The brain knows what the nose smells, but how? Researchers trace the answer

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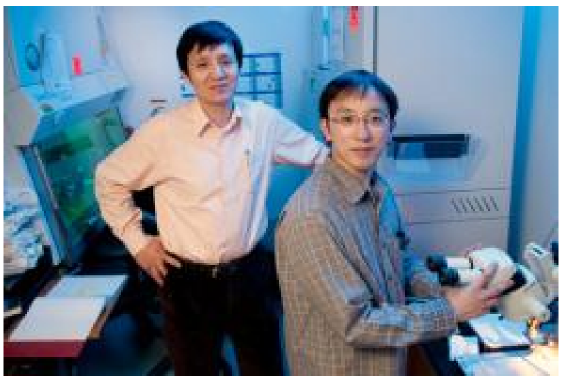

Professor Liqun Luo, left, in his lab with post doctoral fellow Kazunari Miyamichi who is the lead author on the paper to be published in 'Nature' magazine.

(PhysOrg.com) -- Professor of Biology Liqun Luo has developed a new technique to trace neural pathways across the brain. He has mapped the path of odor signals as they travel to the higher centers of a mouse brain, illuminating the ways mammalian brains process smells.

Mice know fear. And they know to fear the scent of a predator. But how do their brains quickly figure out with a sniff that a cat is nearby?

It's a complex process that starts with the scent being picked up by specific receptors in their noses. But until now it wasn't clear exactly how these scent signals proceeded from nose to noggin for neural processing.

In a study to be published in *Nature*, Stanford researchers describe a new technique that makes it possible to map long-distance nerve connections in the brain. The scientists used the technique to map for the first time the path that the scent signals take from the olfactory bulb, the part of the brain that first receives signals from odor receptors in the nose, to higher centers of the mouse brain where the processing is done.

"No one could trace signals across neural connections to a specific type of neuron at a specific location before," said biology Professor Liqun Luo. This is Luo's first study of the mouse olfactory system, but his lab has spent 10 years studying olfactory pathways in the fruit fly. Because mouse brains are so much larger and more complex that those of flies, Luo and postdoctoral researcher Kazunari Miyamichi had to develop an entirely new experimental technique.

Multi-purpose tools

These techniques can be used to do more than just study how mice smell. "The tools we've developed can be applied to trace neural connections of any part of the nervous system," Luo said. The tools could be used to understand how mouse brains process information from their other senses, or how the brain controls movement. The tools could also be adapted for use in rats and other mammalian species, he said.

To trace the neural pathways, the researchers injected mouse brains with two viruses, one after the other.

The researchers first injected a low-grade virus into the higher centers of a mouse brain, where it infected nearby neurons.

This first virus left the neurons susceptible to infection by the second virus, which was injected two weeks later. The second virus – fluorescent red in color – was designed by collaborator Edward Callaway at the Salk Institute.

Genes introduced by the first virus allowed the next virus to infect its way from the higher brain to the olfactory bulb, going in the opposite direction of scent signals. By following the backward progress of the second virus, the scientists could identify the neurons in the olfactory bulb where the virus ended up, thanks to the red fluorescence.

The scientists then sliced each mouse brain into about 60 thin sections, and took photos of all of them through a microscope. They used a sophisticated algorithm to combine the images from 35 mice into a 3-D model of the olfactory bulb designed by graduate students Fernando Amat and Farshid Moussavi in Professor Mark Horowitz's electric engineering group. This allowed them to look for patterns between where the virus started in the higher brain centers and where in the olfactory bulb it finished its journey.

Trigger for innate fear

They found that most of the nerve pathways heading to the higher processing centers that direct the mice's innate like or dislike of certain odors, and trigger a response to them, originated from one region – the top part of the olfactory bulb. This could explain how the mouse brain directs the animal's innate fear response to cat or fox urine.

This is in contrast to the neurons heading to the brain areas which process learned responses to odor. The neurons associated with learned responses are scattered all over the olfactory bulb, and their relative lack of organization could reflect their flexibility in allowing the mice to learn to avoid or be attracted to new smells.

The group also found that each neuron in the brain's higher centers receives signals from at least four neurons in the olfactory bulb, each of which receives input from a large number of like odor receptors. This progressive funneling and processing helps explain how the brain integrates the information from many different odors, Luo said.

In addition, he said, "There might be similar organizational principles in flies and mice, despite the evolutionary distance between them."

Luo said he will use the techniques in this study to take a more detailed look at other parts of the mouse olfactory bulb and brain, with the eventual goal of understanding how the brain processes specific odors. He said he was also working to improve the technique to track neurons across longer distances, allowing him to look in more detail at other pathways in the mouse nervous system.

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