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Monitoring multi-layer neuronal dynamics of epileptiform calcium signaling in the hippocampus of freely behaving mice using a brain-implantable CMOS image sensor

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***Abstract*— Recent advances in microelectronics and nanofabrication have enabled the creation of small compact imaging devices for biomedical applications. In this research, we present a brain-implantable CMOS image sensor that is tiny, energy-efficient, and bio-compatible for studying epileptiform signals in a freely behaving animal.**

***Clinical Relevance*— Epilepsy is one of the most prevalent neurological disorders in the world, with temporal lobe epilepsy (TLE) being the most common type. However, the cause of epilepsy is unknown in more than half of the cases. Therefore, new methods and technology are needed to elucidate the mechanisms behind epilepsy.**

I. INTRODUCTION

Over 50 million people worldwide are inflicted with epilepsy[1]. Despite this, the mechanism of how epilepsy occurs is unclear because of the difficulty in observing large neuronal populations across multiple layers in the brain during seizures. Therefore, we propose a new imaging device that can simultaneously image and measure neuronal calcium signaling in different layers of the hippocampus in the temporal lobe during epilepsy.

II. METHODS

The micro-imaging sensor is 450 x 1500 µm in size, containing 40 x 120 pixels and an imaging area of 7.5 µm^2 per pixel. Then, 305 × 280 µm blue µLEDs were added as a source of excitation light. To keep the device small and lensless, a thin-film absorption filter was placed on the imaging array to block the excitation light and transmit fluorescence from GCaMP6s. All components were attached and wire-bonded onto a flexible printed circuit board that connects to the peripheral electronics. The device was only 0.05 g in weight, and was small enough to allow multiple sites of implantation. Furthermore, since the device was lensless and can be implanted vertically, the field of view and orientation of the device enabled simultaneous imaging of multiple layers of different depths in the hippocampus.

III. RESULTS & DISCUSSION

Our CMOS image sensor can visualize and measure neuronal calcium fluorescence changes from transgenic GCaMP6s mice injected with kainic acid as an epilepsy model. Compared to head-mountable microscopes, our implantable device is smaller, lighter, requires fewer optical components, and can image varying depths simultaneously. Using our device, we were able to observe and characterize different calcium waveforms during epilepsy. Specifically, we found three patterns of neuronal activity that closely resembled previously published results[2].

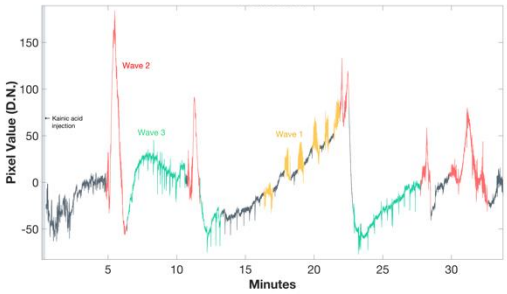

Figure 1. Epilepsy calcium imaging using our µCMOS image sensor. Different waveforms were identified: Wave 1 (yellow), Wave 2 (red), and Wave 3 (green)

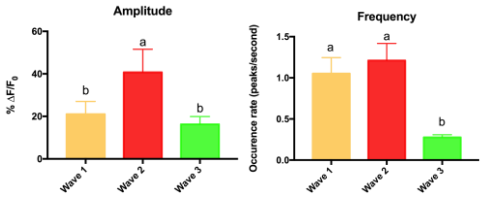

Figure 2. Waveform characterization. Amplitude and frequency values of identified waveforms are statistically different.

IV. CONCLUSION

Our device allows epilepsy researchers to correlate neuronal calcium imaging with behavior since the mouse is unrestrained. Additionally, a closed-loop optical system can also be established by adding µLEDs for optogenetic stimulation. Taken together, our newly developed device can provide insight into the neural mechanisms of epilepsy by imaging the brain during seizure in the same individual.

REFERENCES

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