ATHANASSIOS KALIUDIS

„The question of free will …“

Professor Karl Deisseroth has set himself the task of understanding the brain. To help him achieve this goal, he developed a method called optogenetics, which uses a laser to influence thoughts and decisions.

How would you describe the brain, Professor Deisseroth?

The human brain is a soft yet very dense organ somewhere between pink and brown in color. It weighs approximately one and a half kilograms and has a wrinkled appearance. It is these wrinkles that give us our capacity for highly complex reasoning.

That was a quick jump from the brain’s appearance to our capacity for thought.

Right, and that’s because the two things are so interlinked. Obviously it’s important to start by acknowledging that the brain consists of matter, that it is an organ made up of cells. But it can sometimes feel strange to view it in those terms because, at the same time, the brain is the source of all our thoughts, feelings, desires, memories, and impressions – in other words our entire personality. Everything that makes up who we are as a person comes from this mass of cells we call neurons. How is that even possible?

My question exactly! How is that possible?

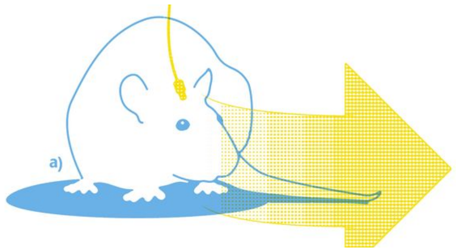
Essentially it boils down to a philosophical question of what the brain actually is. Ultimately, I think two perspectives are correct: the brain is a dynamic object, and it consists both of cells as well as what those cells create. Optogenetics can help us understand how those cells give rise to things such as perception, cognition and action. It is a method that puts us in the role of a composer or conductor in an orchestra of information, telling different cells in different areas of the brain what they should do when, and dictating when and if they should synchronize with each other. We can then observe the perception, cognition and action that occurs as a result.

The field of optogenetics you refer to is your area of specialization. Could you sum up what it involves?

Optogenetics employs laser light in exactly the opposite way to how it is normally used in biology. We don’t use it to observe things, but to make things happen. In simple terms, we employ laser light to make certain neurons fire – in other words, we stimulate them to emit electrical impulses and thus to generate information in the brain. Let me briefly explain how that works. Normally neurons do not react to light. That makes sense, because it’s always dark in the brain. So that means we have to trick them. Using an artificial virus, we inject a photosensitive gene into the brain that converts light pulses into electrical impulses. We employ various other genetic tricks to define exactly which neurons are “infected” with the gene. The advantage of this laser method is the level of precision it gives us in choosing which neurons to activate. It is much more precise than any other method. So far we have applied it to rodents and other mammals, as well as fish and invertebrates. For example, we stimulate very precise and specific neurons in the mouse's brain, observe what happens as a result and use those findings to learn more about their brains.

Typing your name into a search engine brings up a video of a mouse almost immediately. The mouse has a fiber optic cable threaded directly into its brain. Flashing a light through the cable causes the mouse to run in a circle. But when no light passes through the cable, the mouse behaves completely normally.

Yes, that was an experiment we did in 2007. We used our optogenetics method to stimulate the part of the mouse's motor cortex that controls movement toward the left. When the cable lights up, the mouse always runs to the left, in a circle.



<p>What does the mouse feel when we control its decisions? - Gernot Walter</p>

<p>Karl Deisseroth opts to experiment on himself using transcranial magnetic stimulation — his thumb twitches. - Gernot Walter</p>

<p>This form of remote control actually feels surprisingly fine. - Gernot Walter</p>

What does the mouse feel about that? Does it sense it is being controlled by someone else? Or does it actually think it wants to run in a circle?

Obviously we can't know that for sure, but we can see very clearly if a mouse is disturbed or frightened, because it would freeze. We don't observe any of that kind of behavior when we pass laser light through the cable or when we switch it off – everything just seems normal. Based on our assumption that the mouse would be frightened if it felt it was being controlled by an external force, we conclude that the mouse is fine with the situation – though obviously it probably hadn't planned to run to the left in a circle. I tried something similar on myself to find out how it felt. Using transcranial magnetic stimulation, I stimulated the motor cortex that controls my right hand. When I activated the magnetic pulse, my hand twitched. I watched and sensed that I was moving it. But I experienced neither the feeling that I wanted to move, nor the feeling that I was being externally controlled. The movement was simply happening. My right thumb was moving and I was fine with that.

What does that tell us about free will?

Nothing new, really. We are constantly using medicine and psychiatry to influence people's feelings and actions, whether through drugs, brain stimulation or simply talk therapy. Take advertising, for example. Isn't that essentially a way of manipulating your desires? And is optogenetics, fundamentally, any different? It merely shows that our actions and decisions are carried out through electrical signals. But I don't think these findings actually answer the question as to whether or not we have free will. What optogenetics can do, however, is help us phrase this question in more precise terms. For example, is there an organizing force, a principle in the brain, that controls the electrical signals? And if so, how deep within the brain is it located? Some people think there isn't one, or at least not one of any particular interest. Others think this organizing force really does exist. But of course that prompts the question of where this force might come from. Whatever the case, the question of free will remains unanswered, at least for now.

Obviously we constantly influence other people's feelings, even through something as simple as talking to them.

But this form of remote control is surely on a completely different level. How does it actually feel to control a mouse remotely?

It's a powerful and meaningful experience. It forges a connection to the animal and somehow seems miraculous every time it happens. I think what makes the experience so powerful is the immediacy of it, the swift response.

But doesn't it also feel somewhat unsettling?

Yes, absolutely. The precision, immediacy and predictability with which we can trigger actions can certainly feel unsettling at times, and I understand why that might disturb some people.

Could optogenetics eventually be used in a negative way to manipulate human beings?

I don't think so. This technology doesn't really lend itself to that kind of abuse. You have to develop a gene and inject it using a virus. It's all very awkward, time-consuming, expensive and complicated. But obviously we need to contemplate those kinds of possibilities, however unlikely they may seem.

We've been talking about the brain as a generic concept, but is every human brain really the same?

In some ways yes, and in other ways no. We're confident that all human brains have a number of broad principles in common. For example, dopamine neurons do much the same thing in every brain, which include triggering feelings of happiness and contentment. Our experiments on rats and mice support that supposition. But when you take a closer look, things get more complicated. The structure of the brain is not predefined in any real detail. It's a jumble of cells that are arranged differently in each case. So the whole issue is actually rather complex.

Your work extends across many boundaries, from virology and psychiatry to animal behavior, optics, microbiology and chemistry. How would you define your profession?

That's very true! I suppose I primarily see myself as a neuroscientist and psychiatrist.

What prompted your fascination with the brain?

Even as a child I was introspective and interested in how my own brain worked and why I acted in the way I did. Eventually I began to take an interest in the same question for other people, too. Everyone was so different and responded so differently, even to similar things, and I wondered why. Then came my experience of working with psychiatric patients at medical school. Their responses were even less predictable, and sometimes the patients had their own individual conception of reality. I found it fascinating, and I felt a huge affinity for that area of specialization. But I also saw the suffering and distress those people were feeling, and I wanted to alleviate that. There were two illnesses that I found particularly interesting: autism and severe, treatment-resistant depression. Both those diseases are very debilitating for patients and are almost impossible to treat with drugs or any other methods. One of the goals I have set myself in my career is to gain a better understanding of those two diseases.

> » **A vast panoply of mysteries still awaits us.**
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> Prof. Karl Deisseroth, brain researcher and founder of optogenetics

Are you working on a new form of treatment?

As a psychiatrist, I continue to treat patients every week at the hospital, but as a scientist I focus more on the fundamentals. Right now my aim is not to find any one specific therapy, but rather to understand how a brain normally functions. And optogenetics offers us the long-term prospect of finally being able to test our hypotheses more precisely.

How far have we actually progressed along the path toward understanding the brain?

It's hard to say, but we certainly understand less than 50 percent, that much is sure, despite all the progress we have made in recent years. A vast panoply of mysteries still awaits us!

> » **We humans are simply very good at understanding things that we have no real business understanding.**
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Can a brain ever really understand how the brain works?

Someday, yes. I would stake money on humanity being able to achieve that. Put simply, we humans are very good at understanding things that we have no real business understanding! We think symbolically, create maps, construct analogies and break down complexity. And with higher dimensional mathematics, for example, we are able to understand fields that should really be out of our reach. One day we'll crack the brain, too!

Karl Deisseroth

<p>born in Boston in 1971, is a psychiatrist, neurobiologist and bioengineer at Stanford University in California. He is regarded as the founder of optogenetics, a discipline that investigates the brain by stimulating neurons with laser light. He also developed a method of turning post-mortem brains optically transparent and preserving them in this state, enabling the intricacies of the brain's structure to be understood in three dimensions. Deisseroth has received 23 prestigious science prizes for his research work, including the 2018 Berthold Leibinger Zukunftspreis.</p>

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