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RESEARCH NEWS

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Olfaction: When One Plus One Equals Three

Howard Hughes Medical Institute researchers say they are beginning to unravel how the olfactory system perceives an odor that is much richer than the sum of the individual chemicals that compose the odor.

In studies published in the March 10, 2006, issue of the journal *Science*, the researchers have succeeded in capturing the first evidence that the brain creates an `odor image' by combining information about different features of an odorant chemical.

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> **— Linda B. Buck**

The olfactory processing we detected parallels processing in the visual system, noted the study's senior author, Linda Buck, an HHMI investigator at the Fred Hutchinson Cancer Research Center. In the visual system, sensory stimuli are first deconstructed into features, she said. Then they are reconstructed in the brain to form images. In the same way, we think that odorants are being deconstructed by the receptors that recognize different features of the odorant chemical; and what we may be seeing in the cortex is an initial step in the reconstruction of the odor image from its deconstructed features.

Understanding how the brain translates odorant chemicals into odor perceptions has been one of the main goals of Buck and postdoctoral fellow Zhihua Zou. Using a technique that allowed them to compare the responses of about 200,000 brain neurons to different odorants, Zou and Buck compared responses of individual neurons to single odorants versus odorant mixtures. Their studies identified many neurons in the olfactory cortex that responded to combinations of odorants, but not to the individual odorants themselves.

Humans have a limited capacity to detect individual odorants in an odorant mix, said Buck. For example, when two odorants are mixed, individual components may be detected, but they may lose a described quality, such as strawberry. On the other hand, mixing two odorants can create a novel perception. For instance, in certain proportions, a mixture of eugenol (clove) and phenylethyl alcohol (rose) is perceived as carnation, an altogether different scent.

Odorants that enter the nose are detected by odor receptors located on olfactory sensory neurons lining the nasal cavity. The sensory neurons transmit signals to the olfactory bulb of the brain, which then relays the signals to a higher brain area, the olfactory cortex. In earlier studies, Buck and her colleagues discovered 1,000 different odor receptors. They also showed that, much like letters of the alphabet can be used to generate a multitude of different words, the odor receptors are used in different combinations to detect different odorants.

In both the nose and olfactory bulb, each neuron appears to be dedicated to only one type of odor receptor. However, in the olfactory cortex, Buck and her colleagues found something very different. While each neuron in the nose and olfactory bulb receives signals from only one type of odor receptor, each cortical neuron appeared to receive signals from multiple receptors. This was exciting because it suggested that single cortical neurons might combine inputs from different receptors that recognize the same odorant, the odorant's 'receptor code,' said Buck. This could be a first step in the reconstruction of an odor image from its deconstructed features that were denoted by different odor receptors.

Zou and Buck hypothesized that one way this could occur would be if the activation of a cortical neuron actually requires simultaneous signals from different receptors. We reasoned that, if this were the case, a combination of two odorants would stimulate neurons beyond those stimulated by either odorant alone because merging the receptor codes of the two odorants would create new combinations of receptor inputs, said Buck.

To test this idea, Zou and Buck compared neurons in the olfactory cortex that were activated when mice were exposed to odorant mixtures versus single odorants in the mixtures. They exposed mice to individual or paired odorants that smell like clove and chocolate, citrus and fish, or vanilla and apple.

Indeed, when the researchers exposed the animals first to each odorant separately, and then immediately afterward to a mix of the two odorants, they found many neurons that were activated by the subsequent mix, but not by the initial individual odorants.

It was really a beautiful result, and what's more, it was very similar for all three odorant pairs, said Buck. The findings show that the olfactory cortex has a synthetic capacity. While this is consistent with cortical neurons acting as coincidence detectors that require combinatorial receptor inputs, we can't exclude the possibility that the synthetic quality we are seeing is due to secondary inputs from other cortical neurons that respond to the two different odorants. But in either case, the studies indicate that the cortex definitely has a synthetic or integrative capacity that is lacking in the olfactory bulb, she said.

Buck said that future studies will aim at distinguishing these two possibilities. She and her colleagues also plan to continue tracing odor processing to higher brain centers, seeking to detect the logic of how complex odors are perceived there.