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High-speed microscopy reveals electrical activity across the brain

The new technique could help scientists learn how the entire brain works to generate decisions and emotions.

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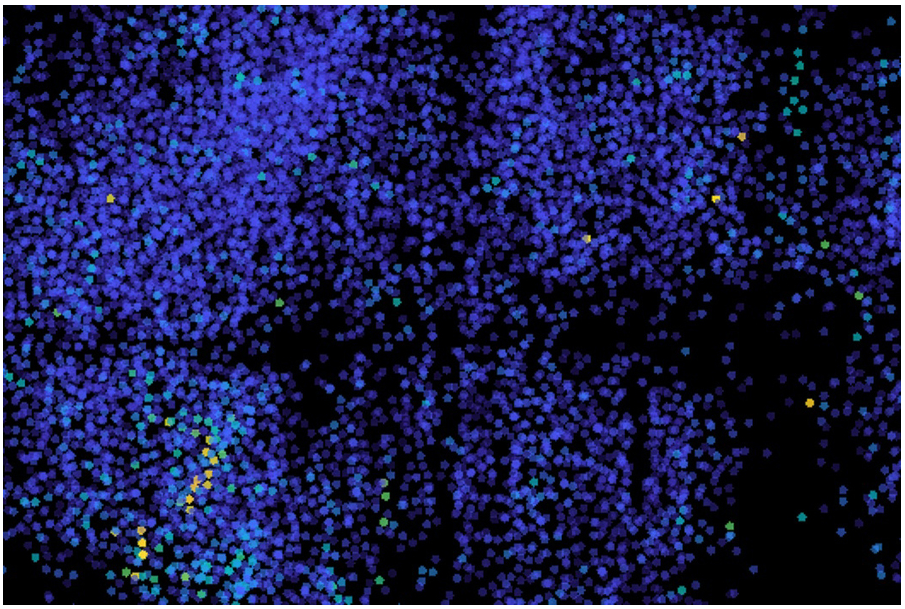

MIT researchers have developed a method for imaging neuron activity in the zebrafish brain. Each colored spot (green and yellow) represents an active neuron.

Credit: Courtesy of the researchers

Within the brain, neurons compute by generating electrical impulses. These signals travel throughout neurons, which are in turn connected in vast networks

that control brain functions such as sensory perception, memory formation, and control of movement.

In an advance that could help neuroscientists map those neural networks, leading to a better understanding of how neural activity underlies behavior and other brain functions, MIT engineers have invented a new microscope that can image electrical activity in neurons distributed across the brain of an entire organism, the experimental model *Danio rerio* (zebrafish).

Using a microscope that they adapted for fast, high-volumetric rate imaging, the researchers were able to track electrical activity across the brain on the scale of milliseconds. This method revealed patterns of neural activity from neurons throughout the brain that were activated in response to ultraviolet light.

“All of the parts of the brain are connected together, so if you want to truly understand the brain, you have to understand how all the neurons work together as an emergent whole,” says Ed Boyden, the Y. Eva Tan Professor in Neurotechnology at MIT; a professor of biological engineering, media arts and sciences, and brain and cognitive sciences; and a member of MIT’s McGovern Institute for Brain Research, Yang Tan Collective, and the Koch Institute for Integrative Cancer Research.

Boyden is the senior author of the study, which appears today in *Nature Methods*. Former J. Douglas Tan Postdoctoral Fellow Zeguan Wang PhD ’24 and former MIT research scientist Jie Zhang are the lead authors of the paper. Other authors include former MIT postdoc Panagiotis Symvoulidis, Picower Institute research scientist Wei Guo, graduate students Davy Deng and Lige Zhang, Koch Institute research scientist Adam Amsterdam, Picower Institute research scientist Takato Honda, Boston College undergraduate Steven Roche, and

Matthew Wilson, the Sherman Fairchild Professor of Neuroscience at MIT and a member of the Picower Institute.

High-speed imaging

One technique often used to measure neuron activity in the brain is calcium imaging. Calcium flows into neurons after they fire an electrical impulse, so measuring calcium levels in the cells can serve as a proxy for neural activity. However, this type of imaging isn't fast enough to capture single spikes of activity.

"Calcium imaging inherently is very slow, so you're talking about imaging activity on the order of seconds or even minutes. Typically that is too slow for us to be able to see a lot of these high-speed neural activities," Zhang says. "Neurons compute using electrical activity, so with voltage imaging, you can get direct observation of that."

To enable direct imaging of voltage, researchers have developed proteins called genetically encoded voltage indicators — fluorescent proteins that can be genetically expressed in neurons. When a neuron fires an impulse, the protein fluoresces, which can be detected with a fluorescence microscope.

In previous work, researchers have used these proteins to image small populations of neurons, usually focusing on one localized part of the brain. Until now, there hasn't been a way to image a large volume, such as the entire brain, with the millisecond-scale resolution needed to see electrical impulses from individual neurons.

To achieve that, the MIT team decided to modify a commonly used microscope known as a light sheet microscope. This type of microscope uses a sheet of laser light to illuminate a thin slice of a sample. By imaging many layers in

sequence, this technique can generate 3D images of a large volume. However, with previous microscopes, the scanning of an entire volume would take too long to be able to capture neuronal impulses across the volume at single cell resolution.

“Different groups of neurons that are distributed across the brain coordinate together at millisecond timescales to generate a lot of behaviors and brain computations,” Wang says. “To understand the principles, we need the technology to observe their activity at the same time, across the whole brain, so we are not missing any important participant neurons.”

To make the imaging process fast enough to image millisecond-scale activity, the researchers increased the image acquisition speed of the microscope’s camera, and they also boosted the scanning speed of the microscope using a technique called remote refocusing.

Using this approach, the researchers showed that they could scan the entire zebrafish brain 200 times per second, or once every five milliseconds.

Mapping brain activity

To test the new microscope, the researchers engineered neurons in larval zebrafish to express a voltage indicator called Positron2-Kv. Although they had hoped that the indicator would end up in every neuron, it produced signals in neurons distributed throughout the brain, with about one quarter of the neurons exhibiting acceptable signals. This was enough, however, to observe patterns of activity across the brain. The researchers imaged the brain as the fish were resting, and they were able to observe single voltage spikes from neurons, as well as rapid bursts of spikes.

Additionally, this technique revealed patterns in how the brain is activated following a stimulus such as ultraviolet light. Immediately following the stimulus, activity was seen in the optic tectum, which receives and processes visual input from the retina. This activity propagated from one side of a part of the brain called the tectum to the other. Stimulus-independent activity also occurred in sequences across sets of neurons in the cerebellum and hindbrain.

The researchers now hope to increase the percentage of neurons that they can image across the brain, as well as the microscope's speed and resolution. They are also working on expanding the use of this technique to other experimental models, including mice.

This approach, they say, could offer neuroscientists a new way to generate hypotheses about what happens in the brain when it engages in specific behaviors, or about how brain activity is linked to states of mind such as daydreaming.

"A big question is simply to understand how neurons work together as a network. And this might be the first time that you could do that, because you can image the voltage of neurons distributed throughout the network," Boyden says.

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Paper: "Voltage imaging of neurons distributed across entire brains of larval zebrafish"