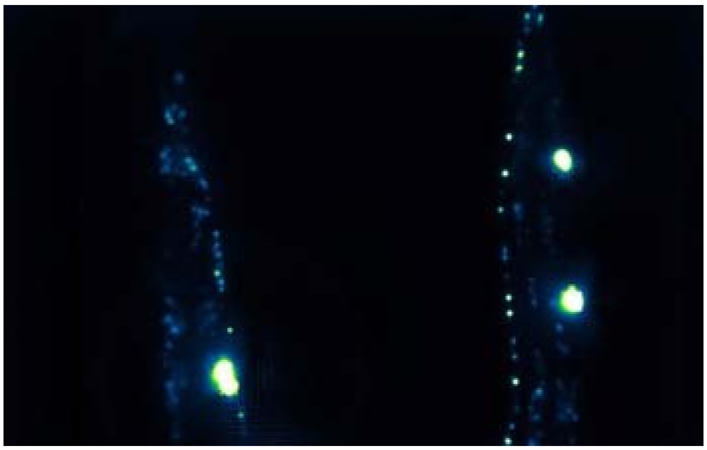
National Science Foundation
WHERE DISCOVERIES BEGIN

Discovery

ENGINEERS ASK THE BRAIN TO SAY, "CHEESE!"

How do we take an accurate picture of the world's most complex biological structure?



New imaging tools to study the nervous systems of living animals, such as this small worm
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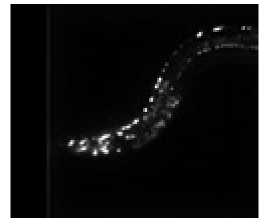
May 19, 2014

Creating new brain imaging techniques is one of today's greatest engineering challenges.

The incentive for a good picture is big: looking at the brain helps us to understand how we move, how we think and how we learn. Recent advances in imaging enable us to see what the brain is doing more precisely across space and time and in more realistic conditions.

The **newest advance in optical imaging** brings researchers even closer to illuminating the whole brain and nervous system.

Researchers at the Massachusetts Institute of Technology and the University of Vienna achieved simultaneous functional imaging of all the neurons of the transparent roundworm *C. elegans*. This technique is the first that can generate 3-D movies of entire brains at the millisecond timescale.



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A new imaging techniq lets researchers simultaneously capture neuronal activity in a w
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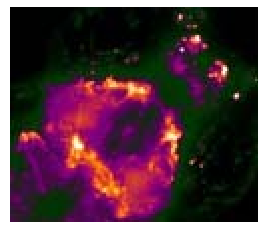

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A new imaging techniq offers new insight into t brains of living animals such as the zebrafish.
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Some methods used to study the brain allow researchers to tap into brains electrical signals
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The significance of this achievement becomes clear in light of the many engineering complexities associated with brain imaging techniques.

An imaging wish list

When 33 brain researchers **put their minds together** at a workshop funded by the National Science Foundation in August 2013, they identified three of the biggest challenges in mapping the human brain for better understanding, diagnosis and treatment.

Challenge one: High spatiotemporal resolution neuroimaging. Existing brain imaging technologies offer different advantages and disadvantages with respect to resolution. A method such as functional MRI that offers excellent spatial resolution (to several millimeters) can provide snapshots of brain activity in the order of seconds. Other methods, such as electroencephalography (EEG), provide precise information about brain activity over time (to the millisecond) but yield fuzzy information about the location.

The ability to conduct functional imaging of the brain, with high resolution in both space and time, would enable researchers to tease out some of the brain's most intricate workings. For example, each half of the thalamus--the brain's go-to structure for relaying sensory and motor information and a potential target for deep brain stimulation--has 13 functional areas in a package the size of a walnut.

With better spatial resolution, researchers would have an easier time determining which areas of the brain are involved in specific activities. This could ultimately help them identify more precise targets for stimulation, maximizing therapeutic benefits while minimizing unnecessary side effects.

In addition, researchers wish to combine data from different imaging techniques to study and model the brain at different levels, from molecules to cellular networks to the whole brain.

Challenge two: Perturbation-based neuroimaging. Much that we know about the brain relies on studies of dysfunction, when a problem such as a tumor or stroke affects a specific part of the brain and a correlating change in brain function can be observed.

But researchers also rely on techniques that temporarily ramp up, or turn off, brain activity in certain regions. What if the effects of such modifications on brain function could then be captured with neuroimaging techniques?

Being able to observe what happens when certain parts of the brain are activated could help researchers determine brain areas' functions and provide critical guidance for brain therapies.

Challenge three: Neuroimaging in naturalistic environments. Researchers aim to create new noninvasive methods for imaging the brain while a person interacts with his or her surroundings. This ability will become more valuable as **new technologies that interface with the brain** are developed.

For example, a patient undergoing brain therapy at home may choose to send information to his or her physician remotely rather than go to an office for frequent check-ups. The engineering challenges of this scenario include the creation of low-cost, wearable technologies to monitor the brain as well as the technical capability to differentiate between signs of trouble and normal fluctuations in brain activity during daily routines.

Other challenges the brain researchers identified are neuroimaging in patients with implanted brain devices; integrating imaging data from multiple techniques; and developing models, theories and infrastructures for better understanding and analyzing brain data. In addition, the research community must ensure that students are prepared to use and create new imaging techniques and data.

The workshop chair, Bin He of the University of Minnesota-Twin Cities, said, "Noninvasive human brain mapping has been a holy grail in science. Accomplishing the three grand challenges would change the future of brain science and our ability to treat numerous brain disorders that cost the nation over $500 billion each year."

The full workshop report was published in ***IEEE Transactions on Biomedical Engineering***.

An imaging breakthrough

Engineers, in collaboration with neuroscientists, computer scientists and other researchers, are already at work devising creative ways to address these challenges.

The workshop findings place the new technique developed by the MIT and University of Vienna researchers into greater context. Their work had to overcome several of the challenges outlined.

The team captured neural activity in three dimensions at single-cell resolution by using a novel strategy not before applied to neurons--light-field microscopy, using a novel algorithm to reverse distortion, a process known as deconvolution.

The technique of light-field microscopy involves the shining of light at a 3-D sample, and capturing the locations of fluorophores in a still image, using a special set of lenses. The fluorophores in this case are modified proteins that attach to neuron and fluoresce when the neurons activate. However, this microscopy method requires a trade-off between the sample size and the spatial resolution possible, and thus it has not been before used for live biological imaging.

The advantage presented by light-field microscopy, here used in an optimized form, is that the technique may quickly capture the neuronal activity of whole animals, not simply still images, while providing high enough spatial resolution to make functional biological imaging possible.

"This elegant technique should have a large impact on the use of functional biological imaging for understanding brain cognitive function," said Leon Esterowitz, program director in NSF's Engineering Directorate, which provided partial funding for the research.

The researchers, led by Edward Boyden of MIT and Alipasha Vaziri of the University of Vienna, reported their results in this week's issue of the journal *Nature Methods*.

"Looking at the activity of just one neuron in the brain doesn't tell you how that information is being computed; for that, you need to know what upstream neurons are doing. And to understand what the activity of a given neuron means, you have to be able to see what downstream neurons are doing," said Boyden, an associate professor of biological engineering and brain and cognitive sciences at MIT and one of the leaders of the research team.

"In short, if you want to understand how information is being integrated from sensation all the way to action, you have to see the entire brain."

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Investigators
Edward Boyden
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Total Grants
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