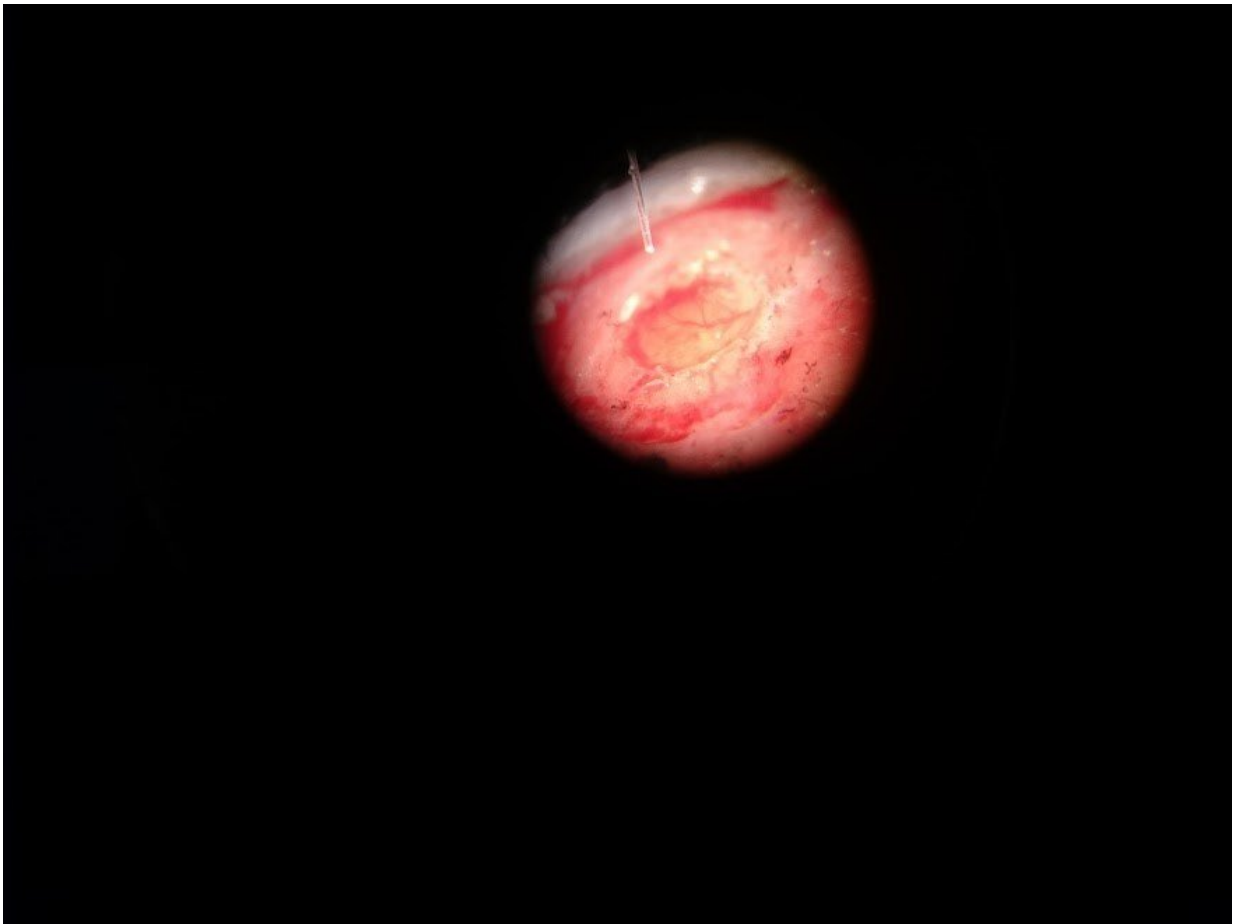


Ultrathin endoscope captures neurons firing deep in the brain

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A new endoscope as small as a human hair was used to image neuronal activity in mice. The optical fiber microendoscope (upper left) is shown just before it is inserted into tissue. Credit: Shay Ohayon, Massachusetts Institute of Technology

Researchers have developed an endoscope as thin as a human hair that can image the activity of neurons in the brains of living mice. Because it is so thin, the endoscope can reach deep into the brain, giving researchers access to areas that cannot be seen with microscopes or other types of endoscopes.

"In addition to being used in animal studies to help us understand how the [brain](#) works, this new endoscope might one day be useful for certain applications in people," said Shay Ohayon, who developed the device as a postdoctoral researcher in James DiCarlo's lab at the Massachusetts Institute of Technology. "It could offer a smaller, and thus more comfortable, instrument for imaging within the nasal cavity, for example."

The new endoscope is based on an optical fiber just 125 microns thick. Because the device is five to ten times thinner than the smallest commercially available microendoscopes, it can be pushed deeper into the brain tissue without causing significant damage.

In The Optical Society (OSA) journal *Biomedical Optics Express*, the [researchers](#) report that the endoscope can capture micron-scale resolution [images](#) of neurons firing. This is the first time that imaging with such a thin endoscope has been demonstrated in a living animal.

"With further development, the new microendoscope could be used to image neuron activity in previously inaccessible parts of the brain such as the visual cortex of primate animal models," said Ohayon. "It might also be used to study how neurons from different regions of the brain communicate with each other."

Acquiring images from a fiber

The new microendoscope is based on a multimode optical fiber, which

can carry different multiple beams of [light](#) at the same time. When light enters the fiber, it can be manipulated to generate a tiny spot at the other end, and can be moved to different positions on the tissue without moving the fiber. Scanning the tiny spot across the sample allows it to excite fluorescent molecules used to label neuron activity. As the fluorescence from each spot travels back through the fiber, an image of [neuron activity](#) is formed.

"To achieve scanning fast enough to image neurons firing, we used an optical component known as a digital mirror device (DMD) to quickly move the light spot," said Ohayon. "We developed a technique that allowed us to use the DMD to scan light at speeds up to 20 kilohertz, which is fast enough to see fluorescence from active neurons."

Because the multimode fibers used for the endoscope scramble light, the researchers applied a method called wavefront shaping to convert the scrambled light into images. For wavefront shaping, they sent various patterns of light through the fiber to a camera at the other end and recorded exactly how that specific fiber changed light that passed through. The camera was then removed, and the fiber placed into the brain for imaging. The previously obtained information about how the fiber changes the light is then used to generate and scan a small point across the field of view.

Imaging living neurons

After successfully imaging cultured cells, the researchers tested their microendoscope on anesthetized mice. They inserted the fiber through a tiny hole in the skull of a mouse and slowly lowered it into the brain. To image the neurons firing, the researchers used a technique called calcium imaging that creates fluorescence in response to the influx of calcium that occurs when a neuron fires.

"One of the advantages of using an endoscope so thin is that as you lower it into the brain, you can see all the blood vessels and navigate the fiber to avoid hitting them," said Ohayon.

In addition to showing that their endoscope could catch detailed neuronal activity the researchers also demonstrated that multiple colors of light could be used for imaging. This capability could be used to observe interactions between two groups of neurons each labeled with a different color, for example.

For standard imaging, the endoscope images the neurons at the very tip of the fiber. However, the researchers also showed that the microendoscope could image up to about 100 microns away from the tip. "This is very useful because when the fiber is inserted into the brain, it may affect the function of neurons very close to the fiber," explained Ohayon. "Imaging an area slightly away from the fiber makes it easier to capture healthy [neurons](#)."

Dealing with bends in the fiber

One limitation of the microendoscope is that any bends in the fiber cause it to lose the ability to produce images. Although this didn't affect the experiments described in the paper because the fiber was kept straight as it was pushed into the brain, solving the bending problem could greatly expand the applications for the device. Various research groups are working on new types of fibers that are less susceptible to bending and computational methods that might compensate for bending in real-time.

"If this bending problem can be solved, it will likely change the way endoscopy in people is performed by allowing much thinner probes to be used," said Ohayon. "This would allow more comfortable imaging than today's large [endoscopes](#) and may enable imaging in parts of the body

that aren't currently feasible."

More information: Shay Ohayon et al, Minimally invasive multimode optical fiber microendoscope for deep brain fluorescence imaging, *Biomedical Optics Express* (2018). [DOI: 10.1364/BOE.9.001492](https://doi.org/10.1364/BOE.9.001492)

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