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Researchers Closer to Learning the Underlying Logic of the Olfactory System

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Researchers from the Howard Hughes Medical Institute have succeeded in mapping the unique patterns of neural activity produced by a wide range of odors, including vanilla, skunk, fish, urine, musk, and chocolate. Revealing these distinct - but often overlapping - patterns of neural activity represents a significant step in understanding how the brain translates complex signals from odorant receptors in the nose into odor perception in the brain, the researchers said.

The research team, which was led by HHMI investigator Linda B. Buck at the Fred Hutchinson Cancer Research Center, published its findings May 23, 2005, in the early online edition of the *Proceedings of the National Academy of Sciences* . Buck's co-authors included postdoctoral fellows Zhihua Zou and Fusheng Li. Buck shared the 2004 Nobel Prize in Physiology or Medicine with HHMI investigator Richard Axel of Columbia University for their discovery of the huge family of odorant receptors and their previous work on the organization of the olfactory system.

> "Just like letters of the alphabet are used in different combinations to form different words, the odorant receptors are used in different combinations to detect different odorants and encode their unique identities."
> **— Linda B. Buck**

Whenever you inhale the aroma of vanilla, the neurons in your brain “light up” with a characteristic pattern of activity. It turns out that pattern is, perhaps unsurprisingly, unique from the pattern of brain activity associated with a whiff of skunk spray.

The process of smelling an odor begins with odorant receptors that are located on the surface of nerve cells inside the nose. When an odorant receptor detects an odor molecule, it triggers a nerve signal that travels to a way station in the brain called the olfactory bulb. Signals from the olfactory bulb, in turn, travel to the brain's olfactory cortex. Information from the olfactory cortex is then sent to many regions of the brain, ultimately leading to the perceptions of odors and their emotional and physiological effects.

Although there are about a thousand different types of odorant receptors in mice, Buck and her colleagues discovered in previous studies that each individual olfactory neuron in the nose only bears a single type of odorant receptor. Independent studies in the Buck and Axel laboratories further showed that signals from neurons with the same type of odorant receptor converge at two specific spots in the olfactory bulb, such that individual structures in the olfactory bulb, called glomeruli, each receive neuronal input from only one type of odorant receptor.

Earlier studies of the olfactory cortex by Buck's group indicated that in contrast to the straightforward mapping of inputs from odorant receptors onto the glomeruli, however, the mapping of odorant receptor inputs onto the olfactory cortex was quite complex.

“We had found that inputs from one type of odorant receptor are targeted to several loose clusters of neurons at specific locations in the cortex, " said Buck. In sharp contrast to the olfactory bulb, where signals from different receptors are segregated, inputs from different odorant receptors overlap extensively in the cortex. Moreover, individual cortical neurons are likely to get inputs from many different odorant receptors.”

Buck's group previously showed that each odorant is recognized by a combination of receptors, and that each receptor can recognize multiple odorants. “So, the odorant receptor family is being used combinatorially,” she said. “Just like letters of the alphabet are used in different combinations to form different words, the odorant receptors are used in different combinations to detect different odorants and encode their unique identities.”

In the new studies, Buck and her colleagues sought further information about how the brain translates these combinatorial receptor codes into distinctive odor perceptions. Because of the complex patterns of receptor inputs in the cortex, it was impossible to predict how odors might be represented in this structure. They therefore decided to investigate the patterns of activity that were triggered by a range of odorants in the olfactory cortex of mice.

“We wanted to find out whether inputs from receptors that recognized the same odorant are all targeted to the same places in the cortex, producing a distinctive spatial map for the odorant,” she said. “Or, whether the inputs from these receptors are sent to different locations in the cortex, resulting in a more distributed representation of the odorant.”

To explore this question, the researchers exposed mice to each of a wide range of odorants—including apple, skunk, floral, fishy, urine, vanilla, musk, woody, garlic, and chocolate. After each mouse was exposed to an odor, the scientists then proceeded to isolate the animal's olfactory cortex and map neural activity by measuring the activity of a marker gene called *c-Fos* in individual neurons across this entire structure.

“We found that a single odorant does not just stimulate one or two spots in the cortex,” said Buck. “Instead it stimulates a very small subset of neurons that are sparsely distributed over a relatively large area. We found that different odorants stimulate different patterns, but the patterns for different odorants partially overlap.”

Importantly, said Buck, the research team found that, despite this very complex patterning, the odor representations are very similar among individuals. “This may explain why odors elicit similar responses in different individuals. For example, most people don't like the smell of skunk odor, but they do like the smell of chocolate,” she said.

The researchers also found that the spatial representations of the odors in the cortex expanded with increased concentrations of the odorants. Buck said this phenomenon could explain why odors can smell different at different concentrations.

She said it was particularly intriguing that odorants with related chemical structures showed highly similar patterns of activation in the cortex. “This finding gives a hint that there is some logic to the way that information is being mapped onto the cortex,” said Buck. “We don't know what that logic is, but it seems as if it has something to do with the molecular features of the odorant.”

The researchers also found, however, that only a small fraction of neurons from the olfactory cortex that receive input from a single type of receptor were activated by concentrations of odorants normally found in the environment. “One intriguing possible explanation for this discrepancy is that the cortical neurons might be acting as `coincidence detectors,'” said Buck. “They might respond only when they get input from more than one type of odorant receptor. And this is fascinating because each odorant is recognized by a combination of odorant receptors."

Buck explained that any odorant is first "deconstructed" by the olfactory system by a combination of receptors. And the signals from those receptors are transmitted separately all the way through the olfactory bulb to the olfactory cortex. "So, if these neurons are really coincidence detectors, what we might be seeing is at least an initial step in the reconstruction of an `odor image' from its deconstructed features," she said.