Worms take the sniff test to reveal sex differences in brain

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Buttery popcorn or fresh green vegetables? Your answer tells a lot about you. Now, scientists say that the way that thousands of tiny worms have answered that question likely reveals a lot about you and your brain, too.

In the experiment at the University of Rochester Medical Center, worms that are hermaphrodites (with characteristics of both females and males) went for the buttery smell, while the males – the other of the two sexes in these worms – opted for the scent of fresh vegetables. But when researchers tricked a few nerve cells in hermaphrodites into sensing that they were in a male worm, suddenly they too preferred the smell of fresh vegetables.

While the olfactory likes and dislikes of the tiny roundworm known as C. elegans is the stuff of distinctive cocktail conversation, trivia is the furthest thing on the minds of Rochester scientists who did the study, which is being published in the Nov. 6 issue of *Current Biology*.

Geneticist Douglas Portman, Ph.D., and graduate student KyungHwa Lee ultimately hope to understand gender differences in diseases like autism, depression, and attention-deficit disorder. Many more boys than girls are diagnosed with ADD and autism, and many more girls than boys are diagnosed with depression. While proposed explanations abound, few scientists debate the notion that the brains of the sexes are in some ways fundamentally different.

The experiments with humble C. elegans, nearly invisible to the naked

eye and common in soil worldwide, make up one way that scientists are exploring the roots of a host of conditions that affect the human brain. The research project was funded by Autism Speaks, an organization dedicated to autism awareness and research.

“For so many diseases, like autism or mood disorders, it’s clear that they either are more prevalent in one sex than the other, or they manifest themselves differently. But no one really knows why,” said Portman, assistant professor of Biomedical Genetics. “We think that sex differences in the brain may play a role. If we can understand these differences, it may give us some clues about how we can diagnose, prevent, and treat these diseases more effectively.”

C. elegans is a one-millimeter-long critter that provides a unique window onto the human brain. Back in 1998, the worm gained fame as the first multi-celled organism to have its genome sequenced. About half of the organism’s approximate 22,000 genes have direct counterparts in people, but its nervous system is far simpler. Indeed, researchers have identified and named every one of the male worm’s 383 neurons, while barely scratching the surface of the hundreds of billions of neurons in the human brain.

Portman and Lee are using the organism to try to work out some of the fundamental rules that govern the nervous systems not only of worms but also people.

“The key to neurons is how they talk to each other. In a human brain, there are trillions of such connections. In a worm, there are thousands – still a considerable challenge to understand, but it’s much more do-able, and it’s a stepping-stone to understanding how the human brain works. The architecture is much simpler to try to understand,” Portman said.

The team is focusing on sex differences in the nerve cells of the critters,

which come in two sexes: males, and hermaphrodites, basically females that are able to reproduce on their own because they can produce both egg and sperm. The two sexes share a core nervous system made up of 294 neurons that are exactly the same; hermaphrodites have eight additional neurons, while males have 87 additional neurons. (The male devotes a large portion of its nervous system to its ability to copulate, but that's another story altogether.)

The team ran hundreds of experiments in which worms in Petri dishes were given 45 minutes to crawl toward one of two scents. One difference stood out: Hermaphrodites more often crawled toward the buttery-popcorn smell of diacetyl, while males preferred the scent of pyrazine, which resembles the smell of fresh vegetables like green peppers and peas.

Then, researchers flipped a key genetic switch in the hermaphrodites, effectively making a few of their neurons think that they were actually part of a male worm. Immediately, they began behaving like males, crawling toward the scent of pyrazine. With a single genetic modification, the hermaphrodites began acting like males. Even though most of these worms looked like regular hermaphrodites, they behaved according to the sexual "identity" of a just a few of their neurons.

"This work reveals an unexpected way that sex can influence the function of the brain," said Portman, who is also a member of the Center for Neural Development and Disease and the Department of Biology. "It would be logical to think that all differences in the behavior of the sexes would result from neurons that are in one sex but not the other. We did not find that. Instead, we found that the behavior of nerve cells that are present in both sexes can be modified by the sexual status of the organism. That tells us that there's a surprising, unexpected dimension of sex differences in brain function.

“It’s far too soon to say what results like this might mean for our understanding of the human brain,” said Portman. “But autism is a perfect example of a disorder where we know very little about what is actually happening in the brain. The incidence of the disorder is increasing, and it’s clear that boys are affected more often than girls. At the same time, it’s unknown how or why a difference in sex chromosomes translates to differences in how brain cells function or to our susceptibility to different disorders. That’s what we hope to learn, ultimately for the benefit of people.”

Source: University of Rochester