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Sensory wiring for smells varies among individuals

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If, as Shakespeare's Juliet declared, a rose by any other name smells as sweet – to you and to me and to anyone else who sniffs it – then one might assume that our odor-sensing nerve cells are all wired in the same way. Alas, they are not, according to a new study from scientists at The Scripps Research Institute.

The researchers developed a new virus-based technique for highlighting individual nerve pathways, then applied it to the olfactory systems of mice. They found that mouse olfactory neurons send signals to two key processing regions of the brain in ways that differ significantly from one mouse to another – a diversity that is likely to be found in humans, too.

"This shows that we still have a lot to learn about olfactory perception and how the brain is wired in general," said Kristin Baldwin, an assistant professor at Scripps Research and senior author of the study, published online on March 30, 2011, by the journal *Nature*.

The Expected Pattern

For the initial stages of odor perception, the wiring pattern in mammals is already well known. Each primary olfactory neuron has root-like input fibers, embedded in the nasal lining, which express odor-specific receptors. When these receptors detect the appropriate "odorant" chemical, their host neuron becomes activated and sends a signal via its output fiber to an initial processing center, the olfactory bulb. There, the

signal terminates in a spherical bundle of fibers known as a glomerulus.

"These odor-specific glomeruli are ordered in a very consistent, stereotyped way in the olfactory bulb so that the spatial pattern of activity that an odor elicits is nearly identical among individuals," said Sulagna Ghosh, a graduate student in Baldwin's lab and the study's first author. "Just by observing which sets of glomeruli are activated in a given mouse, we can predict which smell the animal is perceiving."

But when these olfactory signals go from glomeruli to higher processing centers in the olfactory cortex, does this stereotyped pattern continue? That's the question Ghosh, Baldwin, and their colleagues set out to answer. "We see stereotyped maps in the cortex for other senses such as vision and touch," said Ghosh. "The same regularity is seen in the olfactory systems of flies, but in mammals, the wiring diagram of the olfactory brain has remained poorly understood."

A New Tracing Technique

Signals from activated glomeruli are relayed to higher processing regions of the olfactory cortex via so-called mitral and tufted (MT) neurons. Until now, researchers haven't had precise-enough tools to trace the connections in mammals from an individual glomerulus to its dedicated MT neurons and on to their terminals in the olfactory cortex.

However, Ghosh and her colleagues were able to develop a technique by which they could deliver a highly efficient fluorescent-tracer-expressing virus to individual glomeruli. "Using this, we could tag with different fluorescent colors the separate MT neurons serving a single glomerulus, and then trace their output fibers, called axons, into the cortex," said Ghosh.

Surprising Diversity

Ghosh's technique enabled her to trace the branching axons of any MT neuron to two cortical processing centers, the anterior olfactory nucleus pars externa (AON pE) and the piriform cortex. In both regions, the locations where the MT axons terminated no longer showed the clear pattern seen in the olfactory bulb.

"They turned out to be much more diverse and widely distributed than we expected," said Ghosh.

To help Ghosh and her colleagues compare these patterns from one mouse to another, a collaborating neuroinformatics expert, graduate student Stephen Larson of the University of California, San Diego, set up a software-based 3D anatomical "reference brain." The Scripps Research team then mapped their nerve tracings from individual mouse studies onto this reference.

"We found that MT projections from the same glomerulus in different mice were no more alike in where they landed than were projections from different glomeruli," said Ghosh. In other words, the wiring from the olfactory bulb to these two higher-processing regions is unique in each mouse – and because mice are at least a rough model for other mammals, it seems likely this same olfactory wiring is also unique for each human.

This is puzzling for two reasons: First, it leaves unclear how, during fetal development, axons from adjacent and seemingly identical MT neurons find their way to such different destinations in the olfactory cortex. Second, it begs the question of how mammals can experience the same odor in the same way, if each individual's olfactory cortex has such unique wiring.

Ghosh suggests that the regularity of olfactory experiences – which we infer from our similar descriptions of odors – may arise from a third set of MT neuron projections, into the amygdala, a brain region best known for its role in processing emotion. "The amygdala was the one region we were unable to look at because its distance is greater than our tracer could reach," she said. "It might be an area where there is a more ordered or stereotyped representation."

"What is clear is that our new virus-based nerve-tracing technique should help in resolving these issues, within the olfactory system and beyond," said Baldwin.

More information: "Sensory maps in the olfactory cortex defined by long-range viral tracing of single neurons," *Nature* (2011)

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