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Skinless Ultrasound Micro Needle Transducer for Simultaneous Localized Brain Stimulation and Optical Measurement in-vivo

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***Abstract*—Localized small animal brain stimulations with low frequency (<1 MHz) ultrasound transducers are quite limited due to their wide beam width. Also the size of the transducers is too large to optically monitor brain activities simultaneously. Thus, a skinless micro needle ultrasonic transducer transmitting 10 MHz with the aperture size of 500 μm was developed. The housing of the transducer was replaced by pasting an epoxy on the side wall of the transducer for minimizing the field-of-view blocks of optical microscopy. Due to the miniaturized foot print, optical brain imaging with a calcium transgenic mice could be performed while localized ultrasonic stimulation was delivered to a confined region of somatosensory cortex or visual cortex in a real time. As a result of the localized stimulations, the calcium signal level was increased two or three times higher than the responses in the other cortical area. Also, the artifact response in the auditory cortex which was reported previously could be still found with the periodically bursting stimulation, while the effect was noticeably reduced with the random sequence in bursting the stimulation signal. In conclusion, skinless micro needle transducer with the random transmit sequence could deliver localized stimulation to a small animal mouse brain.**

Keywords— skinless needle ultrasonic transducer, localized stimulation, indirect activation.

I. Introduction

Ultrasound brain stimulations have been receiving a lot of attentions for their feasibility of modulating neuronal activities noninvasively. Many studies have proven that the ultrasonic stimulation using a low frequency (<1MHz) transducer can induce muscle contractions for mice model or modulations in sensory responses. Since the beam size of such a low frequency acoustic beam is a few millimeters, the acoustic stimulation could modulate multiple brain regions in a small animal mouse brain although it probably will be a minor issue in stimulating larger sized brain, e.g., human, monkey brain. Also, the size of the transducer is almost over the mouse head, and optical brain imaging while acoustic stimulation is impossible without changing the structures of the microscopies. Although the studies of mouse brain stimulations are essential in exploring the feasibility of ultrasound stimulation, the previously reported devices cannot mimic the localized stimulations of human brain from mouse model, Moreover, indirect modulations on auditory cortex caused by stimulating visual cortex were reported in recent studies [1]. It was also reported that abrupt applications of stimulations and periodic stimuli burst trains could be regions causing the indirect stimulations [2].

In this paper, a needle acoustic transducer having a smaller beam width was developed to deliver localized stimulations to mouse models, and the physical size of the transducer was significantly reduced by removing the conventional transducer housing and replacing it with thin layer of epoxy. The localized stimulations were demonstrated by using a transgenic mouse in-vivo, and the reduced size enabled recording mouse brain activities while stimulating a mouse brain region. To reduce the indirect activations at auditory cortex, a randomized pulse sequence was developed, and random stimulation burst trains were employed for the localized stimulation. To demonstrate its feasibilities, the calcium level changes at auditory cortex in response to the periodic and non-periodic stimulation burst trains were monitored by recording the calcium level changes in the auditory cortex.

II. Method

A. *Transducer fabrication*

Fig. 1 shows an acoustic stack of the custom-made skinless micro needle ultrasonic transducer. A 500 μm aperture size was built by using PZT-5H with the thickness of 40μm. The thickness of the backing material was 500 μm, and a single 32 AWG conductor was glued to the top of the backing structure

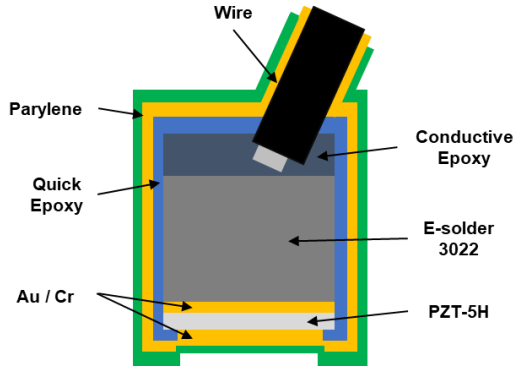

Fig. 1 An acoustic stack of skinless ultrasound micro needle transducer

with a conductive epoxy [3]. The side wall of the transducer and backing region were covered by a quick epoxy to isolate the ground plane which was formed by sputtering Cr/Au on the outer shell of the epoxy and the frontal surface of the transducer from the signal path of the conductor connected to the backing layer. Parylene layer of 12 μm in thickness was loaded for acoustic matching and passivation.

B. *Small animal model preparations*

A transgenic mouse (Thy1-GCaMP6s, Jackson Laboratory, Ellsworth, ME, USA) were prepared for neuronal calcium signal imaging. Mice underwent an acute cranial window preparation surgery to make 2 mm in diameter holes on skull above the barrel cortex and visual cortex. To detect calcium signals indicating the activation of excitatory neurons, a light source transmitting 460 nm laser were transmitted, and the signal from the mouse was received by a CMOS camera (Zyla 5.5, Andor Technology, Belfast, Northern Ireland, UK).

C. *Ultrasonic transmission seqences*

To confirm the feasibility of reducing indirect auditory cortex stimulation by using random burst sequence, both periodic and random burst trains were generated by an arbitrary waveform function generator (AFG3252, Tektronix, Beaverton, OR, USA). The fundamental frequency for both transmit waveform type was 10MHz. For the periodic burst, 300 cycle burst was transmitted in 1.5 kHz for 200 ms. For the random burst sequence, 300 cycle burst was transmitted in a random time, but maintained the duty cycle of 50 % with the periodic sequence.

III. Results

Figs. 2(a)-(b) and figs. 2(c)-(d) show the calcium signal level changes in response to the stimulations on somatosensory and visual cortex, respectively. When the somatosensory cortex was stimulated, the primary sensory cortex was excited by both periodic and random stimulation sequences. However, the responses in the auditory cortex were significantly reduced by using the random stimulation sequence. For the visual cortex stimulation, the responses at the auditory cortex was also reduced by using the random sequence while the responses at visual cortex were similar.

Previously, ultrasound brain stimulation with small animal models utilized lower frequencies than 1MHz with large sized ultrasound transducers which may not be compatible with real time optical imaging systems. Because the beam size of the low frequency acoustic beam was between 2mm and 5mm, it can stimulate wide range of mouse brain and trigger unexpected brain activities. Also, the use of periodical burst sequence cause indirect auditory responses. In the current study, As shown in fig.2, the neuronal activities could be successfully recoded while ultrasound stimulation was delivered. The contrast in the calcium level changes between the targeted region and its peripheral could be identified for confirming the localized stimulation. Also, compared with the periodic stimulation sequence, the indirect auditory cortex responses were significantly reduced by using the random burst sequence. With the development of a high frequency (10 MHz) needle transducer compatible with the optical imaging and the use of the random stimulation sequence, the platform for small animal brain stimulations mimicking localized human brain stimulation was demonstrated.

References

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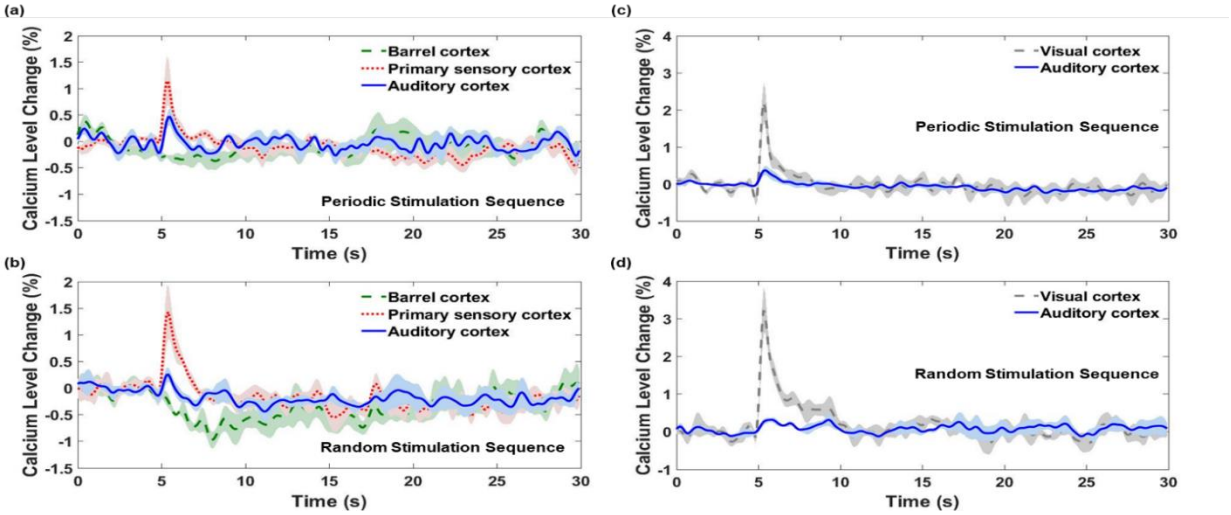

Fig. 2 The average calcium level changes following the somatosensory cortex stimulation by a programmed pulse with PRF(a), and specific PRF(b) for different regions marked with a green dotted line for barrel, red dotted line for primary sensory, blue solid line for auditory cortex. The average calcium level changes following the visual cortex stimulation by a programmed pulse with PRF(c), and specific PRF(d) for different regions marked with a gray dotted line for visual, blue solid line for auditory cortex. Standard error of the mean (SEM) is presented by shaded region.