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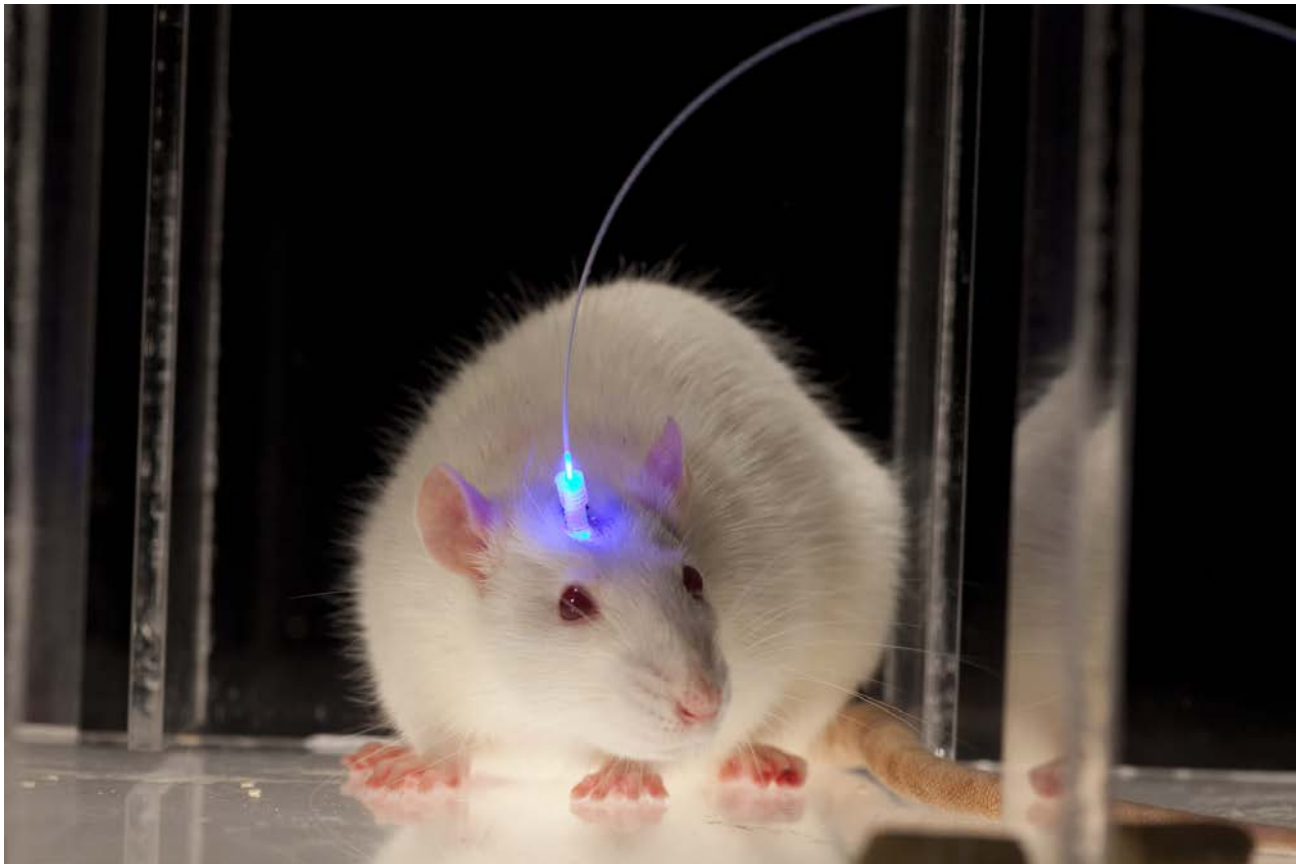
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Optogenetics: understanding the brain, one flash of light at a time

A powerful tool to excite neurons using light is helping researchers to map the brain's connections, and could one day be used to treat blindness, pain and epilepsy. Dyani Lewis reports.



Laser brain: optogenetics lets scientists use light to stimulate specific neurons and see the results.

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Late one night in the summer of 2004, a Stanford PhD student named Ed Boyden flashed a pulse of blue light on to a genetically modified rat neuron. To his delight, the neuron fired in response.

“It was one in the morning and it was almost too good to be true,” recalls Boyden, who has since launched his own bioengineering lab at MIT.

His seminal experiment has revolutionised neuroscience. Being able to excite neurons – the cells that send and receive signals in the brain – with simple flashes of light has given researchers unprecedented control over the brain’s workings.

The technique – dubbed ‘optogenetics’ – is enabling scientists to tease apart how each of the 86 billion-odd neurons stuffed into our skulls makes us tick. Others have more practical applications in their sights, hoping to take optogenetics out of the lab and into the clinic to treat conditions including blindness, chronic pain and epilepsy.

Boyden, along with Karl Deisseroth, a fellow grad student who has gone on to run his own lab at Stanford, wasn’t the only one to stumble upon the idea of making neurons light-sensitive. In 1999 Nobel laureate Francis Crick had **speculated [1]**: “It is conceivable that molecular biologists could engineer a particular cell type to be sensitive to light.”

But other methods developed in the early 2000s were clunky and unreliable. Boyden and Deisseroth’s was the first that **really worked [2]**.

The normal trigger for neurons to transmit an electrical signal is the opening of ion channels in their membranes – molecular gates that allow electrically charged ions to pass through. Deisseroth and Boyden doctored their rat neurons to include a light trigger. The key component is channelrhodopsin, a light-sensitive protein. When channelrhodopsin is zapped by light, it opens the ion channel, and the neuron fires off its electrical signal.

Channelrhodopsins are naturally found in single-celled algae and microbes. Linking light detection to electrical signals enables these microbes to swim towards light.

Most channelrhodopsins only work in the salty conditions where these organisms live. But in 2003, Deisseroth and Boyden got their hands on **one from the freshwater green alga [3]** *Chlamydomonas reinhardtii* [4].

Neurons are finicky cells to work with, according to Boyden. “You just sort of look at them funny and they die,” he says. “Did we know it was going to work? The honest answer is it was luck.”

When details of the light-excitable neurons were published in 2005, others were dubious that the luck would hold. “There was a lot of scepticism,” says Boyden.

OPTOGENETICS IS EXQUISITE IN ITS PRECISION; RESEARCHERS NOW HAVE A TOOL THAT CAN DISSECT OUT INDIVIDUAL NEURONS.

But a handful of labs were soon demonstrating the potential of optogenetics to excite small populations of neurons inside live animals. For the first time, researchers could connect the dots between specific neurons and the behaviours they control. In 2007, for instance, Deisseroth's lab used optogenetics to **wake narcoleptic mice [5]** from their slumber with a flash of blue delivered by an optic fibre inserted directly into the brain.

The optogenetics toolkit has also expanded. Researchers have riffed on the winning formula that Boyden and Deisseroth first dreamed up, creating ion channels that respond to wavelengths from across the rainbow, and versions that switch neurons *off* as well as *on*.

Optogenetics quickly established itself as an essential tool in brain labs around the world. In 2010 it was hailed by *Nature Methods* as **Method of the Year [6]**, and by *Science* magazine as an **Insight of the Decade [7]**. The burgeoning field has also yielded a steady crop of awards for Deisseroth, Boyden and others involved in developing the revolutionary technique.

“It's really been huge, and that's why so many labs have adopted it,” says Lucy Palmer, who heads up the neural networks lab at the Florey Institute of Neuroscience and Mental Health in Melbourne.

Before optogenetics came along, neuroscientists had only coarse tools for unpicking what different regions of the brain do – how they form memories, encode personality traits, and control movements and behaviour. Optogenetics is exquisite in its precision; researchers now have a tool that can dissect out individual neurons. Light-sensitive channels can be targeted to specific populations of neurons that share a unique genetic signature, and these cells can be either turned on or off depending on the protein deployed. “We're able – for the first time – to control one brain region,” says Palmer.

Activating neurons with optogenetics is also whip-fast. And for understanding neural networks, speed matters. Whereas drugs alter neural activity for minutes or hours at a time, light triggers activity from channelrhodopsin-studded neurons in milliseconds – as fast as would occur naturally. This means neurons can be triggered or silenced in real time, their function tested and their connections traced.

Armed with optogenetics, scientists are already making great strides. Decades-old theories of how memories form have **finally been confirmed [8]**, and complex behaviours and emotions such as **compulsive grooming [9]**, **fear [10]**, **depression [11]** and **the urge to kill [12]** have been sparked and muted at will.

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Beyond the brain, too, optogenetics is starting to leave its mark. In recent years, researchers have moved into cells outside of the nervous system, creating **light-sensitive muscle cells [13]** in the heart and **vocal cords [14]**.

While optogenetics continues to pay dividends in the lab, a handful of start-ups are developing optogenetic treatments destined for the clinic. It's a leap that Pankaj Sah, director of the Queensland Brain Institute in Brisbane, sees as "inevitable". In patients with epilepsy, for instance, "if you knew which cells were causing the seizures, and then as soon as the seizure started you could just silence those cells, you could pretty much stop the seizure," he says. "And you wouldn't have to take drugs every day."

But putting optogenetics to work in humans has its challenges. The technique, as it is currently used in the lab, is highly invasive. An optogenetic treatment would first require gene therapy to deliver the channelrhodopsins to specific brain cells using a virus, and then a means of delivering light to those cells. In mice, that's usually via an optical fibre inserted directly into the brain.

Sah doesn't see these hurdles as insurmountable, especially given that electrodes are already embedded in peoples' brains to still the tremors of Parkinson's disease – a technique called deep brain stimulation.

The trailblazing trials for the field are likely to be less invasive, though. Two companies, **Allergan based in Dublin [15]** and **Gen-Sight Biologics based in Paris [16]**, have commenced trials of optogenetics to treat blindness caused by retinitis pigmentosa, a condition that destroys the light-sensing cells of the retina. The idea is to work with the cells just downstream of the destroyed retinal cells. Known as retinal ganglion cells, they are not normally light sensitive but by using a virus to ferry in channelrhodopsin genes, they can be made so. Similar trials last year in monkeys **restored light sensitivity [17]**.

The treatment isn't expected to fully restore vision, but could help people to detect enough light to get around.

Meanwhile, others are looking to peripheral neurons to get around the need to penetrate the skull with light. One company, for instance, is **testing a treatment for chronic pain in pigs [18]** that prevents neurons from sending pain signals to the brain using a flexible LED skin patch to deliver light.

One hope is that the power of optogenetics to tweak brain circuits could one day transform our ability to treat anxiety, depression and schizophrenia.

But that will have to await teasing out exactly what those circuits are.

For now, untangling the messy biology of the brain is where the technique's forte lies.

"I'm a firm believer that what we want to do is to accelerate basic science to understand what we're doing," says Boyden.



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