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PRESS RELEASE (2024/12/26)

Scientists uncover insights into neuron function by simultaneously measuring two key signals in living animals

By simultaneously measuring membrane voltage and calcium levels in neurons, scientists reveal that these two signals encode different sensory information.

Fukuoka, Japan – Researchers from Kyushu University have developed an innovative technique to non-invasively measure two key signals, membrane voltage and intracellular calcium levels, at the same time, in neurons of awake animals. This new method offers a more complete understanding of how neurons function, revealing that these two signals encode different information for sensory stimuli. The research was published in *Communications Biology* on September 16, 2024.

Neurons are cells that act as the brain's fundamental building blocks, transmitting information through electrical signals. When a neuron receives a stimulus, changes in membrane voltage (the electrical charge across the neuron cell membrane) trigger the neuron to activate, causing rapid changes in membrane voltage to propagate along the neuron as an electrical signal. These changes in membrane voltage then lead to changes in intracellular calcium (calcium levels inside neurons).

Historically, measuring membrane voltage has involved invasive techniques using electrodes. As a non-invasive alternative, scientists have developed techniques to measure calcium activity using fluorescent proteins that are sensitive to calcium ions as sensors, providing an indirect proxy for neuron activity. However, these different methods mean that the two signals have almost always been studied separately, making it challenging to understand how they interact in real-time and to identify their distinct functions in living animals. Now, new advancements in the development of fluorescent proteins that respond to changes in membrane voltage mean that both calcium ion sensors and membrane voltage sensors can be used simultaneously.

"Simultaneous measurement of intracellular calcium ions and membrane voltage can help us to understand how neurons encode information for sensory processing in neuronal circuits," says senior author Professor Takeshi Ishihara from Kyushu University's Faculty of Science.

In collaboration with the Faculty of Computer Science and Systems Engineering at Kyushu Institute of Technology, Ishihara and his colleagues developed a method to simultaneously measure intracellular calcium and membrane voltage in neurons of living animals. By capturing images under the microscope at a high speed of 250 frames per second and using cutting-edge image processing, the researchers were able to detect small and rapid fluctuations in the fluorescent intensity of the calcium ion sensors and membrane voltage sensors.

Using this newly developed technique, the scientists focused on how olfactory neurons in *Caenorhabditis elegans*—tiny nematodes commonly used as a model organism in neuroscience research—respond to odorants.

The researchers found that when exposed to odors, these neurons altered their membrane

voltage and intracellular calcium levels. Importantly, the research team revealed for the first time that these signals encode separate information. While the membrane voltage indicated the presence of an odor, intracellular calcium levels reflected the odor's concentration. By simultaneously measuring both signals, the researchers were able to better understand how the brain processes and distinguishes sensory inputs.

Additionally, the authors identified two ion channels that are essential for the change of membrane voltages triggered by sensory stimulation. The team also found that a protein called ODR-3, which is involved in signal transmission in neurons, plays an important role in stabilizing membrane voltage. This prevents neurons from improperly firing in response to irrelevant stimuli, and regulates the timing and magnitude of responses to odors.

In the future, simultaneous measurements of membrane voltage and intracellular calcium could also be obtained in the neurons of more complex animals, or in other types of neurons, potentially revealing insights about information coding in neuron circuits.

Sharing his concluding thoughts, Ishihara says, "These high-speed simultaneous measurements reveal the different functions of the membrane voltage and intracellular calcium ion signals induced by the sensory stimuli. These findings could lead to a better understanding of sensory processing in the central nervous system, not only in simple model systems like nematodes, but in higher organisms too."

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For more information about this research, see "Mechanism of sensory perception unveiled by simultaneous measurement of membrane voltage and intracellular calcium," Terumasa Tokunaga, Noriko Sato, Mary Arai, Takumi Nakamura, and Takeshi Ishihara, *Communications Biology*, DOI: https://doi.org/10.1038/s42003-024-06778-2

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia. Through its VISION 2030, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

About Kyushu Institute of Technology

Kyushu Institute of Technology (Kyutech) is a Japanese national university that was originally founded in 1907 and opened in 1909 as a private institution called the Meiji College of Technology. Throughout more than 115 years of its history, Kyutech has been contributing to industrial development in Japan through research and education in engineering fields. Currently, Kyutech aims to foster inter-disciplinary and innovative research with its 12 research centers in various research fields such as space, environment, energy, AI, IoT, data science, LSI, robotics, and biology. Kyutech also promotes international research collaborations with overseas universities for establishing an international industry-academic alliance which brings

Kyutech a diverse research environment to its laboratories. For the future, Kyutech will continue contributing to local and global society through its technology, knowledge, and education.

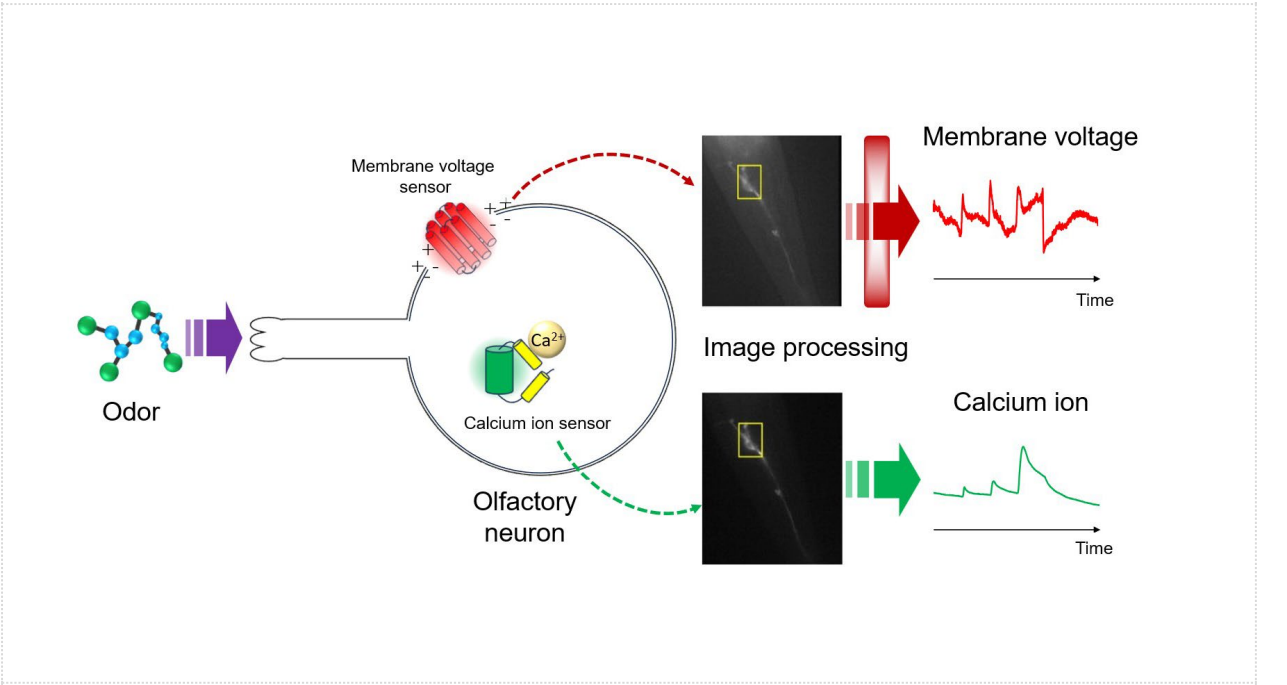

Fig. 1. When triggered by an odor, rapid changes in membrane voltage and intracellular calcium ion levels occur in nematode olfactory neurons, causing membrane voltage sensors and calcium ion sensors to fluctuate in fluorescent intensity. Using high-speed capture under a microscope, followed by image processing, the researchers simultaneously measured these changes, showing that the two signals encode different information about the stimuli. (Modified from Tokunaga et al., (2024) Commun Biol < https://doi.org/10.1038/s42003-024-06778-2>)

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