Making sense of smell

Four CSHL investigators find in olfaction a window on major brain questions

In an effort to understand neural circuits underlying complex behaviors in people, multiple neuroscience labs at CSHL are probing basic cognitive processes in model organisms, including the mouse and fruit fly. It is research that is providing a foundation for the development of next-generation diagnostics and therapies for neurological and psychiatric illnesses. We focus here on four CSHL investigators who study olfaction separately, but in common pursuit of knowledge about how perception is linked to behavior.

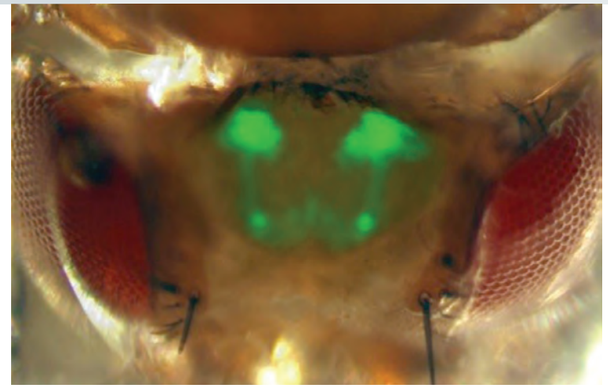
Koulakov: Dimensions of the problem

"Olfaction is the last frontier of our senses, the one that is still almost completely mysterious to us," Alexei Koulakov tells a visitor to his lab, filled with purring computers and diagram-covered whiteboards. An associate professor, he is working on a theory of olfaction, to address a key question: How does the brain of a mammal transform raw sensory inputs into knowledge about the world that can drive behavior?

Koulakov notes we have considerable difficulty describing and defining smells. While we can imagine an infinite range of colors within the band of wavelengths to which receptors in our eyes are sensitive, no olfactory analog is apparent. There is, for instance, no olfactory analog of "red" or "bluish-green." Although we know that humans have 350 different types of olfactory receptors, and we know a great deal about the composition and structure of the molecules that waft about in the air, "we don't really know anything about the internal space, the sensory space, that our olfactory system creates in the brain."

Humans do seem able to classify certain things that are salient, such as "skunk" or "strawberry." But the question is whether these are disconnected perceptions, if they coexist in a single perceptual space, Koulakov says. "This is the big question: is the sense of smell a patchwork, or is there a unifying principle?"

Four on olfaction: (l to r) Glenn Turner, Alexei Koulakov, Stephen Shea, Florin Albeanu



Position of mushroom body (green) in fly's head, in a composite image.

It boils down to a problem of dimensionality. If olfaction is what Koulakov calls a patchwork, it would be necessary to plot human olfaction in 350 separate dimensions—each the product of a separate evolutionary process involving each of the 350 receptor types. Olfaction in mice, creatures that deeply depend on their sense of smell, would occupy a 1200-dimensional space, reflecting their vast number of receptor types. Such a space is something "we have no way of comprehending," says Koulakov.

He hypothesizes, however, that there is an organizing principle behind olfaction. "My research is trying to determine if olfaction is a synthetic sense," he says, "meaning rather than hundreds or thousands of dimensions to understand at once, there might be 10 or 20, each of which would be represented by the activity of some combination of receptors."

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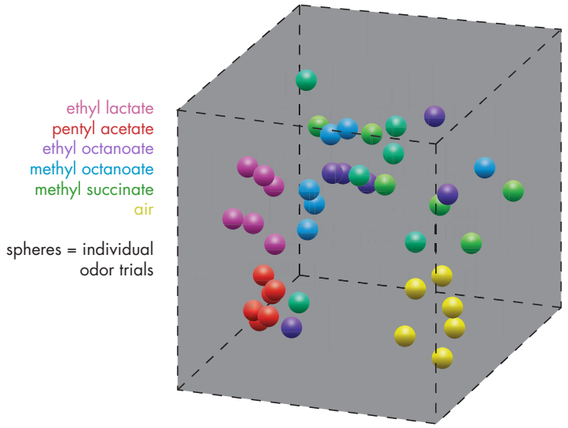
Three of Koulakov's CSHL colleagues are conducting experiments to determine how chemical odorants are represented by neurons, in the olfactory bulb of the mouse and the mushroom body of the fruit fly. This work will show how chemical space maps onto neural space. The next step, says Koulakov, "is to see how the output signal from these neurons propagates to the cortex, where it is processed into percepts" — units of perception, like "citrus" or "gasoline."

Turner: Thresholds between odors

Glenn Turner, an assistant professor, has been looking closely at how odors detected by sensory receptors in the antennae of fruit flies are represented by neurons in a portion of the fly brain called the mushroom body, or MB [see above]. One attraction of the fruit fly is its size. In its MB, there are only 2500 small neurons, called Kenyon cells. "The fact that we can get a fairly complete view of a whole brain area at the cellular level is something you just can't get in a mammal," Turner says. Prior research shows that neurons in the antennae respond broadly to many odors, and yet, the Kenyon cells that receive this raw signal are much more odor-selective, each firing in response to a much narrower range of odors.

Neuroscientists call this sparse representation, and it is a hallmark of the capacity to learn. If neurons respond in a very specific way to specific odors, then memories can be formed and recalled. But how? "When we expose a fly to the same odor over and over, we do not get exactly the same response in the mushroom body," says Turner. "Despite that variability, the animal still knows that it was the smell of an orange. It also knows that different oranges are the same fruit, even though their odors may vary a bit. And, it knows how to tell an orange from a tangerine and a tangerine from a grapefruit or lemon."

Some of Turner's recent work addresses this "threshold" problem of distinguishing one odor from another. The fly has 50 olfactory receptor types, "and while different receptors have different odor 'preferences,' there should be some overlap," he says. In the illustration [next page], five color-coded chemical odorants are listed at the left of the 3-dimensional grey cube, which is a mathematical construct of the olfactory space of a fly, as measured by the firing rates of 60 MB neurons in multiple trials in which the five odors were presented. This representation reduces a 60-dimensional problem by translating the data into three dimensions that we can readily grasp.



Note that dots of certain colors congregate in compact groups, while others don't. Groups that are spatially distinct suggest that the corresponding odorants form distinct representations in the fly's brain.

What amazes Turner is the fact that flies, like people, "seem able to make specific associations with pretty much any odor that comes along." It's a function of having receptors of overlapping sensitivity that sample broadly, yet neural processors that enable discrimination even of very similar odors.

Albeanu: Using light to dissect a circuit

Florin Albeanu, an assistant professor, is studying olfactory circuitry in the mouse brain. Not only does the mouse have 1200 olfactory receptor types; its brain subjects signals coming in from these receptors to a more involved series of processing steps, compared with the fly. Albeanu focuses on the mouse olfactory bulb (OB). Its circuit includes input (from receptors in the nose) and output (to various cognitive areas of the cortex), but it also responds to feedback *from* the cortex as well as slower, neuromodulatory signals from other regions.

Unlike Turner, Albeanu cannot see and take measurements from the totality of the structure he works with; only about 15% of the OB is experimentally accessible in living animals for imaging experiments. Yet this is enough for Albeanu to pursue his aim of "understanding the general principles that transform inputs into outputs in the OB."

As shown in the illustration [next page], inputs into the bulb's glomeruli from odor receptors in the nose are sent on to mitral cells, although only certain ones. Mitral cells are themselves part of a circuit modulated by interneurons. This schema sets up the problem Albeanu and colleagues most recently solved: What do signals from mitral cells connected to the same glomeruli look like, and how does lateral communication, across the layer of mitral cells, modify the output that mitral cells, in turn, send to the cortex?

Albeanu built tools to measure electrical signals in these circuits and to image them. The cells are stimulated by shining beams of colored light into the OB input layer in mice whose glomeruli have been genetically engineered to be capable of photoactivation. By switching the cells "on" and tracing their output, the team can isolate individual mitral cells connected to the same glomeruli, which they call sister cells. Last October they reported on how sister cells vary in their output. "Although synchronized by default, they become offset in their firing with respect to one another as we present odors to the mouse," says Albeanu, "probably because they are modulated by signals coming in from other glomeruli, connected to different receptor-types in the nose."

An interim conclusion: "There are many more information output channels *leaving* the olfactory bulb than the number of information types *entering* it." The work thus revealed a previously unobserved complexity in sensory coding, which Albeanu speculates may help the cortex rapidly make highly accurate odor distinctions.

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As they begin now to collect data on how mitral cells communicate with the cortex, the team will study how the cortex sends feedback to mitral cells and modulatory interneurons in the OB. They will do these studies "in real time, as the animal is learning something about the environment." For in the end, it's not a problem of simply tracing circuits, but of understanding "how the circuit suddenly, almost instantly, makes sense of a stimulus that it encounters."

Shea: Olfaction and emotional salience

This question of salience is central in the work of Stephen Shea, an assistant professor interested in the olfactory system as a window on social decision-making. Is this sensory system biologically optimized to process data on the basis of its emotional salience? This is pertinent to questions about how the human brain fails to process social and emotional cues in illnesses such as autism and schizophrenia.

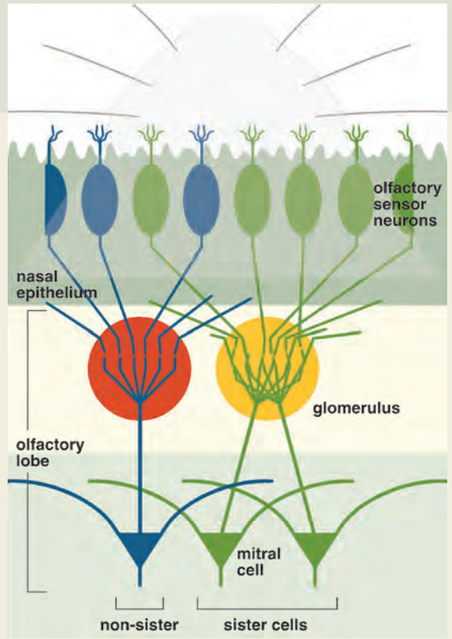
"In order to understand how social cues are perceived and decisions made in the mouse, we need to speak the mouse's language," Shea explains. This language provides mice with ways of detecting, discriminating and remembering one another. Odors, and to a lesser extent vocalizations, enable a mouse to learn, for example, about whether another mouse is friend or foe or wants to mate.

Neurochemicals such as oxytocin and noradrenaline are involved in modulating social decision making in mammals. Produced in the locus coeruleus, in the brainstem, noradrenaline is carried via axonal projections to the mouse's OB. "A mouse is mating, or giving birth or meeting a new mouse—situations in which oxytocin and noradrenaline are released in large quantities. We're studying how that release interacts with information that's arriving at that same time through the olfactory system." It has been postulated that the animal stores or imprints this nexus of signals, biochemically, as the basis of forming an emotionally salient memory.

Shea's team has completed a remarkable set of experiments in which anesthetized mice, exposed to a virtual-reality version of a social encounter, could be shown to "remember" this simulated encounter after waking up. The simulated encounter consisted of introducing the scent of another mouse into the nose of the sleeping mouse. "We were able to effectively create a memory, under conditions in which we could study neural manifestations of the process."

Shea's lab is now perfecting means of recording from awake animals, which will enable them to show this olfactory-centered memory-formation process occurring in the context of natural behavior. Preliminary clues are intriguing: mice have been shown to respond to individuals they remember via olfactory memory by showing less interest, which correlates with reduced mitral cell firing rates. An encounter with a new prospective mating partner produces the opposite result. "We hypothesize the sensory information is sent downstream to deeper brain structures, where some interpretation or behavioral decision is made," Shea says.

The picture of olfaction that emerges in these four CSHL labs—from the uptake of raw sensory data, to the recognition of patterns, to the formation of percepts, to the imprinting of their salience at particular moments in time—inspires a sense of awe over what even simple brains can do. It also makes a vivid case for the value of research on model organisms, work that has placed us on a path toward understanding the brain dysfunctions underlying some of the most perplexing and devastating human illnesses. **Peter Tarr**



The mystery addresed by researchers is how signals from sensors in the nose are recognized and processed by successive brain layers to form perceptions that a mouse can act upon.