A low-invasive micro imaging device for measuring neural activities implanted in the mouse deep brain

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Abstract

A low-invasive micro-imaging device implantable into the mouse brain is demonstrated. The device consists of a CMOS image sensor and LEDs to excite fluorophore. To reduce damage in implantation, the LEDs are embedded into the CMOS image sensor to make the surface flat. The fundamental device characteristics and some preliminary experiments *in vivo* are shown.

Fluorescent measurement plays an important role in brain science, because it can measure specific neural activities such as short-term memory, learning in the hippocampus. Conventionally, an optical microscope is used to observe such fluorescence, but it is difficult to apply it to a freely-moving rodent such as a mouse. Recently, some head-mounted optical microscopes for a rodent have been developed [1]-[3]. They are however still heavy for a freely-moving mouse and difficult to observe neural activities in the deep brain such as the hippocampus.

To address the issue, we have been developing an imaging device that is directly implanted in the mouse deep brain. It consists of a dedicated small CMOS image sensor and LEDs to excite fluorescence on a flexible substrate. The surface of the sensor is coated with a color filter to block an excitation light as well as to pass a fluorescent light. Whole device is covered with a parylene, which is a biocompatible, water-tight, high-resistive, and transparent polymer material. We have implanted the device in the hippocampus of a mouse, and measured neural activities of the un-tethered situation [4], [5]. Although neural activities were observed just after the implantation, we found that implantation damage must be reduced for long-term observation.

In this presentation, we demonstrate a lower invasive imaging device for the implantation of the mouse deep brain. The CMOS image sensor is designed in a 0.35 μm standard CMOS technology with four input/output ports to minimize wiring, which makes an implanted mouse move easily. The specification of the chip is summarized in Table 1. The chip photo is shown in Fig. 1. For an implantable device, the thickness and width of the device and the surface flatness are essential factors to reduce invasiveness when implanted. The image area is designed so large to observe neural activities in the hippocampus of a mouse. To make the surface flat, two cavities were formed in the both sides out of the image area, and then the LED was buried in the cavity so as to flatten the device surface. Figure 2 show the comparison of the device structure. This structure enables to reduce the thickness of the device. By back-lapping the device, we reduced the thickness of the device to about 150 μm. In Fig. 3(a), the buried LEDs turn on. Figure 3(b) shows the SEM photograph of the device. A cannula is installed in the device as shown in Fig. 3(c).

We implanted the ultra-thin device into the hippocampus of the mouse brain, and succeeded to observe fluorescence in the mouse brain. The implantation place is shown in Fig. 4. The implanted mouse can move around freely as shown in Fig. 5. Figure 6 shows the experimental results captured by the implanted device in the mouse brain. A fluorophore was injected into the mouse brain with a cannula,

which is attached in the device as shown in Fig. 3(c). The results of the immuno-staining of the brain slice after the implantation show that almost neural structures remain if the device thickness is less than 200 μm. We will present experimental results of the observation of neural activities by using the device.

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Figure 1: Chip photograph

Table 1: Chip specification

Technology	0.35μm 2-poly 4-metal Standard CMOS
Operating voltage	3.3 V
Die size	452 μm × 3900 μm
Pixel size	7.5 μm × 7.5 μm
Pixel number	42×160
Pixel array area	315 μm × 1200 μm
Fill factor	43%
I/O number	4 (w/o LED inputs)

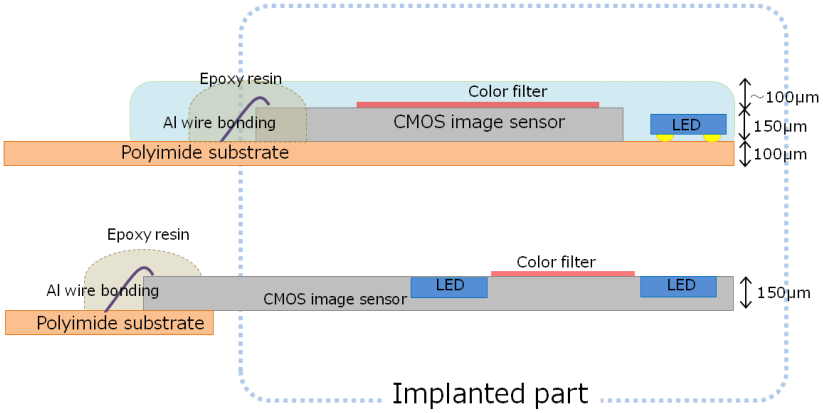

Figure 2: Comparison of device structure. Upper: previously developed implantable device. Lower: Present device. LEDs are buried in the sensor chip.

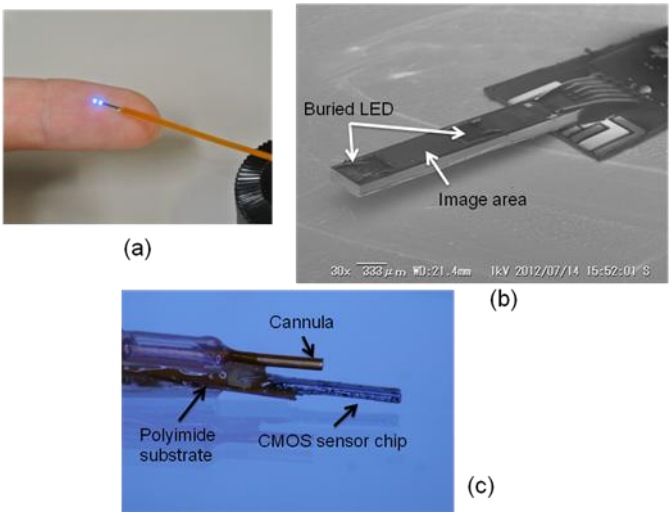

Figure 3: Assembled device. (a) LEDs turn on. (b) SEM photograph. (c) A cannula is installed.

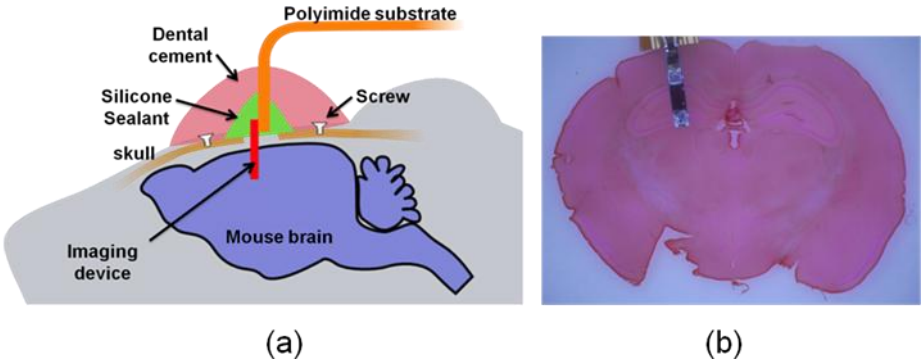

Figure 4: Implantation method (a) and place (b). (a) Schematic cross-sectional view of the implantation place. The device is fixed in the skull. (b) The implanted device is place on the hippocampus of the brain slice.

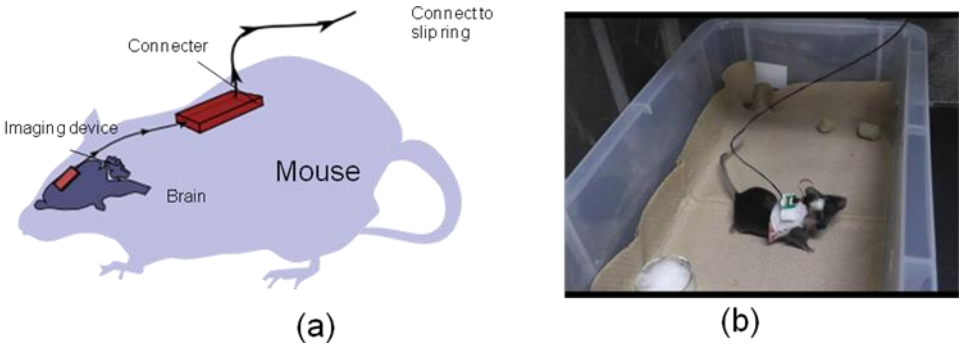

Figure 5: A mouse that the device is implanted. (a) Schematic illustration of the implantation system. (b) A freely-moving implanted mouse.

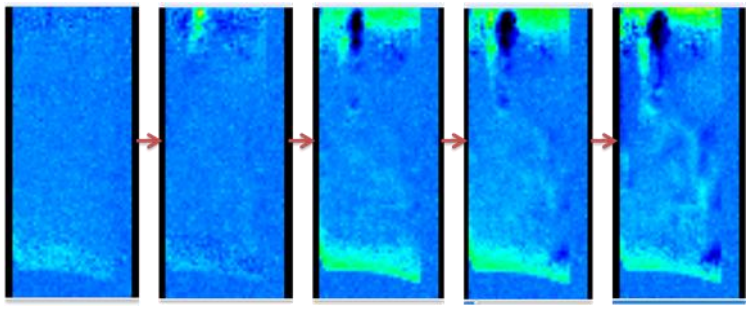

Figure 6: Captured images of the flow of fluorophore injected through the cannula. The time course of flow can be captured clearly.