NEUROSCIENCE

# Navigating space in the mammalian brain

## A study of bats reveals how hippocampal place cells code large-scale environments

By **Emma R. Wood**[1] *and* **Paul A. Dudchenko**[2]

How does the brain represent the world and allow spatial navigation? One mechanism is hippocampal place cells—neurons that fire according to where an animal is in its environment. Different place cells fire according to different locations, and together they are thought to provide a cognitive map that supports spatial navigation and memory (*1*). Place cells have been described in a range of mammalian species, including mice, bats, marmosets, and humans. However, most studies have used rats in small enclosures or mazes. Thus, it is unknown how such representations might underpin larger-scale, real-world navigation. On page 933 of this issue, Eliav *et al.* (*2*) show that in bats flying in a large (200-m-long) enclosure, most place cells fire in several different locations and with varying spatial scales. Such multiscale representations are likely the most efficient way for a finite number of neurons to encode large distances.

Neurophysiological recordings in rats exploring relatively small "open-field" environments (~1 $m^2$) or running along short tracks 1 to 2 m long have revealed that a given place cell in the hippocampus typically fires when the rat is in a single area within the apparatus (called its place field) (*1*, *3*, *4*). In the few experiments that have investigated bigger open-field environments and longer tracks, place fields are typically slightly enlarged compared with those in smaller environments (*4*–*6*), and individual place cells in CA1 (the main output region of the hippocampus) fire in multiple, irregularly spaced locations (*5*, *6*), with more place fields per cell in tracks of increasing length (*6*). Within a given environment, the different place fields of each hippocampal neuron are of a fairly uniform size, but there is an anatomical gradient, with the most dorsal hippocampal place cells having the smallest fields and ventral hippocampal cells having the largest fields (*3*, *7*). Together, these studies suggest that the hippocampus provides an ensemble place code, whereby different combinations of neurons are active in any given location, and that coding of different spatial scales is provided by different neurons across the dorsal-ventral hippocampal axis.

But how does the mammalian brain represent much larger spaces, on the spatial scale that animals would need to navigate in their natural environment? Eliav *et al.* wirelessly recorded from dorsal CA1 place cells in bats as they flew along a 200-m-long tunnel between two feeding stations. They found not only that place cells expressed multiple, irregularly spaced place fields in this very large environment but also that the size of the different place fields expressed by a given neuron varied widely: The mean ratio of the largest:smallest field was 4.4:1, but this was as high as 20:1 in some cells (see the figure). By contrast, and consistent with observations in rats, in a shorter 6-m-long tunnel, place cells expressed only one or two fields, the average field size was smaller than in the 200-m-long tunnel, and fields of the same cell were of a similar size (mean ratio <2:1).

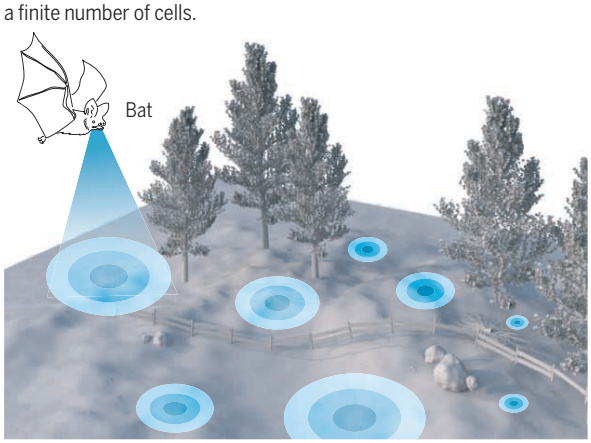
These findings of multiscale coding by individual place cells may help answer a puzzling question: How can a finite population of place cells encode the large environments in which mammals navigate in the wild, at both large and small spatial scales? The modeling by Eliav *et al.* shows that the multiscale coding mechanism seen in the bats is a particularly efficient mechanism for coding large environments. It needs fewer neurons for accurate decoding of the current location of the bat than other ensemble coding mechanisms based on individual cells having multiple fields of the same size and other cells having fields of different sizes (as had previously been assumed).

It will be important to determine the extent to which multiscale coding by individual neurons is a general property of hippocampal coding across species and across different types and scales of environments. A preliminary study of rats following a moving robotic feeder in an 18.6-$m^2$ open-field environment reported that cells in dorsal CA1 exhibited the same type of multiscale coding as found in the tunnel-flying bats (*8*). This indicates that this type of firing may be a general principle of hippocampal coding of large-scale space across mammalian species. Moreover, perhaps in large, continuous spaces, multiscale place cell representation may be the rule.

As with many elegant studies, the work of Eliav *et al.* points to promising new avenues of research. One key question is how multiscale encoding arises. The two main inputs to CA1 (where the multiscale place cells have been described) are the CA3 and the medial entorhinal cortex (MEC). CA3 also contains place cells; indeed, the dorsal-ventral gradient of small-large place fields was described in CA3 neurons in rats (*7*). Conversely, the MEC contains a different type of spatial cell called grid cells. Each grid cell fires in multiple locations arranged in a regular hexagonal grid pattern that repeats across the environment (again with a dorsal-ventral arrangement of grid field size and spacing) (*9*, *10*). Grid cells are thought to be important for path integration, where animals use self-motion signals to estimate distances and directions

### Navigating large, complex spaces

Eliav *et al.* found that bats exhibit multiscale place cell coding. Individual place cells in the hippocampus fire according to a range of spatial scales (place fields of a single place cell indicated by circles), allowing optimal processing of a large environment with a finite number of cells.




GRAPHIC: N. DESAI/*SCIENCE*

[1]Centre for Discovery Brain Sciences and Simons Initiative for the Developing Brain, University of Edinburgh, Edinburgh, UK. [2]Division of Psychology, Faculty of Natural Sciences, University of Stirling, Stirling, UK.
Email: emma.wood@ed.ac.uk; p.a.dudchenko@stir.ac.uk

traveled. Eliav *et al.* suggest a feed-forward model whereby the multiscale fields in CA1 result from convergence of inputs from multiple CA3 place cells with different spatial scales onto each CA1 place cell. Predictions of this model that still need to be tested are that CA3 neurons should not show multiple fields in large environments and that either grid cells should not show multiple fields or grid cell inputs do not contribute to the firing of CA1 place fields in large environments.

A second question is whether there is a continuum of multiscale coding across environments of all sizes or whether (as suggested by Eliav *et al.*) multiscale coding occurs only in sufficiently large environments. And if the latter, what behavioral, perceptual, and neural mechanisms trigger the transition from small-scale to large-scale encoding of space?

The study of Eliav *et al.* provides a marker for the need to examine spatial coding in ethologically relevant environments. The multiscale place cell coding mechanism that they demonstrate may allow both fine-scale spatial localization and localization on a more extended scale, which would be required for navigating accurately between very distant locations hundreds of meters or kilometers apart. It will be interesting to see whether similar multiscale spatial representations occur in humans or nonhuman primates navigating (virtual or real) large, open spaces and whether multiscale coding by individual neurons occurs in other, nonspatial domains, such as the coding of time (*11*). ■

**"...the multiscale coding mechanism seen in the bats is a particularly efficient mechanism for coding large environments."**


**REFERENCES AND NOTES**

1. J. O'Keefe, J. Dostrovsky, *Brain Res.* **34**, 171 (1971).
2. T. Eliav *et al.*, *Science* **372**, eabg4020 (2021).
3. M. W. Jung, S. I. Wiener, B. L. McNaughton, *J. Neurosci.* **14**, 7347 (1994).
4. J. O'Keefe, N. Burgess, *Nature* **381**, 425 (1996).
5. A. A. Fenton *et al.*, *J. Neurosci.* **28**, 11250 (2008).
6. P. D. Rich, H.-P. Liaw, A. K. Lee, *Science* **345**, 814 (2014).
7. K. B. Kjelstrup *et al.*, *Science* **321**, 140 (2008).
8. B. C. Harland *et al.*, bioRxiv 10.1101/2021.02.15.431172 (2021).
9. T. Hafting, M. Fyhn, S. Molden, M.-B. Moser, E. I. Moser, *Nature* **436**, 801 (2005).
10. V. H. Brun *et al.*, *Hippocampus* **18**, 1200 (2008).
11. C. J. MacDonald, K. Q. Lepage, U. T. Eden, H. Eichenbaum, *Neuron* **71**, 737 (2011).


10.1126/science.abi9663

MEDICINE

# CRISPR diagnostics

## New CRISPR enzyme activities add to the nucleic acid detection arsenal

By **Omar O. Abudayyeh** and **Jonathan S. Gootenberg**

Although clinical diagnostics take many forms, nucleic acid–based testing has become the gold standard for sensitive detection of many diseases, including pathogenic infections. Quantitative polymerase chain reaction (qPCR) has been widely adopted for its ability to detect only a few DNA or RNA molecules that can unambiguously specify a particular disease. However, the complexity of this technique restricts application to laboratory settings. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has underscored the need for the development and deployment of nucleic acid tests that are economical, easily scaled, and capable of being run in low-resource settings, without sacrifices in speed, sensitivity or specificity. CRISPR-based diagnostic (CRISPR-dx) tools offer a solution, and multiple CRISPR-dx products for detection of the SARS-CoV-2 RNA genome have been authorized by the US Food and Drug Administration (FDA). On page 941 of this issue, Jiao *et al.* (*1*) describe a new CRISPR-based tool to distinguish several SARS-CoV-2 variants in a single reaction.

There are multiple types of CRISPR systems comprising basic components of a single protein or protein complex, which cuts a specific DNA or RNA target programmed by a complementary guide sequence in a CRISPR-associated RNA (crRNA). The type V and VI systems and the CRISPR-associated endonucleases Cas12 (*2*, *3*) and Cas13 (*4*, *5*) bind and cut DNA or RNA, respectively. Furthermore, upon recognizing a target DNA or RNA sequence, Cas12 and Cas13 proteins exhibit "collateral activity" whereby any DNA or RNA, respectively, in the sample is cleaved regardless of its nucleic acid sequence (*4*, *6*). Thus, reporter DNAs or RNAs, which allow for visual or fluorescent detection upon cleavage, can be added to a sample to infer the presence or absence of specific DNA or RNA species (*4*–*8*).

Initial versions of CRISPR-dx utilizing Cas13 alone were sensitive to the low picomolar range, corresponding to a limit of detection of millions of molecules in a microliter sample. To improve sensitivity, preamplification methods, such as recombinase polymerase amplification (RPA), PCR, loop-mediated isothermal amplification (LAMP), or nucleic acid sequence–based amplification (NASBA), can be used with Cas12 or Cas13 to enable a limit of detection down to a single molecule (*8*). This preamplification approach, applicable to both Cas12 and Cas13 (*6*, *7*), enabled a suite of detection methods and multiplexing up to four orthogonal targets (*7*). Additional developments expanded CRISPR-dx readouts beyond fluorescence, including lateral flow (*7*), colorimetric (*9*), and electronic or material responsive readouts (*10*), allowing for instrument-free approaches. In addition, post–collateral-cleavage amplification methods, such as the use of the CRISPR-associated enzyme Csm6, have been combined with Cas13 to further increase the speed of CRISPR-dx tests (*7*). As an alternative to collateral-cleavage–based detection, type III CRISPR systems, which involve large multiprotein complexes capable of targeting both DNA and RNA, have been used for SARS-CoV-2 detection through production of colorimetric or fluorometric readouts (*11*).

FDA-authorized CRISPR-dx tests are currently only for use in centralized labs, because the most common CRISPR detection protocols require fluid handling steps and two different incubations, precluding their immediate use at the point of care. Single-step formulations have been developed to overcome this limitation, and these "one-pot" versions of CRISPR-dx are simple to run, operate at a single temperature, and run without complex equipment, producing either fluorescence or lateral flow readouts. The programmability of CRISPR makes new diagnostic tests easier to develop, and within months of the release of the SARS-CoV-2 genome, many COVID-19–specific CRISPR tests were reported and distributed around the world.

The broader capability for Cas enzyme–enhanced nucleic acid binding or cleavage has led to several other detection modalities. Cas9-based methods for cleaving nucleic acids in solution for diagnostic purposes have been combined with other detection platforms, such as destruction of undesired amplicons for preparation of next-generation sequencing libraries (*12*), or selective removal of alleles for nucleotide-specific detection

McGovern Institute for Brain Research at MIT, Massachusetts Institute of Technology, Cambridge, MA, USA. Email: omarabu@mit.edu; jgoot@mit.edu