The 83rd JSAP Autumn Meeting 2022 Highlighted Presentations

October 24, 2022

Head-mounted CMOS imaging device for blood flow and fluorescent measurement

Contributing to the development of brain science and drug discovery by developing an ultra-compact CMOS imaging device that can simultaneously measure cerebral blood flow and neural activity

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summary

- **By placing a 0.5-g ultra-compact imaging device on the surface of the mouse brain, researchers succeeded in measuring blood flow and neuronal activity almost simultaneously under free-running conditions without damaging the brain, which had been a difficult feat to achieve.**

- **Using a device that can observe the brain surface while alternately illuminating green and blue LED light sources, they measured changes in the amount of hemoglobin in the blood, including changes in the calcium fluorescence (*1) content of mice genetically engineered to express GCaMP.**

- **The simultaneous measurement of blood flow and neural activity will be beneficial in the research on the pathogenic mechanism of diseases such as cerebral infarction and migraine, including brain functions via behavior, leading to the development of advanced technologies such as drug discovery and brain-machine interfaces.**

Makito Haruta et al. developed an ultra-compact CMOS imaging device at the Nara Institute of Science and Technology (NAIST), to observe detailed brain activity in freely behaving mice. This technology is a lens-less imaging method that enables the simultaneous measurement of blood flow and fluorescence, to elucidate the relationship between blood flow and neural activity in the brain. By utilizing this device, it is now possible to study mouse and brain activities from an unprecedented angle. This device is expected to be used to elucidate the mechanisms of diseases related to cerebral blood flow and neural activity, such as cerebral infarction and migraine, for drug discovery and to elucidate brain functions via the detailed measurement of brain activity under free-running conditions.

detail

Novel device for measuring the active brain in real time

When the brain is active, the blood flow in the active region increases. Therefore, cerebral blood flow is an important indicator of brain activity and condition. Blood flow is also closely related to brain pathology. When blood flow is reduced owing to the narrowing of blood vessels, brain function is impaired. Several diseases are related to cerebral blood flow, such as cerebral infarction and migraine headaches.

PET and fMRI are conventionally adopted to measure brain activity in humans. For studies with animals, in addition to methods based on the same principles as those used for humans, there are also methods that adopt fluorescence microscopy; nevertheless, it is crucial to perform measurements under anesthesia or with the head immobilized by training or other means. Regardless, the animal must be immobilized under anesthesia or training, and the animal's head must be immobilized. Under such conditions, the experimental animal is subjected to unnecessary stress, and the brain activity to be observed cannot be considered pure.

To address this problem, the research group developed an ultra-compact imaging device that combines a CMOS image sensor and LED, and by implanting it in the head of a mouse, established a technology that enables the long-term observation of brain activity without placing a burden on the mouse.

Specifically, using green light, which is strongly absorbed by hemoglobin (*2), as a light source, blood vessels on the surface of the brain can be observed with a CMOS image sensor. In addition to enabling the clear observation of minute blood vessels, this technology also enables the measurement of blood flow and blood flow velocity.
A blue LED adopted as a fluorescence excitation light source and a light absorption filter (long-pass filter) on the image sensor were utilized to detect changes in the fluorescence intensity of GCaMP, which is a fluorescent calcium probe used to observe neural activity. Elements other than the blood flow can be observed simultaneously by alternately turning these two light sources. At (the Japan Society of Applied Physics Autumn Meeting), Dr. Haruta presented the results of a study on the relationship between blood flow and direct neuronal activity together with calcium fluorescence imaging in mice genetically engineered to express GCaMP.

According to Haruta, "this device is equipped with LEDs for blood flow observation and fluorescence excitation. The device is equipped with LEDs for blood-flow observation and fluorescence excitation. Because blood flow measures endogenous signals, it can be measured without staining. In addition, we attempt to simultaneously measure blood flow and neural activity by combining the measurement with genetically engineered mice with fluorescent probes, which has already been established.”

The range of applications can be expanded by altering the combination of light mounted on the device and the genes expressed in the mice. For example, it is possible to combine optogenetics, which induces or inhibits neural activity via optical stimulation, with the observation of blood flow or measurement of neural activity.

Simultaneous Measurement of Blood Flow and Nerve Activity Opens the Possibility of Drug Discovery

This device, which is based on the fusion of different fields of neuroscience and semiconductor engineering, adopts the semiconductor packaging technology, biomedical implantation technology used in the biomedical field, and fluorescence microscopy and fluorescence imaging technology, using genetically engineered mice that have been cultivated in the neuroscience field. By altering the size of the device, it is possible to adjust the area of the brain that can be measured, and observe the interaction of multiple areas.

According to Haruta, "our greatest advantage is that we can design the image sensor itself and fabricate a device that fits the research."

Recently, significant progress has been made in brain research owing to technological developments. Haruta et al. 's novel imaging device is a groundbreaking technology that could inspire brain scientists to experiment, connect, and advance several previously unproven findings.

The results of this study will be utilized in the development of novel therapies and drug discovery. It can also be adopted to examine the pharmacokinetics and effects of drugs during development. In particular, the ability to measure blood flow velocity can provide valuable data for the development of more effective drugs.

According to Haruta, "this technology will allow us to get closer to the mechanisms of diseases involving cerebral blood flow and neurological activity. We are currently conducting joint research on cerebral infarction and migraines. In addition, because we can comprehensively observe brain activity in mice under free-running conditions, we believe that studying the relationship between behavior, blood flow, and neuronal activity could benefit technologies such as brain-machine interfaces.

annotations

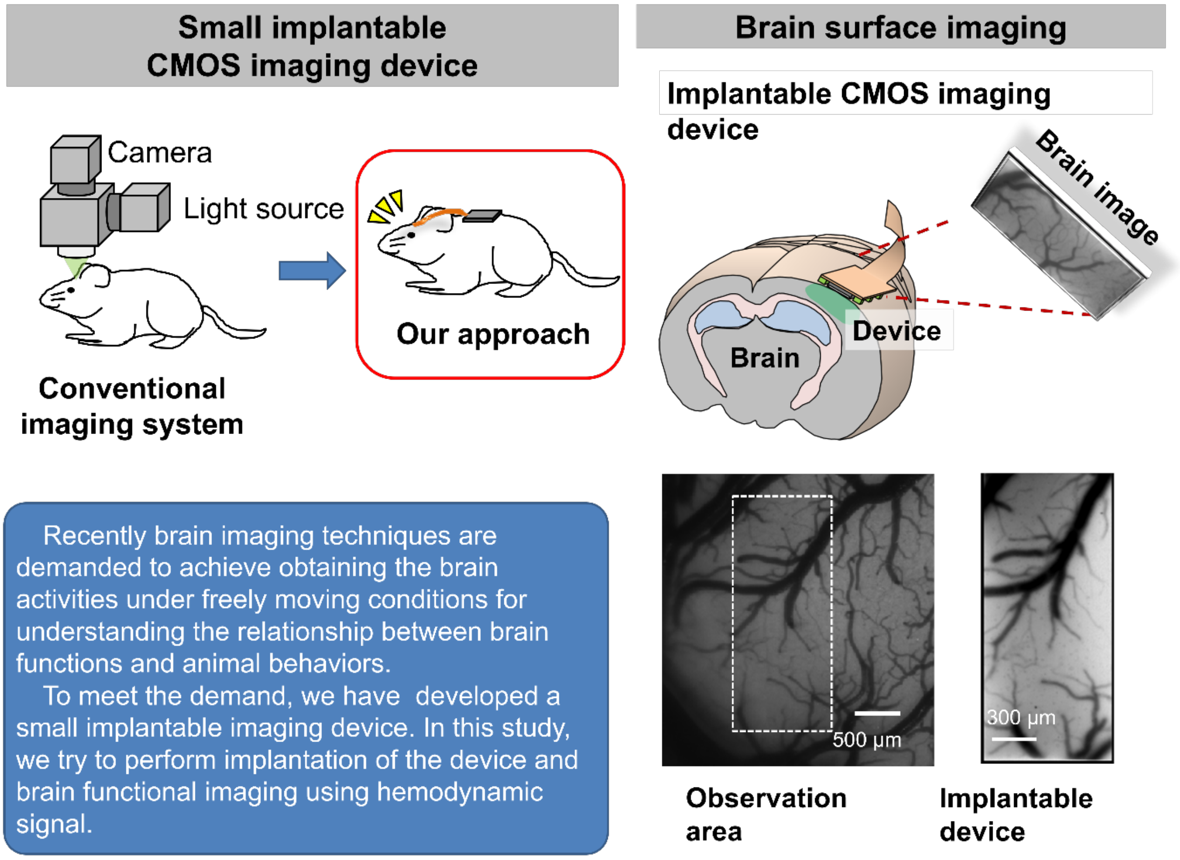
*** 1 Calcium fluorescence imaging of mice expressing GCaMP**

GCAMP binds to calcium and emits fluorescence. When neurons are active, calcium flows into the cells. Therefore, by expressing GCAMP in mouse neurons via genetic recombination, it is possible to directly observe neuronal activity by measuring the fluorescence emitted by GCaMP.

***2 Absorption spectrum of hemoglobin**

Red blood cells are associated with hemoglobin. Because hemoglobin absorbs light of a specific wavelength, the amount of hemoglobin can be determined, and blood flow can be estimated by shining light on it and measuring the amount of light absorbed by the hemoglobin.

Figures



Conventional imaging systems that utilize lenses require the mouse to be immobilized; however, this technology can measure brain activity in free-moving mice (top left). The device was fixed on the dura mater without skull removal, thereby allowing imaging without damaging the brain (upper right panel). Even minute blood vessels can be comprehensively observed (bottom right panel).