain cells, almost like watching the switches inside a computer click on and off. By improving this method, my lab recently achieved something no one had done before: we imaged the millisecond timescale electrical activity of neurons distributed across an entire brain [3]!

The ability to write and read brain activity using optogenetic, and modified optogenetic tools, respectively, is an incredibly powerful way to learn about the brain. It can reveal normal patterns of brain activity, identify which patterns go wrong in diseases so we can try to fix them, and inspire new kinds of artificial intelligence that more closely mimic brain processes.

Surprising Discoveries Using Optogenetics

There are many more examples of fascinating discoveries made using optogenetics. A team from Harvard University, for instance, found that a relatively small group of cells deep in the brain controls different aspects of parenting behavior in mice, involving movement, motivation, and social interaction (Figure 3) [4]. When the researchers changed the activity of these brain cells, the way mice cared for their offspring changed as well. Discoveries like this give brain scientists hope that we can one day build a kind of “map” showing which brain cells are responsible for which behaviors and functions.

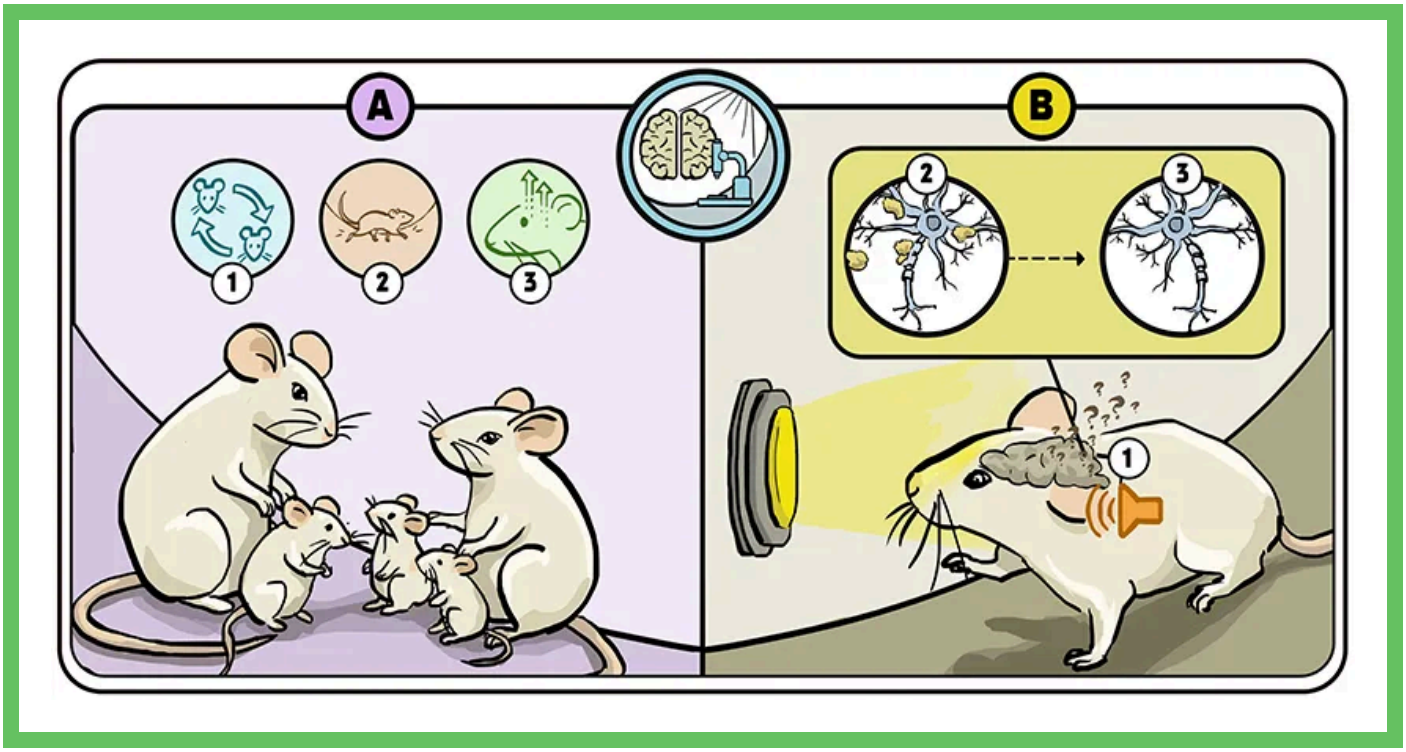

Figure 3 - Two surprising discoveries.
(A) One team of scientists discovered that parenting behavior in mice is controlled by a small group of brain cells. By changing the activity of these cells, they could alter how much the parents interacted with their pups (1), how they moved to care for them (2), and how protective they acted toward them (3). **(B)** My collaborators and I found that a treatment using flickering light and a clicking sound (1) can help reduce symptoms of Alzheimer disease, partly by reducing abnormal protein clumps around brain cells (2), thus keeping those cells healthier (3). The initial principle of this therapy was discovered *via* optogenetics.

Optogenetics is also helping scientists search for new treatments for brain diseases. One of my favorite examples comes from a collaboration between my lab and another team at the Massachusetts Institute of Technology [5]. In mice modified to model Alzheimer's disease, the team used optogenetics to activate brain cells with 40 light flashes per second, delivered to the brain with an optical fiber, and saw that this helped reverse some of the molecular problems associated with the disease. Even more surprising, they later showed that they could get a similar effect without optogenetics—no optical fiber needed—by showing mice a flickering light accompanied by a clicking sound—basically a special kind of "movie". This approach is now being tested in people. Imagine if

would be a truly stunning achievement made possible by optogenetics.

Toward a Simulation of the Brain

One of the things I am most excited about is building a complete model of the brain inside a computer—a simulation. To do that, we must understand the brain's building blocks as well as we understand the parts of a computer chip. In the brain, those building blocks are molecules that interact with each other and with electric fields. If we can fully understand how these molecules behave and interact, we might reach what I call the "microchip moment"—the point where we can study the brain through accurate computer simulations. That would be a huge step toward truly understanding how the brain works.

In my view, the path to this goal is to combine three powerful toolsets. The first two are optogenetics and live imaging, which let us control and watch the electrical activity of brain cells in real time, as I have already described. The third is expansion microscopy [6], which allows us to expand brain tissue so we can map its tiny molecular parts in great detail. By entering all this structural and activity data into computer models that behave like real brain circuits, I hope we can start to answer big questions: What gives rise to our feelings? Why do we have feelings at all, while computers might not feel anything, even when they process similar information? Understanding this could teach us something deep about what it means to be human, and perhaps even help us become kinder to others and better at resolving conflicts.

Problem-Solving Tip: Learning the Skill of Being Lucky

The toughest problems in science—and in life—do not come with ready-made "recipes" that tell us what to do. Solving them requires a set of skills, and one of the most important is learning how to be lucky. Over many years of tackling hard challenges in my lab, I have found principles that help us be more "luc
at discovering powerful solutions. The idea is simple: luck is something you

you want instead of only moving forward from what you already know; systematically listing and organizing all possible solutions to a problem, then drilling down on the ones that are most promising and practical; and learning from failure in ways that bring you closer to success. If you want to explore specific strategies, you can read some of my online articles like this. The main message I want to leave you with is this: luck does not have to be random—it can be engineered, and it is worth taking the time to learn how.

Glossary

Neurons: ↑ Brain cells that send and receive electrical and chemical messages, working together like a computer network.

Optogenetics: ↑ A method that lets scientists turn brain cells "on" or "off" with light.

Causality: ↑ The idea that one action directly leads to a certain result.

Fluorescence: ↑ A colorful glow that happens when a molecule absorbs light of one color and then emits a second, different color.

Alzheimer's Disease: ↑ A brain illness that slowly harms memory and thinking, often making it hard for older people to remember, plan, and recognize others.

Simulation: ↑ A computer-made version of a system—like a brain—that behaves like the real thing, so researchers can study and test it efficiently.

Microchip: ↑ Small electronic devices that process information inside computers.

Expansion Microscopy: ↑ A technique where scientists make brain tissue swell like a sponge so its tiny details become big enough to see clearly under a normal microscope.

Conflict of Interest

ESB is an inventor on numerous patents related to optogenetics, expansion microscopy, and other technologies here described. ESB is a co-founder of Cognito Therapeutics, Eratos Therapeutics, and Expansion Technologies, w

Acknowledgments

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Further Resources

- The Brain Prize 2013 - Optogenetics
- Ed Boyden: A light switch for neurons (TED)
- Ed Boyden, PhD - Toward Computer Simulations of the Brain

AI Tool Statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

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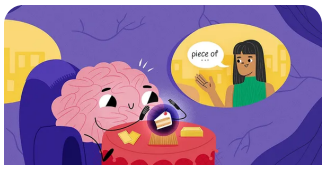

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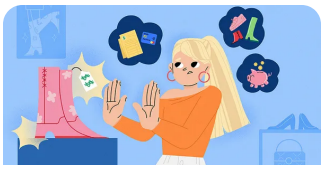

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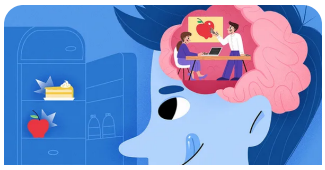

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