NATURE | NEWS

Flashing fish brains filmed in action

Fast imaging in larval zebrafish produces first neuron-level vertebrate brain-activity map.

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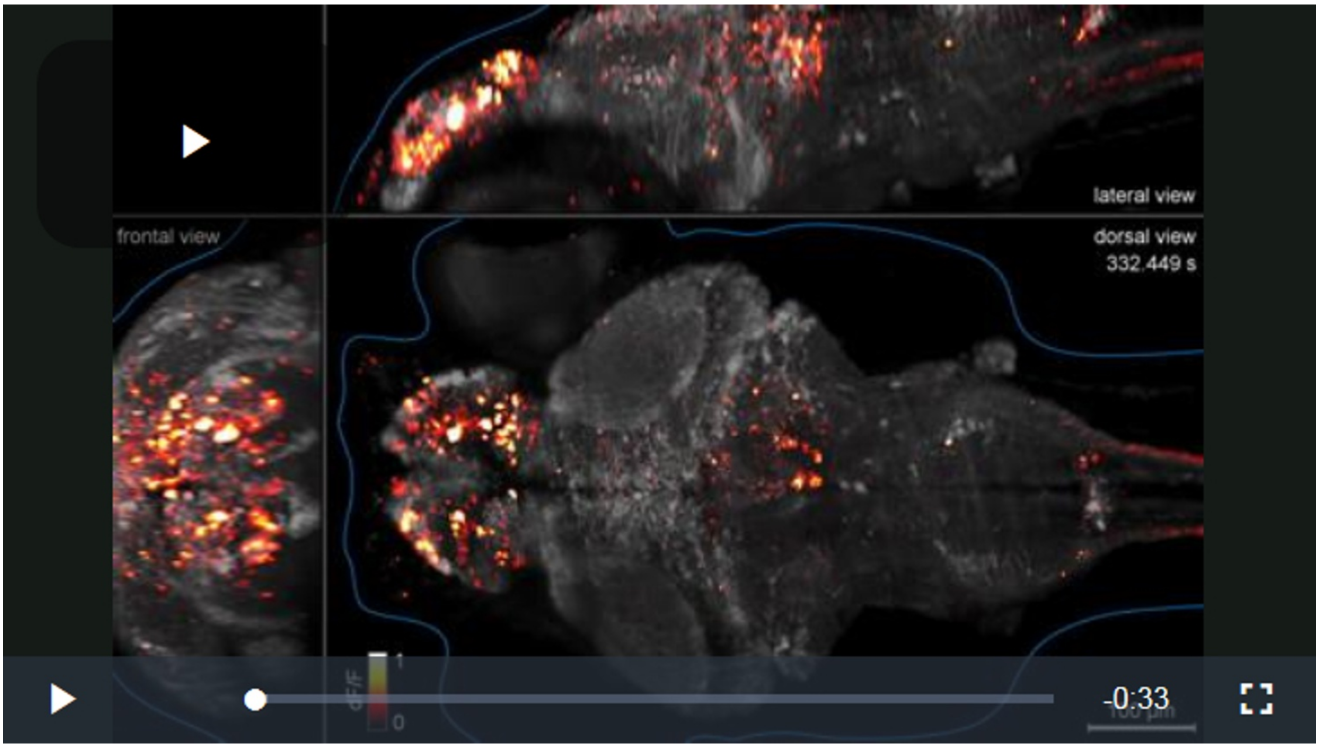
18 March 2013



At first glance, it looks like an oddly shaped campfire: smoky grey shapes light up with red sparks and flashes. But the video actually represents a different sort of crackle — the activity of individual neurons across a larval fish brain. It is the first time that researchers have been able to image an entire vertebrate brain at the level of single cells.

“We see the big picture without losing resolution,” says Phillipp Keller, a microscopist at the Howard Hughes Medical Institute's Janelia Farm Research Campus in Ashburn, Virginia, who developed the system with Janelia neurobiologist Misha Ahrens. The researchers are able to record activity across the whole fish brain almost every second, detecting 80% of its 100,000 neurons. (The rest lie in hard-to-access areas, such as between the eyes; their activity is visible but cannot be pinned down to single cells.) The work is published today in *Nature Methods*[1].

“It’s phenomenal,” says Rafael Yuste, a neuroscientist at Columbia University in New York. “It is a bright star now in the literature, suggesting that it is not crazy to map every neuron in the brain of an animal.” Yuste has been leading the call for a big biology project[2] that would do just that in the human brain, which contains about 85,000 times more neurons than the zebrafish brain.

The resolution offered by the zebrafish study will enable researchers to understand how different regions of the brain work together, says Ahrens. With conventional techniques, imaging even 2,000 neurons at once is difficult, so researchers must pick and choose which to look at, and extrapolate. Now, he says, “you don't need to guess what is happening — you can see it”.

The increased imaging power could, for example, help to explain how the brain coordinates movement, consolidates learning or processes sights and smells. “It allows a much better view of the dynamics throughout the brain during different behaviours and during learning paradigms,” says Joseph Fetcho, a neurobiologist at Cornell University in Ithaca, New York.

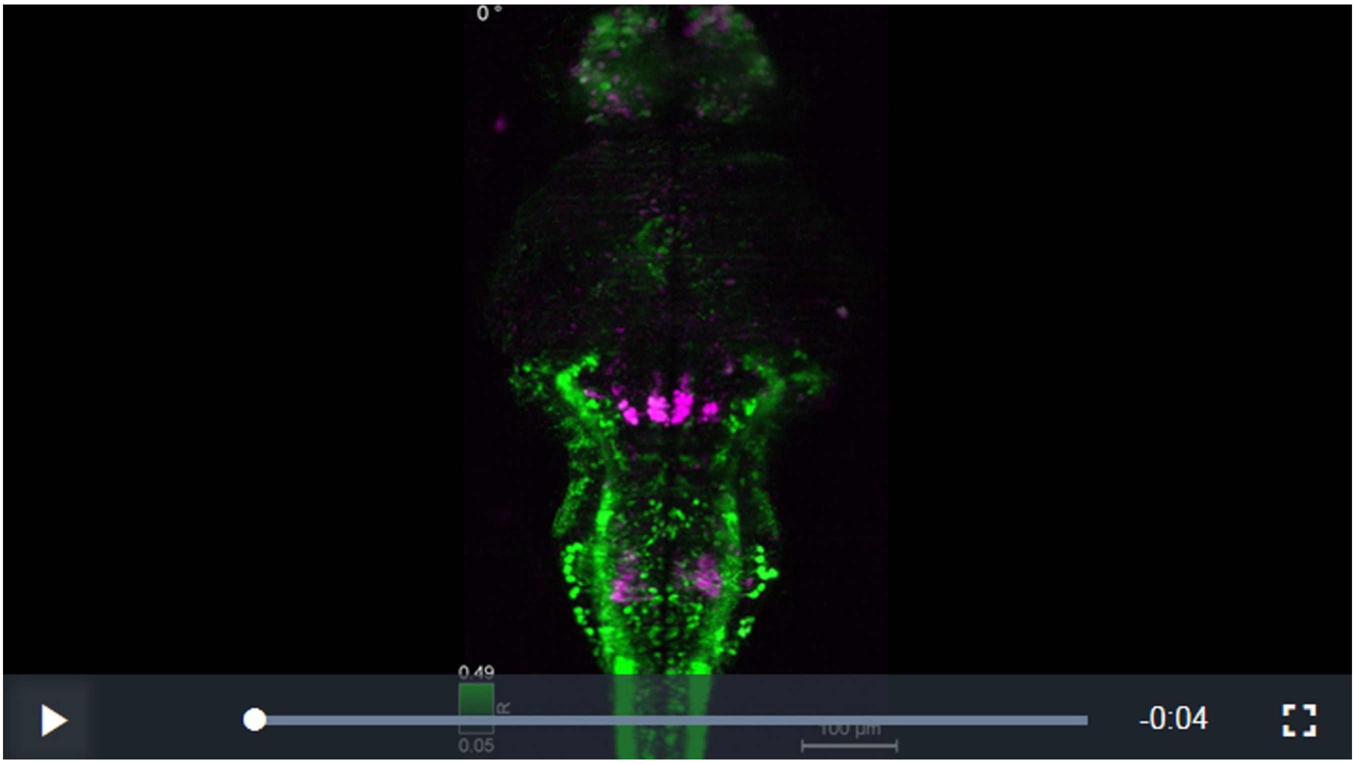
Light, camera, activity

The imaging system relies on a genetically engineered zebrafish (*Danio rerio*). The fish's neurons make a protein that fluoresces in response to fluctuations in the concentration of calcium ions, which occur when nerve cells fire. A microscope sends sheets of light rather than a conventional beam through the fish's brain, and a detector captures the signals like a viewer watching a cinema screen. The system records activity from the full brain every 1.3 seconds.

Ahrens, Keller and others have previously used light-sheet microscopy to image developing embryos over days[3]; for the latest study, they modified light detectors and other aspects of the system to increase the rate of imaging tenfold. In a series of hour-long experiments, each of which generated 1 terabyte (1 million megabytes) of data, the researchers were able to see populations of neurons in distinct regions that correlated to their activity (see video above).

The technique does have its limitations. For one thing, it works best in zebrafish embryos, which are transparent. Ahrens and Keller think that it could work in intact mammal brains, but it would require surgery and would cover only a small fraction of the brain.

Another limitation is that neither the protein sensor nor the imaging system yet works fast enough to distinguish whether a neuron has fired once or several times in quick succession. But Fetcho says that it is fast enough to start to understand how activity flows through the brain. “No one is anywhere in the ball park of this for any other animal model.”



Nature | doi:10.1038/nature.2013.12621

References

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2. Alivasatos, A. P. *et al. Science* **339**, 1284–1285 (2013).
3. Tomer, R., Khairy, K., Amat, F. & Keller, P. J. *Nature Meth.* **9**, 755–763 (2012).