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What Makes Worms Turn for Food?

Wriggling worms are motivated by their sense of smell - lingering when they detect the tempting aroma of their favorite bacterial snack, or twisting and turning to explore new territory when that aroma fades. In new studies, Howard Hughes Medical Institute scientists have now shown how odor-sensing neurons in the worm can activate or inhibit other neurons that control crawling and turning. The studies have begun to explain how neurons are capable of carrying information over minutes or even hours - timescales that are much longer than the millisecond timeframes measured by many neuroscience experiments.

The research team, led by Howard Hughes Medical Institute investigator Cornelia Bargmann, published its findings in the November 1, 2007, issue of the journal *Nature*. Bargmann is at The Rockefeller University, and other co-authors were from Stanford University. The scientists say their findings demonstrate that transient changes in sensory cues can trigger sustained behaviors like food-seeking and mating.

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> **— Cornelia I. Bargmann**

The keen sense of smell in *C. elegans* has provided a unique opportunity for Bargmann to understand the interface between genetics and experience. On the one hand, many responses to odors are genetically determined, like the favorable response by human infants to the smell of vanilla. On the other hand, a bad experience, like getting sick after eating a particular food, can create a lifetime aversion to its smell.

While the human brain has billions of neurons, the *C. elegans* brain has only 302, of which 32 are dedicated to smell, making it an ideal model for studying the relationship among genes, neural circuits, and behavior. Yet, the brains of worms and humans share many of the same features of wiring and function, and many of the genes found in *C. elegans* are also in humans. "When we understand the worm's brain, we'll be in a much better position to understand the complex functions of the human brain," Bargmann noted.

Researchers have analyzed the genetics and connectivity of the worm's neural wiring extensively, said Bargmann. But studies of *C. elegans* have lagged behind in the ability to record from neurons in behaving animals; of knowing when specific neurons are active, she said.

In their latest studies, Bargmann and her colleagues wanted to observe precisely which neurons were activated when worms responded to olfactory information. To get this information, they used a genetic labeling technique that permitted them to tag specific neurons with a fluorescent marker. The marker glowed more intensely when neurons were active, allowing the researchers to easily see which neurons were firing in response to olfactory stimuli.

To corral the worms, the researchers constructed tiny microfluidic chambers a mere 25 microns high, about a tenth the diameter of a human hair. The chambers were only slightly taller than the worms, restricting the worms to lateral movement, making their two-dimensional meanderings easier to track under a microscope. The researchers could also direct narrow streams of odorants to the worms in the chambers them.

The team began by applying the fluorescent label to AWC neurons. Previous studies had shown that these neurons help worms respond to odors by controlling the turning behavior that worms use to seek food. When Bargmann and her colleagues presented the worms with an alluring odor, they saw no response in the fluorescently labeled AWC neurons.

We spent quite a bit of time giving the worms odors, but seeing the AWC neurons do nothing, Bargmann said. It took us quite a while to realize that we needed to take odors away for the neurons to activate. AWC neurons are food-seeking neurons, so if the food is there, they are not active. It's only when the food is removed that they are activated to trigger behaviors to find food.

Bargmann pointed out that the roundworm is not the only animal to use the absence of sensory information to activate neurons. Photoreceptors in mammals, including humans, are active in the dark, but silenced by light. Molecular similarities in the worm olfactory system and mammalian visual circuitry suggest that this machinery may have been conserved by evolution from worms to mammals, she said.

The researchers next labeled the interneurons that connect the sensory neurons to the worms' behavior circuitry. They found that when they removed the odorant, the olfactory neurons activated AIB interneurons, which enhanced turning behavior. When they inactivated the olfactory neurons by adding odorant, AIY interneurons were turned on and repressed turning behavior.

This told us that the sensory neurons could split the information, so that one interneuron responds when the odor goes away, and the other responds when the odor appears, said Bargmann. But the most interesting thing was that odor removal produced a persistent signal in AIB interneurons. It lasted as long as a couple of minutes. So, this system transforms a transient piece of information into long-lasting activity.

Using their findings of the specific molecules that these neurons use to signal to one another, the researchers created mutant worms in which that signaling was disrupted. In this way, they could switch off or on each element of the circuit and observe how turning behavior was affected.

By controlling odorant streams in the tiny chambers, the researchers also tested what kinds of changes could alter the worms' behavior. We were basically asking this system what computation it was doing about odors, said Bargmann. Does it know exactly how much odor is present? Does it know where the odor is coming from?

The answer to both questions, she said, is no. The circuitry wants to compare how much odor exists now to how much odor there used to be.

Such studies, said Bargmann, offer researchers a way of thinking about neuronal circuits on a longer time scale than other related experiments. People usually study neuronal function at times of milliseconds, or seconds at most, she said. That is the time domain at which people do things like throw a baseball or perceive a face. But behaviors like feeding, mating or exploration can take place over minutes or even hours. So, we know that there have to be ways neurons can carry information for these longer times, and we think that is what we are seeing in these experiments that hasn't been easy to see before.