'Fly guy' makes memory breakthrough

December 10 2008

Francois Bolduc

Dr. Francois Bolduc keeps more than 300,000 fruit flies in a basement laboratory, where he manipulates their genes and then tests their mental abilities. He's called the "fly guy," and he may sound like a comic book villain, but Bolduc is no mad scientist.

A new recruit to the University of Alberta's Faculty of Medicine & Dentistry, Bolduc has shown that genetically disrupting a specific gene called FMR1 in a fruit fly's brain will wipe out its long-term memory. Bolduc has also found a class of drugs that helps fruit flies with this disrupted gene to regain their memories. The news is significant for humans, because FMR1 may malfunction in people with intellectual disabilities like Fragile X syndrome, and there are currently no clinically available treatments.

Fragile X syndrome is the most common cause of genetically defined developmental delays in humans, affecting 1 in 4,000 males and 1 in 8,000 females. Children with Fragile X syndrome may have learning and memory problems, epilepsy and autism.

"We know that 87 per cent of the genes found in human mental retardation have homologs in fruit flies, so we're confident that we're on to something here," said Bolduc, whose research was recently published in *Nature Neuroscience*.

Bolduc's test of long-term memory in fruit flies began by exposing them to two smells in succession that were different but "equally repulsive" to the flies. One of the smells was paired to a foot shock, and the other was benign. From this, the flies learn to avoid the odor that leads to a shock, even in the absence of a future shock. This memory lasts for about a week—one-fifth of a lifetime to an average fruit fly.

In his long-term memory experiment, Bolduc found just 10 per cent of the fruit flies without the FMR1 gene avoided the smell that led to a shock, while 50 per cent of the normal flies knew enough to steer clear of it.

"The evidence clearly showed that the flies without the FMR1 gene really weren't operating at the same capacity as the control group," said Bolduc, who arrived at the University of Alberta this year from the Cold Spring Harbor Laboratory in New York.

A well-functioning FMR1 gene is thought to help "quiet" new protein synthesis in the brain, enabling normal mental performance. After four years of research, Bolduc was not only able to demonstrate the cognitive deficiencies of fruit flies without a FMR1 gene, he was also able to show that adding more of the Fragile X protein than is normal in a fruit fly's brain also debilitated its mental capacity. He also identified the pathways

that interfered with the function of the protein, and he determined where in the flies' brains the protein functioned. Perhaps most significantly, he enhanced memory performance in Fragile X flies by pharmaceutically decreasing protein synthesis. Fragile X flies that were fed drugs that reduced the production of protein in the brain remembered to avoid the smell associated with a shock almost as much as the normal flies.

The next step, he said, is to translate the findings into the creation of drugs to treat the condition in human patients.

"Right now there is no medical treatment—absolutely nothing that we can use routinely in the clinic—so we have a long way to go. We're probably about 10 years away, but I think we're on the right track," said Bolduc, an assistant professor in the Department of Pediatrics.

Bolduc also believes the new knowledge of the FMR1 gene will likely apply to a number of other syndromes involving reduced cognitive function.

Source: University of Alberta