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Development of a CMOS image sensor for *in situ* brain functional imaging in freely-moving mouse

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1. Introduction

In recent years, imaging technologies as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are being rapidly developed and becoming powerful tools for brain science. Although these measurement technologies have an advantage of non-invasiveness, temporal and spatial resolutions are limited and it is difficult to image deep regions inside a brain as hippocampus in a small animal. We have been developing CMOS imaging devices which are capable of real time *in vivo* fluorescent imaging in a brain with small invasion. In our previous works, we have successfully demonstrated functional imaging of a hippocampus in mouse's brain under anesthesia [1]-[3]. In this work, we develop a CMOS image sensor for brain functional imaging in freely-moving mouse.

2. Preliminary experimental trials of brain functional imaging in freely-moving mouse

CMOS Image Sensor Chip

We have already succeeded in fluorescent imaging in mouse's hippocampus under anesthetized conditions [3]. The sensor chip is shown in Fig. 1, and the specifications of the sensor are summarized in Table I. We implemented via holes on the sensor chip for illumination with LEDs mounted on the backside of the sensor chip. We also implemented on-chip stimulation/measurement electrodes on the sensor chip. The positions of the electrodes were designed to stimulate and observe the mouse's hippocampus effectively. The pixel array has a curved outline that is effective to minimize damage to the brain tissue. The sensor chip was mounted on a polyimide flexible substrate and sealed with epoxy resin [1]. We have performed preliminary freely-moving experiment with this image sensor.

Preliminary experimental trials in freely-moving mouse

We inserted the image sensor device shown in Fig. 1 into CA1 region of the mouse's hippocampus (Fig. 2). After the insertion, we fixed the sensor device in the skull with dental cement (Fig. 3). An experimental setup is shown in Fig. 4. The mouse was placed in a 20×30cm cage equipped with a wiring harness through a slip-ling connector, as shown in Fig. 5. For luminescent imaging, we injected substrate MCA which is transformed to fluorescent substrate AMC by serine protease [2] in the brain. Figure 6 shows intensity signals observed with the implanted CMOS image sensor. It was confirmed that our CMOS imaging device kept its function in freely-moving situations. However, the result also shows the pixel values are affected by mouse's action, as shown in Fig. 6. We consider the action of the freely-moving mouse makes the connection between the sensor and the wiring harness worse and the contact face between CMOS image sensor and brain organization instable. We also verified the damage in the brain caused with the inserted sensor device was acceptable, as shown in Fig. 7. All the experiments were carried out following the Institutional Guidelines of Nara Institute of Science and Technology.

3. Development of CMOS image sensor for brain functional imaging of freely-moving experiment

To realize less invasive and more effective brain functional imaging in a freely-moving mouse, we designed a new CMOS image sensor that is suitable for imaging of the mouse's hippocampus. We used 0.35μm 2-poly 4-metal standard CMOS process. The sensor has a 120×266 pixel array of 3-transistor active pixel sensor. The layout is shown in Fig. 8, and the specifications of the sensor are summarized in Table II. The thin and long outline was adopted to achieve an observation in deeper region with a less invasion to the mouse's brain. The packaging of the sensor is being developed and the functional demonstration will be reported at the conference.

4. Conclusion

We have developed a CMOS image sensor for *in situ* brain functional imaging in a freely-moving mouse. Based on preliminary experimental trials, we designed a new image sensor with thin and long outline. The development of the sensor packaging and functional characterization are now underway and will be reported at the conference.

Acknowledgements

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References

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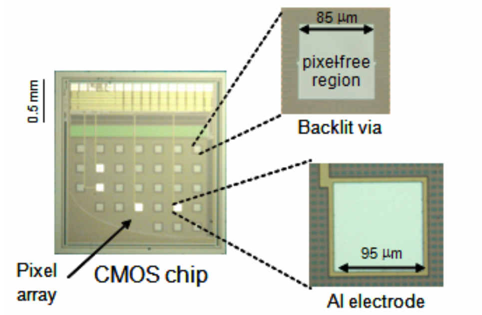
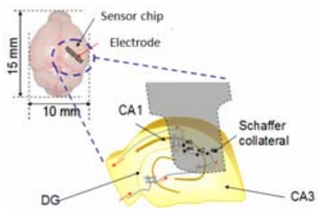


Fig.1. CMOS sensor chip for *in vivo* brain imaging

Table I Specifications of the CMOS sensor chip (Fig. 1).

Technology		0.35 µm std. CMOS 4M2P
Operating voltage		3.3 V
Chip size		2 mm x 2.2 mm
Image pixel	type	3-transistor APS
	number	224 x 164 (non-rectangular)
	size	7.5 x 7.5 μm^2
Photodiode	type	Nwell-Psub
	size	19.75 μm^2
Backlit via	size	85 x 85 μm^2
	number	26
Electrode	size	90 x 90 μm^2
	number	4
Image sensor output		Serial analog voltage



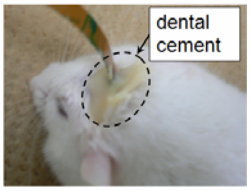


Fig.2. Implant configuration Fig.3. Fixing with dental cement

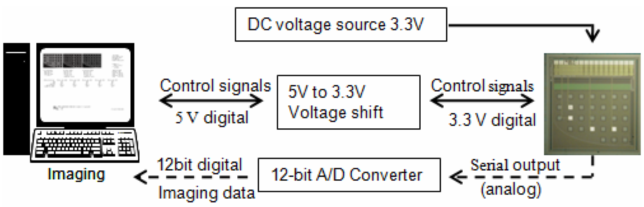


Fig.4. Experimental setup for *in vivo* brain imaging

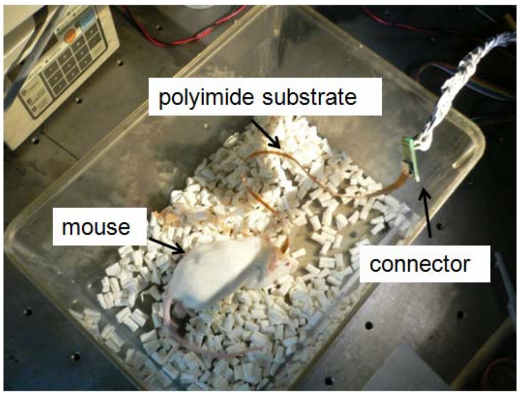


Fig.5. Cage for freely-moving experimental trials

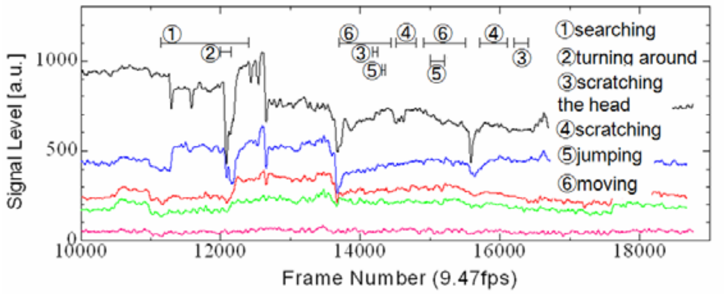


Fig.6. The relationship between the action of the mouse and the pixel values

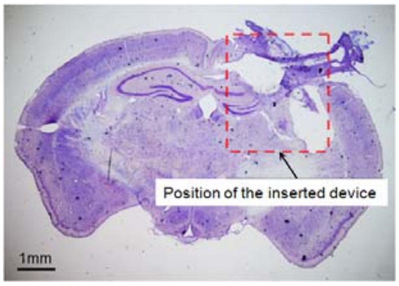


Fig.7. The brain slice after the insertion

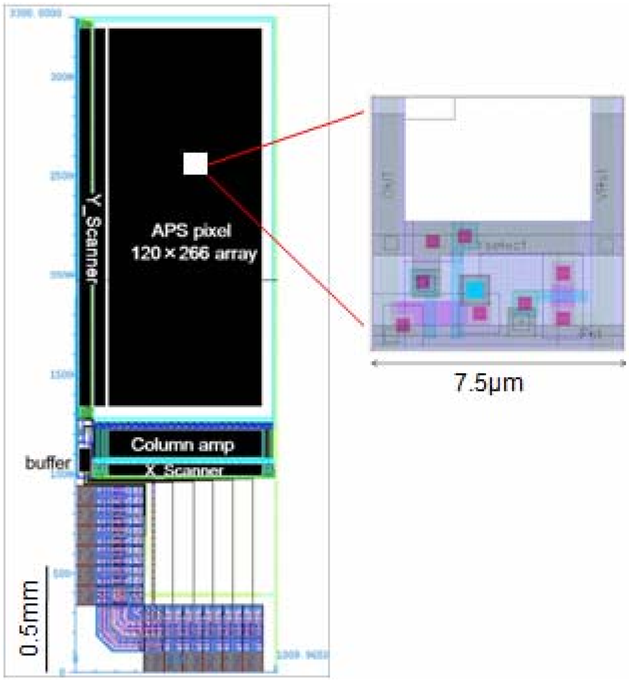


Fig.8. Layout of CMOS image sensor for freely-moving mouse

Table II Specification of CMOS image sensor for freely-moving experiment

Technology		0.35 µm std. CMOS 4M2P
Operating voltage		3.3 V
Chip size		1mm × 3mm
Image pixel	type	3-transistor APS
	number	120 × 266
	size	7.5 x 7.5 μm^2
Photodiode	type	Nwell-Psub
	size	19.75 μm^2
Image sensor output		Serial analog voltage