



A light-sensitive algal protein energised neuroscience

To understand how the brain forms memories, feelings and behaviours has long been a dream for researchers. Karl Deisseroth, Peter Hegemann and Georg Nagel are awarded the 2026 Nobel Prize in Physiology or Medicine for discoveries leading to *optogenetics*, which makes it possible to switch on, or off, the activity of individual nerve cells in a living brain. This method is now being used in laboratories around the world to reveal the brain's mysteries.

"My own brain is to me the most unaccountable of machinery — always buzzing, humming, soaring, roaring, diving, and then buried in mud. And why? What's this passion for?"

These are Virginia Woolf's words in a letter to a friend in 1932. Many people share her fascination with the brain. How can this organ, which only weighs around 1.3 kilograms, hold childhood memories, daydreams and creativity? How can it be the cause of joy, love and jealousy? How does it control the pace of heartbeats, the rhythm of breathing and the sleep cycle?

Since ancient times, researchers have attempted to understand this biological mystery. In the twentieth century, they successfully identified which regions of the brain govern various physiological functions. This provided invaluable understanding, but the methods available at the time were relatively blunt and could not prove that a specific type of nerve cell directly caused a certain feeling or behaviour. The image of the brain that emerged was therefore like a blurry photograph, missing many details.



Figure 1. Scientists dreamed of using a switch for nerve cells.

One of those who dreamed of more precise tools to explore the brain's exceptionally complex network of nerve cells was Francis Crick (Nobel Prize 1962). A few decades after the ground-breaking discovery of DNA's double helix in 1953, he began investigating the mechanisms that underlie human consciousness. He envisioned ways to activate individual nerve cells in a living

brain. The signals in nerve cells are extremely rapid. To match this speed, he concluded that it would probably be ideal to use light. If molecular biologists could somehow manipulate nerve cells and get them to react to light, they might be able to control neural activity (Figure 1). Crick admitted that his idea sounded far-fetched, but perhaps not impossible to achieve.

His vision of the future has now become reality. Karl Deisseroth, Peter Hegemann and Georg Nagel are awarded the 2026 Nobel Prize for their discovery of a molecular switch for nerve cells. Using light, researchers are now able to switch individual neural circuits on or off in the brain. They can bring memories to life, create feelings, drive behaviours and study the types of neurons that are involved in various psychiatric and neurological disorders. Optogenetics is fundamentally transforming our understanding of the brain. It has also provided important insights into how the nervous system interacts with various cells in other areas of the body, such as in the heart and gut.

It all started with the curiosity of one researcher. In the early 1990s, Peter Hegemann at the Max Planck Institute for Biochemistry in Martinsried, asked a simple question: How can the unicellular alga *Chlamydomonas* react so rapidly to light?

Hegemann investigates how a swimming alga senses light

Chlamydomonas is famous for its ability to swim towards light. When researchers stir this green alga into a petri dish, the liquid turns a faint green colour. If they then illuminate one side of the dish, the green colour shifts towards the light source, as the microscopic algae swim towards it (Figure 2). The algae sense the light with an eyespot, a tiny orange dot on the cell's surface that contains a light-capturing molecule, retinal.

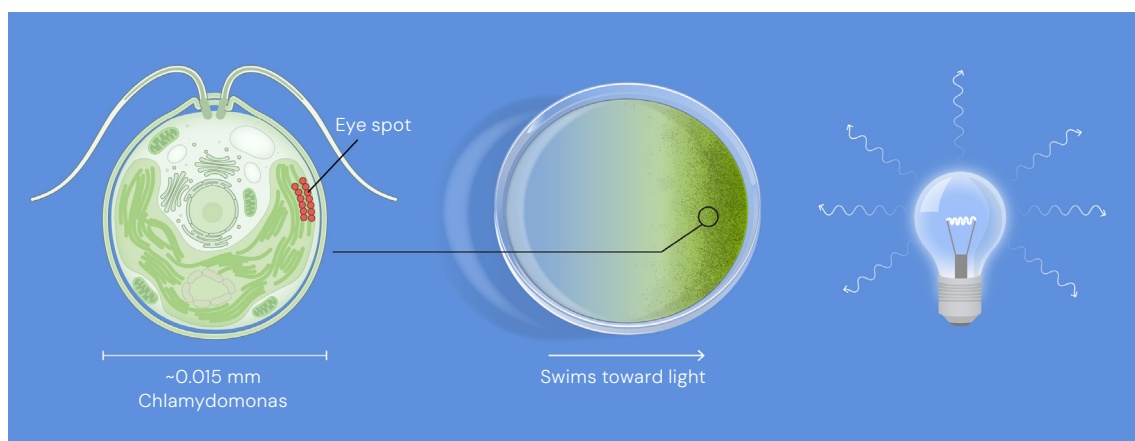


Figure 2. The alga *Chlamydomonas* senses light using its eyespot. When light is sufficiently strong, it swims towards the source.

Hegemann investigated the algal eyespot. Using minuscule electrodes, he measured the electrical signals that arose in *Chlamydomonas* when the eyespot was illuminated. The algae reacted incredibly quickly. Just half a millisecond after light reached the eyespot, an electrical impulse occurred.

Compared to other biological systems that researchers knew of at the time, this was remarkably fast. For example, light reaching a human eye triggers a complex chemical chain reaction that involves many different steps. The final protein in this chain — an ion channel — forms an opening in the cell surface through which charged ions can flow, creating an electrical signal. The entire process takes at least 10 milliseconds. So how could the response to light be more than twenty times faster in *Chlamydomonas* than in our own eyes?

The fast light reaction in algae ignites Hegemann's curiosity

Hegemann could only think of one explanation for this ultrafast response: the process must be much simpler in *Chlamydomonas* than in a human eye. In the early 1990s, he formulated the hypothesis that a single protein complex both captured light and acted as an ion channel. However, his proposal was met with scepticism. At the time, researchers knew of many different types of ion channels, but none of them could react to light on their own.

To test his hypothesis, Hegemann attempted to isolate *Chlamydomonas*'s light-sensitive protein. However, this was easier said than done. When the proteins in the algal eyespot were removed from their natural setting, they became unstable and easily damaged, making them difficult to study. However, around the turn of the millennium, after years of setbacks, the research group made an intriguing finding. Japanese researchers had mapped the DNA of *Chlamydomonas* and made the genetic code for thousands of genes available. Among them, the Hegemann group found two genes that had significant similarities with known genes for light-capturing proteins. Could either of these contain the code for the protein they were looking for?

To answer this question, Hegemann contacted a colleague: Georg Nagel at the Max Planck Institute for Biophysics in Frankfurt. He had the necessary knowledge to take the next decisive step towards what would come to revolutionise neuroscience.

Hegemann and Nagel discover a remarkable protein

Nagel used egg cells from frogs to study proteins. When he received the two *Chlamydomonas* genes, he injected copies of them, separately, into different batches of frog eggs, which then began to mass produce the two unknown proteins (Figure 3). The proteins ended up on the surface of the egg cells, in the surrounding membrane. Nagel could then investigate how they functioned, and he quickly discovered that the hypothesis formulated by Hegemann a decade earlier was correct: the newly discovered proteins were ion channels that opened when exposed to light (Figure 3).

These proteins were named channelrhodopsin-1 and channelrhodopsin-2. We will leave the first of these behind and concentrate on the second, which paved the way to optogenetics.

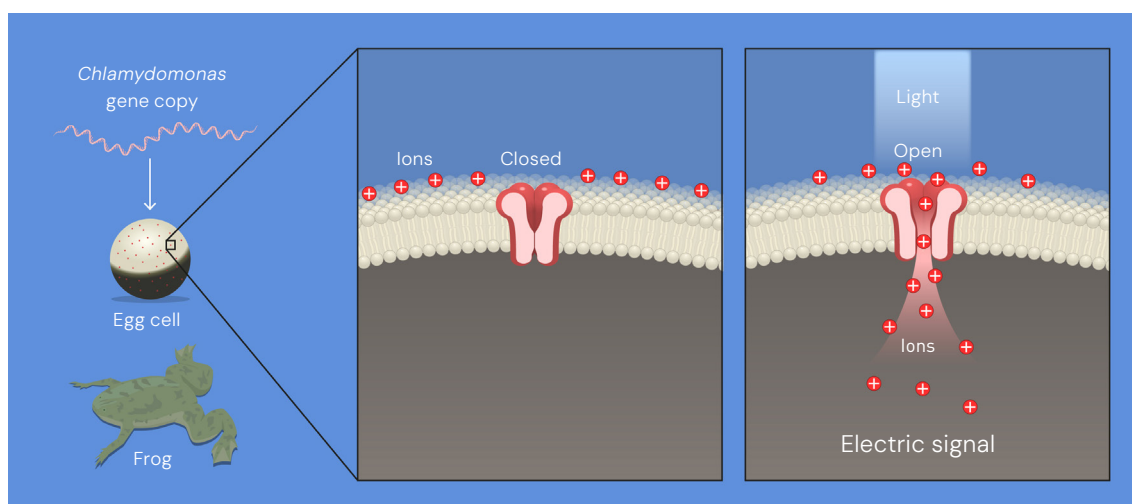


Figure 3. When Nagel and Hegemann introduced the *Chlamydomonas* genes in frog eggs, they began to produce ion channel proteins that ended up on the surface of the eggs. When the researchers illuminated the ion channels, they opened. Ions then flowed through the channels, creating an electric signal.

The algal protein activates human cells

Just as in Hegemann's experiment, Nagel's characterisation of channelrhodopsin-2 showed that it reacted exceptionally strongly and rapidly to a pulse of light. A channel opened through the surface of the frog egg cell within 0.2 milliseconds. Positively charged ions then flowed through the channel, producing an electrical signal (Figure 3).

Hegemann and Nagel realised that they had made a revolutionary discovery. They tested introducing the gene for channelrhodopsin-2 into embryonic human kidney cells and in kidney cells from hamsters. The cells became light-sensitive: when they were exposed to light they produced an electrical signal.

In 2003, Hegemann and Nagel published the results of their experiment. They proposed that channelrhodopsin-2 could be used as a powerful tool to generate electrical impulses in cells using light. After this, a young scientist at Stanford University took the baton.

Meeting psychiatric patients was decisive for Deisseroth

In the 1990s, when Karl Deisseroth started to study medicine, he was considering becoming a neurosurgeon, but part of his training was done at a psychiatric clinic. There, he was struck by the patients' suffering and their need for help. At the same time, he began to wonder how the brain can work so differently in different people. Why do people with depression find it so difficult to feel joy? What causes autism, or schizophrenic delusions?

In parallel with his medical studies, he gained a PhD in neuroscience. In the laboratory, he used thin brain slices and examined them in petri dishes. His research yielded important insights, but he realised that in order to understand the diseases he encountered in the clinic, he needed to study how nerve cells function in a living brain.

Other researchers were trying to develop methods that made it possible to control the activity of specific nerve cells in the manner proposed by Francis Crick. However, many of them were concerned about wasting time and money on something that appeared to be an unrealistic dream. Deisseroth realised that he had to take the risk of failing; the treatments he was able to offer his patients were rarely effective and often produced debilitating side-effects. If he were to find a better way of helping them, he needed a more profound understanding of the brain.

Success! Moving algal protein into nerve cells

When Deisseroth started his own research group, they began to search for a protein they could use to trigger electrical impulses in nerve cells. They tested numerous candidates and when Deisseroth heard about the discovery of channelrhodopsin-2, he wrote to Georg Nagel and asked whether he could have access to the DNA encoding the protein.

When the DNA arrived in Deisseroth's lab, he introduced it into rat nerve cells cultured in petri dishes. He worried that the sensitive nerve cells would be negatively affected by the foreign gene, but they began to produce channelrhodopsin-2 with no apparent problems. When the research group exposed the nerve cells to blue light, the cells reacted immediately. The light provoked a nerve signal that could be propagated to other nerve cells.

In 2005, Deisseroth's research group published their discovery. They had achieved a decisive milestone, although Deisseroth understood that he had a long journey before reaching his goal: the ability to control the activity of nerve cells in live animals.

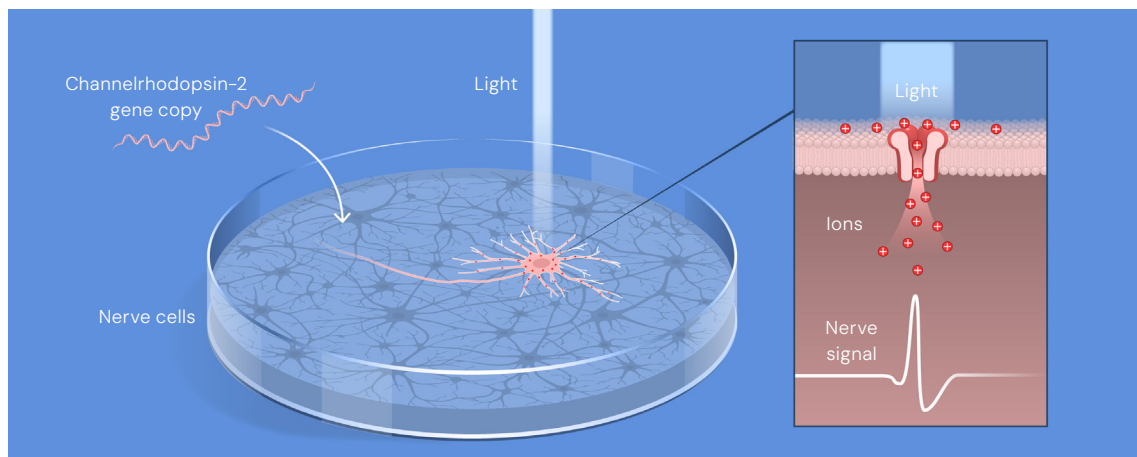


Figure 4. Deisseroth introduced the gene encoding channelrhodopsin-2 into nerve cells that he cultured in a petri dish, making the nerve cells sensitive to light. Using blue light, the researchers were able to trigger a rapid nerve signal.

Optogenetic control of nerve cells in a living brain

Karl Deisseroth now began numerous collaborations, including with Peter Hegemann and Georg Nagel. He also shared his discovery with other researchers who understood its enormous potential. With Deisseroth's lab at the forefront, researchers soon found more proteins that can turn nerve cells on and off, and which are activated by different wavelengths of light.

In 2006, this new method was given the name optogenetics. One year later, Deisseroth successfully activated nerve cells in the brains of living mice (Figure 5). His research group introduced the gene for channelrhodopsin-2 into a specific nerve cell type in the motor cortex, the area of the brain that governs movement. They then illuminated the nerve cells with a thin optic fibre that they fed into the brain through a small hole in the skull. This allowed them to control movements of the mouse whiskers.

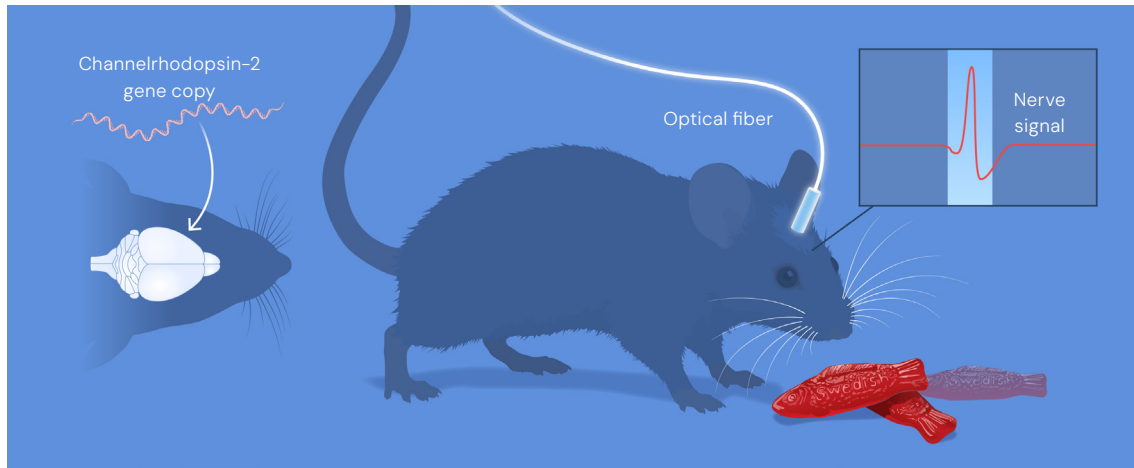


Figure 5. Deisseroth's research group delivered the gene for channelrhodopsin-2 to the brains of living mice. They then inserted a thin optical fiber into the brain. When they illuminated the nerve cells through the optical fiber, a nerve signal was triggered that induced movement of the whiskers.

The same year, working with other researchers, Deisseroth used optogenetics to wake sleeping mice in a controlled manner. The research group introduced channelrhodopsin-2 into a recently discovered type of nerve cell that they suspected controlled wakefulness. When they shone light on the nerve cells, the mice woke up, confirming the hypothesis.

Another famous piece of work from the infancy of optogenetics was published in 2012. Together with Susumu Tonegawa (the 1987 Nobel Prize for discoveries in immunology), Deisseroth successfully activated an engram, the specific pattern of neural pathways that is formed when a memory is created. The researchers studied the brains of mice as they experienced fear, and noted which nerve cells appeared to form the memory of the experience. When they later reactivated these nerve cells, the mice showed signs of fear, despite not being in danger at the time. This was the first experiment in which researchers could demonstrate exactly which nerve cells are necessary for a specific memory.

A new epoch in neuroscience

The ability to activate individual types of nerve cells in the brain has fundamentally changed our understanding of this incredible organ. An adult human brain has around 90 billion nerve cells, each of which forms thousands of connections with other nerve cells. In many cases, the pathway from a nerve cell stretches to a completely different area of the brain, while nerve cells that govern entirely separate physical functions can be closely intermingled.

Thanks to optogenetics, researchers can now discover exactly which of the nerve cells in a complicated bundle control different brain functions. For example, they have identified neural circuits that govern the sense of pain, social behaviours, thirst, food consumption, reward and attention. They have also found nerve cells responsible for diverse functions, from controlling the circadian rhythm to causing a fever when the immune system is activated.

When researchers studied more complex behaviours, such as how mice care for their young, they discovered that the various components of a behaviour can be controlled by separate neural circuits. One circuit governs, for example, how mice gather their young in a nest, another regulates the way that they groom them.

Optogenetics can also be used to map the nervous system and cell functions outside the brain. Deisseroth has demonstrated that heart rhythm can affect our emotions; if the heart is forced to work harder, this can reinforce feelings of anxiety. Other researchers have identified specific cells in the gut that can explain why some people would rather eat sugar than sweeteners, to give just a few of very many examples.

Hope for new medical treatments

The hope that the knowledge generated by using optogenetics will lead to new medical treatments has begun to come to fruition. The method has provided greater understanding of the distinguishing features of psychiatric and neurological disorders such as depression, anxiety, schizophrenia, Alzheimer's disease and Parkinson's disease.

Researchers have also taken the first steps towards using optogenetics as a medical treatment. In ongoing clinical trials they attempt to restore vision in people who have become blind due to retinitis pigmentosa, a disease that destroys the eye's rods and cones. When they inserted a channelrhodopsin-like protein in the retina of a blind person, the person regained some vision. Using special glasses emitting light, the person was able to discern and grasp objects on a table.

There are also hopes that optogenetics could improve cochlea implants. Currently, these implants stimulate the auditory nerve using electricity. If it were instead possible to use optogenetics, the implant may be able to activate the auditory nerve with greater precision.

Optogenetics: a transformative method in neuroscience

Karl Deisseroth, Peter Hegemann and Georg Nagel are awarded the 2026 Nobel Prize in Physiology or Medicine for their discoveries that led to an incredibly powerful tool that has transformed neuroscience. Optogenetics continues to unravel one of humanity's greatest mysteries: how the brain works.

The 2026 Nobel Prize in Physiology or Medicine

“For their discoveries concerning light-gated ion channels and optogenetics”



KARL DEISSEROTH

Born 1971. Ph.D. 1998 and MD 2000 from Stanford University, USA. D.H. Chen Professor, Professor of Bioengineering and of Psychiatry and Behavioral Sciences, at the Howard Hughes Medical Institute and Stanford University, USA.



PETER HEGEMANN

Born 1954. Ph.D 1984 at the Max Planck Institute for Biochemistry, Martinsried, Germany. Hertie Senior Professor of Neuroscience, Humboldt University of Berlin, Germany. The prize awarded discoveries were made at the Max Planck Institute for Biochemistry, Martinsried, Germany



GEORG NAGEL

Born 1953. Ph.D. 1988 at the University of Frankfurt, Germany. Professor of Molecular Plant Physiology at the Department for Molecular Plant Physiology and Biophysics – Botany I, University of Würzburg, Germany. The prize awarded discoveries were made at Max Planck Institute for Biophysics, Frankfurt, Germany.

Key Publications

Harz, H., Nonnengasser, C., **Hegemann, P.** The photoreceptor current of the green alga *Chlamydomonas*. *Philos. Trans. R. Soc. Lond. Ser. B: Biol. Sci.* 1992:338:39–52.

Nagel G, Ollig D, Fuhrmann M, Kateriya S, Musti AM, Bamberg E, **Hegemann P.** Channelrhodopsin-1: a light-gated proton channel in green algae. *Science*. 2002:296:2395–2398.

Nagel G, Szellas T, Huhn W, Kateriya S, Adeishvili N, Berthold P, Ollig D, **Hegemann P**, Bamberg E. Channelrhodopsin-2, a directly light-gated cation selective membrane channel. *Proc. Natl. Acad. Sci. U. S. A.* 2003:100:13940–13945.

Boyden ES, Zhang F, Bamberg E, **Nagel G**, **Deisseroth K.** Millisecond-timescale, genetically targeted optical control of neural activity. *Nat. Neurosci.* 2005:8:1263–1268.

Aravanis AM, Wang LP, Zhang F, Meltzer LA, Mogri MZ, Schneider MB, **Deisseroth K.** An optical neural interface: *in vivo* control of rodent motor cortex with integrated fiberoptic and optogenetic technology. *J Neural Eng.* 2007:4:S143–156.

Science editors: Abdel El Manira, Sten Linnarsson, Thomas Perlmann, Per Svenningsson and Anna Wedell, the Nobel Committee for Physiology or Medicine

Text: Ann Fernholm

Translation: Clare Barnes

Illustrations: Mattias Karlén

© The Nobel Assembly at Karolinska Institutet