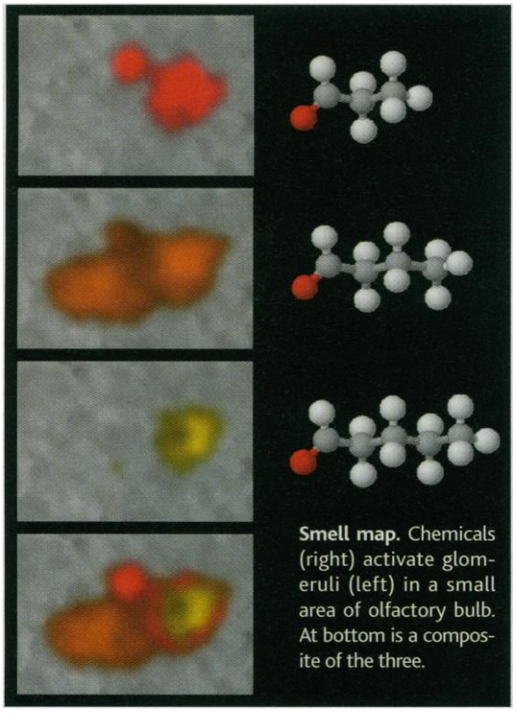
NEUROBIOLOGY

## Mapping Smells In the Brain

A whiff of perfume or the smell of wood smoke may dredge up complex memories, but every smell starts as a simple code. Now, a team at Duke University Medical Center in Durham, North Carolina, has developed a powerful new tool for reading the brain's smell code.

Each sensory system has a code for the information it receives. For example, hearing uses a frequency code, while the olfactory system encodes odors by chemical composition. There are over 1000 different olfactory receptor proteins found on neurons in the nose, each of which recognizes a particular chemical feature of some odor molecules. The neurons send their signals to the brain's olfactory bulb, where each of thousands of little clusters of neurons called glomeruli receives input from olfactory neurons with just one receptor type. That means each smell should activate a unique pattern of glomeruli—the "code" for that smell.



**Smell map.** Chemicals (right) activate glomeruli (left) in a small area of olfactory bulb. At bottom is a composite of the three.

Researchers want to know how the brain uses that code to process olfactory information further, and now Duke neuroscientist Lawrence Katz and graduate student Benjamin Rubin have developed an essential tool for doing so. In the July issue of *Neuron* they report that they have used an optical imaging technique to see the patterns of glomeruli that respond to particular odors in rat brains—the first time that's been done in living mammals.

"This is really a breakthrough," says Randolf Menzel of the Free University of Berlin, who studies olfaction in honeybees. He and others note that because the olfactory system is so well characterized molecularly and structurally, the technique should offer neurobiologists a rare opportunity to examine and manipulate the ways the brain processes specific sensory information.

Katz and Rubin decided to try a technique on the olfactory bulb that had been used for years on the visual system. Developed by Amiram Grinvald of the Weizmann Institute of Science in Rehovot, Israel, the method, called intrinsic signal imaging, involves shining light on a patch of brain surface of a living animal. An analysis of the light bouncing back can reveal changes in blood oxygenation (via changes in light absorption by hemoglobin) or changes in the light-scattering properties of neural membranes, both of which reflect changes in neural activity.

Rubin tried the technique on rats, removing or thinning the part of the skull lying over their olfactory bulbs, then measuring the pattern of optical signals in the bulbs when the anesthetized animals were exposed to different odors. The technique worked beautifully, says Katz, with a resolution "10-fold better than in the visual system," enabling Rubin to clearly visualize individual glomeruli. Each odor produced a unique pattern of active glomeruli.

The optical imaging is a vast improvement over earlier methods, which entailed exposing a rat to an odor for 45 minutes (an unnaturally long time), then killing it and looking for changes in the uptake by the olfactory bulb of a labeled form of glucose, which also indicates neuronal activity. That approach can test only one odorant per animal, and, Menzel adds, "one never knows whether the neuronal ... code might not change" under such long stimulation. Katz and Rubin, he says, "used stimulation which is rather natural" in concentration and timing.

That advantage, coupled with the high resolution and the flexibility of being able to expose a single animal to many odors at different concentrations and under various conditions, is what has researchers so excited. What's more, the imaging can be used to guide other techniques. For example, once researchers identify the glomeruli that respond to a particular odorant in a living animal, Katz says, it is "not that difficult" to use electrodes to examine how the glomeruli interact, enabling researchers to check the hypothesis that active glomeruli turn up the contrast in their signal by inhibiting the responses of their neighbors.

Olfaction is also "perfect for looking at learning and memory," Katz says, "because one thing rodents learn very well is odors." He and others are eager to ask how the glomerular code for an odor may change if the rat learns to associate a smell with, say, food, something Menzel has already shown to be the case in honeybees. The possibilities don't stop there.

Katz's team now has the technique working in mice, and because the mouse odorant receptors have been cloned, researchers can use genetic engineering to generate receptor molecules tagged with a fluorescent protein, enabling them to associate specific glomeruli with specific receptors, or even genetically change the receptors or their neurons to see how that affects olfactory processing. What's more, optical imaging can likely be done on higher olfactory processing areas in the cerebral cortex, where smells may interact with other perceptions or memories, to ask how the patterns from the olfactory bulb are translated and transformed in those areas.

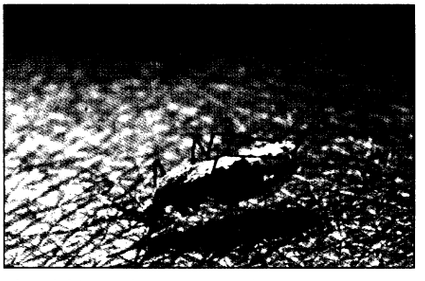
Indeed, says Grinvald, the possibilities opened by Rubin and Katz's result are already drawing new participants into the field of olfaction. "I know of two very good groups that jumped on this project as soon as they heard that the imaging is working so well," he says. Others are bound to follow.

—MARCIA BARINAGA

INFECTIOUS DISEASES

## Gene Sequencers Target Malaria Mosquito

A group of insect geneticists, genome researchers, and funding officials has put together a plan to open a new front in the war against malaria: the sequencing of the genome of *Anopheles gambiae*, the mosquito primarily responsible for spreading the disease in Africa. "*Anopheles* would be the first insect disease vector to be sequenced," says Carlos Morel, director of the United Nations' Special Program for Research and Training in Tropical Diseases, which hosted a meeting earlier this month in Geneva to discuss strategy. The participants will submit proposals to major biomedical agencies in Europe and the



**Bloodthirsty bug.** *Anopheles gambiae* is the leading malaria vector in Africa.

CREDITS: (TOP) LAWRENCE KATZ AND BENJAMIN RUBIN; (BOTTOM) OSF/ANIMALS ANIMALS