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New research finds that collective neural activity is shaped like the surface of a doughnut

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High-level brain functions result from the orchestration of activity between many thousands of neurons in neural networks. For grid cells, these neural network conversations result in our understanding of location, our capacity to navigate, and our mental maps.

"This discovery provides one of the first insights into how brain cells operate collectively, as a society. It provides an unprecedented glimpse into how large networks of neurons produce properties that cannot be inferred from the activities of single cells. These collective codes are the clue to all high-level cognitive functions of the brain," said Edvard Moser, a professor of neuroscience and co-director of the Norwegian University of Science and Technology's (NTNU) Kavli Institute for Systems Neuroscience.

A theory of how the brain organizes information

In neuroscience, theory and experiment go together like map and terrain. Without a map, you'd be lost in the unknown. Without access to the neural landscapes, you're stuck just speculating.

One of the most promising neuroscience theories in the last fifty years predicts how neural networks in the brain organize information. It proposes that neural networks are self-organized, and that the activity is defined not by sensory or motoric input, but by the specific way cells in the network are connected.

This theory is called continuous attractor networks (CAN), and it has never before been tested. Testing it would require analyzing the simultaneous recorded activity from hundreds or thousands of cells in the same brain network, while the animal is actively performing different tasks. This has not been possible—until now.

Four critical advances have made this research possible.

NTNU's Kavli Institute for Systems Neuroscience has co-developed and discovered two of the four advances. The first is a recently developed super-tool called Neuropixels, which provides researchers access to neural activity from hundreds to thousands of cells, while the second is the most well understood high-level brain function, namely the network of grid cells in the entorhinal cortex that generates the brain's GPS.

NTNU's Department of Mathematical Sciences has developed the third component, advanced topological methods.

Last but not least is the most promising CAN theory, pioneered at ELSC at the Hebrew University of Jerusalem.

Seeing if the map fits the landscape

"We wanted to resolve the question of whether grid cell dynamics are an inevitable product of the animal's experience in space, or if the grid cells' hexagonal pattern arises from the intrinsic design of the neural network itself," said Richard Gardner, a postdoc at the Kavli Institute for Systems Neuroscience and co-first author of the paper.

The researchers set up three experiments with conditions that put the network's intrinsic behavior to the test.

In the first experiment, the rat freely explores an open landscape. In this environment, single cells usually produce perfectly hexagonal grid patterns. In the second experiment, the rat runs along a wagon wheel shaped maze. These types of linear paths are known to distort grid patterns. In the third experiment, the rat rests in REM sleep stage and in slow-wave sleep stage. REM is short for rapid eye movements and is known to be the sleep stage where dreams occur. In the slow-wave sleep stage, the brain doesn't receive motoric or sensory input from the body or the environment, nor does it simulate sensory experiences such as happens with dreams in REM sleep.

This last experiment would turn out to be the real test for the theories, because it would either support or reject one of the strongest predictions from the CAN theory of grid cells. All experiments were done by using Neuropixels probes to extract raw brain data from hundreds of grid cells in the same neural network.

Can we understand the landscape via the map?

"During the experiments, neuroscientists coded the rat's movements as neural activity per unit of time. Every grid cell in the recorded network is given the value of 1 or 0 per unit of time, depending on whether the cell is active or not. During the analyzes, mathematicians then use topological and geometrical methods to decode the data from cell activity and back to behavior again," said Nils A. Baas, a professor of mathematics at NTNU.

Mathematical models reduced the dimensionality of the brain data from several hundred down to three dimensions, which is easier for the human eye to grapple with, and models counted the number of holes in the data—what we call the shape of data. And there, out of the previously unshapely giant cloud of grid cell data, the surface a torus emerged.

"What we found was that the joint activity of the grid cell network resided on and moved along the surface of a torus, a doughnut. For the awake rat, the activity moved across the doughnut in synchrony with the animal's movement in the room. At any given time, we could describe the rat's network activity by coordinates on that doughnut," said Edvard Moser.

"I was surprised by how well the model's decoding turned out. We fused local data from single cells to represent a global behavior. To me, that is a few levels deeper than the torus itself. This is one of the first really interesting application of topological methods on experimental neural data that I've seen," Baas said.

Results were replicated in all experiments

The results were also replicated, regardless of the experiment. No matter if the single cell grid data looked good or poor, no matter what the rat was doing—whether it was freely exploring, running along a linear maze, or sleeping in either REM stage or in slow-wave sleep stage—the joint activity from the population of grid cells firmly moved along the surface of a doughnut. The results support the strong predictions about brain dynamics posed by CAN theory.

"It was remarkable to observe the rigidity of grid cell representations across various conditions, including two different stages of sleep, where this result was far from obvious or expected," said Yoram Burak, an associate professor in physics at ELSC, the Hebrew University of Jerusalem.

"It was one thing to find the torus in the animals when they were moving around in the box—and then we looked when they were sleeping and I couldn't believe it. Finding the torus during sleep surprised me the most but that was after already being surprised by the maze—the maze was supposed to disrupt the regularity but there was the torus. It's always a torus, even when we think it might not be," said Benjamin Dunn, an associate professor at NTNU's Department of Mathematical Sciences.

"What was surprising to me was how well this novel methodology works and how clear the results were. I think it's largely because of the very clear activity structure in the grid cell network, due to the strong constraint on grid cells. The results fit very nicely with the theory of grid cells serving a very particular role for providing a basic metric of space," Gardner said.

"Until recently, the field of topology has been mostly of theoretical interest, but this finding shows that the tools are an important part of understanding our brain," said co-first author Erik Hermansen, a Ph.D. student in NTNU's Department of Mathematical Sciences.

"First and foremost, this study teaches us something about what neural networks in the brain can do. For more than a decade, theoreticians like myself developed theories that attempt to explain grid cell activity. Due to the present study we can now confirm key predictions that were made by these theories. This is very exciting for me personally," Burak said.

Spontaneous grid cell activity aligns to our external world

So, what is the significance of seeing that the network activity of grid cells is always unfolding on the surface of a doughnut?

"Only one theoretical model in neuroscience has predicted what the activity of grid cells should be like regardless of the animal's state, the CAN theory. These findings tell us something about the way the network of neurons is connected. The doughnut exists in the connectivity between the cells," Edvard Moser said.

CAN theory proposes that grid cells with similar functions, cells that are active at nearby places in space, are strongly connected, in a reinforcing way. Cells that are active at distant locations are weakly connected in a mutually inhibitory way. From this follows two premises: (1) If this theory is correct, the only way to get hexagonal grid cell patterns from single cells is if the joint network activity moves along on the surface of a doughnut. (2) The activity structure is a result of the brain's intrinsic wiring rules. Thus, the doughnut remains, regardless of where the animal is or what the animal is doing, whether it is using the grid cells to navigate its external environment or not.

The results show that the grid cell pattern is created internally by the connections between grid cells and is not created by the input from the sensory systems, from the outside.

How can this self-organized, highly structured, constrained and robust dynamic that is generated independent of the environment and emerge from pre-configurations within the entorhinal cortex itself, be flexible enough to support navigation?

"Whenever the rat is actively exploring and navigating the world, its sensory system has to coordinate and align the internal grid cell pattern, the torus map, with the external environment. The grid pattern and the environment have to be in synchrony; the grid pattern must be stably anchored to landmarks in the landscape. This is a job that the entorhinal cortex and the larger areas of the brain have to do all the time. This is what happens in navigation whenever there is sensory input. If there is no sensory input, the map will just drift around. However, the internal relationship between grid cells will remain the same, so when we plot it onto a torus the joint network activity will still move around on the surface of a doughnut, although the activity is no longer aligned to the rat's navigation in the external environment," Edvard Moser said.

"It is absolutely possible that the activity continues to represent where the rat is imagining it is or even dreaming that it is. You can imagine sensory inputs from landmarks and places just as well as you actually perceive them. But there is no way for us to tell, because we don't know what the rat is thinking or dreaming," he said.

An inside out approach for investigating high-level cognitive functions

Gardner says that grid cells were an ideal aspect of the research in helping make the larger doughnut pattern clear.

"This was an ideal system to introduce the use of these kinds of methods to the field. Grid cells are remarkable for having such a strong constraint on their activity, which has this very particular kind of shape to it. The circuit of grid cells are a very unusual of a high-order neural system where we have a good understanding of how to interpret the activity of the cells—the "neural code" they use. It is very special in that way. It's a really beautiful system to work with," Gardner said.

"This study demonstrates a new approach to doing neuroscience, which I think is going to see more and more usage as time goes on. A methodology for extracting dynamics from networkwide neural activity as a starting point for analysis, and just looking at what's there. Finding structure in the data that is intrinsic to the cell populations themselves," he said.

"We can now explore other parts of the brain, where we expect similar tricks are used but where the underlying features might be more abstract, like emotions or social behavior," Hermansen said.

"It's a promising approach for uncovering signals in the brain which may be hidden from us because they don't relate to anything that we can see or measure externally. This may be particularly relevant for understanding the brain circuits involved in higher cognition, which deal with highly abstract information that is difficult for us to make sense of," Gardner said.

Nearly 20 years ago, the Mosers discovered the activity structure of single grid cells. What they found was a hexagonal grid pattern that functions as the brain's metric and coordinate system for space. Today they have uncovered the activity structure from the population of grid cells representing a spatial module. What they found was the surface of a doughnut. The doughnut exists in the connectivity between the cells.

The research was published in *Nature*.

More information: Richard J. Gardner et al, Toroidal topology of population activity in grid cells, *Nature* (2022). DOI: 10.1038/s41586-021-04268-7

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