

## How fruit flies sniff out their environments

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Credit: Hong lab

Fruit flies—Drosophila melanogaster—have a complicated relationship with carbon dioxide. In some contexts, CO<sub>2</sub> indicates the presence of tasty food sources as sugar-fermenting yeast in fruit produces the molecule as a by-product. But in other cases, CO<sub>2</sub> can be a warning to stay away, signaling an oxygen-poor or overcrowded environment with too many other flies. How do flies tell the difference?

Now, a new study reveals that fruit fly olfactory neurons—those



responsible for sensing chemical "smells" such as CO<sub>2</sub>—have the ability to talk to each other through a previously undiscovered pathway. The work provides insights into the fundamental processes by which <u>brain</u> cells communicate with one another and also gives new clues to solving the longstanding mysteries about <u>fruit flies</u> and CO<sub>2</sub>.

The research was conducted in the laboratory of Elizabeth Hong (BS '02), assistant professor of neuroscience and Chen Scholar of the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech. A paper describing the study appears in the journal *Current Biology* on September 6.

"CO<sub>2</sub> is an important but complex signal found in all sorts of different situations in the natural environment, and it illustrates a core challenge neurobiologists face in understanding the brain: How does the brain process the same sensory signal in different contexts to allow the animal to respond appropriately?" says Hong. "We tackle this question using the fly olfactory system, one of the best-studied and well-characterized sensory circuits. And even still, with this research, we discovered a surprising new phenomenon in how the brain processes sensory signals."

Olfaction, or the sense of smell, was the original sensory system to evolve in all animals. Though humans are primarily visual, the majority of animals use olfaction as the main method of understanding their environments: sniffing out food, avoiding predators, and finding mates. Fruit flies are a particularly manageable model for understanding the biological mechanisms underlying the <u>sense of smell</u>: a fruit fly only has about 50 different odorant receptors, whereas a human has around 400 to 500, and mice have more than a thousand.

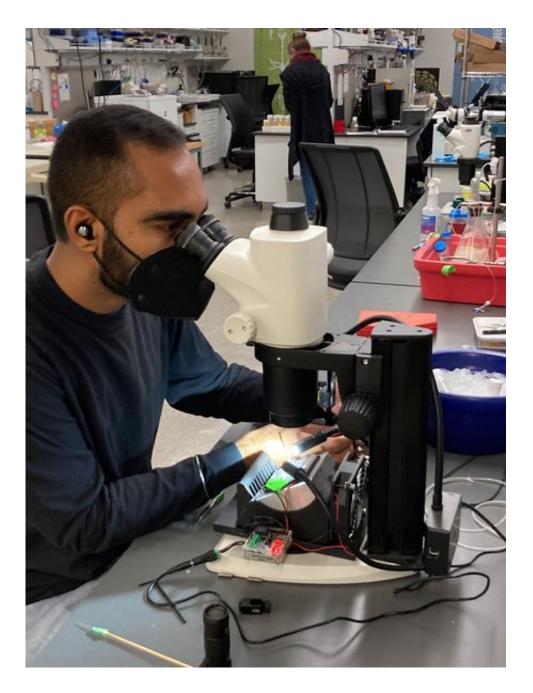
A fly's "nose" is its two antennae. These antennae are coated with thin hairs called sensilla, and inside of each sensillum are the olfactory neurons. Odors—like CO<sub>2</sub> or the volatile esters produced by rotting



fruit—diffuse into tiny pores on the sensilla and bind onto corresponding receptors on the olfactory neurons. Neurons then send signals down the sensillum and into the brain. Though we don't have antennae, an analogous process happens in your own nose when you lean in to catch a whiff of delicious cooking or recoil from bad smells.

In fruit flies, while most odors activate around 20 different types of sensory neurons at once, CO<sub>2</sub> is unusual in that it only activates a single type. Using a combination of genetic analysis and functional imaging, researchers in the Hong laboratory discovered that the output cables, or axons, of the CO<sub>2</sub>-sensitive olfactory neurons actually can talk to other olfactory neural channels—specifically, the neurons that detect esters, molecules that smell particularly delicious to a fruit fly.





Neurobiology graduate student Pratyush Kandimalla works to tether a fly for experiments. Credit: Hong lab

However, this olfactory crosstalk depends on the timing of CO<sub>2</sub> cues. When CO<sub>2</sub> is detected in fluctuating pulses, such as a wind-borne cue from a distant food source, the CO<sub>2</sub>-sensing olfactory channel sends a



message to the channels encoding esters, signaling to the brain that delicious food is upwind. However, if CO<sub>2</sub> is continually elevated in the local environment, for instance from a rotting log, this crosstalk is quickly shutoff, and the CO<sub>2</sub>-sensitive neurons signal directly to the brain to avoid the source.

This is the first time that olfactory neurons have been shown to talk to one another between their axons, processing incoming information before these signals ever reach the brain. The results cut against the prevailing dogma in neuroscience that information processing is limited to the integration of inputs by neurons; the new findings show that signals are reformatted at the output end as well.

The scientists also discovered that how flies behave toward  $CO_2$  also depends on the timing of  $CO_2$  signals. "We found that the behavior of the animal is affected by the temporal structure of the  $CO_2$  signal," says Hong. "When the fly walks into a cloud of elevated  $CO_2$ , it tends to turn away from the direction it was traveling. But in an environment where  $CO_2$  is pulsing, the fly will run upwind toward the source of the odor. This difference in how flies behave toward fluctuating  $CO_2$ , versus sustained  $CO_2$ , parallels the dependence of the crosstalk from the  $CO_2$ -sensing neurons to attraction-promoting food-sensing neurons."

Understanding fruit fly olfaction, particularly with respect to sensing CO<sub>2</sub>, is a long-standing goal for Caltech researchers. Decades ago, researchers in the laboratory of David Anderson— Seymour Benzer Professor of Biology; Tianqiao and Chrissy Chen Institute for Neuroscience Leadership Chair; Investigator, Howard Hughes Medical Institute; director, Tianqiao and Chrissy Chen Institute for Neuroscience—discovered that flies avoid CO<sub>2</sub> as a chemical indicating an overcrowded environment. But recently, researchers in the lab of Michael Dickinson—Esther M. and Abe M. Zarem Professor of Bioengineering and Aeronautics and executive officer for Biology and



Biological Engineering—discovered that flies can also be attracted to  $CO_2$ , when using it to sniff out a source of food.

"Our work builds on these prior studies and provides one possible neural solution for how CO<sub>2</sub> could be triggering opposing behaviors in flies in varying contexts. It has been a highlight of having my lab at Caltech to have the opportunity to directly interact with David's and Michael's labs and discuss the connections between our work and theirs," says Hong.

The next major question is to understand how these parallel olfactory axons are talking to one another. The team ruled out most forms of classical chemical transmission that neurons use to communicate, and the mechanisms by which <u>olfactory neurons</u> are able to send and receive messages between their axons are mysterious. Solving this problem may provide new insights into how animal brains detect and process sensory information.

**More information:** Dhruv Zocchi et al, Parallel encoding of CO2 in attractive and aversive glomeruli by selective lateral signaling between olfactory afferents, *Current Biology* (2022). <u>DOI:</u> 10.1016/j.cub.2022.08.025

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