

ELSE KRÖNER-FRESENIUS-STIFTUNG

Else Kröner Fresenius Preis für Medizinische Forschung 2017

# The Biological Basis of Psychiatric Disorders



### Dear Readers, Friends and Partners of the Else Kröner-Fresenius-Stiftung,

Some 20 percent of people in Europe suffer from mental disorders. This creates tremendous burdens for patients and their relatives, particularly because our capacity for treating mental disorders is limited and existing therapies are often far removed from the root causes of the problem. In recent years, evidence has accumulated that many psychological problems are caused by biological changes in the brain. As a result, the consequences for our understanding of mental disorders will be dramatic, potentially revolutionizing the way we treat them.

The Else Kröner Fresenius Preis für Medizinische Forschung has been designed to give a leading international researcher in a specific area of medicine the resources to intensify his research and achieve breakthroughs. In addition, it is intended to help support the next generation of researchers. The prize was first awarded to Yale University immunologist Prof. Dr. Ruslan Medzhitov in 2013, on the 25th anniversary of Else Kröner's passing. The four million euro prize is the largest award for medical research, and is given every four years.

The Else Kröner-Fresenius-Stiftung congratulates prizewinner Prof. Dr. Karl Deisseroth and thanks the jury for its painstaking and expert work. Our hope is that the prize will lay the foundation for significant advances in the diagnosis and treatment of mental disorders.

Prof. Dr. Michael Madeja  
Member of the Board, Else Kröner-Fresenius-Stiftung



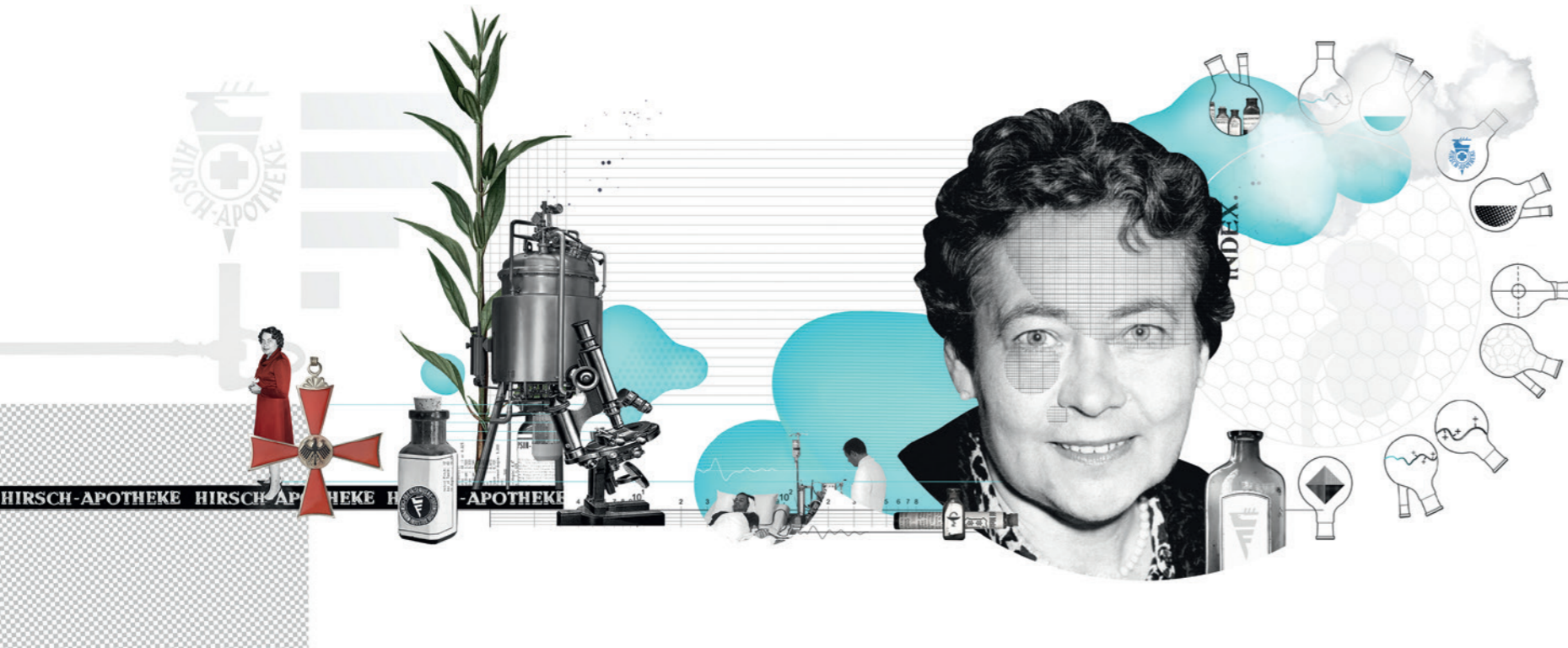
### Dear Readers,

For centuries, man has searched for the roots of mental disorders. It was not until the 19th century that it became clear for the first time that psychological problems could be caused by damage to the brain. Today, modern psychiatry has shown that mental disorders are often the result of many different factors.

Psychological processes are based on biological activity, including neuronal interactions and hormonal signaling. Understanding these processes requires the most sophisticated technologies and cutting-edge methods – precisely what Professor Dr. Karl Deisseroth brings to the table in his groundbreaking work.

I am pleased that such a remarkable scientist has been awarded the prestigious Else Kröner Fresenius Preis für Medizinische Forschung. His research is advancing the global research community's understanding of neurological and psychological illness.

Prof. Dr. Johanna Wanka  
Federal Minister for Education and Research



Else Kröner

## »If not us, then who?«

Else Kröner (1925–1988) was one of Germany's most successful entrepreneurs. She turned Fresenius into an international healthcare company, employing nearly 260 000 individuals and donated her entire estate to found the Else Kröner-Fresenius-Stiftung, one of Germany's largest charitable foundations.

She was born Else Fernau in Frankfurt am Main on May 15, 1925. At the age of three, she lost her father, and shortly thereafter moved with her mother to the house of Dr. Eduard Fresenius, a Frankfurt pharmacist who owned the Hirsch Pharmacy and had established the Fresenius Company in Bad Homburg. Fresenius' own marriage was childless, and he looked after Else as if she were his own daughter. In 1944, Else began as a trainee at the Hirsch Pharmacy. Shortly thereafter,

she decided to study pharmacy. Dr. Fresenius died before Else had completed her studies. In his will, he left both the Hirsch Pharmacy and the Fresenius Company (which by then employed only a handful of workers, as it had been greatly damaged in the war) to Else.

Barely 21, Else Fernau assumed responsibility for both the pharmacy and the Fresenius company. The company was heavily in debt, and only 30 of the firm's 400 employees were kept on. But Else Fernau – renamed Kröner after her marriage to Dr. Hans Kröner – soon began to rebuild the business. Else Kröner managed the company until 1981. When it became a publicly-held corporation, she served as chairwoman of the board of directors until her death on June 5, 1988.

## Else Kröner Fresenius Preis für Medizinische Forschung 2017

Else Kröner's question, »if not us, then who?« is a symbol of her social engagement. During her life, she supported numerous humanitarian initiatives, and founded the Else Kröner-Fresenius-Stiftung in 1983. The Foundation's goal is to facilitate medical research and support suffering patients. Upon her death, she allocated the entirety of her estate to the Foundation.

First awarded in 2013, the prize is conferred every four years, and comes with an endowment of four million euros. In 2017 the Else Kröner Preis für Medizinische Forschung is awarded in the field of the biological basis of psychiatric disorders to:

**Karl Deisseroth, MD, PhD**

**D. H. Chen Professor of Bioengineering and of Psychiatry and Behavioral Sciences, Stanford University; Investigator, Howard Hughes Medical Institute**

*for his discoveries of optogenetics and of hydrogel-tissue chemistry, and for developing circuit-level insight into depression.*

The previous Prize Winner:

2013 – Immunology: Ruslan M. Medzhitov, PhD, Sterling Professor of Immunobiology, Yale University; Investigator, Howard Hughes Medical Institute



The Awardee Karl Deisseroth

**Brilliant, creative, fearless**

**The building that houses Karl Deisseroth's laboratory is located near a vineyard in the hills of Palo Alto, a few miles from Stanford University's main campus. There is not a lot of room to spare at the main campus, but here Deisseroth and his interdisciplinary team have been given two complete floors. We wanted to know: how does he work? Where do his ideas come from? What does the future hold for him? We spoke to those closest to him and visited the man himself in his lab.**

Noted neuroscientist and psychiatrist Karl Deisseroth opens the door to his office promptly at 9 a.m., our agreed-upon meeting time. It is windowless and not quite 90 square feet, and a Venetian blind covers the glass door. Papers and scientific journals are piled on the desk where Deisseroth, 45, writes his own papers, drafts future projects, and works on applications for research grants that will provide funds to help him study the brain's complex wiring. Together with his team, he is looking for new methods to help us understand what exactly happens in the brain when someone exhibits symptoms of mental illness.

Deisseroth's already presented two such visionary methods to the greater public. He pioneered the field of optogenetics, a method that uses light to turn nerve cells on and off (see box next page). Since 2005, when he published one of his several key groundbreaking papers on the method in *Nature Neuroscience*, optogenetics has been used in thousands of labs worldwide. It has been applied to better understand illnesses such as schizophrenia, anxiety disorders, depression and Parkinson's disease. Four years ago, Deisseroth produced another global breakthrough with the invention and development of hydrogel-tissue chemistry (one form of which is his CLARITY technique, a way to make brain tissue transparent that results in neural cell networks becoming visible at high resolution even within the fully intact adult mammalian brain (see box p. 10).

Optogenetics has thus far chiefly been used in animals, and hydrogel-tissue chemistry on postmortem animal and human tissues, but the insights gained have already helped doctors guide their clinical work. »Karl Deisseroth is leading the way in demonstrating that it is possible to translate findings from rodent brains to human brains,« says Stanford Professor Robert Malenka, one of Deisseroth's mentors. »The discoveries are incredibly important for the field of psychiatry, and will eventually lead to more sophisticated approaches to diagnosis and treatment.«

But it wasn't clear that this would be Deisseroth's path in life, even though he came from a family of scientists: His father is an oncologist, his mother a chemist. »I actually wanted to be a writer. I am fascinated with words, and how their rhythms can stir emotion,« Deisseroth says. He took classes in creative writing at Harvard University, and wrote short stories and poems. At the same time, he decided to pursue his interest in the natural sciences, and ended up majoring in biochemistry. In the neurosciences, he found a way to combine his interests. »When I study the brain, it's to answer the same questions,« he says. »How do such complex emotions come from the simplest chemical components?«

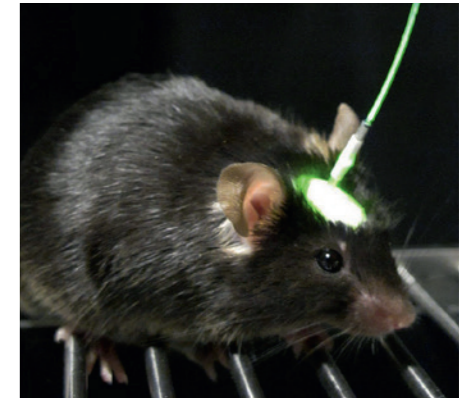


### It is about understanding the brain

In 1992, Deisseroth enrolled in medical school at Stanford; he later earned a doctorate in neuroscience there as well, and launched his lab in 2004. He has been a full professor of bioengineering and psychiatry since 2012, and is a member of the renowned National Academy of Sciences. In 2014, he became an investigator at the Howard Hughes Medical Institute, and was accepted to the Leopoldina, the German National Academy of Science. *Nature Methods*, a leading journal of the natural sciences, named optogenetics »Method of the Year« in 2010. He is one of the minds behind the billion-dollar U.S. BRAIN Initiative, which was launched by a small group of neuroscientists and the Obama administration in 2013. The project's aim? Nothing less than developing and applying tools to understand all neural systems, from the simplest to the most complex of all – the human brain.

For Deisseroth, every success is a stimulus for new ideas. Robert Malenka, codirector of the Stanford Neurosciences Institute, describes Deisseroth as »brilliant, creative, driven, and visionary.« Deisseroth conducted research in Malenka's lab as a postdoc from 2000 to early 2004, before establishing his own lab at Stanford. »I knew he was special and decided that I would give him whatever resources he needed so that he could pursue his own ideas,« Malenka says. Deisseroth used this opportunity to focus on a demanding project dealing with the stem cells that develop into neural cells. He worked with methods that were new to Malenka's lab, and published his results in *Neuron*, a leading neuroscience journal, in 2004 – even though he spent up to three-fourths of his official workweek at his medical residency in psychiatry.

Most of all, Malenka remembers Deisseroth's high tolerance for frustration. »If experiments were not working – that would drive him to work harder to figure out what was going on,« Malenka says. »He was able to accept that doing really good science is challenging and that failures are part of the normal process.«

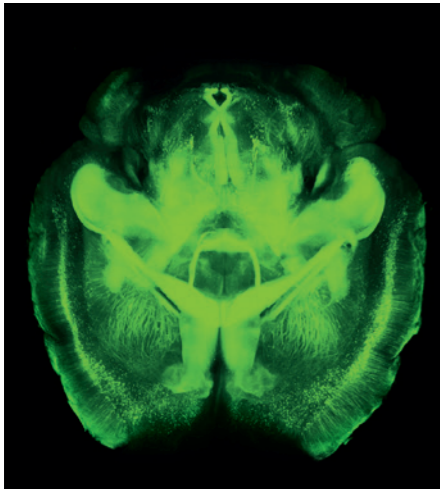


#### Optogenetics

Using optogenetic techniques, researchers can study the activity of cells in the brains of living organisms. This is accomplished by genetically introducing protein-based ion channels into neuron cell membranes that react to light pulses. These proteins work like switches, and can be activated or deactivated using fiber optic cables inserted into the relevant brain regions – thereby turning the nerve cells on or off. Optogenetics thus offers unprecedented causal access to the inner workings of the brain. A decade ago, Karl Deisseroth's team demonstrated the technique's effectiveness by steering a mouse in circles and stopping and starting it using pulses of light.

More on the history of optogenetics:

Deisseroth, K.: Optogenetics: 10 years of microbial opsins in neuroscience. *Nature Neuroscience* **18**, 1213–1225 (2015), doi:10.1038/nn.4091



Brain of an adult mouse

#### Hydrogel-tissue chemistry

Because the outsides of nerve cells are covered by a layer of fat, studying the brain's neural networks with a microscope is a challenging task: Researchers must first cut brain tissue into thin slices, then photograph it. The pictures are then reconstructed into a 3-D image of the brain using computer software. Karl Deisseroth and his team figured out a way to wash out the layer of fat, after converting the brain into a unique hydrogel-tissue chemical hybrid that allows fat removal without disintegration. The resulting preparation is transparent (one version of the hydrogel-tissue chemistry approach is even called CLARITY, since it allows the cleared brain to be examined as a whole). With the help of various dyes, specific networks – for example, the ones responsible for mental illness – can be isolated and studied.

Malenka is convinced that this perseverance was the deciding factor that led Deisseroth and his team to finally use optogenetics not just in petri dish neural cells, but also in animals. »Most investigators would have given up.« But Deisseroth was »fearless,« Malenka says. »That might be the single best word to describe him.«

#### »At night, we both get our laptops out«

While he was a postdoc, Deisseroth met his now-wife, Michelle Monje. Today, she is a successful scientist with her own lab at Stanford, specializing in researching brain tumors in children. »I am driven by my patients and lack of good therapies for many of them« Monje says. When she talks about her husband, she describes him as a tireless worker whose day almost always ends in the early hours of the morning.

Together, they have four children between the ages of one to eight, and split the household and child-rearing responsibilities. Deisseroth also has a fifth child, a 20-year-old son from his graduate school days. He describes family life like this: »I get up early, and I make breakfast and lunch boxes for the kids. Then I take the kids to daycare and school, and I'm at the lab around nine,« Deisseroth says. »My wife usually picks the kids up in the afternoon, and then we all meet back at the house. And when the kids have been tucked in for the night, we both get our laptops out.« The two do not have any joint projects, but regularly trade ideas back and forth.

Her husband values and fosters independent thinking and creativity in his trainees, Monje explains. She sees this as the secret of success behind his lab. Malenka describes Deisseroth's lab as a »playground for creativity, filled with fantastic resources that attracts the best and brightest young talents.« For many students and postdocs, working with Deisseroth is a career stepping-stone: Feng Zhang and Edward Boyden (both key participants as graduate students in the early optogenetics tests) now lead their own laboratories at the Massachusetts Institute of Technology (MIT) in Boston, and Zhang is now famous as

well for his genome editing work. Meanwhile Kwanghun Chung and Viviana Gradinaru (key players in hydrogel-tissue chemistry work beginning as postdocs in Deisseroth's group) both lead their own laboratories, at MIT and Caltech, respectively.

When Karl Deisseroth talks about an average day in the lab, he explains exactly what it is that his colleagues contribute. And with every word he speaks, he makes it clear that he truly values each individual. Ailey Crow, an IT and optical technology expert, describes her boss as »humble and understated for his position.«

Crow sees Deisseroth's method of selecting and introducing new colleagues as a key to the lab's success: »He's assembled a large group of intelligent, ambitious, and driven scientists. Karl provides just enough guidance to ensure that all projects, even technology development efforts, stay focused on furthering our understanding of the brain.«

Molecular biologist Li Ye describes Karl Deisseroth as someone who always sees »the big picture,« and is always aware of thinking across disciplines. In his lab, 35 individuals from a wide variety of backgrounds have found a common workplace, from neuroscientists and biologists to optical and IT engineers and chemists. »Karl has a crystal clear vision about where the field and the lab are going,« says Li Ye. »Karl makes a great effort to push people out of their comfort zones and pair them with colleagues with vastly different backgrounds.«

Deisseroth is proud of his group's scientific output – not just of their biological research results but also of the technical innovations they have made. And now he has presented the Else Kröner-Fresenius-Stiftung a research plan that he says is more ambitious than any other his team has taken on. He would like to not only develop new techniques, but then also implement and use them immediately, in order to examine what happens in the brain when symptoms of depression are exhibited. These new techniques will be based on optogenetics and on hydrogel-tissue chemistry, and with them, Deisseroth will focus on the brain's circuitry (see interview p. 13).

This restless approach to research is in stark contrast to Deisseroth's calm in-person manner. It is as if he has all the time in the world for whomever he is speaking with at any given moment. But how does he get his ideas? At his desk, he says – when it is absolutely quiet, when he can read and think, and no outside distraction interrupts him. »That's why the blinds are closed. It's almost a kind of meditation, when all of the different threads suddenly come together.« Other people may get their ideas when they are in motion – jogging, for example. But not Deisseroth. »I just feel distracted,« he says.

Deisseroth also gets input from conversations with his researchers. »I try not to have too many formal meetings,« he says. »I love to talk to everybody, and see what the different teams are working on.« On this particular morning, he is speaking with Ailey Crow about a presentation for a speech she is working on. The speech touches on research on the

»Karl's Lab is a playground for creativity, filled with fantastic resources that attracts the best and brightest young talents«

Robert Malenka



Karl Deisseroth likes the stimulating interchange of ideas – here with his colleague Ailey Crow.

zebra fish's nervous system: Which cells are activated when a fish exhibits a specific behavior? The team is hoping to find out while using Deisseroth's optogenetic methods.

The neuroscientist's morning commute passes through the heart of Silicon Valley. Countless high-tech start-ups populate the area, many of them founded by graduates of Stanford University. And their numbers are constantly growing, especially in the biotechnology field. »This environment is, of course, extremely stimulating,« says Deisseroth. He himself helped found two different companies, both of which he still scientifically advises. »But the business world isn't for me. I belong right here, in the research lab.«

**For more information**

**on Karl Deisseroth's work:**

<http://web.stanford.edu/group/dlab/>

Interview with Karl Deisseroth

## »Achieving causal understanding can make any kind of treatment more powerful«

»Cracking the Neural Code« Program (CNC Program) is the name of the lab run by Karl Deisseroth. In his work as a neuroscientist he is driven by his experience as a psychiatrist and his encounters with patients. How can we help them better?

**What drives you in your daily work in the lab?**

The brain itself is such a fascinating place, but also my early encounters with patients with autism, treatment-resistant depression, schizoaffective disorders, and anorexia were among the key moments that inspired my research interest in understanding brain circuits. Currently available treatments like medication or talk therapy often do not work adequately in these classes of patients, and I still want to know how we can help them.

**Do you still see patients?**

Yes. I spend one week per year as the overnight attending physician for the inpatient hospital (covering the Emergency Room, too) and over the weekend. I also have a half day outpatient clinic that runs year-round. Some of the outpatients suffer from autism, but I mostly focus on patients with major depression. This is a disease that is particularly difficult to understand: as far as we can tell, everything about patients' brains seems structurally and physically intact. And yet among other symptoms, they feel deeply hopeless, they cannot imagine positive or useful consequences of their actions. And they can have a reduced ability to feel reward or pleasure or motivation; this very distressing state is called anhedonia.

**How do you treat them?**

I use medications alongside cognitive-behavioral techniques, but I also try to help some patients with brain stimulation



For Karl Deisseroth the understanding of neuronal networks is the basis for future therapies.

treatments. One of these is called TMS, transcranial magnetic stimulation, where we bring magnetic field-generating coils close the head of a patient to stimulate nearby brain cells. It has been around for a long time and I was one of the treating physicians on the study that led to its approval in the USA for depression. But I can tell you both from my clinical experience and from the actual data which were published, the effects are very small at the population level. We have to do better.

### What will the focus of your future work be – using the prize?

With this award my team and I will focus on depression and on depression related symptoms while studying animal models with a couple of new techniques. These are based on our new optical-technology discoveries as well as optogenetics and CLARITY. We are at a point where we can look at brain-wide dynamics – analyzing interactions among many different regions in real-time while the brain is in action. It is only since last year that we achieved the ability to ask questions like: Not just what can region A do, but what can region A and B and C do together? Or, what happens to the influence of region B on region C, when I stimulate region A?

This circuit approach is extremely powerful since with latest technologies, we can see in rodents that highly specific, fast

modulation of circuit activity underlies very specific cognitions and action patterns, such as those involved in anxiety, hedonic behaviors, and social interactions.

### Can mice really help to understand complex mental illnesses such as depression?

We do not claim that animals experience depression as people experience. But we can induce animals to express symptoms that are similar to those of depressive people. Anhedonia for instance: healthy mice prefer certain rewarding things just like people. For example, they prefer sugary water over regular water. However, if we put them under chronic stress, this preference is lost and they don't care. And then there is hopelessness. We can put rodents in a challenging situation that requires effort to resolve. Stressed animals or depressed-like animals will not try as hard as healthy animals and give up much earlier. We have identified circuit dynamical processes that cause or correct these particular behavioral states.

### Using optogenetics, you can modulate specific behaviors in mice. Can you understand that people might be scared of optogenetics in humans and have ethical concerns?

Of course. I certainly do not want anything or anybody to control me or my brain, so I understand these fears and do not want to dismiss the ethical aspects at all. But it is still a long journey to using optogenetics directly in patients as we use it in rodents. For example, it entails brain delivery of microbial opsin genes via viral vectors along with fiber optic neural interfaces where you obviously have to know a lot more about the safety of the method in humans.

The reason why the direct use of optogenetics may be particularly unsettling to some people might be that it is more precise and target-specific than any of the currently available interventions such as medications or everyday stimulants like caffeine. However, we don't plan to do anything like that.

Rather, we can use the results and observations from our optogenetic experiments to understand the brain more deeply, and this has led to new ideas and hypotheses also for clinical studies.

### Are clinical studies translating results from »bench to bedside« already underway?

Yes. For example, last year the first optogenetics-guided clinical trial was published, showing that TMS delivered to a prefrontal-cortex brain region is safe and effective, for patients suffering from cocaine addiction, in inhibiting cocaine use. Though a relatively short-term study, this work provided important proof of principle for treating psychiatric and addictive diseases directly based on results from optogenetics in animals (see graph p 26 / 27).

### Will you run clinical studies as well?

Personally I will not run clinical trials; there are specialists who are very good at that. I am a psychiatrist, but first and foremost a basic scientist. For patients, I think the biggest thing I can do is drive basic science forward and help everyone understand. I am certain (in fact we already know) that achieving causal understanding can make any kind of treatment more powerful. For example, we will be able to combine pharmacotherapy and brain stimulation methods in patient-specific ways to be more precise and effective.

### What does this award mean for you and your lab?

The prize will allow us not only to expand our work, but also to take up a particularly high-risk project of great importance that would otherwise not be feasible. I am both proposing the development of novel technologies and tackling a very difficult problem (depression). When I proposed new technology development in the past, it was generally in the setting of a very simple, well understood assay or readout, like a movement



»We do not claim that animals experience depression as people experience. But we can induce animals to express symptoms that are similar to those of depressive people«

Karl Deisseroth

of an animal. Likewise, when I have studied more complex behaviors such as those relating to anxiety and depression, the technologies involved had been better established. So this combination of still-developing technologies and complex behaviors is a big challenge and a great responsibility.



Laudation for Karl Deisseroth

## Seeking to Understand the Brain »in Action« is Bold and Visionary

**The Else Kröner Fresenius Preis für Medizinische Forschung 2017 acknowledges both, groundbreaking past achievements and bold visions for the future. Prof. em. Dr. Peter McGuffin headed the jury that screened the long list of applications. »But in the end the ten of us who formed the jury were unanimous that Karl Deisseroth was our winner,« says the psychiatrist and geneticist.**

»Genius« is a word often used by the popular media to describe prominent persons in all sorts of fields but it is a word that I have rarely if ever seen before, being used by a scientist who has been asked to provide a critical review of the work of a contemporary. However, one of the expert reviewers who we, the jury, invited to comment on Karl Deisseroth's application for the 2017 Else Kröner Fresenius Preis unabashedly described him as a genius and the other assessors who provided detailed written reports were equally fulsome in his praise. Whittling the initial long list of nominations for the prize down to a manageable shortlist was quite a task – and all of those who made the shortlist were truly outstanding. But in the end the ten of us who formed the jury were unanimous that Karl Deisseroth was our winner.

### Karl Deisseroth's contributions to date

A fundamental problem about exploring the biological underpinnings of mental disorders is that the brain is not only the body's most complicated organ, it is also the most inaccessible. One of Deisseroth's major contributions has been the development of a set of methods, that he has named

optogenetics, which make possible the detailed study of brain function in living, free moving animals. Optogenetics involves using genes that occur naturally in some simple single celled organisms such as bacteria and algae and transferring them into mammals, such as mice, in such a way that they are expressed in nerve cells (neurons) in the brain. The genes in question carry the code for a class of light sensitive proteins called opsins. When incorporated into neurons, opsins make their way to the cell membranes, the surface areas where neurons communicate with each other. This means that by using light sources such as lasers, specific parts of the brain can be either activated or »switched off« by the experimenter to study functional effects. Over the last decade or so since

»One of the expert reviewers described him as a genius – and the other assessors were equally fulsome in his praise«

Peter McGuffin

he first began developing optogenetics, Deisseroth has been unstintingly generous in helping literally hundreds of neuroscientists around the world establish these revolutionary techniques in their own laboratories.

But if that were not enough, Deisseroth has also invented another experimental tool called CLARITY. A longstanding problem for researchers who want to carry out fine grained studies of the brain using microscopes is that the fats (lipids), that are vital components of membranes, make the brain opaque. Therefore it needs to be cut into very thin slices to render it sufficiently translucent to be studied. This in turn limits the extent to which within-brain connections can be visualized. CLARITY is now changing all of that. The CLARITY method allows large regions of the brain or even whole brains to be embedded in a water based gel, with the architecture preserved intact and the lipids dissolved away. Thus CLARITY is a superb complementary method for studying the anatomical basis of the functional brain connections revealed by optogenetics.

### The future plans

The proposal for Deisseroth's future research put forward for the prize could be seen as risky. Possibly too risky as he has said in his interview (p. 13), to be funded by a conventional research grant. But it was described by one of the prize reviewers as »bold and visionary« and the jury agreed. He seeks to understand the brain »in action,« and thence unravel the functional role of large scale neural oscillations, literally »brain waves.« Current technology has both temporal and spatial limitations and we do not really have any good methods to noninvasively measure neural dynamics in humans.

Deisseroth's prize winning proposal put forward three innovations, that have high potential. Optoencephalography (OEG) should enable whole cortex recordings of wide-scale

neural dynamics with cellular and genetic specificity. Another approach called frame-projected independent-fiber photometry (FIP) would move this resolution into deep brain areas. These are to be coupled with yet another new method called CAPTURE (a development from CLARITY) to rapidly acquire anatomical connectivity linking the functional results with knowledge of the anatomical circuits.

Together these tools should provide completely novel means for testing specific hypotheses about key circuits and oscillatory phenomena involved in complex behaviors and thence to much improved understanding of the biology of psychiatric disorders.



Prof. em. Dr. Peter McGuffin has been researching the genetic causes of diseases like schizophrenia since the 1970s. Born in Northern Ireland, he continued his scientific career in Wales, and later on at the prestigious King's College London. The clinical psychiatrist authored many publications. He became emeritus in 2013, but continues active research. McGuffin headed the jury for the Else Kröner Fresenius Preis für Medizinische Forschung 2017.

## Else Kröner Fresenius Preis für Medizinische Forschung 2017

# The Jury

**In the fall of 2015, following extensive and intense deliberation, the Else Kröner-Fresenius-Stiftung announced that the Foundation's 2017 Prize for Medical Research would be awarded in the field of the biological basis of psychiatric disorders.**

»There have been breathtaking advancements in our understanding of the cellular biology of the connectivity between nerve cells as well as in the imaging of the central nervous system. This will open up new possibilities in the diagnosis and treatment of psychiatric disease,« says Prof. Dr. Stefan Endres, chair of the Else Kröner-Fresenius-Stiftung scientific committee. »Making these advances visible, and fostering them further, is the prize's primary goal.«

For the jury, the Else Kröner-Fresenius-Stiftung was able to secure ten renowned researchers and clinicians from five countries. Peter McGuffin, professor emeritus for

Psychiatric Genetics at King's College (London), was named as jury head. The Else Kröner-Fresenius-Stiftung scientific committee accompanied the multi-stage selection process. It was represented by Prof. Dr. Hans-Peter Schuster, Prof. Dr. Stefan Endres (Chair since January 2017), and Prof. Dr. Christine Klein.

Forty applications were received following a call for submissions. Researchers could nominate themselves, provided their application was supported by letters of recommendation from two leading researchers from different countries. For the first round of competition, nominations were based on two criteria: an overview of the most important aspects of applicants' research and the potential impact of their work in the future.

After a formal examination of all applications on the part of the Else Kröner-Fresenius-Stiftung, the jury met for the first time in March 2016 to narrow the field of candidates. The deciding factors were (1) candidates' record of groundbreaking achievements and (2) their clear potential to make meaningful contributions to the field in the future. Seven candidates were then asked to submit more detailed applications describing their proposed research plans and how they would use the prize to support their work over the following five years.

Experts in psychiatry and neurology helped the jury come to a decision and select a winner. Each full application was evaluated by three reviewers, excerpts of which were anonymized by the Foundation and forwarded to the applicants. Candidates answered further questions about the contents of their proposals and, in several instances, refined their research plans.

In November 2016, the jury met again. A thorough discussion established the fact that more than one applicant was qualified for the award. Among this elite group Karl Deisseroth's unique past results and the excellence of his proposed research program stood out. His nomination, forwarded by the jury to the board of the Else Kröner-Fresenius-Stiftung was unanimously approved.

»The deciding factors were the record of groundbreaking achievements and their clear potential to make meaningful contributions to the field in the future«

Stefan Endres

Robert Freedman has been researching the foundations and possibilities of medical therapies used to treat and prevent schizophrenia. At the same time, he uses psychotherapy to help patients. »For many years, there was a line dividing psychotherapy and pharmacotherapy; people belonged either to one camp or the other. That's no longer true for most practicing psychiatrists,« Freedman says. For medicine in general, psychiatric research and the search for the root cause of illness have become more important. »We know that 30 percent of patients who come to a general physicians office come with a psychiatric problem.« For many of his patients, it is important that he clarifies »the biological basis for their ailments, and explains to them what's happening in their brains, and how we can help them.«



Robert Freedman, MD, Professor at the Department of Psychiatry, University of Colorado Denver, USA



Fritz Henn, MD, PhD, Professional Lecturer at the Icahn School of Medicine at Mount Sinai, New York; Brookhaven National Laboratory, USA

Fritz Henn's main focus is the neurobiological cause of depression. Together with his task force, he recently discovered nerve cell circuits heavily involved with the manifestation of depression. Using fMRI and PET imaging technology, he has been able to make them visible. Researchers hope to one day alleviate the symptoms of depression by stimulating these nerve cells. »I think we are getting to the point where we really are starting to understand circuits involved in psychopathology,« says Henn, formerly the director of the Central Institute of Mental Health in Mannheim. »If we then can combine that with an understanding of the genes that can alter those circuits, we may find a point at which we can intervene and really create a significant therapeutic result.«

For Thomas Insel, the early detection of mental disorders is key, which he describes as disorders of the brain. »For brain disorders, behavior is the last thing to change,« says Insel, former Director of the National Institute of Mental Health in the USA. »There are changes in the brain a decade or more before you see the first sign of a behavioral change.« The earlier these changes are detected, the further in advance treatment plans can be developed and the more effectively they can be dealt with. So-called »machine learning,« in particular, offers the promise of revolutionary advances in medicine: Computer programs can be trained to recognize the patterns of illness early, thereby improving outcomes for people with a broad range of brain disorders.



Thomas Insel, MD, Verily Life Sciences (Alphabet), USA

Marion Leboyer studies the role the immune system plays in the development of mental disorders. In the field of immunopsychiatry, researchers are hoping to discover new mechanisms and biomarkers that can improve diagnoses and therapies. »It's only in the recent past that we've been able to understand the role that genetic factors in the immune system play when it comes to how individuals react to psychological stress or infection,« says Leboyer. »We react very individually. And this means that the likelihood that an individual will develop a psychological illness has to do with his or her genetic disposition.« Discoveries in this field include conditions such as autism, bipolar disorder, depression or schizophrenia.



Marion Leboyer, MD,  
Professor of Psychiatry at the faculty of  
the Université Paris-Est, Inserm, France

What do genes, neuropsychological symptoms and environmental factors have to do with the development of mental health problems? That is what psychologist Terrie Moffitt wants to know. As part of a larger study, she is looking at participants from birth to middle age. »If you follow people long enough, virtually everyone will experience a spell of mental disorder at some time in their life – from fear and depression to substance abuse,« Moffitt says. New technologies allow a better understanding of mental illness and are key to research in the field. »The Else Kröner Fresenius Preis für Medizinische Forschung injects important funds into a lab that is already poised to make discoveries, Moffitt says, »enhancing the chances of a breakthrough.«



Terrie Moffitt, PhD, Professor,  
Duke University, Durham, USA,  
and King's College, London, UK



Wolfgang Maier, MD, Professor for  
Psychiatry at the Universitätsklinikum  
Bonn, Germany

Wolfgang Maier's research focuses on the genetic foundations of diseases such as schizophrenia, bipolar disorder, and, most recently, Alzheimer's. He hopes that the Else Kröner Fresenius Preis für Medizinische Forschung can help end the stigmatization of people with mental health problems. »Historically, these illnesses were misunderstood, and even sometimes seen as evidence of bad character,« Maier says. Today, it is widely understood that genetic and psychosocial factors, as well as personal biography, contribute to the development of psychological conditions. According to Maier, »the prize will help focus public attention on major breakthroughs in psychiatric research.«



Barbara J. Sahakian, PhD, DSc,  
FMedSci, Professor of Clinical  
Neuropsychology at the University  
of Cambridge

Barbara Sahakian is interested in the impact of neurodegenerative diseases and psychiatric disorders on cognitive skills. In the case of schizophrenia, for example, in addition to psychotic symptoms, such as hallucinations and delusions, patients also have motivational problems and cognitive symptoms, including impairments in concentration, learning, and memory. The consequences can be dramatic: »Patients often find that cognitive problems prevent them from staying in education or earning a living,« says Sahakian. She is studying the effects of cognition-enhancing drugs and cognitive training using games on mobile devices in people with schizophrenia and depression in order to improve patients' well-being and ability to function.

Patrick McGorry is a specialist in youth mental health. His research tackles the early detection of mental illnesses, three-fourths of which present before the age of 25. »Psychosis almost never begins overnight, but develops gradually over a time – often months or years before the first presentation of hallucinations or delusions.« Warning signs including relationship problems, major mood changes and vocational failure may be the first signs of a more serious and persistent illness. Such indicators can already be recognized early so that patients can expect a much better outcome. McGorry is convinced that dividing mental disorders into stages – already a common practice in oncology – would enable better matching of treatment and help prevent progression to later more disabling stages of illness.



Patrick McGorry, MD, PhD, FAA,  
FASSA, FRCP, FRANZCP. Professor at  
the Center of Youth Mental Health,  
University of Melbourne, and Orygen,  
the National Centre of Excellence  
in Youth Mental Health, Australia

For almost 30 years, Myrna Weissman and her team have tracked families over multiple generations to trace the roots and development of depression. »In families where the grandmother suffered from depression, for example, the risk that her children and grandchildren will develop the illness can be two to six times greater,« Weissman says. Natural predispositions can interact with concrete events, like the death of loved ones or conflict with family members. Weissman places particular weight on awarding the Else Kröner Fresenius Preis für Medizinische Forschung to a successful researcher in the middle of their career who works actively to mentor younger scientists. That way, she says, »they will be able to use the money to find very excellent young people and further some of the work they're doing.«



Myrna Weissman, PhD, Diane  
Goldman Kemper Family Professor  
of Epidemiology and Psychiatry,  
Columbia University College of  
Physicians and Surgeons; New York  
State Psychiatric Institute, USA

The Future of Psychiatry

## Seven Burning Questions We are Trying to Answer

### Early detection

### How long before obvious symptoms develop does a mental illness start?

Mental illness often makes itself known when a patient's behavior, emotional makeup, or sense of perception conspicuously changes. But changes in the brain's structure may very well have happened years before the first symptoms appear. When did those changes actually begin? How can we reliably recognize them using imaging methods? And how can we use these insights to aid in early detection and prevention of serious disease progression?

### Diagnosis

### Will we someday be able to detect mental illness from a simple blood test?

It is easy for doctors to use an inflatable cuff to diagnose high blood pressure or a blood glucose meter to test for diabetes. Simple methods like this have proven elusive in diagnosing psychological suffering, and finding equivalent methods for psychiatric illness is extremely difficult: With few exceptions, mental illnesses can have multiple causes. Researchers are looking for so-called biomarkers – in this case, molecules that could serve as indicators of mental illness – that can be found with a blood test.

### Pharmacotherapies

### How do we find new medicines with more specific effects?

Very broadly, the medications used to treat depression or schizophrenia today work by engaging with the brain's hormonal signaling. These psychotropic drugs have been around for decades, and they help many patients, but not all. And they often have side effects, because they simultaneously affect multiple regions of the brain. Researchers are looking for new, more specific compounds and for tests that can explain which drugs work with which patients.

### Psychotherapies

### How do psychotherapies affect the biological causes of mental illnesses?

With the help of psychotherapies, patients not only learn how to better live with their suffering, but also how they can positively influence their symptoms, and even heal their illness. We now know that emotional trauma can affect the regulation of genes, which in turn play a role in stress. Can psychotherapies measurably change these molecular processes? And could this help us understand why psychotherapy helps some patients and not others?

### Classification

### In light of new insights into biological causes, do we need to reorganize clinical classifications?

The World Health Organization is in the process of revising their mental illness diagnostic guide. The ICD-11 should appear in 2018, and will establish definitions of mental illnesses that will in turn form the basis for research and therapies. To date, ailments were categorized according to symptoms. There are strong discussions about the new version, as there are vigorous efforts afoot to categorize illnesses based on new insights into genetic factors or imaging instead.

### Social acceptance

### What can we do to fight the stigmatization of patients?

»It's easier to say ›I have cancer‹ than ›I have schizophrenia,« says Myrna Weissman, an epidemiologist who focuses on psychiatry at Columbia University College of Physicians and Surgeons in New York. It is a concise expression of what many people with mental illness experience. In many people's minds, a patient's symptoms are attributed to a difficult personality, and not to an illness. In countries the world over, there are a variety of organizations fighting this stigma. Their hope? That their fight will be easier when we can more easily identify and explain the biological roots of these afflictions.

### Imprint

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### Epidemiology

### Is the frequency of occurrence of mental illness higher in industrialized nations?

Studies from Europe and the USA show that some 20 percent of the population suffer from a mental illness. And we often hear that that number is rising. Health insurance companies are reporting more instances of depression, anxiety, and sleep disorders. But are the numbers of psychiatric patients actually rising? Or could the higher reporting rate actually reflect the rise in awareness – thanks to educational campaigns – faster diagnosis on the part of doctors, and the increasing willingness of the afflicted to seek help?

## Research College »Translational Psychiatry« Of Flies and Men

**If you want to achieve outstanding research results, you need not only the best working conditions; you also need time. With its program to support young researchers, the Else Kröner-Fresenius-Stiftung provides both. This year, the Research College »Translational Psychiatry« will start in Munich. The goal is to take new discoveries drawn from basic research and introduce them as quickly as possible into clinical practice. Here, we introduce two young talents.**

**David Popovic (28),  
Clinic for Psychiatry and Psychotherapy, LMU Munich**

»Ever since I was a student intern working with mentally ill, elderly individuals, I've always asked myself, why do some people get these illnesses and some don't? It might sound strange, but it may very well be that little flies, of all things, could help us answer these kinds of questions.

After my Physikum, or preliminary examinations, I spent some time at the Harvard Medical School, where Prof.



Edward Kravitz had his »Fruit Fly Fight Club« lab. I wanted to know how these fruit flies would change and develop if they're constantly defeated in the fight for food. So I started by having »normal« flies repeatedly go up against a special kind of highly aggressive conspecific. These »normal« flies lost all of their fights and so we had created a group of »chronic losers.« These flies showed unusual behavior, which we called »depressive-like.« In confrontations with »normal« flies they would give up early and lose in 70 percent of the fights. As another feature, they did not like sugary food as fruit flies usually do.

In the next step, we changed one of the fruit flies' genes. That gene corresponds to a gene in humans that is linked with antidepressive effects. These altered flies seemed to be more resistant. After all their defeats against the highly aggressive opponents they did not show a change in their way of fighting. They also preferred sweets.

Of course, you can't directly transfer these observations to humans. Nevertheless, fruit flies produce neurotransmitters such as serotonin or dopamine, and have a system to transmit stimuli that resembles the human nervous system.

At the moment, I'm focusing more on schizophrenia. As a junior doctor, I'm working with adolescents, many of whom have already shown the first symptoms of a psychological illness – be it a cognitive disorder or a disturbance in perception.

Within the framework of the Else Kröner Research College, I'll focus on the connection between psychosocial stress and an increased risk of schizophrenia. Using MRT imaging, I'll look at patients' brain structures, and look for proof of specific disease patterns.

Research projects like this take time. Creative work is only possible when it's not done on the side. You have to concentrate on it. In the truest sense of the word, the Else Kröner Research College has given me a priceless opportunity.«



**Laura Albantakis (30),  
Max Planck Institute of Psychiatry, Munich**

»When I started my studies, I wanted to be a vascular surgeon. But at some point, I realized I was lacking intense patient contact. I saw a BBC report on developmental disorders in children and adolescents, and it was a turning point for me. The program focused on autism, and it made me realize that that's what I wanted to do.

My doctoral dissertation topic came from the Clinic for Child and Adolescent Psychiatry at the University of Würzburg. I looked at the »brain-derived neurotrophic factor,« or BDNF, which is a protein that's important for the growth of nerves in the brain, and which seems to play a role in the development of autism. I examined how the concentration of BDNF in the blood develops over a span of years and if I could find differences between healthy and autistic children. I wanted to know if this protein could serve as a biomarker and help facilitate making an autism diagnosis.

I came to the conclusion that BDNF levels in the blood of autistic children between the ages of four and six years are in fact, higher than in healthy children of the same age. However, with the onset of puberty, BDNF levels in autistic patients seem

to be lower than in healthy study participants. This might be a result of the development of sexual hormones.

As an Else Kröner Research College fellow, I'd like to find out how the concentration of the BDNF protein changes in adult patients with autism. Continual research is important, and I love the direct contact I have with patients as a doctor.

I hold »autism office hours« at the Max Planck Institute of Psychiatry in Munich. And in the hospital ward, I work with patients who suffer from a wide range of psychological illnesses. In the near future, I'll transfer to the Outpatient Clinic for Social Interaction Disorders.

Psychological illnesses are a heavy burden for patients – and the health care system – to bear. When we know more about them, and know how to better treat them, we'll do a better job as a society on the whole.«

The Else Kröner-Fresenius-Stiftung provided a million euros to the three-year »Translational Psychiatry« Research College. With the funds, the young doctors (who are on their way to becoming clinician scientists) can be exempted from clinical work for one full-time year and two part-time years to do research in this field.

The work takes place in Munich at the Clinic for Psychiatry and Psychotherapy at the Ludwig Maximilians University and at the Max Planck Institute of Psychiatry, in collaboration with the International Max Planck Research School for Translational Psychiatry. This cooperative effort locks basic applied research and work with patients closely together.

The college's spokespeople are Prof. Dr. Peter Falkai (LMU) and Dr. Elisabeth Binder (MPI). To date, seven fellows have been accepted to the program. The fellows' translational research culminates in a PhD in Medical Research.

Translation der Ergebnisse – translating the results

# Vom Labor ans Patientenbett – From bench to bedside

Mit vollkommen neuartigen Methoden erforscht Karl Deisseroth die Arbeitsweise des Gehirns. Auf Basis seiner Ergebnisse laufen bereits erste klinische Studien mit Patienten. *Karl Deisseroth is researching how the brain works using completely new methods. The first clinical studies involving patients are based on his results and already underway.*

**2005** *nature neurosciences* \* Karl Deisseroth veröffentlicht 2005 seine ersten Publikationen zur Optogenetik. *Karl Deisseroth published his first articles on optogenetics in 2005.*

**2007** Diverse lichtempfindliche Proteine reagieren jeweils auf verschiedenfarbiges Licht. 2007 zeigt Deisseroths Team, dass sich mit Hilfe optogenetischer Methoden bestimmte Verhaltensweisen von Nagetieren steuern lassen. *Various light-sensitive proteins react to different colored lights. In 2007, Deisseroth's team used optogenetic methods to control specific behavior patterns in mammals.*

Bereits in den 1970er Jahren forschen Wissenschaftler an lichtempfindlichen Eiweißen aus Mikroben. Dank neuer genetischer Methoden lassen sich solche Proteine 30 Jahre später in tierische Neurone einschleusen und diese so verändern, dass sie auf Lichtimpulse reagieren. Sie lassen sich »an- und ausschalten« und erlauben Einblicke in die Funktion neuronaler Netzwerke.

Researchers have been looking at light-sensitive microbial proteins since back in the 1970s. 30 years later, thanks to new genetic methods, these proteins could be implanted in animal neurons. The proteins altered the neurons, causing them to react to light impulses. They could be turned on and off, so to speak – giving researchers an inside view into how neural networks function.

**2013** CLARITY *Karl Deisseroth made another breakthrough in 2013, when his team prepared postmortem brains in such a way that they became transparent. Using color stains, they made neural networks in the tissue visible.*

2013 gelingt Karl Deisseroth ein weiterer Durchbruch: Sein Team präpariert Gehirne post mortem so, dass sie transparent werden. Durch Anfärbungen können neuronale Netzwerke sichtbar gemacht werden.

Karl Deisseroth made another breakthrough in 2013, when his team prepared postmortem brains in such a way that they became transparent. Using color stains, they made neural networks in the tissue visible.

**2013** Forscher stimulieren das Gehirn von Ratten mit optogenetischen Methoden. *Researchers stimulate rats' brains using optogenetic methods.*

**2016** + *Ärzte behandeln Patienten mit transkranieller magnetischer Stimulation (TMS). Doctors treat patients using transcranial magnetic stimulation (TMS).*

*Researchers the world over now use optogenetics to explore the causes of mental illnesses using animal models. Karl Deisseroth's team determined that one area of the brain in cocaine-addicted rats was less active than the same area in non-addicted rats. Researchers stimulated the area, thereby suppressing the animal's desire for the drug. The results made a clinical study possible: a team of addiction researchers using Deisseroth's tools stimulated the corresponding area of the brain in human patients, successfully counteracting cocaine's addictive pull.*

Forscher weltweit nutzen die Optogenetik in Tiemodellen, um die Ursachen von psychischen Leiden zu ergründen. Karl Deisseroths Team erkennt, dass ein Hirnareal bei kokainsüchtigen Ratten weniger aktiv ist als bei anderen. Die Forscher stimulieren es und unterdrücken so das Verlangen der Tiere nach der Droge. Die Erkenntnisse ermöglichen eine klinische Studie: ein Team von Suchtforschern, das Deisseroths Erkenntnisse nutzt, regt das entsprechende Hirnareal bei Patienten an und zeigt, dass sie so der Kokainsucht entgegensteuern können.

Researchers the world over now use optogenetics to explore the causes of mental illnesses using animal models. Karl Deisseroth's team determined that one area of the brain in cocaine-addicted rats was less active than the same area in non-addicted rats. Researchers stimulated the area, thereby suppressing the animal's desire for the drug. The results made a clinical study possible: a team of addiction researchers using Deisseroth's tools stimulated the corresponding area of the brain in human patients, successfully counteracting cocaine's addictive pull.

**2017** Drei neue Methoden / *Three new methods:*

- 1 Optoencephalography (OEG)
- 2 Frame-Projected Independent-Fiber Photometry (FP)
- 3 CAPTURE (basiert auf / based on CLARITY)

**Zukunft Future** *320 Millionen Menschen weltweit leiden laut der WHO an Depressionen. According to the WHO, 320 million individuals suffer from depression worldwide.*

Mit dem Preisgeld möchte Karl Deisseroth mehr über die neuronalen Netzwerke von Hirnregionen herausfinden, die bei Depressionen eine Rolle spielen. Er entwickelt dafür drei neue Methoden, die er kombinieren will. Die Hoffnung für die Zukunft: die Schaltkreise im Gehirn zu verstehen und zu beeinflussen – ob über Hirnstimulation, gezieltere Pharmakotherapien oder eine Kombination von beidem.

With the prize money, Karl Deisseroth hopes to learn more about neural networks in different regions of the brain that play a role in depression. To do so, he has developed three new methods which he hopes to combine. His hope for the future? That he will understand the brain's circuitry and ultimately learn how to influence it using brain stimulation, focused pharmacotherapies, or a combination of both.

\* Illuminating next-generation brain therapies. Ferenczi, E. and Deisseroth, K.: Illuminating next-generation brain therapies. *Nature Neuroscience* 19, 414–416 (2016), doi:10.1038/nn.4232