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A multi-modal implantable CMOS imaging device with two-color light source for intrinsic signal detection in a brain

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Abstract

Long-term measurement of continuous brain-activity change is important to understand brain functions which control animal behaviors. In this study, we developed an implantable CMOS imaging device with two-color light sources for measuring intrinsic signal of a rat brain. One light source is a green LED with wavelength of 535 nm for observing a brain surface, while the other light source is a red LED with wavelength of 630 nm for measuring intrinsic signals. The device switches rapidly between green light and red light. The new implantable imaging device demonstrated intrinsic signal imaging under implantable state.

1. Introduction

In order to measure brain functions under animal behavior, a small implantable imaging device and a long-term measurement system are needed. In recent researches, some methods using a miniaturized microscope [1] or an optical fiber scope [2] have been developed for behavior experiment of a small animal such as a rat and mouse. These devices observed new findings of brain activities under animal behaviors. They could not, however, be fully implanted into the animal head and could not measure brain activities in long-term. These devices induced stress to the animals in the behavior experiment. In order to alleviate these problems, we developed an ultra-small implantable CMOS imaging device in our previous work [3]. For this device, we designed a dedicated image sensor in 0.35-μm CMOS technology [4]. Our proposed device is so small that it can be fully implanted by introducing contact imaging, which needs no bulky optics such as an objective lens. The weight of this device is only 0.02 g. The value is 1/1,000 of an adult rat or 1/10,000 of an adult mouse. We have successfully measured blood flow rate in a rat brain by using the device under freely-moving condition [3].

In this study, we demonstrate multi-modal sensing of imaging an intrinsic signal which is arisen by redox reactions of hemoglobin in the blood. This technique is suitable for long-term measurement because it does not require the brain staining with dyes. For intrinsic signal imaging under implantable state, we mount two-color LED light sources on the small implantable CMOS imaging device. One is a green light source for observing brain surface, and another is a red light source for measuring intrinsic signals. Thus, it makes possible to perform a stable brain functional observation with a long-term behavior experiment.

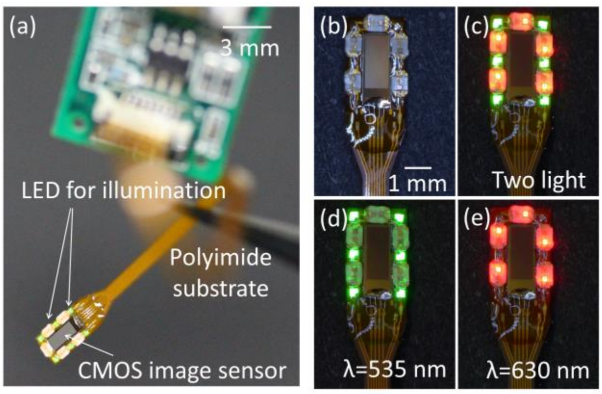

Fig. 1 Multi-modal implantable CMOS imaging device with two-color light source. (a) A photograph of the device. This device has different illumination patterns. This figure shows four patterns that are Extinction (b), Simultaneous lighting (c), Green LEDs (λ=535 nm) lighting (d) and Red LEDs (λ=630 nm) lighting (e).

2. Implantable CMOS imaging device with two-color light source

We have developed an implantable CMOS imaging device for intrinsic signal imaging of a small animal's brain (Figs. 1a). The new device has a CMOS image sensor that is mounted on a polyimide printed circuit substrate. The device specification is shown in Table I. For the biological use, the device is coated and waterproofed with a parylene film.

Table I Specification of the CMOS imaging device

Size (device head)		4.3 mm × 2.3 mm × 0.35 mm
Total length		66 mm
Substrate		Polyimide flexible substrate
Waterproof		Parylene film
Light source		Green LED (λ = 535 nm) × 6, Red LED (λ = 630 nm) × 5
CMOS image sensor	Technology	0.35-μm 2-poly 4-metal standard CMOS process
	Pixel size	7.5 μm × 7.5 μm
	Pixel count	120 × 268
	Fill factor	44%

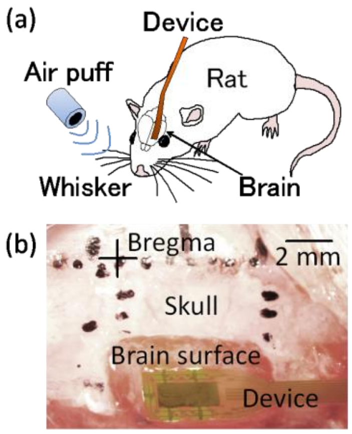

Fig.2 Intrinsic signal imaging arises from whisker sensory responses using the implantable CMOS imaging device. (a) Overview of an implantation with the device and whisker-stimulation experiments. (b) Implanted device on the brain surface.

The main feature of the device is integrating with two-color light sources (Figs. 1b-e). Green LEDs with an emission wavelength of 535 nm are located around the sensor as light sources for observing a brain surface condition. This wavelength is one of absorption spectral peaks of hemoglobin in the blood [5]. Thus, the device enables to acquire fine images of the brain. Red LEDs with an emission wavelength of 630 nm are used for measuring intrinsic signal changes in the brain. At this wavelength, intrinsic signals arise from oxyhemoglobin (HbO_2) in the brain, because hemoglobin (Hb) absorption is higher than HbO_2 absorption [5]. The change of light intensity indicates the change of HbO_2 to Hb.

3. Implant and whisker stimulation experiments

For measurement of intrinsic signal of the brain, we performed surgery to implant the CMOS imaging device into the head of the rat (Fig. 2a). First, the rat was anesthetized by urethane anesthesia and the head skin and skull of the target area were removed. Figure 2b shows a surgical image under a microscope. Next, we put the device on the brain surface by a manipulator.

After the surgery, the green LEDs were turned on. The brain surface images of the rat were clearly obtained under green-LEDs light (Fig. 3b). We show an area where the device acquired image by comparison with the microscope image in a dotted frame in Figure 3a.

Next, the green LEDs were turned off and the red LEDs were turned on for intrinsic signal imaging. Figure 3c shows an image under the illumination of the red light source. This image shows few blood vessels, because the absorption of Hb and HbO2 in red light-source is weaker than the absorption in green light-source. The image under red light illumination results in reducing noises from vital signals.

4. Detection of intrinsic signals

The intrinsic signals in the brain are correlated closely with the brain activity. We performed intrinsic signal imaging using the implantable CMOS imaging device with red light-source at 630 nm. In this experiment, we observed nerve responses which were produced by sensory stimuli with air puff (Fig. 2a). We measured the intrinsic signal of the primary somatosensory cortex. We obtained sequential images at a frame rate of 58 fps. Figure 3d shows the responses measured by the imaging device. Intrinsic signal changes arise at the bottom of the images. We demonstrate intrinsic signal imaging using the implantable CMOS imaging device with red LEDs light-source.

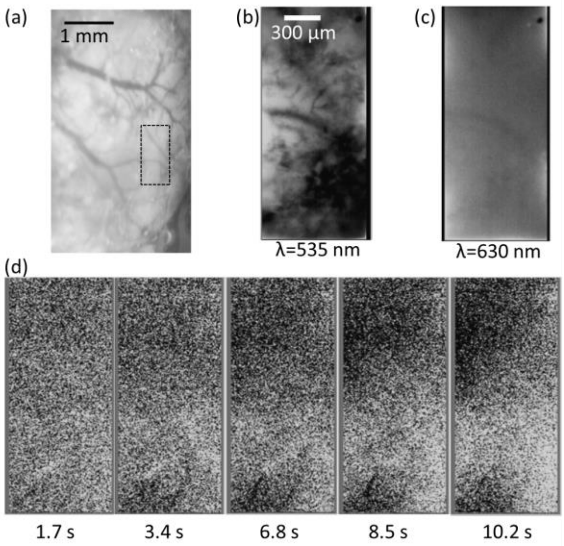

Fig.3 Intrinsic signal imaging with the implantable CMOS imaging device. (a) Gray scale image of a brain surface under a microscope. Black dot frame is an imaging area with the device. (b) Brain surface image captured by the device with green LED lights. (c) Brain surface image with red LED lights. (d) Neural responses of the intrinsic signal were evoked by whisker stimulation.

5. Conclusions

We have developed the implantable CMOS imaging device for measuring intrinsic signal from the brain activity. We successfully obtained fine images of the brain surface. Moreover, we performed intrinsic signal imaging which was measured by using our device at the primary somatosensory cortex of the rat. In the next work, we will try to observe brain functions related to behavior by comparing the intrinsic signal in the brain and the animal behaviors.

Acknowledgements

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