Mavericks

The Mind's Cartographer

Amanda Schupak, 11.14.05

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Researchers have given us an atlas of the brain. Molecular biologist Julie Simpson is drawing a street map.

For six minutes Julie H. Simpson sits motionless on a laboratory stool, her eyes glued to a microscope. Holding a pair of finely pointed forceps in each hand, she delicately dissects the head of a fruit fly and lifts its brain onto a waiting slide. "On the weekends," she says, finally looking up from the scope's eyepiece, "the lights are on motion-sensor and they'll go out on me. I have to wave my arms to get them back on."

When the slide is finished, Simpson will have transferred the brains from four more *Drosophila melanogaster,* each a perfect genetic clone of the others, to the hole of a clear three-ring-binder reinforcement, the kind you find in a school-supply store. A swipe of clear nail polish fixes the brains in place.

This benchwork could consume the rest of Julie Simpson's life, and she's only 32 years old. Over the past four years she has collected and photographed 400 of these slides--"Gorgeous," Simpson mutters whenever she sees a good one--at a lab at the University of Wisconsin at Madison. Each photo shows the outline of a bulbous *Drosophila* brain, pocked with brilliant bits of green, blue and red fluorescence against a pitch-black background. Each spot of color is a place inside a fly's brain that controls a specific motor behavior such as walking, grooming and courtship.

With each slide, Simpson inches closer to one of science's more monumental goals: producing a functional brain map as precise as a street map--first of the fly, eventually of humans. With detailed knowledge of the brain's byways, neuroscientists will able to understand how and where information is stored and thus pursue targeted treatments for epilepsy, paralysis, depression and attention deficit disorder.

Neuroscientists have labored to produce relatively crude maps of human brain regions, which can locate the origins of particular behaviors in swaths of thousands of neurons. In her short career Simpson has already begun locating motor-control neighborhoods of just 10 to 100 neurons in fruit flies. "There is no textbook, "she says. "We didn't even know where these neurons were, and now we're seeing their outline."

There are maybe a dozen labs in the world mapping the neural circuitry of fruit flies. Some have chosen to focus on one area of brain function, such as olfaction or fear response. But Simpson has ambitiously chosen to chart motor control, which encompasses a wide range of behaviors and poses many unanswered questions. How many neurons are used in walking or climbing? One of Simpson's emerging theories is that it may be only a precious few brain cells that keep a fly or a person from, say, forgetting how to walk. "We understand so little about how normal memory takes place," says Simpson. "If we knew that it was really only one or two synapses storing so much information we would have a better sense of how fragile things really are."

Drosophila makes an excellent proxy for human brain research. Maybe two-thirds of our DNA has an equivalent in its genome and, even though fly brains have only 200,000 neurons to our 100 billion, they're organized much like ours, with activities such as sensory processing assigned to distinct regions. Conveniently, the animals reproduce fast, racing from embryo to adult in 14 days.

Simpson's experiments depend on the use of genetically altered flies, but they also mix in some very low-tech techniques. She has produced 450 lines of *Drosophila,* each with a gene mutation that turns off production of a necessary protein at high temperatures. Heat them up and the flies behave abnormally, for example going into seizures or paralysis. When they cool off, they become themselves again. Simpson's favorites are ones that turn into sex addicts when the heat's on.

Attached to the mutated genes is a hunk of DNA that acts like a car's ignition, starting the mutant genes up with the right protein key. Simpson's key is GAL4, a gene and protein originally extracted from yeast. Each fly line was designed to produce GAL4 in a different group of neurons, causing the mutant genes to be expressed only in those areas. Because GAL4 also turns on a fluorescing protein in these neurons, Simpson can locate them when she takes brain scans.

To demonstrate, she heats a glass vial to 102 degrees Fahrenheit by submerging it in a bucket of hot water. She takes a rubber hose with a pipette on one end and a mouthpiece on the other and sucks 20 healthy looking flies from a small glass jar, then blows them into the the heated vial. These happen to be so-called seizure-mutant flies. Within seconds of being exposed to heat, the flies are going bananas. "They look like popcorn in the vial," says Simpson.

When she removes them from the test tube, their motor-control protein kicks back into action and the flies go back to normal. Simpson then grabs any five flies from these genetic lines and scans their brains with a powerful confocal laser microscope that produces what are essentially optical salami slices of the fly brain. A software program builds out of these slices a 3-D image. Wherever she sees GAL4 neurons glowing brightly in the scans is where the mutant gene in question is being expressed.

Of particular interest to Simpson is the seizure gene because, by locating seizure-inducing cells, she might be able to point toward which types of neurons cause epilepsy in humans. Epilepsy is triggered in various parts of the brain, yet experts admit they're at a loss to pinpoint which zones are more influential. "If you overactivate the whole brain you'll get seizures," Simpson explains. "But can you do that to just a few neurons and trigger the same thing?"

Says W. Allen Hauser, professor of neurology at Columbia University: "Anything that would give you clues to things that would turn off seizures readily could be applicable for a lot of things. If you're able to turn off neuron circuits specifically for seizure, then maybe you can for depression or ADHD."

Simpson was hardwired to live the scientific life. Her father, a Columbia University geochemist, would take her mother (a nurse) and young Julie on long family car trips, pointing out rock formations and collecting bottles of water at every stop for chemical analysis when he got home. "I thought it was irritating at the time; now I wish I had paid more attention," she says. His work moved the family from a base in Nyack, N.Y. to Egypt, Italy and Australia.

After getting a degree in molecular biology from Princeton, she earned a doctorate from UC, Berkeley on the nervous system development of fruit flies. Her curiosity next took her to the lab of renowned geneticist Barry Ganetzky at the University of Wisconsin at Madison, home to a large collection of temperature-sensitive mutant flies. Simpson arrived with the notion that she could use these flies to locate only those neurons essential for normal behaviors--the minimal circuitry, she calls it--to produce a precise functional map. When Simpson presents her research goals to colleagues, some are hopeful and eagerly supportive. "But half the people I speak to say, 'You're insane, it's too open-ended,'" Simpson says. "I think they are both right."

Next year Simpson is moving her crates of slides and 1,000 genetically modified fly lines to Janelia Farm, a $500 million retreat in Ashburn, Va. for elite bioresearchers, part of the Howard Hughes Medical Institute. She was one of 5 chosen out of 300 applicants. "What attracted us was the bold nature of Julie's project," says Gerald Rubin, director at Janelia Farm. "We want people who are willing to risk their careers on their ideas."

Simpson's project may not see its end for decades, and she is not fazed by its scope. "I'm not going to get bored for a long time," she says.