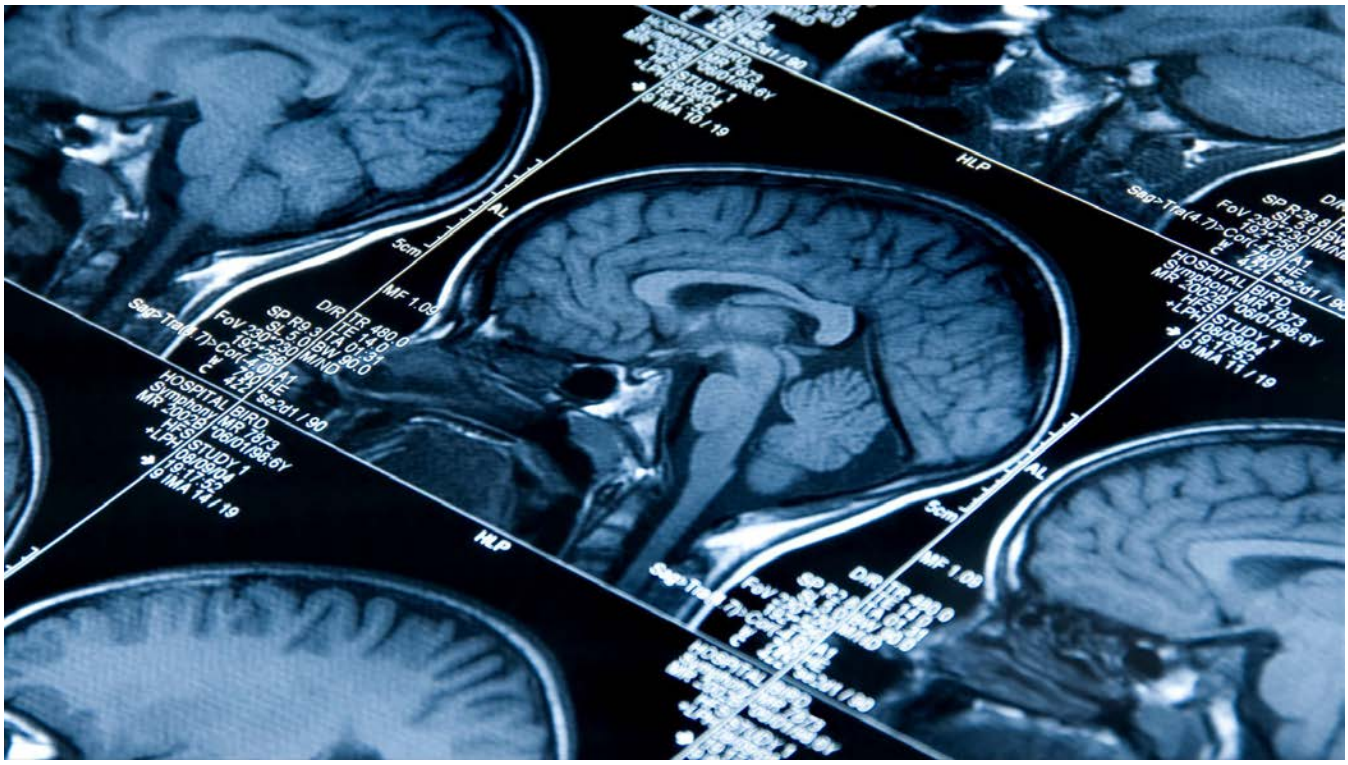
FAST FORWARD

THIS SCI-FI TOOL LETS YOU SHINE A LIGHT ON THE BRAIN



WHY YOU SHOULD CARE

Optogenetics offers neuroscientists a chance to solve decades-old mysteries and promises therapeutic breakthroughs.

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This OZY original series brings to you Medical Breakthroughs – and the people behind them – that could change how doctors treat us, find fixes to today's diseases and make our lives truly better.

Famed neuroscientist and Nobel laureate Santiago Ramón y Cajal believed that in the central nervous system (CNS) — the brain and spine — nerves don't regenerate. It was a dismal proclamation but one that held for nearly 100 years. Until now.

The CNS puzzle, Ramón y Cajal admitted then, belonged to future scientists. Today, optogenetics, a burgeoning young field of neuroscience that controls neural activity with light, is illuminating the mechanisms behind nerve regeneration — and showing how to overcome neuroscience's oldest mystery.

Nobel Prize–winning biologist Francis Crick had laid the groundwork for the development of optogenetics in the 1970s, when he laid out a challenge for neuroscientists: Find a way to stimulate select pathways of neurons, to study neurological activity. After all, "neurons are individual computational units," says Ed Boyden, one of the pioneers of optogenetics. To study their mechanics, one needs to run comparable code through specific systems. Crick even predicted that light could be a way to do so.

WITH OPTOGENETICS, YOU CAN DIRECTLY CONTROL NEURONS WITH MILLISECOND PRECISION BY SHINING LIGHT.

JOSUE ORDAZ, INDIANA UNIVERSITY SCHOOL OF MEDICINE

But it was only just over a decade ago that a few intrepid researchers began taking Crick up on his offer. In 2004, Boyden and his partner Karl Deisseroth showed that by inserting light-activated proteins into neurons in a Petri dish, they could guide neurons' electrical activity. Optogenetics works because when these proteins — usually inserted into neurons by a virus — are activated by light, they alter neurons' electric potential, either increasing or inhibiting their firing.

Now, this ability to precisely target specific neural pathways in real time (unlike drugs) is making optogenetics a staple in labs worldwide. Recent research on PNS regeneration has shown optogenetics, among other things, to triple the growth of neurons in a petri dish and to improve the growth of axons — the long, branching, transmitting end of neurons — in muscle tissue implanted into mice. Optogenetics has even managed to improve regeneration in the CNS.

“With optogenetics, you can directly control neurons with millisecond precision by shining light,” says Josue Ordaz of Indiana University School of Medicine.

But how is this useful for studying nerve regeneration? Why does our CNS have trouble regenerating in the first place, given what an advantage it would be?

Simply put, evolution is poker. Some animals, such as flatworms and axolotls (a type of salamander), were dealt simple nerve systems, slower metabolisms and little armor. For them, regeneration was the path of least resistance and greatest reward.

Mammals were dealt complex nervous systems, mobility and robust armor around the brain and spine. Humans, in particular, got Earth’s most complex supercomputer. Trying to weave in new nerves, proverbial transistors, in a live circuit — in hopes that every new axon plaits properly into the mesh of neurons — is quite the gamble. Dozens of genes control hundreds of growth factors and inhibitors, many of which have a myriad of other functions, such as tumor suppression. So, natural selection took the easy bet: Double down on the armor we were dealt.

Over the decades, scientists nailed down a plethora of mechanisms behind the disparity in our nervous systems’ regenerative capabilities. Nerves depend on a support crew, glial cells, to repair, support and produce insulation (myelin) for them. The CNS and PNS have different myelin-repairing cells. In the PNS, multiple Schwann cells tend to the axons of every neuron. After an injury, so-called oligodendrocytes in the CNS have to repair up to 50 neurons, and they often release growth inhibitors. Glial cells proliferate into thick, fibrous scar tissue that, unlike most scars, provides a hostile growth environment, choking out new axons. Glial scars also diminish the expression of growth factors, while pumping out growth inhibitors.

All this ado to stop regrowth may have paradoxically been evolution’s way to protect us. But optogenetics is illuminating better strategies than simply accepting neural degradation.

There's a saying that "neurons that fire together, wire together." The more often neuron neighbors fire together, the more apt they become to do so. By stimulating neural pathways, optogenetics exaggerates this effect, improving neuroplasticity, which is important to regeneration. Optogenetics has also been used to stimulate the growth of dendrocytes (the receiving end of neurons), trigger the proliferation of oligodendrocytes (which improves the repair of myelin), ameliorate glial scarring and improve the expression of biomolecules that support neuron growth. According to Ordaz, it may increase the available calcium in cells, which aids in the expression of genes.

This has led to positive results with Alzheimer's, epilepsy, Parkinson's, multiple sclerosis, stroke, spinal cord injuries and memory improvement. There's just one catch: Most optogenetics research has been limited to animals.

"Optogenetics requires two major things: expressing the [LAPs] in a cell-specific manner," says Ordaz, "and shining light sufficient to stimulate these neurons." This makes it invasive. To get the blue or green light that activates the LAPs in the brain or spine, scientists often implant fiber optic cables in animals.

However, they are rapidly developing less invasive optogenetics tech. Scientists can now bind a molecule co-opted from bioluminescent animals to specific proteins in targeted cells. Recently, Shuo Chen, with the RIKEN Brain Science Institute, developed a method that uses nanoparticles to convert near-infrared light, which better penetrates tissue, into LAP-stimulating blue light. Chen says that its efficiency leaves much to be desired, but it's far less invasive than fiber optics.

Moreover, as gene therapy advances, targeted cells could soon be altered to produce LAPs. Several human trials using optogenetics to treat advancing blindness — the very mission for which Zhuo-Hua Pan, one of the pioneers of optogenetics, helped develop the technology — are already underway.

But more important than optogenetics' exciting-but-uncertain future in therapeutic treatments for disease, the technique has, in 13 years, already become neuroscience's equivalent of the CRISPR gene-editing tech. It is indispensable for illuminating the mysteries of why regeneration is so hard — and how to approach Ramón y Cajal's puzzle.

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