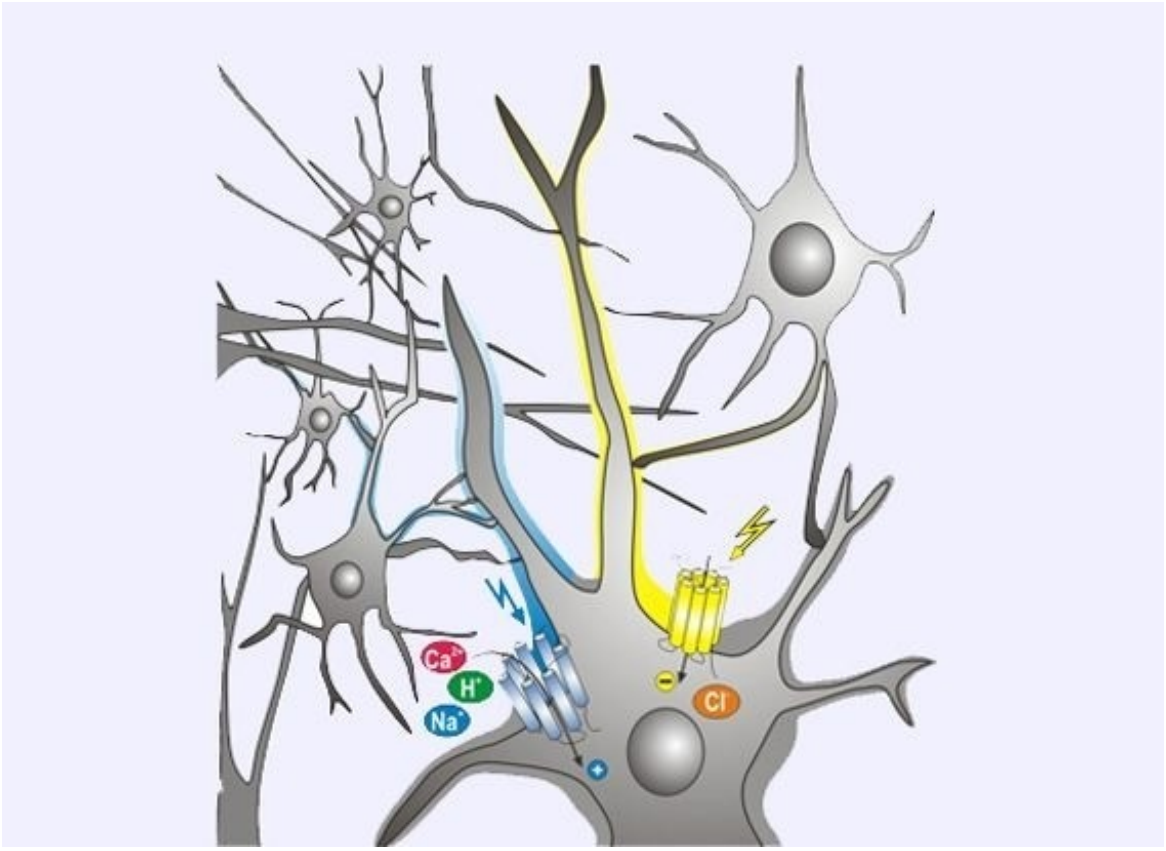
Website address:
https://www.gesundheitsindustrie-bw.de/en/article/news/how-can-light-be-used-to-control-the-behaviour-of-neurons

How can light be used to control the behaviour of neurons?

The control of the behaviour of individual neurons simply by switching light stimuli on and off sends neuroscientists into raptures as it reveals insights into as yet hidden and complicated processes in the brain. Thanks to optogenetics, this particular science fiction became reality a few years ago. Working with researchers from the Bernstein Center at the University of Freiburg and the Friedrich Miescher Institute for Biomedical Research in Basel, scientists in the teams of Dr. Birthe Rubehn and Prof. Dr. Thomas Stieglitz in the Department of Microsystems Engineering (IMTEK) have developed a multimodal implant which allows the genetic modulation, control and measurement of cell activity.



Channel rhodopsins spark impulses in neurons that are excited by light of a specific wavelength.

Three years ago, the journal Nature Methods declared optogenetics the "method of the year 2010". Optogenetics uses a combination of techniques from optics and genetics for carrying out detailed investigations in living tissue on the molecular, cellular and network level. Light-sensitive proteins, so-called opsins, from algae and bacteria can be genetically modified and introduced into cells to control the cells' electrical activity using light.

Algae and bacteria use opsins to generate energy. Opsins are ion channels with different spectral sensitivities. They are located in cell membranes and their ability to conduct certain ions is controlled by visible light. The modification of genes of the channel proteins restricts the expression of opsins to specific cells. This forms the basis for optogenetics. Neuroscientists use gene shuttles or vectors, i.e. customised viruses, to deliver the light-sensitive proteins to specific areas in the brain of living animals. The modification of the genes leads to the exclusive expression and incorporation of the opsin molecules in specific brain cell types.

Light switches neurons on and off

Fibre-optic probes are inserted into the brain in order to illuminate a small brain area. This provokes a specific activity within specific neurons and potentially also a specific behaviour in the experimental animals. The advantage of the technique is that the animals can move around freely, which they cannot do with brain electrodes attached to their head. Moreover, the technique is more cell-type specific and non-invasive. "Electricity stimulates all cells that are in or close to the stimulated area," said Prof. Dr. Thomas Stieglitz, head of the Department of Biomedical Microtechnology at the University of Freiburg, going on to point out another advantage of using light: "Electrical stimulation does not allow us to record the activity of all cells simultaneously as electricity interferes with the amplifier. This does not happen with light and we can therefore

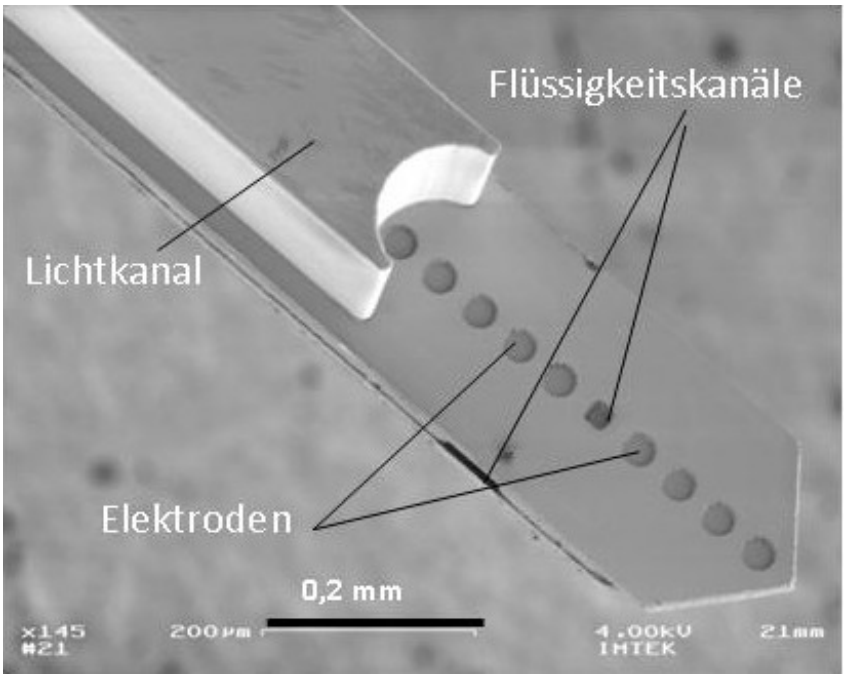
measure the signals in real time."

Plastics increase flexibility

Five years ago, Stieglitz more or less stumbled across optogenetics and became fascinated by the question as to whether the necessary equipment could also be manufactured from polymers whose compatibility with brain tissue was already proven. His basic idea was that plastics would make the devices more flexible than other materials. "Things that are more flexible are associated with fewer relative material movements and the material adjusts more easily to brain movement," said Stieglitz, pointing out that he prefers to use polyimides and a standard polymer that are frequently used in the field of microengineering as they are stable, insensitive to light and not cytotoxic.

In addition, optogenetic experiments had been rather laborious up until that point: a syringe had to be used to apply the vector to the targeted brain area and researchers had to wait several weeks before they could insert the fibre-optic probe for the light that would ideally also lead to a change in the animals' behaviour. The long waiting time was necessary for the cells to build the light-sensitive ion channels.

Prototype: a multimodal system



Prototype of the 3-in-1 microimplant.
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In order to improve the situation, Stieglitz and Rubehn came up with the idea to construct smaller devices by optimising the implant material and shape. In addition, the new devices would also be able to carry out different functions, i.e. be multimodal.

"We wanted to do away with having to use two or three systems one after another. What we had in mind was a single device that would allow us to target specific brain areas," said the engineer. In the new microimplant, the fluid channel used to transfect the nervous tissue with the vector ends in an area bordered by the recording electrodes and the optical waveguide. This area is just one

eighth of a square millimetre in size. “This set-up allows us to inject the substances needed for genetic modification, emit the light for stimulating the nerve cells and measure the effect all at the same time,” said Stieglitz explaining what their new 3-in-1 chip looks like and how it works. Proof-of-concept was provided by Stieglitz’s cooperation partner Prof. Dr. Andreas Lüthi and his colleagues from the Friedrich Miescher Institute for Biomedical Research in Basel who are specifically focused on the mechanisms of fear. Using anatomical landmarks, Lüthi and his team of researchers have successfully tested the prototype in mouse brains. The prototype did not yet use the new fluid channel and the vector had to be injected with a cannula several weeks before the actual recordings.

Can optogenetics be used in medical therapy?

Stieglitz feels that the prototype is still a bit difficult to handle, so he and his colleagues are already working on the optimisation of the implant. At present, the three channels used to guide light, liquids and electronics still need to be attached with small plugs to the heads of the mice. In the long term, Stieglitz hopes that the device will work with no wires at all by attaching a tiny light-emitting diode at the tip at the probe and using radio waves for data transfer and energy supply. The fluid channel currently used to inject the substances that are necessary for genetic modification is only used once. Stieglitz and his team are therefore working on a second version whose injection channel is biodegradable, i.e. dissolves over time.

Thomas Stieglitz and his team work closely with optogeneticists and neuroscientists. “We plan to develop a complex device that enables basic scientists to better understand how the brain works,” said Stieglitz. He believes that such devices will pave the way for completely new experiments in neurobiology, including in Freiburg’s new BrainLinks-BrainTools cluster of excellence.

However, time will tell whether optogenetics is a suitable tool for medical treatment. “In the past, scientists have often been over-optimistic about a new finding, in stem cell therapy, for example, a field where many false hopes have been raised. And this is not fair to those concerned,” concluded Stieglitz.

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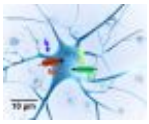
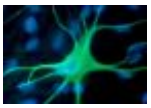


Optogenetics: switching cell activity on and off with light



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