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"together we can and we will make a difference"

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ABSTRACT

A Fabry-Perot cavity milled with a focused ion beam on a tapered fiber tip is proposed for in vivo neural activity recording as an optical method. Optical fiber micro-tips are good candidate devices for sensing applications in a small volume and difficult to access locations, such as neuroscience research. The fiber-based probe is electrical artifact-free, labeling free, and feasible for a portable system compared with conventional in vivo neural recording networks. Optical signals and electrical neural activity from the rat somatosensory cortex were simultaneously recorded. This fiber-based probe promises the enhanced ability to extracellular recording of the neural activity in neurophotonics applications. It has a potential capability compared with optrode in optogenetics techniques. Therefore, a single fiber optic probe can be used for simultaneous optical stimulation and optical recording.

Keywords: Neuron, optical recording, single-unit recording, tapered fiber tip, milled Fabry Perot, refractive index, ion channel

INTRODUCTION

Various technologies have been developed for in vivo neural recordings of the mammalian brain (Kim, 2013). Microelectrodes with diverse shapes and materials have been introduced to measure the brain electrophysiological properties, including in vivo whole-cell patch clamping (Kodandaramaiah, 2012) and multichannel electrodes (Royer, 2010). However, in general, the electrophysiological recording has limitations in the number of recordings, even with state-of-the-art techniques. It is also vulnerable to environmental electric noises and artifacts caused by electrical stimulation or movements. Moreover, most microelectrodes are unable to reliably record chronic neural activity (Bjornsson, 2006).

In recent years, optical neural recording techniques are promising tools. The optical instruments have several advantages compared with the traditional electrophysiological recording method, such as immune of electrical noise, simultaneous imaging of a lot of neurons, or selective recording from genetically-targeted neurons. Optical approaches have been suggested with both extrinsic and intrinsic schemes.

The methods for intrinsic neural recording employ the change of optical properties in brains such as

blood flow/oxygenation, cellular volume change, or refractive index (RI) change without the addition of external indicators. Those properties can be detected using various optical techniques, including laser Doppler flowmetry (LDF) (Fredriksson, 2012), near-infrared (NIR) spectrometry (Villringer, 1993), functional optical coherence tomography (FOCT) (Lazebnik, 2003), diffuse optical tomography (DOT) (Zeff, 2007), and surface plasmon resonance (SPR) (Kim, 2012). Although functional imaging is noninvasive, they have a low temporal resolution and raise issues related to the considerable size and the high cost of the system. To address these issues, it needs to develop a high spatiotemporal imaging technique with a miniature and inexpensive detection system for functional brain imaging and individual neuron activity. The extrinsic monitoring techniques use a chemical or genetic modification of the neuronal cells to fluorescence signals neuronal activity, such as calcium indicators and voltage-sensitive fluorescent proteins. Although extrinsic voltage-sensitive dyes allow simultaneous measurement of different locations without stimulation artifact and the fluorescent signals induced by the dyes have been shown to reflect neural activity, there are concerns

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about its pharmacological effects and photodynamic damage to the cells (Ebner, 1995). In these methods, the detection area usually covers the whole brain, resulting in high temporal latency and poor spatial resolution. In addition, they require bulky and expensive equipment and immobilization of subjects for accurate monitoring. Because of the limitations of conventional intrinsic optical methods, there is a need for a technique offering higher spatial resolution and lower temporal latency for the optical in vivo recording of brain activity. Fiber-optic techniques allow minimally invasive imaging from the cortex to the deep-brain. The use of the fibers for in vivo neural recording and brain imaging offers key mechanical benefits regarding device size, portability, and flexibility, as well as advantages concerning the performance and availability of fiber optic components (Kim, 2012).

Thus, we employed an optical fiber approach to developing a portable and implantable Fabry Perot on tapered fiber tip (FP-TFT) sensor capable of in vivo neural recordings because the optical fiber is flexible, thin, and light. We applied our sensor to detect changes in the optical characteristics at the sensor tip induced by neural activity.

PRINCIPLE OF OPTICAL PROBE

The first assumption in this analysis is that the change in the nerve's dielectric constant will directly affect the FP-TFT cavity RI change.

Changes in the RI of electrically stimulated nerves have been previously reported by measuring the birefringence and scattering changes. The reason for these changes is proposed to be a reorganization of axon membrane protein molecules (Kalatsky, 2003) and changes in ionic concentration near the nerve membrane (Menon, 1997). Moreover, these hypotheses are still in controversy.

Another possible assumption is that the change in the aCSF region's dielectric constant is a fundamental factor of the wavelength shift of FP-TFT spectrum and is strongly dependent on the corresponding recorded extracellular potential. The key factor affecting the RI around the FP-TFT sensor was assumed to be the presence of the Na^+ and K^+ ion of the nerve.

Figure 1 shows a schematic of a FP-TFT sensor located close to the channel of a neuron.

FP-TFT sensor has a high sensitivity to the RI change in the gap of the cavity. The FP-TFT signal results from the integrated RI changes within a tiny measurement volume. The RI can be altered by changing the ionic composition and/or fractional volume change between different organelles. A similar response was reported for the SPR sensor. It is proven that the optical SPR signals were emanated from neural activities evoked by stimulation with simultaneous electrical recording and pharmacological analysis (Kim, 2012).

In this work, we demonstrate the measurement of neural signals in a rat brain for single-unit recording based on measuring the RI using a FP-TFT sensor.

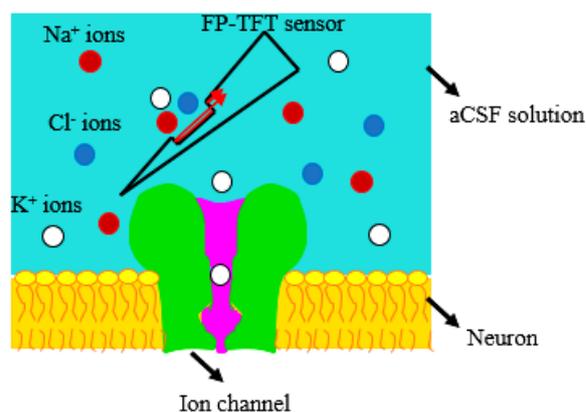


Fig. 1: The two-dimensionally reduced model for neural recording system with FP-TFT probe. The nerve membrane was in close proximity to the FP cavity. The gap region was filled with aCSF fluid, which included only K^+ , Na^+ and Cl^- ions and water molecules (other ions were not included).

EXPERIMENTAL SETUP

Figure. 2 shows the schematic of the experimental setup. In this experiment, a Bragg METER system was used for monitoring the FP-TFT spectrum (Fiber Sensing, FS2100). The FP-TFT lead-in fiber is connected to one source channel of the BraggMETER, and the reflected spectrum from the tip arrives at the detector in the same channel. The data from the BraggMETER was recorded on a computer.

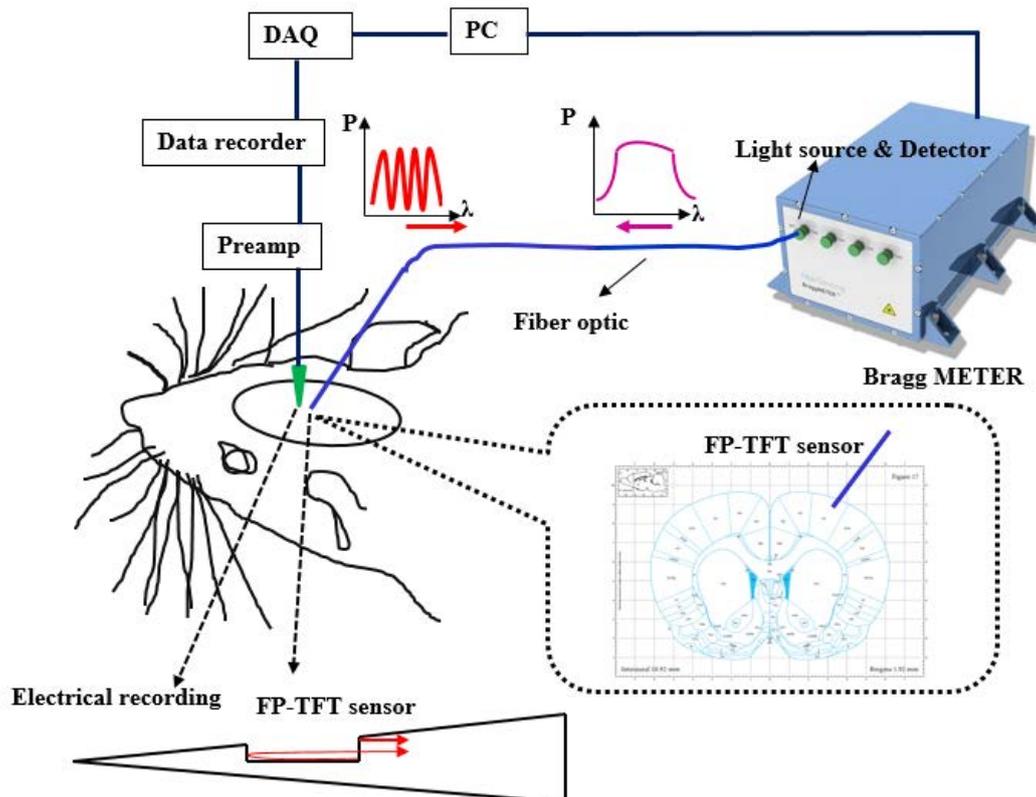


Fig. 2: Schematic of FP-TFT sensor for in vivo extracellular neural recording. A FP-TFT sensor and tungsten electrode were closely located to the target region, and the wavelength shift caused by changing RI of neural was recorded.

The recorded data was processed by a program code in the Labview software. In this study, the fiber optic probe was fabricated with a micromachining technique (focused ion beam) that allows for creating tiny cavities or microcavities. The optical fiber micromachining are manufactured by femtosecond laser micromachining (Liao, 2012) and focused ion beam (FIB) milling (André, 2014).

The Fabry-Perot cavities were milled using a dual-beam FIB-SEM TESCAN system (LyraXMU) on tapered optical fiber tips. The TFTs were fabricated using dynamic chemical etching (Nikbakht, 2015). The TFT length and cone angle are controlled by this technique. Unlike traditional dynamic chemical etching, where the fiber is moved relative to the meniscus position, the relative position of etchant and fiber is controlled by a syringe pump. The volumes of acid in the container and the surface level are changed by the syringe pump. Therefore, the length of the fiber dipped in the acid changes. All the tips were created by single-mode fibers (SMF-28).

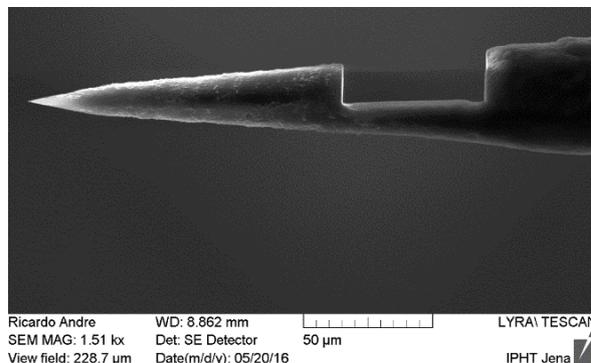


Fig. 3: SEM micrograph of a Fabry-Perot cavity milled in a TFT.

For optical single-unit recording, the probe was inserted into the brain tissue with brain surgery protocols. For this purpose, Male Wistar rats weighing about 280 g were anesthetized with Ketamine (80 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) with supplemental doses as required. After mounting the animal into the stereotactic frame, a first incision is made to open the skin above the skull. The skin is gradually pulled to the side to reveal the cranial sutures. After early cleaning the skull with hydrogen peroxide, the bregma and the lambda can be easily identified (marked spots).

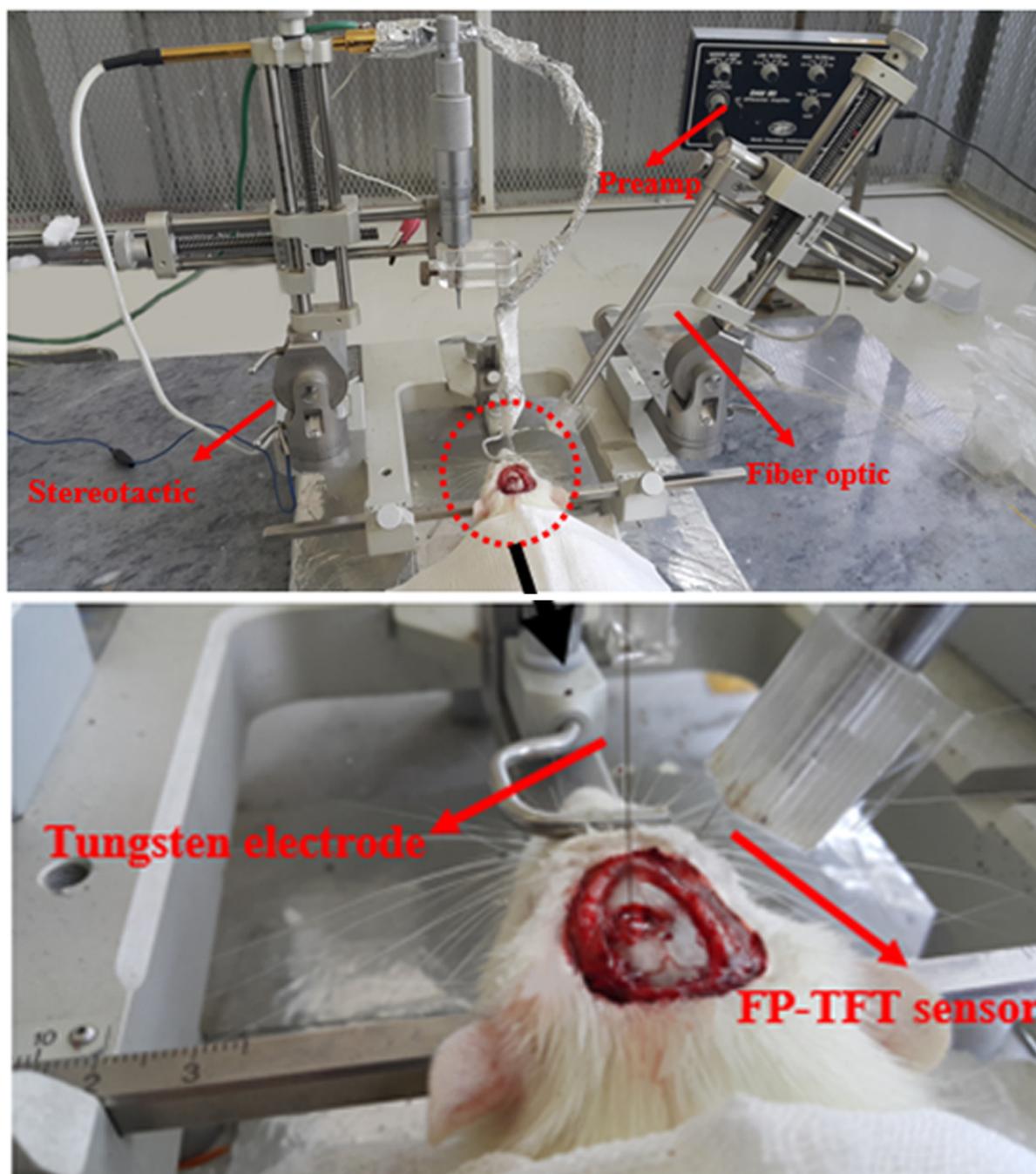


Fig. 4: The experimental setup photo for electrical and optical recording from the anesthetized rat.

A small craniotomy was created with a dental drill at the desired position on the skull, without puncturing the dura. The dura is later removed using fine forceps to minimize damage to the cortex. For an optical recording of the neural activity, the fiber probe was attached to one of the stereotactic arms. The surgery was carried out according to established animal care guidelines and standard protocols (Riahi, 2015). A photo of the brain surgery for guiding the fiber probe inside the brain is shown in figure 4.

RESULTS AND DISCUSSION

For optical recording, the skull and the dura were removed over the somatosensory cortex (approximately 4.0 mm and 1.0 mm lateral and anterior to the bregma, respectively), which is known to process the neural signal from the rat somatosensory. A FP-TFT probe was inserted into the cortex to a depth of 300–600 μm from the surface. All procedures were performed following the guidelines concerning the use of experimental animals.

Electrically spontaneous signals were recorded from the contralateral brain by a DAQ board (NI 4462, National Instruments, Austin, Tex.) with a sampling rate of 10–20 kHz. Single-unit recording of spontaneous neural activity in the somatosensory cortex was obtained optically with the FP-TFT probe and electrically with a tungsten wire microelectrode, which was also inserted into the cortex. The electrical response was obtained after bandpass filtering (1–500 Hz) and 1000× amplification with a differential amplifier.

Fig 5 shows the FP-TFT spectrum in air and the spectrum after inserting the probe inside the brain. Electrical recording of spontaneous neural activity from the rat somatosensory cortex is shown in fig. 6.

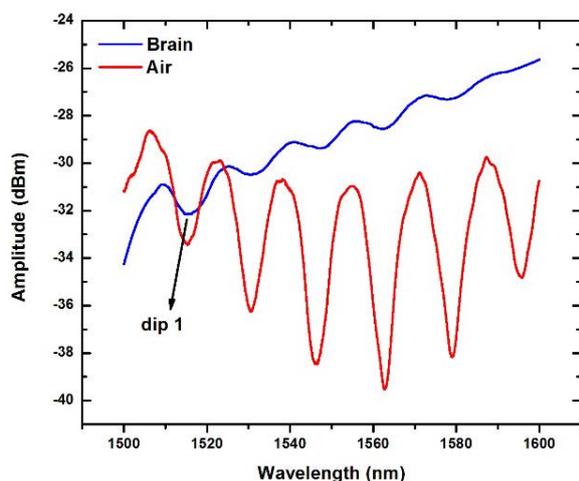


Fig. 5: FP-TFT spectrum in air and brain.

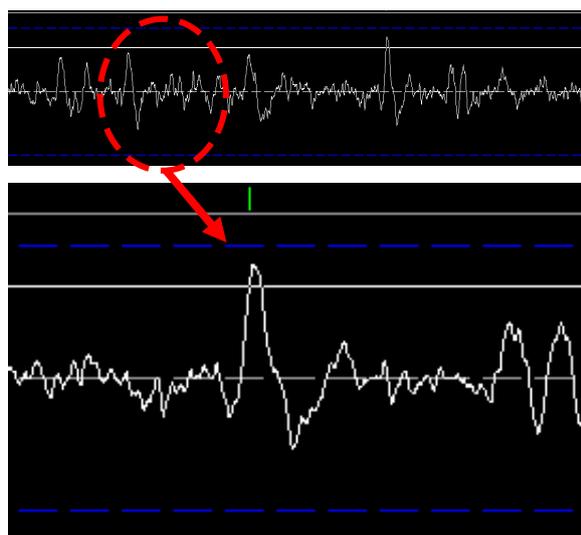


Fig. 6: Electrical recording of single-neuron activity from the rat barrel cortex.

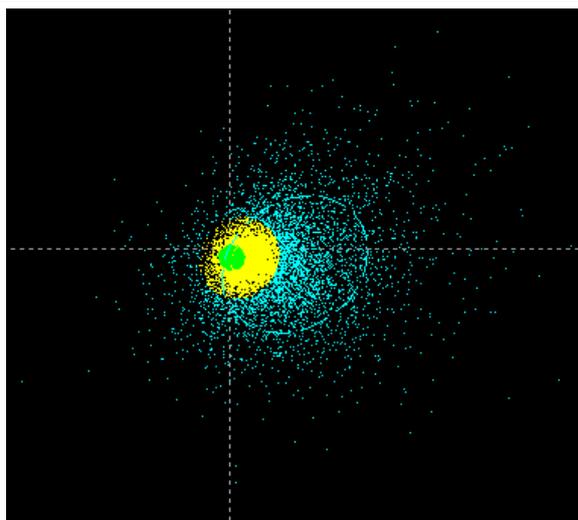


Fig. 7: Cortical action potentials recorded from a tungsten electrode showing three clusters and average and 95% percentiles of the waveforms on the electrode contacts.

The green color clustered in figure 7 is our targeted single neuron, as shown by a single trace in figure 6. Figure 8 shows the optical signals recorded by FP-TFT sensor, located close to the tungsten electrode. The wavelength shift was measured tracing dip 1 in figure 5. The obtained results show the optical recording is in accordance with the electrical recording.

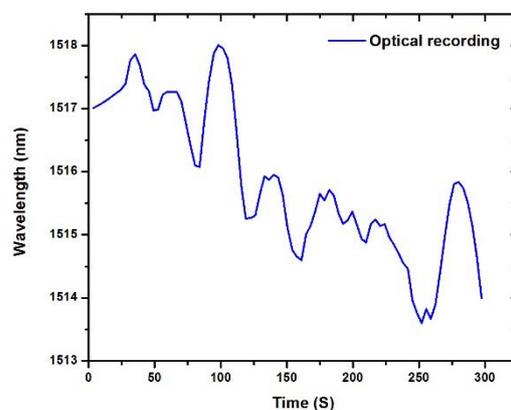


Fig. 8: Optical signals recorded by the FP-TFT sensor.

Optical fiber micro-tips are promising devices for neural optical recording, stimulation, and sensing applications in a small volume and difficult to access target points, such as neuropharmacology research. To our knowledge, this probe is the first report of the successful measurement of in vivo single-unit recording neural activity with fiber optics. This flexible and simple fiber system can also be capable of in vivo chronic recording and localized optical stimulation as an alternative to conventional

microelectrodes. This approach may also induce less cellular damage compared with standard fiber optic or stiff microelectrodes.

CONCLUSIONS

The *in vivo* detection of neuronal activity from the brain is essential in the study of neural circuits. Electrophysiology is a golden method in neuroscience research, but the electrical recording is vulnerable to electrical noise and artifacts and has a limitation in the number of channels. It is also impossible to electrically record the activity exclusively from specific types of neurons. To overcome these drawbacks, we developed an optical probe based on focused ion beam milled Fabry-Perot cavities in

optical fiber micro-tips for optical neural recording. With spontaneous neural activity, the ion concentrations in the target area will be changed, leading to changing the RI around the fiber probe. Due to its small size and immunity from electromagnetic interference, the FP-TFT sensor can integrate with optrodes in optogenetics techniques for neuroscience applications. Also, the fiber optical neural recordings can be used for freely moving animals in behavioral neuroscience research.

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