A Few Good Neurons

Remembrances of things past do not necessarily involve a great many nerve cells.

Cornelia Bargmann joins forces with a tiny worm to study how the brain's wiring influences behavior.

Matthew Septimus

"We are watching the nervous system translate experience into its own language."

CORNELIA BARGMANN

IF YOU'VE HAD THIS UNPLEASANT EXPERIENCE, YOU WON'T FORGET IT: You ate something bad and got sick as a dog. Even years later, the thought of eating that particular food again makes your stomach turn.¶ This response, called conditioned taste aversion, is one of the strongest forms of learning in mammals, says Cornelia I. Bargmann, an HHMI investigator at the Rockefeller University. "All it takes is a single experience to form very long-lasting memories." And the process is not unique to mammals. Fish, snails, and the cuttlefish (a relative of octopus and squid) show a similar response. In the November 10, 2005, issue of *Nature*, Bargmann's team reported that *Caenorhabditis elegans*, a nematode with only 302 neurons, does too.

If a worm with so few neurons can learn such a sophisticated behavior, just how many neurons does it take to establish a memory? Theoretically, only two: a sensory neuron to detect a stimulus and a motor neuron connected to a muscle that will carry out a behavior. But in actuality, neural circuits are never quite this simple and invariably involve more—though not necessarily a great many—cells.

The laboratory of Eric R. Kandel, an HHMI investigator at Columbia University who won the 2000 Nobel Prize in physiology or medicine for his work on memory, has studied the sea slug *Aplysia*. This animal rapidly learns to associate a noxious stimulus, like an electrical shock, with an innocuous cue, such as a light touch on its siphon. It will subsequently withdraw its gill in a protective behavior in response to just the light touch.

The circuit that underlies such classical conditioning can be reduced to about 20 or 30 neurons if one focuses on only one aspect of gill movement, says Kandel. In the full-blown behavior, 50 to 60 neurons are likely to be involved.

Bargmann doesn't yet know what the circuit looks like that controls conditioned taste aversion in nematodes, but she estimates that, here too, some 60 neurons are involved. Significantly, her team used molecular tools to watch as one type of neuron in the circuit increased production of the neurotransmitter serotonin (which strengthens signaling between neurons) in response to bad food, in this case, toxic bacteria. When the scientists knock out the receptors for serotonin, they inhibit learning.

"We are watching the nervous system translate experience into its own language," says Bargmann. The worm experiences an infection from eating the wrong bacteria, and the nervous system transforms that experience into an increase in serotonin, a molecular language that the nervous system understands. The fact that it is the same neurotransmitter that Kandel's lab saw in classical conditioning in *Aplysia* leads Bargmann to suggest that scientists might be beginning to unravel the grammar of this molecular language common to all creatures.

So how many neurons do we humans need to remember a particular Rembrandt masterpiece or to recall a conversation we had with a close friend? There are no specific answers yet, but Kandel and others predict that the molecular aspects of memory storage in humans will be similar to those in *Aplysia* and other model systems. The size of the human brain, however, adds enormous complexity. Even simple circuits, such as those described above, will be layered many times over. And there will be a concomitant increase in combinatorial options to mix and match pathways. "We can't dissect out each bit yet," says Kandel, "but eventually we will." ■ —RABIYA TUMA

Table for One?

Have a question about nematode behavior? Ask Cornelia Bargmann. She's figured out what makes some of these 1-millimeter-long worms social eaters while others prefer to eat alone, and she can tell you how they know bad food when they smell it. The HHMI investigator at the Rockefeller University has also determined how the worms, known as *Caenorhabditis elegans*, can recognize and distinguish among thousands of odors in their environment. Their keen sense of smell and small number of neurons make *C. elegans* an ideal model for Bargmann and other researchers to understand the interface between genetics and experience. Since neuronal genes, like most other genes, are conserved among all animals, she expects that her research on the worm's brain will improve understanding of the human brain. The gene she found that determines whether a worm prefers a table for one or family-style dining, called *npr-1*, is related to human proteins involved in appetite and anxiety regulation.