MICROSCOPY

A tiny macroscope to look into complex behavior

A macroscope mounted on the head of a freely moving transgenic rat can help shine light on complex behaviors.

A macroscope is a microscopy device able to image at the mesoscopic scale, typically from hundreds of micrometers to centimeters. Such devices have been used to record neural activity in the brains of behaving rodents, mostly by measuring intracellular calcium dynamics in neurons. Usually the head of the animal needs to be restrained to ensure that the brain position remains stable relative to the imaging system, which limits the range of behaviors that can be studied. Alternatively, the use of miniaturized head-mounted microscopes allows for functional imaging in freely moving animals, which introduces the possibility of studying more sophisticated behaviors. However, most head-mounted microscopes can image only a relatively small field of view—typically less than 1 mm^2, which is not compatible with the recording of neural activity across multiple brain regions. Also, these systems often cannot correct for image contamination caused by changes in blood flow due to neural activity, a phenomenon known as hemodynamic response.

To overcome these limitations, David Tank and his team at Princeton University have developed cScope, a head-mounted macroscope able to image a field of view larger than 30 mm^2 at the mesoscopic scale, without the need for animal head restraint. This is a low-cost 3D-printed plastic device equipped with two independent illumination sources, one for fluorescence imaging and one for hemodynamic response correction. The name cScope stands for "cortical macroscope," underlining the ability to image various regions of the neocortical surface simultaneously, including sensory and motor regions as well as association regions.

The researchers also developed new strains of transgenic rats expressing the genetically encoded calcium indicator GCaMP6f in a large proportion of neurons in the brain, by using pan-neuronal enhancers known to drive expression throughout the nervous system. In rats, fluorescent reporters are usually delivered by viral injection, which labels only a small region of tissue; therefore, the generation of transgenic rats expressing GCaMP6f in the neocortex, hippocampus, cerebellum, and other regions allows scientists to make the most of the large field of view available with the cScope.

Cartoon of a macroscope mounted on the head of a rat. Reproduced with permission from Scott et al. (2018), Elsevier.

The team demonstrated the use of cScope to image spatiotemporal activity patterns across multiple brain areas, by imaging neuronal calcium dynamics in rats performing an evidence-based decision-making task. In this task each rat was exposed to random sequences of light flashes from its right and left sides, and it received a reward when it oriented toward the side with more flashes. The researchers observed that stimulus identity during cue presentation could be inferred from the activity in visual cortical regions, while the rat's behavioral choice could be predicted on the basis of the activity in parietal cortical regions. These results confirm that complex behaviors recruit multiple brain regions, and that cScope can help scientists map activity in distant brain areas during behavioral tests.

The combination of cScope and transgenic rats expressing the GCaMP6f calcium sensor expands the application of head-mounted microscopes into the mesoscopic scale and enables studies of global neural activity during a range of natural behaviors, including navigation, sleep, and social interactions. The authors of the study anticipate that cScope could also be used to image hemodynamic response, in addition to fluorescent reporters, in the brains of various animal models, including wild-type rats and even larger animals such as marmosets.

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Research papers

Scott, B. B. et al. Imaging cortical dynamics in GCaMP transgenic rats with a head-mounted widefield macroscope. *Neuron* **100**, 1045–1058 (2018).