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Head-mounted microscope brings unprecedented view of neuronal activity in mice

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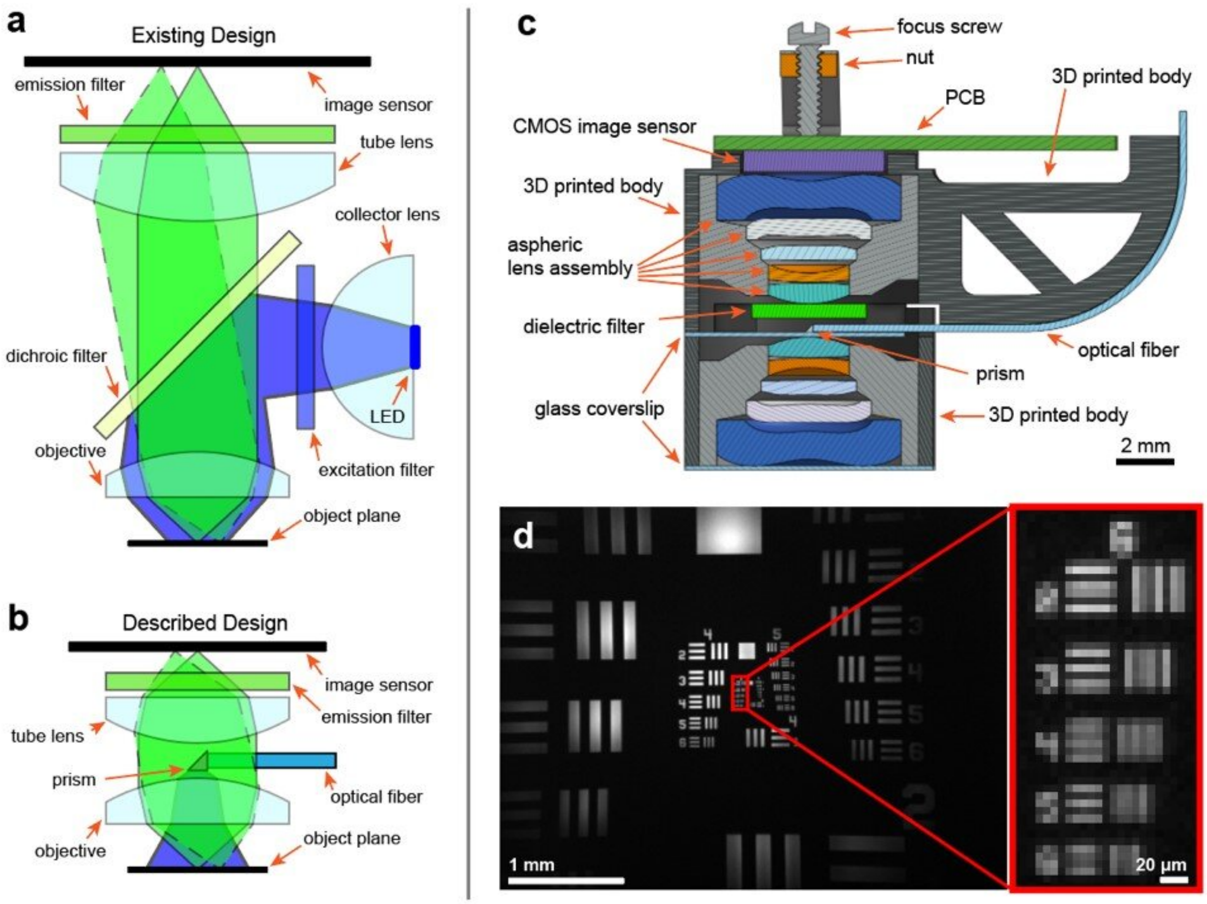

A schematic of the components of standard head-mounted microscopes (a) and the new design (b-c), which eliminates the standard illumination optics resulting in a device that is significantly more compact and lightweight. Panel (d) shows that the microscope retains high resolution, with the ability to distinguish lines just over 4 μm wide. Credit: Joseph R. Scherrer, Massachusetts Institute of Technology

Miniature microscopes attached to the heads of living mice have enabled researchers to gain important insights about the neuronal pathways behind complex behaviors. Now, researchers report a new generation of head-mounted microscopes that achieve a field of view of about four millimeters (mm) in diameter, an order of magnitude larger than previous designs while weighing significantly less.

Researchers demonstrated the microscope's capabilities by recording activity in thousands of neurons in four freely moving mice. Joseph R. Scherrer from the Massachusetts Institute of Technology will detail the new research at Optica's Biophotonics Congress being held in Vancouver, British Columbia and online 23—27 April 2023. Scherrer's presentation is scheduled for 24 April at 14:15-14:30 PDT (UTC—07:00).

"A chief goal of neuroscience is to understand how thought and behavior are generated by the coordinated activity of large populations of neurons. Although there has recently been an explosion of new tools for recording thousands of neurons at once, this increase comes at a cost; neuroscientists using these tools are limited to studying unnatural and simplistic behaviors in head-restrained animals," said Scherrer.

"Our new optical design overcomes this limitation, allowing scientists to make the same kinds of large-scale observations of neural activity but in freely-moving animals performing natural and complicated behaviors. Ultimately, it is unrestricted studies of these complex behaviors that will be critical to understanding how our own brains generate the richness of human behavior."

A broader window into brain activity

While scientists can use a variety of methods to track brain activity in laboratory animals that are fixed in one position, head-mounted microscopes are uniquely valuable for studying behaviors that involve movement, such as social interaction and navigation. However, existing head-mounted microscopes for small animals such as mice have been limited to a field of view of less than one mm, limiting the number of neurons that can be recorded simultaneously to several hundred at most.

Having a larger field of view is important to uncovering the neuronal basis behind complex behaviors, which involve large collections of neurons working together across different regions of the brain. In addition to its large field of view, the new device is significantly lighter than previous head-mounted microscopes at just 1.4 grams, allowing it to be used for longer periods without impeding movement.

The benefit of the lighter device allows the research team to use multiple microscopes at once in the same animal to image even more neurons across multiple brain regions or in the spinal cord.

To accomplish this, the researchers used a light-guide and coupling prism to introduce excitation of the light instead of the dichroic filter used in previous designs. This reduced the size and weight of the illumination options and allowed the researchers to use cutting-edge lens assemblies designed for smartphone cameras. In contrast with previous attempts to achieve a larger field of view which sacrificed resolution in the process, the new design has sufficient resolution to distinguish individual neurons across the entire field of view.

Tracking neurons by the thousand

The research team demonstrated the new microscope by simultaneously recording more than a thousand neurons in multiple freely moving mice. By measuring the movement of calcium through neuronal complexes, they were able to decode the position of a mouse in a maze and quantify the amount of position information contained in different regions of the brain.

Using tiny fluorescent beads to assess the image resolution, researchers showed that the microscope had a resolution of four micrometers (µm) at the center of the field of view and about five µm at the edges. Compared to existing head-mounted microscopes, neuron somas are typically 10–25 microns in diameter, making the resolution enough to resolve individual neurons and distinguish them from one another.

Researchers say the new microscope can help scientists develop and test computational models of cognition across large neural populations and between multiple brain regions. Since there is substantial variability in how well head-mounted microscopes work from mouse to mouse, they noted that future improvements in the surgical techniques used to attach the microscopes could help to reduce variability and further improve the results.

"We are working to make these tools widely available to neuroscientists as low-cost, turnkey systems," said Scherrer. "In future design iterations, we hope to incorporate other recently-developed miniature optical technologies that will further increase performance."

More information: Conference: www.optica.org/en-us/events/co … ophotonics_congress/

Provided by Optica

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