Published online: May 31, 2017

EMBO reports

Science & Society

# Understanding the brain in health and disease

*An interview with Karl Deisseroth, Professor of Bioengineering and Psychiatry at Stanford University*

Esther Schnapp & Holger Breithaupt

**Today, Karl Deisseroth was awarded the 4 million euro 2017 Else Kröner Fresenius Prize for his discoveries of optogenetics and of hydrogel-tissue chemistry, and for developing circuit-level insight into depression. We asked him how his and related work enhances our understanding of the brain and psychiatric diseases at the molecular level.**

See also: **K Deisseroth** (June 2017)

**EMBO reports (ER)**: Dr. Deisseroth, what are the prospects of understanding the molecular basis of mental diseases such as schizophrenia, depression or autism, for which there are no or only limited animal models available?

> *"It's hard to understand how a system goes wrong if you don't understand its key principles of operation in the first place."*

**Karl Deisseroth (KD)**: There are many steps that we need to take before we achieve that goal, which is worthy and important, but difficult. The first one is basic understanding. It's hard to understand how a system goes wrong if you don't understand its key principles of operation in the first place. So, even before we think about disease models, we need a fundamental understanding of brain function. To take your example of schizophrenia, many different domains are dysfunctional in these patients. For example, there is a failure in the assessment of reality, perhaps due to failure of communication between one part of the brain and another, but we have essentially zero concrete and causal knowledge of how these processes normally take place. That's the first step: understanding how different parts of the brain causally interact with each other—not just looking at correlations but the causal, brain-wide dynamic principles—and how the brain operates as a unit. You can do that in animals perfectly well, and then start to perturb function in various ways.

**ER**: How can we study brain function? What are the roles of novel techniques such as optogenetics, hydrogel-tissue chemistry, etc?

**KD**: One unifying theme of optogenetics, and of hydrogel-tissue chemistry, which includes the CLARITY concept, is that these both maintain the brain in an intact state to allow high-resolution analysis of structure and function. I started as a single cell patch clamper, I worked with tissue culture and slices of brain tissue, I've done a lot of biochemical and molecular work, so I do not denigrate reduced-system research. But to approach the broader questions, one has to use tools that give you cellular resolution within the intact system. Optogenetics keeps the brain intact and operating and achieves causal cellular-scale control. This can operate on any time scale—acute or chronic—and we've developed ways of simultaneously interacting with many areas of the brain using multiple fiber optics for example. Hydrogel-tissue chemistry is carried out after life in the same animal in which we have studied brain-wide and causal dynamics during complex behaviors. What we've done is figured out ways to align the living and post-life data sets at cellular resolution and look at individual cells that were involved in a particular behavior and study their molecular phenotype and local wiring. That is the sort of integration that I think is going to be valuable.

> *"One unifying theme of optogenetics, and of hydrogel-tissue chemistry (. . .) is that both maintain the brain in an intact state to allow high-resolution analysis of structure and function."*

**ER**: Can you give an example of the insights that have been gained using these techniques?

**KD**: One of the most striking ones has been relevant to the depression symptom of anhedonia, which is the loss of ability to feel reward or motivation or pleasure from things that normally are sources of reward or motivation or pleasure. It's a fundamental symptom of depression according to the diagnostic criteria we use, and it's a source of great disability, suffering, and morbidity. It's also a major basic question—how and why an individual loses the ability to feel normal rewards.

About a year ago, Emily Ferenczi, who was a graduate student in my laboratory at the time, published an interesting experiment. Several other groups had found that elevated prefrontal cortex activity correlated

EMBO, Heidelberg, Germany. E-mail: esther.schnapp@embo.org
**DOI** 10.15252/embr.201744400

Published online: May 31, 2017
*EMBO reports*


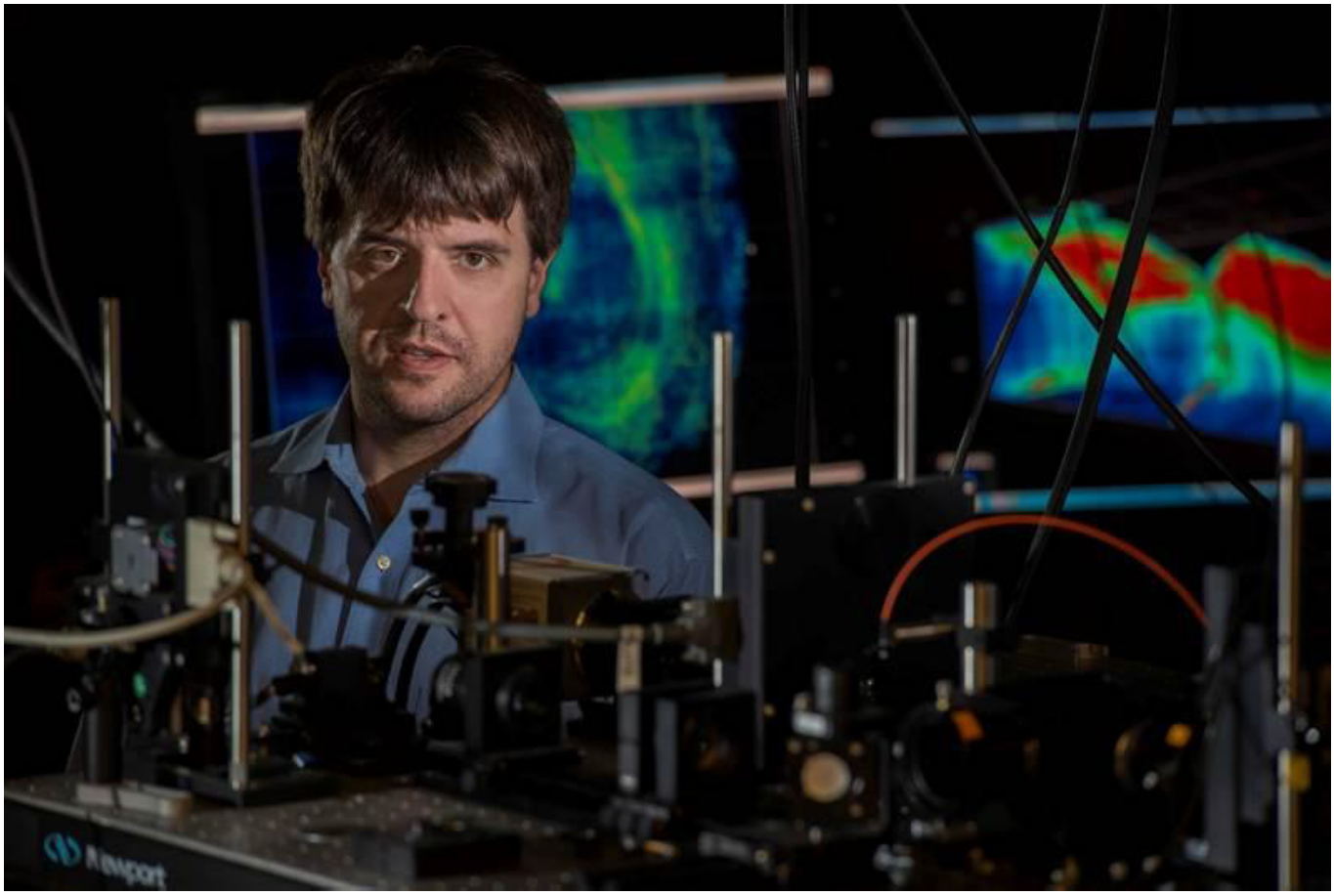


Photo credit: Steve Fisch.

with depressive and anhedonic symptoms, and she wanted to do a causal test of what might be going on. She used optogenetics to elevate prefrontal cortex activity in rats and saw anhedonic behavior as a result, which is interesting by itself, going beyond correlation to causation. For example, rats no longer preferred sugar water as much versus regular water, which is one way we can assess hedonic behavior in rodents. Then she used a variety of brain-wide readouts and found that this elevated activity in the prefrontal cortex was affecting how two other, completely distinct, brain regions were interacting with each other. And indeed, the elevated prefrontal cortex activity was keeping the ventral tegmental area dopamine neurons from recruiting the ventral striatum accumbens activity that normally is part of manifestations of reward or pleasure. Without an intact brain and the causality that optogenetics enables, we would not have the capability to look at both normal and maladaptive behaviors in this ultimately illuminating way.

**ER**: You're also a practicing physician. How important is this direct contact with patients for your research?

**KD**: It is important for my research and it's important for me personally, it's part of my identity. I have an outpatient clinic and I do about a week of inpatient attending work in the hospital where I field ER visits and consults from other services. Even though we do mostly fundamental work in the laboratory, it's incredibly valuable to tell the students "here's what really matters to my treatment-resistant depression patients or for my autism spectrum patients; here's what that symptom really looks like and how it affects them". That affects our motivation and even how we set up experiments. I had a patient who told me that when he'd just look at a neutral thing like a piece of paper on a table, it would make him feel really bad—this piece of paper had no meaning and he'd just feel terrible about it. It made me think about how anhedonia may arise, how valence becomes attached to or detached from sensory stimuli, which is the sort of thing that we've been working on.

**ER**: Do you think that any of the recent techniques that have been developed could be used to treat patients?

**KD**: My laboratory is not working on that because we think there's so much that needs to be done on a basic level to understand normal brain function. But we already see optogenetically guided clinical trials and this gets back to the reward question. In 2013, Antonello Bonci, now at the National Institute on Drug Abuse, published a very interesting paper using optogenetics in cocaine-addicted rats. They found they could make these seriously addicted rats no longer

***Karl Deisseroth*** is the D.H. Chen Professor of Bioengineering and of Psychiatry and Behavioral Sciences at Stanford University, and an Investigator of the Howard Hughes Medical Institute. He received his undergraduate degree from Harvard University and his PhD and MD at Stanford University where he also completed postdoctoral training, medical internship, and adult psychiatry residency. Deisseroth is a board-certified psychiatrist by the American Board of Psychiatry and Neurology and practices at Stanford with specialization in affective disorders and autism spectrum disease. He is Associate Chair of both the Department of Bioengineering and the Department of Psychiatry and Behavioral Sciences at Stanford.

Over a period of twelve years, Deisseroths laboratory created and developed optogenetics, hydrogel-tissue chemistry, and a range of supporting and enabling methods. He has employed these technologies to discover the neural cell types and connections that cause adaptive and maladaptive behaviors, and disseminated the technologies to thousands of laboratories around the world. He was selected a Howard Hughes Medical Institute Investigator in 2013 and was elected to the US National Academy of Medicine in 2010, to the US National Academy of Sciences in 2012, and to the German National Academy of Sciences (Leopoldina) in 2014.

For his discoveries, Deisseroth has received the NIH Directors Pioneer Award (2005, the Zuelch Prize (2012), the Perl Prize (2012), the BRAIN prize (2013), the Breakthrough Prize (2015), the BBVA Award (2016), the Massry Prize (2016), and the Harvey Prize from the Technion in Israel (2017), and he was the sole recipient for optogenetics of the 2010 Koetser Prize, the 2010 Nakasone Prize, the 2011 Alden Spencer Prize, the 2013 Pasarow Prize, the 2013 Richard Lounsbery Prize, the 2014 Dickson Prize in Science, the 2015 Keio Prize, the 2015 Lurie Prize, the 2015 Albany Prize, the 2015 Dickson Prize in Medicine, and the 2017 Redelsheimer Prize, in addition to the 2017 Else Kröner Fresenius Prize.

seek cocaine by elevating activity in their prefrontal cortex—you can see how this is relevant to what I was talking about before. Then, informed by this animal finding, a couple years later, he and his colleagues described an optogenetically guided clinical trial, using the discovered causal principle to test a specific and targeted transcranial magnetic stimulation (TMS) treatment. TMS is an approved, non-invasive treatment, but the problem with TMS is that we don't know really how to use it; there's a lot of brain you could stimulate and it might vary from person to person, and symptom to symptom—without a known causal target it's very hard to develop it as a therapy. Using optogenetics, Bonci and his colleagues had indeed found a causal target; then, in cocaine addicts, they tested TMS in homologous structures and they saw a powerful reduction of cocaine consumption in these patients. So that's what we are starting to see: the knowledge, the insight, the fundamental understanding to guide treatment.

**ER**: Do you think we should invest more funding into brain research, given the apparent increase in mental and brain disorders?

**KD**: I think this is one of our most important responsibilities, to ensure that brain research is adequately supported. There is an epidemiological and human suffering issue as you mentioned. We're seeing elevated suicide rates, we're seeing increased autism diagnoses. Anxiety and depression are not nearly as well treated as they should be; we're seeing increased PTSD incidence. From the human suffering standpoint, it's important to increase our support and investment in brain research, both basic, for the reasons I mentioned earlier, and clinical.

**ER**: Do you think that researchers should get more involved in translational and clinical research?

**KD**: Although it would be natural for me to say yes, I'm actually going to say no, because I think we need more basic research. I would just say to basic researchers, stay informed, and if you're at a conference go and look at some clinical posters, but don't change what you're doing. Do the basic research, that's what we need.

**ER**: You already mentioned TMS, there is also deep brain stimulation, which is being used for treating Parkinson's and depression—how do you see the value of these and other emerging technologies to treat mental disorders?

**KD**: Deep brain stimulation is interesting because it's clearly effective for treating Parkinson's disease, but it only helps some patients and it only helps some symptoms and it only helps for a little while. So, we still need to understand DBS much better. But for other disorders—memory or depression—we haven't yet seen the effects we'd hoped for with multi-centered placebo-controlled studies. DBS is a great treatment, but it's brain surgery: implanting an electrode, and pushing everything out of the way as it goes down into the brain—you want to understand what you're doing before you explore the space of possibilities with DBS. As with TMS, I'm a strong supporter, but we need a basic understanding of what we're doing.

**ER**: TMS, DBS, and other treatments for depression and schizophrenia are basically changing human behavior with drugs or with a device. Do you see ethical issues with this?

**KD**: Even talk therapy, by the way, changes the brain and changes behavior, so this is not limited to medicine or stimulation. This is something we take seriously; of course as interventions become quicker and more precise, it doesn't change the fundamental ethics, but it heightens the clarity of the ethical issue. When you think about a treatment that changes behavior quickly and specifically, you have to wonder, is this going to be misused in some way? I don't have all the answers, but I know it's something we all

have the responsibility to discuss and, as technology advances, we need to grow the ethics along with the technology. It's not a fundamentally new issue to neuroscience or psychiatry, but we need to keep the ethics discussions healthy and active.

> *"We already see optogenetically guided clinical trials (. . .) they saw a powerful reduction of cocaine consumption in these patients"*

**ER**: As diagnostics have improved recently, how do you think this might influence our idea of what is normal behavior?

**KD**: In psychiatry, diagnostics have historically been, and still are, essentially verbal: patient self-report and physician checklists—not even quantitative necessarily. This is still the state of the art for diagnosis. That said, diagnoses are advancing. We're starting to see genetic testing, we're starting to see efforts in terms of activity levels inferred from EEG and other biological markers. Even if none of these have reached the level of typical clinical care yet, they will eventually influence clinical care or diagnosis. That's what we need in psychiatry: We need to know that we're measuring something quantitative and reproducible. Two patients can have depression, but they can have completely non-overlapping symptoms; thus, we need to understand what we need to measure in a patient-specific way. And that will guide all therapies including the new, causal circuit-level therapies.

**ER**: Do you also see a shift in the definition of what is normal: that we now diagnose someone with depression or autism if he or she is just a bit more withdrawn or a bit more unhappy?

**KD**: With autism, the increased diagnosis rate likely relates to an increased awareness. You may indeed have had children who were sort of simply written off as odd—and may have suffered from being written off as odd, in not getting the support they needed to bring them into more effective social interactions, for example. So increased diagnosis may be positive in many cases. The key thing with depression—and this is something fundamental to psychiatry—is that there are many kinds of depression, and there are different severities of depression; it can be recurrent and associated with suicidality, or take a mild and treatment-responsive form. Again, increased awareness may have led to more people getting treatment. But you raised the question if there are cases of unnecessary treatment, and there are in all fields of medicine. Where is that line and if you move that line too far in one direction or the other, do you end up excluding people who would benefit from treatment? This is an active discussion in every field of medicine, and psychiatrists are trained carefully to minimize treatment of patients who don't need treatment. These are not issues that are unknown to psychiatry, they are actively discussed, and we have to be careful at the same time to not exclude patients who could benefit from treatment. We have to not arbitrarily move that line without careful consideration.

> *"From the human suffering standpoint, it's important to increase our support and investment in brain research, both basic (. . .) and clinical."*

**ER**: What do you think is the role of organoids or GWAS studies to understand mental disorders? This question again may be related to better diagnosis.

**KD**: The genetic studies, and organoid studies, are quite powerful. As we look at large numbers of patients and as we identify more and more genes of interest, we start to understand the complexity. There is great promise that we may be able to look at the genetic signatures of patients and home in on a set of genes and get a picture of what the underlying vulnerability might be. If that guides diagnosis and treatment, that would be great. We're not there yet, but the promise is clear. If we could merge that information with our causal, brain-wide dynamical understanding, we could say, for example, with this genetic makeup, the patient is likely to have impaired communication between the prefrontal cortex and amygdala. Since we know from optogenetic animal models that enhancing this connection ameliorates PTSD or anxiety, we could then give this patient a principled, precision, causal treatment. That's a hope. We're nowhere near that point yet, but I think that what we're doing could help, and the addiction work proves an underlying principle.

> *"There is great promise that we may be able to look at the genetic signatures of patients and home in on a set of genes and get a picture of what the underlying vulnerability might be."*

Organoids are interesting as well. You might have a patient and you could take skin cells or other cells and make iPS cells and make organoids. The question is what do you measure in those organoids, do they preserve enough key properties and are they consistent enough? Is there some measurable parameter that is both consistent across different organoids and causally representative of brain-wide dysfunction? People are working hard on this. Again, we're not there, yet.

**ER**: What do you think is the future potential of optogenetics and new microscopy techniques, and other novel technologies to help us understand brain function and structure?

**KD**: Looking into the future, as you mentioned, we and others are advancing microscopy methods for both structure and function, that's part of what we'll be doing after the prize. We've been working on this for years and we are in a situation now where computational methods are becoming limiting. We now have unique and remarkable data sets from which we are extracting useful findings, as in Emily Ferenczi's work that I mentioned earlier, but we haven't fully tapped the potential of these data sets, because we don't really know what to look for in terms of spatial and temporal patterns within the vastness and diversity of brain-wide, high-resolution structural and functional data sets. We now can form new hypotheses, but we also need new ideas from theoretical and computational neuroscience. That's going to be a very interesting process: finding patterns that the eye can't necessarily pick out

easily. And maybe those will turn out to be part of the key set of principles that we need.

**ER**: Sort of the holy grail of understanding the human brain is, in a way, understanding human consciousness. This is a bit more philosophical question perhaps: Do you think we are getting there?

**KD**: Most systems neuroscientists and most psychiatrists think about consciousness even if they don't admit it in writing—I certainly do. Most people also think that a brain-wide understanding is essential as this property cannot emerge from—or can be fully represented in—just a local circuit of 10, 20, or 1,000 neurons. So I hope that some of these big principles may also in the long run emerge from intact brain analyses. But it's a thorny problem. Even talking to another person, to a patient, or a healthy person, I don't know what their consciousness is. It's very hard to measure these subjective states, but I think the brain-wide, causal analyses are going to be part of the answer.

**ER**: What would you like to do now with the prize money that otherwise you couldn't have done?

*"In the future, we plan to use our new technologies to study complex behaviors."*

**KD**: Normally, we work on developing technologies but when a technology is new, our initial tests of it will be well-studied, easily measurable behaviors. Anhedonia for example is important and mysterious and we've had some results, but it is a simple behavior in a rodent, measured by sugar consumption. In the future, we plan to use our new technologies to study complex behaviors. We're trying to understand motivational and hope-related behaviors that are more challenging to measure, and are not as deeply understood, and to do so we're bringing our new technologies—some not even published yet—to bear, while developing them further to address these complex questions. That's the unique opportunity: to take such a big risk. It is something that would be hard to justify in other circumstances. The exciting thing for me is to have the confidence to do something that I know is needed, and take a big jump forward.

**ER**: Can you maybe explain briefly what these new technologies would be like?

**KD**: They all share this principle of not only brain-wide intervention but also brain-wide readout during behavior. There are several of these we have designed that are largely optical in nature, but they all have this bi-directional, global, cellular resolution, and readout quality, and that's what we are hoping to advance in the next few years.

**ER**: Dr. Deisseroth, thank you very much for the interview.

*The interview was conducted by Esther Schnapp and Holger Breithaupt.*