Flies navigate using complex mental math

December 16 2021

Scientists can image the brains of flies to study how they navigate. Here, a fly walks in place inside a visual arena that makes the fly feel as if it is traveling in various directions. Credit: Maimon Lab

The treadmills in Rachel Wilson's laboratories at Harvard Medical School aren't like any you'll find at a gym. They're spherical, for one, and encased in bowling ball–sized plastic bubbles. They're also built for flies.

Inside these bubbles, fruit flies walk in place as they navigate a 360-degree virtual reality environment.

A similar scene unfolds 200 miles away, in Gaby Maimon's lab at the Rockefeller University, where flies attached to tiny tethers browse their own virtual worlds. By monitoring the flies' brain signals, researchers in these two labs have discovered a key mechanism behind insect navigation.

These little flies, with brains the size of poppy seeds, navigate the world using mathematics that most of us mere mortals forgot after high school. The feat requires performing calculations with data gleaned from the senses and using geometry to compute the body's traveling direction. Howard Hughes Medical Institute Investigators Wilson and Maimon and their colleagues report the work in two new studies released together December 15, 2021, in the journal *Nature*.

Researchers had previously located the fly brain's compass—a set of neurons arrayed in a donut-shaped structure that keeps track of which direction the fly is facing. But scientists didn't understand how flies knew which way they were traveling, Maimon says. "Not which way their body is facing, but which way they are moving in the real world." The new papers identify for the first time which neurons in the brain are tracking both body movement and orientation, and how the signals combine to track a path through the environment.

"To actually lay bare a sophisticated mechanism for navigation as they do is truly significant for neuroscience. Not just fly neuroscience or insect neuroscience or navigational neuroscience—it's significant for neuroscience," says Vivek Jayaraman, who was not part of the new research. Jayaraman, head of mechanistic cognitive neuroscience and senior group leader at the HHMI's Janelia Research Campus, first reported the fly brain compass in 2015.

Mental maps

Insects have remarkable navigation abilities. Scientists knew fruit flies could perform path integration, or "what we'd call dead reckoning," says Wilson. This is the process of tracking past movements to predict where you are on a map. For instance, if you get out of bed in the middle of the night to go to the bathroom, she says, you can navigate by mentally mapping which side of the bed you're on, how many steps you've taken, and which direction you turned.

For an insect, she says, "that's a computation that seems fairly sophisticated for a tiny brain." Understanding how a tiny brain does this computation, she says, could help scientists understand how more complex brains do other kinds of complicated computations.

Wilson and Maimon were both studying fly brain nerve cells thought to be involved in such mental math. Wilson realized while listening to a Zoom seminar by Larry Abbott, an author on the Maimon study, in 2020, that the two of them were thinking on parallel tracks. "So I sent Gaby a message in the chat," she says. It became evident that they each held pieces of the same puzzle, so Wilson and Maimon decided to collaborate.

Both teams showed that two types of brain cells (called PFNd and PFNv cells) track a fly's heading (which way it's facing) and its velocity (speed) as it walks. Since a fly has a nearly 360-degree field of vision, Jenny Lu, a graduate student in the Wilson lab, wanted to watch flies navigate in a 360-degree virtual reality environment. She improved on existing spherical treadmills for flies by adding an immersive virtual reality environment and placing the entire contraption in a clear plastic bubble, so that a camera underneath could record fly movement. By tracking neural activity as the fly navigated, the Wilson team found that both cell types are involved in making geometric calculations.

The neurons keep track of sideways and backward movements and register the compass direction in which the fly is moving. An animal could be facing north and walking forward, or facing west and walking to the right, Wilson says, and the brain would know that in both cases, the animal is actually moving in the same direction: northward.

That ability to adjust one's orientation relative to both the body and the outside world is crucial for dead reckoning, she notes. If you didn't account for sideways as well as forward movement on your late-night trip to the bathroom, for instance, you might bump your shin on the bed or run into a wall.

Math for flies

Cheng Lyu, a graduate student in the Maimon lab, was interested in a mathematical understanding of how information from PFNd and PFNv cells is combined in the brain. He used clever experiments to show that these brain cells use a type of math called vector arithmetic to calculate which way the fly is traveling.

A vector, Maimon explains, is a quantity with a magnitude and a direction. Scientists represent a vector with an arrow. So, a short arrow pointing to the right could indicate slow movement towards the east. And a long arrow pointing up could signify a speedy pace to the north. For navigation, a vector is a handy way to communicate direction and speed. And in the fly brain, adding multiple vectors together can tell the fly both its precise direction of travel and its speed.

Lyu, Abbott, and Maimon discovered that the fly's brain uses PFNd and PFNv cells to do this vector arithmetic. As the scientists report, a neural circuit in the fly brain can rotate, scale, and add the four vectors represented by different PFNd and PFNv populations to track the fly's direction of travel relative to its body orientation.

To visualize this computation during flight, the researchers tethered flies to a platform in the center of a miniature arena and imaged their brains. Starlike dots displayed on the arena's walls made the flies feel like they were traveling in various directions.

Inside the fly brain, activity patterns from PFNd and PFNv cell groups formed a sine wave, a type of regular, repeating wave that shows up often in physics and mathematics. The height and position of the waves vary depending on which way the fly was traveling, the team discovered. By adding the PFNd and PFNv waves, the fly was able to mathematically calculate if it was moving northward, eastward, etc.

"This part of the brain is literally adding vectors," Maimon says. By doing this math, the fly can determine not only which direction it's moving, but how fast it's going in that direction.

The new work provides insight into how animal navigation systems work, says Barbara Webb, a professor of biorobotics at the University of Edinburgh in Scotland who was not involved in the research but has previously studied insect navigation. "It is pretty amazing that we can actually unravel it at this level of specific neurons and connections," Webb says. "I find that really exciting."

What remains unclear, Webb says, is whether other animal brains, such as mammals," use the same mechanisms that flies do. Primates that need to navigate a jungle, for example, face a different set of challenges than an insect that can fly the shortest path between points.

It's also uncertain how navigational data in the brain translates into behavior—the flies' actual steering mechanism. "We now have a deep sense of how brains implement one fundamental type of computation, but we're still only scratching the surface on how the brain works, overall," Maimon says.

In today's era of neuroscience, he adds, "the approachable fly brain may continue to be a place where we figure things out first, giving us a blueprint for understanding larger brains, like our own."

More information: Jenny Lu et al, Transforming representations of movement from body- to world-centric space, *Nature* (2021). DOI: 10.1038/s41586-021-04191-x

Cheng Lyu et al, Building an allocentric travelling direction signal via vector computation, *Nature* (2021). DOI: 10.1038/s41586-021-04067-0

Provided by Howard Hughes Medical Institute

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