Analysis of worm neurons suggest how a single stimulus can trigger different responses

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Worm brain: All the neurons within this microscopic roundworm are highlighted, with the large cluster at one end representing the brain. Coelomocytes, a type of immune cell, appear as dots along the body.

Even worms have free will. If offered a delicious smell, for example, a roundworm will usually stop its wandering to investigate the source, but sometimes it won't. Just as with humans, the same stimulus does not always provoke the same response, even from the same individual. New research at Rockefeller University, published online today in *Cell*, offers a new neurological explanation for this variability, derived by studying a simple three-cell network within the roundworm brain.

"We found that the collective state of the three neurons at the exact moment an odor arrives determines the likelihood that the worm will move toward the smell. So, in essence, what the worm is thinking about at the time determines how it responds," says study author Cori Bargmann, Torsten N. Wiesel Professor, head of the Lulu and Anthony Wang Laboratory of Neural Circuits and Behavior. "It goes to show that nervous systems aren't passively waiting for signals from outside, they have their own internal patterns of activity that are as important as any external signal when it comes to generating a behavior."

The researchers went a step deeper to tease out the dynamics within the network. By changing the activity of the neurons individually and in combination, first author Andrew Gordus, a research associate in the lab, and his colleagues could pinpoint each neuron's role in generating variability in both brain activity and the behavior associated with it.

The human brain has 86 billion neurons and 100 trillion synapses, or connections, among them. The brain of the microscopic roundworm Caenorhabditis elegans, by comparison, has 302 neurons and 7,000 synapses. So while the worm's brain cannot replicate the complexity of the human brain, scientists can use it to address tricky neurological questions that would be nearly impossible to broach in our own brains.

Worms spend their time wandering, looking for decomposing matter to eat. And when they smell it, they usually stop making random turns and travel straight toward the source. This change in behavior is initially triggered by a sensory neuron that perceives the smell and feeds that information to the network the researchers studied. As the worms pick up the alluring fruity smell of isoamyl alcohol, the neurons in the network transition into a low activity state that allows them to approach the odor. But sometimes the neurons remain highly active, and the worm continues to wander around – even though its sensory neuron has detected the odor.

By recording the activity of these neurons, Gordus and colleagues found that there were three persistent states among the three neurons: All were off, all were on, or only one, called AIB, was on. If all were off, then, when the odor signal arrived, they stayed off. If all were on, they often, but not always, shut off. And, in the third and most telling scenario, if AIB alone was active when the odor arrived, everything shut off. "This means that for AIB, context matters. If it's on alone, its activity will drop when odor is added, but if it's on with the rest of the network, it has difficulty dropping its activity with the others," Gordus says.

AIB is the first neuron in the network to receive the signal, which it then relays to the other two network members, known as RIM and AVA; AVA sends out the final instruction to the muscles. When the researchers shut off RIM and AVA individually and together, they found AIB's response to the odor signal improved. This suggests that input from these two neurons competes with the sensory signal as it feeds down through the network.

Scaled up to account for the more nuanced behaviors of humans, the research may suggest ways in which our brains process competing motivations. "For humans, a hungry state might lead to you walk across the street to a delicious smelling restaurant. However, a competing aversion to the cold might lead you to stay indoors," he says.

In the worm experiments, the competition between neurons was influenced by the state of the network. There is plenty of evidence suggesting network states have a similar impact on animals with much larger and more complex brains, including us, says Bargmann, who is also a Howard Hughes Medical Institute investigator. "In a mammalian nervous system, millions of neurons are active all the time. Traditionally, we think of them as acting individually, but that is changing. Our understanding has evolved toward seeing important functions in terms of collective activity states within the brain."