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Why did the nematode cross the maze?

To get to the other side, TERRENCE BELFORD discovers. But how they remember the route teaches researchers a lot, for a little

TERRENCE BELFORD
SPECIAL TO THE GLOBE AND MAIL

Aaron Wheeler, a 32-year-old assistant professor at the University of Toronto, is plumbing the depths of brain chemistry with experiments so inexpensive to stage that they make the average high-school science project look lavish.

His findings are catching the attention of researchers around the world not only for what they suggest about the workings of the brain and memory, but also for the almost negligible costs to achieve them.

The research by Dr. Wheeler, a Canada Research Chair in bioanalytical chemistry, is a model of simplicity. In a nutshell, he took nematodes -- tiny, blind worms -- and ran them through an equally tiny maze. The lure for the worms was a particularly tasty bit of E. coli bacteria.

Drawn by its scent, the millimetre-long worms navigated the glass-sided maze, which measured only 3x4 centimetres and was only 150 microns deep. In some runs, the threadlike worms had to negotiate four right-hand turns; in others, four turns to the left.

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Amazingly, even when the food was removed and there was no scent to follow, the nematodes remembered where it had been before, and set off again to the spot where the E. coli used to be. Because the agar gel base they crawled upon was replaced between tests, they weren't able to follow an old scent.

The conclusion had to be that somewhere in that microscopic brain lay a chemical linked to memory. And if the worms found no bacteria waiting, they showed little interest in repeating their feat.

In short, Dr. Wheeler showed that a worm with just 302 neurons in its brain is capable of memory and could even be trained.

"It was quite a surprise," he says. "It was also an amazing feat for the worms. They had to travel . . . what would be the equivalent of miles for us to get to the food. That meant a memory that could take them that far."

Dr. Wheeler repeated the experiments using mutant nematodes deficient in brain chemicals such as dopamine. While those worms were capable of locating the food, they were incapable of remembering where they had found it -- reinforcing other research that found dopamine is key to memory function in humans.

Perhaps best of all, Dr. Wheeler's research was so inexpensive it opens the door for a floodgate of future work, especially in experiments require mass screening.

"The total cost was literally just a few dollars to build that little maze," explains Dr. Wheeler. "The worms you can get for free, and they are such prolific breeders that just three or four will become thousands within less than a week."

His findings and the bargain-basement cost of the experiment have drawn considerable attention in the research community.

"Wheeler's work is terrific in that it raises more questions than it answers," says Dr. Catharine Rankin, a psychology professor at the University of British Columbia with an international reputation as a nematode-based researcher.

"The next step has to be focusing on some of those unanswered questions," she says. "How, for example, does a worm know its right from its left? The nematodes were lying on different sides of their body as they made their way through the maze, so how did they know which was right?"

She also poses other questions worth further investigation, such as: What chemicals are involved in producing memory? Do those chemicals diminish with age? Do worms' memories begin to fail as they near the end of their 10- to 20-day lifespan?

"I think it is groundbreaking -- it is that important. It shows something with just 302 neurons has a memory," Peter Roy, an assistant professor in the UofT's medical genetics and microbiology department, says of his colleague's experiments.

"This will be the basis for genetic and pharmacological research well into the future," predicts Dr. Roy, a recognized leader in research into the *Caenorhabditis elegans* (C. elegans) strain of nematodes.

He supplied Dr. Wheeler with the C. elegans worms for the maze tests, and explains why they were perfect subjects: "If you were to study the human brain to see what chemicals produce what reactions, you would be faced with searching trillions of neurons. In C. elegans you have just 302."

The lure of nematode research is manifold, Dr. Roy adds. Nematodes offer researchers many of the basic body systems studied in higher mammals -- but in a greatly simplified form. They have a tiny brain, a nervous system, circulatory system, respiratory and digestive systems, and even a skin of sorts.

Dr. Wheeler hit on his groundbreaking experiment almost by accident. His previous work revolved around studying microfluidics, the chemical contents of cells suspended in droplets of water. He was looking for new ways to test pharmacological discoveries.

"By chance, I was talking with Peter Roy and we decided to try looking at his worms in droplets to examine their cell chemistry," Dr. Wheeler recalls. Then came the suggestion that the worms be introduced to a maze to see how they reacted.

"The maze was just one of those ideas that came up in conversation," Dr. Wheeler says. "The cost was so cheap - free worms and a few dollars to have a technician build one -- we thought, why not?"

Cost is a major factor in most research, he notes. His success in working with C. elegans means large-scale studies are easily affordable.

"One of the great advantages of C. elegans is that you can do really large screenings," Dr. Wheeler notes. "You can do research on a desk top with C. elegans that you would need a multi-storey building full of rats to equal, if they were the test subjects.

Nor are nematodes without their charm, he adds. His research assistant, Dr. Jainhua Qin (who has since returned to her native China), became so fond of some of her short-lived subjects that she even named a few of them.

Dr. Wheeler financed his initial experiments through the grant package received when he was named a Canada Research Chair last September. He is now seeking funding for the next phase of experiments, which will use hyper-sensitive chemical detectors that can sense elements the size of a single molecule.

He intends to repeat the maze runs to see which chemicals in nematode brains are linked to memory. Identifying those chemicals could lead, for example, to medicines to improve human memory, perhaps with application to diseases such as Alzheimers.

Nematode-based researchers have made some stunning findings already. In the past five years, such researchers have won two Nobel prizes. The 2002 prize went to three scientists, one Briton and two Americans, who used nematodes to study cell death; the 2006 award recognized two American scientists who discovered RNA interference, a key to gene regulation.

With that sort of backdrop, Dr. Roy is confident his colleague will find the required funding to take his memory research to the next level.

"There is always money for great science," Dr. Roy says. "And this is great science."

Microscopic lab stars

Nematodes -- whose name comes from the Greek *nema*, or thread -- are the most numerous multicelled animals on Earth, with more than 20,000 species. And the simple roundworms, especially the *Caenorhabditis elegans*
(C. elegans) strain, are becoming the test animal of choice for a growing number of scientists around the world ever since a U.S. researcher wrote the first paper on them in 1974.

At one time, fruit flies were the favourite subject for genetic researchers because of their similarities to humans, but the flies present challenges that nematodes do not, says Peter Roy, an assistant professor in the University of Toronto's medical genetics and microbiology department.

"The problem with fruit flies is that they don't stay in place," says Dr. Roy, a recognized leader in C. elegans research. "First the egg becomes a larva, and the larvae start to crawl out of the test wells you keep them in, then they change into flies and fly all over the place."

The one-millimetre long C. elegans, by comparison, is a homebody. Place a newborn in one of the 96 tiny "wells" that make up a typical laboratory test station and three days later the worm reaches sexual maturity, breeds with itself (they are hermaphroditic) and produces up to 300 young, who three days later start creating their own large families. Some time between the age of 10 and 20 days, the worm dies.

Nematodes are popular with scientists because they have body parts similar to higher mammals -- a brain, nervous system, circulatory system, and respiratory and digestive systems -- but in much simpler form.

Currently about 1,500 nematode-based researchers are at work around the world, says Dr. Catharine Rankin, a well-known nematode researcher and psychology professor at the University of British Columbia.

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