Creating Internal Maps

Combining complementary skills, a team of neuroscientists studies how flies navigate their surroundings.

SOME COLLABORATIONS CLICK FROM THE START. TAKE THE CHANCE meeting three years ago at Janelia Farm Research Campus between Michael Reiser, a group leader at Janelia, and Charles Zuker, an HHMI investigator then at the University of California, San Diego (UCSD). The two had never spoken before, but within a day or two, Reiser says, Zuker was suggesting his graduate student as a perfect fit for the project.

The partnership seemed so promising that Zuker arranged to work with Reiser through Janelia Farm's Visitor Program, where scientists from around the world conduct research of their own design for a few weeks or several years (see Web extra sidebar, "Visitors Welcome"). "We all hit it off beautifully," he says.

The researchers weren't just simpatico. They brought together complementary talents and knowledge that enabled them to explore an important question: do fruit flies commit details of their surroundings to memory? Humans and other vertebrates make spatial memories all the time. You can return to your car in a crowded parking lot, for example, by referencing landmarks stored in memory. So-called place neurons in the hippocampus, a brain structure crucial to memory, confer this ability. "In essence, the cells are creating an internal map of the outside world," says Zuker.

But how do neurons register this information? Reiser believes it might be possible to dissect mapping of spatial memory by analyzing the process in fruit flies, where brain cells can be precisely targeted for manipulation. "The fly presents a real sweet spot to try to answer this question," he says.

At the outset, Reiser brought his LED-based display that projects different background patterns, providing potential navigation landmarks for flies. Zuker brought small, hot and cool tiles that his lab had developed to study how the insects sense temperature.

The job of melding these technologies fell to the third member of the partnership, Tyler Ofstad—Zuker's graduate student and an M.D./Ph.D. candidate at UCSD. After a year of R&D in Reiser's lab, handled largely by Ofstad with what Zuker calls "devotion, drive, and maniacal commitment," the team had built a shallow, circular arena, about 20 centimeters across, with a clear glass lid. Most of the arena's floor was a warm-to-the-touch 36°C. One tile, however, was only 25°C, pleasantly cool for fruit flies. Each time the flies entered the arena, they typically wandered, but "once they found the cool spot, they stopped and stayed there," says Ofstad. The flies were allowed 10 five-minute trials to learn the location of the tile. To follow the flies' movements, the researchers were among the first to use software designed by Janelia Farm fellow Kristin Branson that Reiser describes as "the world's best fly tracking program."

The cool tile looked the same as the rest of the floor, so the only landmarks in the arena were patterns of bars projected on the wall. To determine whether the flies used this background to guide them to the cool tile, the researchers rotated the floor and walls of the arena after each trial so that the location of the cool floor tile changed, but its position relative to the wall patterns stayed the same.

The flies quickly learned to pinpoint the cool spot. After 10 attempts, the insects could find the tile in under 60 seconds, less than half the time of their first try, the group

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reported June 8, 2011, in *Nature*. Moreover, when the trained flies encountered an arena without a cool tile, they congregated where the tile should have been, based on the visual background.

Then the team tricked the flies, rotating the thermal pattern on the arena floor after each trial but leaving the wall stationary, so that the background pattern no longer corresponded to the location of the cool tile. The flies were baffled. When given the chance to find the cool tile in the dark, they also made no headway. Given this evidence, the researchers concluded that "flies can form memories about spatial locations," says Ofstad.

Next the researchers wanted to know which part of the fly brain remembers the location of the cool spot. They switched off certain brain cells in the flies, using genetic tools developed in the lab of Janelia Farm director Gerry Rubin that allow scientists to target small groups of identified neurons. When neurons in a structure called the ellipsoid body were shut down, the flies couldn't navigate the arena. Thus, this structure might be crucial for storing or retrieving spatial information in the insects. The role of the ellipsoid body isn't clear, but Zuker says it would be the first place to look for the fly equivalent of place neurons.

The researchers have gone their separate ways—Ofstad has returned to San Diego to finish clinical work for his M.D., and Zuker has moved his lab to the Columbia University College of Physicians and Surgeons in New York City. The team, however, is hatching a plan to use fruit fly vision and behavior to decipher another aspect of brain function. "When you find the unique synergy that helps some of the magic come out of exciting scientific problems, you want more of it," Zuker says. ■ –MITCH LESLIE

WEB EXTRA: To read more about the Visitor Program at Janelia Farm, visit www.hhmi.org/bulletin/nov2011.