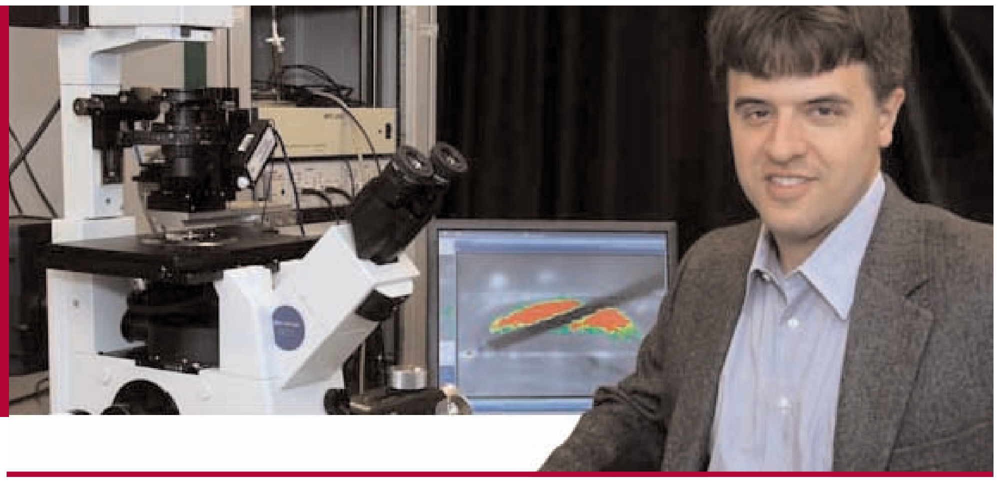
PRECISION PSYCHIATRY
ENGINEERING THERAPIES FOR BETTER MENTAL HEALTH

Disorders such as depression, autism, and schizophrenia can be devastating for the people they afflict, but their underlying causes are subtle.

Karl Deisseroth
Assistant Professor
Bioengineering and Psychiatry
PhD 1998 Stanford; MD 2000 Stanford



BY DAVID ORENSTEIN

To study and treat these problems, psychiatrists need research tools and therapies, both drugs and devices, that are just as subtle and precise. So far there haven't been any. Assistant Professor of bioengineering and psychiatry Karl Deisseroth is working to change that by applying the technology and precision of engineering to the subtlety of psychiatry.

"You don't hear those two words—engineering and psychiatry—put together in the same sentence very often," Deisseroth observes. By putting the two fields together in the lab, he hopes to develop treatments that are less painful, faster acting and more effective than the less precise treatments available today.

The brain, when you get down to it, is fundamentally an electrical circuit," Deisseroth says. "What we're doing here is [developing] tools, bioengineering based tools, to observe circuit dynamics and to control circuit dynamics on a millisecond (thousandth of a second) timescale," Ultimately these efforts are meant to develop new therapies that will fine-tune the faulty circuitry underlying disease.

Improving observations

To watch individual brain circuits operate, Deisseroth's lab is working to engineer a visualization tool that is faster and sharper than brain imaging systems available today, such as functional magnetic resonance imaging (fMRI). The technology highlights what parts of the brain are activated by a stimulus, such as a sound heard by a patient, but the observations depend on changes in blood flow in the brain, which can take a few seconds. It is also imprecise in that it only shows what is going on in relatively large parts of the brain, not in its small circuits.

Deisseroth's system allows for much more precise observations—currently in animal models of disease rather than human patients—because it has millisecond responsiveness and cellular resolution needed to view intact circuit operation in real time. The system uses a fluorescent dye that is sensitive to the voltages produced by brain circuit activity. In the lab, the dye can be injected into animal brain tissue. As dyed circuits light up and darken again in response to electrical activity, the action is captured by very fast, high-resolution video cameras. Deisseroth can observe how different stimuli, such as a dose of an antidepressant drug, can affect circuit operation.

Improving interventions and therapies

Improved observations will enable research that may speed Deisseroth to his goal of improving therapies for depression, schizophrenia and autism. Fixing the faulty circuitry that underlies those disorders might be a matter of tuning either the production of new neurons or the activity of new neurons in an area called the hippocampus, which plays a vital role in mood and memory, and has been shown to be structurally abnormal in all three disorders. The hippocampus of every mammal naturally has adult stem cells and when these transform into neurons, those new neurons hook right into hippocampal circuits and alter how they function. Although it is not clear why, it turns out that virtually all treatments for depression correlate with an increase in stem cells becoming neurons, Deisseroth says, even if that is not what they were explicitly designed to do.

"This is how we learn and remember and adapt to our environment," Deisseroth says. "The brain is designed to change. And it is designed to change rapidly and it is designed to change in response to external stimuli."

Deisseroth is working on two approaches that involve stem cells. One avenue is to find ways to promote neuron production from stem cells in the hippocampus. In 2004 Deisseroth and his colleagues at Stanford reported success in stimulating hippocampal stem cells to become neurons more often and more plentifully than they would without intervention. The experimenters encouraged neuron production with small molecular agents known to affect the electrical properties of brain circuits. The experiment could ultimately lead to clinical techniques to improve hippocampus circuitry.

"THE BRAIN, WHEN YOU GET DOWN TO IT, IS FUNDAMENTALLY AN ELECTRICAL CIRCUIT. WHAT WE'RE DOING HERE IS [DEVELOPING] TOOLS, BIOENGINEERING BASED TOOLS, TO OBSERVE CIRCUIT DYNAMICS AND TO CONTROL CIRCUIT DYNAMICS ON A MILLISECOND (THOUSANDTH OF A SECOND) TIMESCALE."

Another way Deisseroth seeks to tune circuitry in the hippocampus is by electrically stimulating closely connected parts of the brain such as the prefrontal cortex, an area of the brain behind the forehead. Deisseroth is currently participating in a 16-site clinical trial of a promising, painless therapy called transcranial magnetic stimulation (TMS). The therapy focuses a fast, strongly varying magnetic field at a small—about a cubic centimeter—part of the brain. The field induces an electric current that excites brain circuits in that area. Deisseroth says the excitation of prefrontal cortex circuits might encourage stem cells in connected circuits of the hippocampus to become neurons, although he acknowledges that another possibility is that the excitation stimulates existing cells to make more neurotransmitters. If the trial's results are positive, the study could lead to TMS winning federal regulatory approval.

The beauty of bioengineering

The productive combination of psychiatry and electrical engineering apparent in Deisseroth's research is exactly what Stanford had in mind when the School of Engineering and the School of Medicine joined forces to establish the Department of Bioengineering and to house it between the two schools in the Clark Center.

As a jointly appointed member of psychiatry and bioengineering, Deisseroth has two offices, and works with two chairs and two deans, but the arrangement is hardly burdensome. "I can walk over to my clinic and see patients and then I can walk back here and go meet with people in electrical engineering or the Center for Integrated Systems," Deisseroth says. "As you can tell they are really synergistic, engineering and psychiatry. They are very intimately and intellectually linked."