HHMI
HOWARD HUGHES MEDICAL INSTITUTE

RESEARCH NEWS

NOVEMBER 08, 2001

Researchers Discover Precise Olfactory Map

Each day, we use our noses to help make sense of our surroundings. We may not be as dependent on our olfactory capabilities as dogs or mice, but we are able to recognize and "assign an odor" to many thousands of chemicals in our environment.

These chemicals, called odorants, are detected in the nose by roughly 1,000 different odor receptors. Understanding how signals from those receptors are arranged in higher regions of the brain to yield diverse odor perceptions has been a longstanding goal for researchers. Now, researchers have taken a step toward that goal with a series of experiments that shows how signals from different odor receptors are arranged in the brain's olfactory cortex. The findings provide new insights into the processes that underlie odor perception.

> "We're going step by step, but we're getting closer and closer to what one might think would be the end point of actual odor perception in the brain."
> **— Linda B. Buck**

In an article published in the November 8, 2001, issue of *Nature* , Howard Hughes Medical Institute investigator Linda Buck and colleagues Zhihua Zou, Lisa Horowitz, and Jean-Pierre Montmayeur at Harvard Medical School reported genetic studies in mice that uncovered a precise sensory map in the olfactory cortex. The researchers also showed that this map is virtually identical in different individuals.

Odor molecules that enter the nose are detected by odor receptors located on the surface of olfactory neurons. There are about five million olfactory neurons, which are located in the olfactory epithelium on the wall of the nasal cavity. Each of these neurons extends a long process, called an axon, to the olfactory bulb of the brain. Once in the olfactory bulb, the axon enters a spherical structure, called a glomerulus, where it makes contact with neurons in the bulb.

The bulb neurons, in turn, extend axons to make contact with neurons located in the olfactory cortex. When odor receptors on an olfactory neuron detect an odorant, the neuron is activated. This sets off a chain reaction whereby signals are transmitted from the neuron in the nose to connected neurons in the bulb and then to neurons in the olfactory cortex.

Buck and her colleagues previously found that each olfactory neuron in the nose has only one of the 1,000 different types of odor receptor. They also found that one odorant can be detected by several different receptors. They then showed that different combinations of receptors detect different odorants. It appears that each odorant has a unique combinatorial "receptor code," Buck said.

In the nose, the 5,000 or so neurons with the same receptor are scattered in one of four spatial zones. In the olfactory bulb, however, the axons of neurons with the same receptor converge in a few invariant glomeruli, creating a map of odor receptor inputs that is nearly identical in different individuals.

But what happens to odor signals at higher levels of the nervous system to generate different odor perceptions and emotional responses? "It had been shown that if you place a tracer in one region of the olfactory cortex, it would back-label neurons in many parts of the bulb, " Buck said. "These findings made it clear that there was no point-to-point connection between the bulb and cortex. So, some suggested there may be little or no organization of inputs to the olfactory cortex. The most extreme view was that the inputs were random and the brain was able to take that random information and sort out different smells."

To find out how signals derived from different odor receptors are represented in the olfactory cortex, Buck and her colleagues engineered mice to express a tracer, called barley lectin (BL), along with just one type of odor receptor at a time. The BL tracer crosses gaps between connected neurons, called synapses, and labels chains of connected neurons. The scientists genetically inserted the BL tracer into the odor receptor gene *M5* or *M50* — choosing those two receptor genes because they are expressed in different zones of the olfactory epithelium. For the sake of comparison, the researchers also engineered mice to express the tracer gene in all olfactory sensory neurons.

When the researchers used the tracer to follow the wiring of the *M5BL* or the *M50BL* mice, they found that the neuronal connections extended through the olfactory bulb and showed up in the olfactory cortex as discrete clusters in different regions. In contrast, the mice in which all olfactory neurons were engineered with BL showed labeling throughout the olfactory cortex. A particular surprise, however, came when the researchers compared different mice with the same odor receptors labeled.

"We were amazed to find that the labeling was for the most part the same from mouse to mouse," said Buck. "Also, the labeling was bilaterally symmetrical in the two sides of the brain." Such a "stereotyped sensory map" in the olfactory cortex has important implications for understanding how the brain processes odors, said Buck.

"The fact that this information is highly organized in the olfactory cortex, and is the same in different individuals, implies something about the perception of odors among different individuals," said Buck. "It provides a potential explanation as to why the odor of, say, a skunk smells bad to all people, and roses smell sweet."

The tracer studies also provided information about the neural processing of odors. "It appears that information from different receptors is being combined in the cortex, while that’s not true in the nose or the olfactory bulb," she said. "There, the information from different receptors is segregated in different neural structures. So, we may be seeing the beginning of processing of the combinatorial receptor code that we know exists for each odorant."

The olfactory cortex is actually composed of several distinct brain structures, each of which may have a different function. The researchers found that information from both the M5 and M50 receptors is targeted to several of these structures, rather than to just one of them. This indicates that inputs from the same receptors are being processed in parallel in different cortical areas–a scheme that may allow the same receptor inputs to be combined or modified in several different ways to achieve different effects.

Intriguingly, the researchers could not detect any inputs from the M5 or M50 receptors into the brain’s amygdala — the structure involved in processing information associated with intense emotion. Odor receptors for fear-inducing smells, such as those of a predator, should wire into the amygdala, said Buck. This finding hints that the amygdala might receive information from only a subset of odor receptors–-"receptors that detect odorants that are important to the animal—in terms of emotions or instinctive responses."

Buck and her colleagues are developing more powerful tracers to extend their mapping beyond the olfactory cortex and into higher cortical areas. "We’d like to know what happens next," she said. "We’re going step by step, but we’re getting closer and closer to what one might think would be the end point of actual odor perception in the brain."