Smart Dura: A monolithic optoelectrical surface array for neural interfacing with primate cortex

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***Abstract*—Chronic interfacing with the brain to record and stimulate neural activity with high spatiotemporal resolution is highly desirable to advance the understanding of neural circuits and design of novel therapeutics. Traditional neural interfaces mainly rely on electrical recording and stimulation, which have inherent limitations such as lack of specificity and a large volume of tissue activation. With the advent of optogenetics, hybrid opto-electrical platforms have emerged as new bidirectional interfaces. In this paper, we introduce our groundwork towards the Smart Dura, a novel device that will ultimately integrate high density recording electrodes and light sources in the form of a chronic implant that can cover large cortical areas in the primate brain (300 mm^2) for adaptive recording and stimulation of neural activity in a closed loop. Smart Dura has two main components, the electrical dura for recording and the optical dura for optogenetic stimulation. As the first step to implement this platform, we have implemented the electrical dura as a high density, transparent and flexible µECoG array, as well as the optical dura, which is a high-density LED array, independently. Both the electrical and optical dura are implemented in flexible polymer substrates that provide mechanical compliance with the brain tissue and can be integrated together in a vertical stack. Here we present the fabrication, bench top characterization and acute *in vivo* validation of both the electrical and optical dura. This work paves the way towards the ultimate Smart Dura, a functional device that can replace the native dura as a chronic, large-scale bidirectional interface to study cortical brain activity in non-human primates (NHPs), with the potential for translation to humans.**

Keywords—bidirectional interfaces, µECoG, LED array, optogenetics, non-human primates, cortex.

I. Introduction

The neural circuits that mediate human cognition and behavior, among other aspects of the human mind, are still not well understood due to, in part, their inherent complexity and the limited amount of information extracted from brain activity with current neuroscientific tools. This neuroscientific challenge is increasingly driving a broader multidisciplinary research community to develop new techniques and methods to decipher the function of neural circuits. Thanks to the development of such an interdisciplinary field, new optical techniques have been developed to monitor and manipulate neural populations. One of the most notable advancements is the groundbreaking optical technique known as optogenetics, which provides cell-type specific manipulation of neurons with millisecond temporal precision [1]. Optogenetics has been widely adopted in small animal models (i.e., mice and rats) due to their fast life cycles, small sizes, and simpler anatomies [2]. However, the upscale of optogenetics to large brains in larger animal models like NHP remained challenging. Recently, viral vector techniques, such as convection enhanced delivery (CED) of optogenetic vectors [3],[4], have been demonstrated to provide optogenetic expression in large cortical areas in NHPs, expanding the utility of optogenetics to large animal models [5]. Leveraging the use of optogenetics and combining it with traditional electrophysiological recording technologies into one platform could lead to powerful and complementary new ways to explore the brain function [6]. As with optogenetic techniques, hybrid opto-electrical neural interfaces have been demonstrated in small animal models but have been challenging to scale up in large animal models, such as NHPs.

In NHP research, one of the most ubiquitous devices used for optical access to the cerebral cortex is the traditional artificial dura. The artificial dura is an elastomer-based passive device that replaces the native dura and is used to create a stable optical window to the NHP cortex. This device can provide optical access for the duration of many months, although without simultaneous electrophysiological recordings. Yazdan-Shamorad et al. tested heterogeneous methods of combining artificial dura with ECoG arrays and external light sources but struggled to achieve the same levels of stability achieved by the simple passive artificial dura [3]. Homogenous integration of electrodes on soft polymers has been demonstrated in spinal cord implants with desired flexibility and stability [7], showing the capabilities of polymer-based electrode arrays. More recently, Griggs et al. demonstrated the use of a commercially available ECoG array molded in an artificial dura, named multi-modal artificial dura (MMAD), for simultaneous electrophysiology and optical access [8]. The MMAD showed the capability of recording ECoG signals in optogenetic experiments using external light sources for optical stimulation. In this paper, we discuss the design of a novel microfabricated device that improves the current capabilities of the MMAD by providing larger optical access, higher density of recording electrodes and integrated light sources into one platform. We call this

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device, Smart Dura, since it can enable a read/write access to the brain tissue. This platform can be used for adaptive neural recording and stimulation in a closed loop.

The first generation Smart Dura is fabricated in two parts, the electrical dura and the optical dura, which are integrated together with the potential to become a chronic implant. The Smart Dura is microfabricated on soft elastomeric substrates with elastic properties and a form factor that provides mechanical compliance with brain tissue. Future generations of the Smart Dura will replace the native dura and can reduce tissue growth and infection for chronic stable interfacing with the brain. Because of the monolithic integration of light sources, the Smart Dura obviates the need for external light sources and serves as a multimodal platform to monitor and manipulate neural populations within the same device. This will be a major advancement in the field and can be used to unlock the potentials of optogenetic and bidirectional interfaces in primate brains.

II. Methods

A. Animals

We validated our electrical dura on a pig-tailed macaque (*macaca nemestrina*, Monkey M, 18.4 kg) and our optical dura on a rhesus macaque (*macaca mulatta*, Monkey H, 14 kg). Animal care and experiments were approved by the University of Washington's Office of Animal Welfare, the Institutional Animal Care and Use Committee, and the Washington National Primate Research Center (WaNPRC).

B. Electrical Dura

1) Design and Fabrication

The electrical dura is a transparent and flexible µECoG array with platinum (Pt) surface electrodes patterned on polydimethylsiloxane (PDMS) and Parylene C biocompatible substrates (figure 1A). The electrical dura is fabricated using microfabrication technology at the wafer scale, leveraging the capabilities of high-resolution lithography techniques for parallel, high-throughput fabrication of high-density electrodes for electrophysiology recording with high spatial resolution. Neural electrodes have been fabricated in PDMS [7] and Parylene C substrates [9]. We have designed a novel microfabrication process that combines both materials to enable high resolution micro lithography on Parylene C, while still providing the high level of mechanical compliance of PDMS. The resolution of our lithographic techniques enables a trace width and pitch of 4 µm or smaller, allowing for an electrode count of up to 512 electrodes on each single thin-film layer, covering an area of 300 mm^2 for high density electrophysiology recording without significantly compromising the optical access. The recording electrodes can be made as small as 5 µm in diameter for high spatial resolution recording. Despite the ability to obtain such small features, our initial designs feature lower electrode counts to reduce the complexity of backend electronics and slightly larger electrode diameters to reduce the impedance, improve SNR and record stable signals such as local field potentials (LFPs) and electrocorticography (ECoG) signals. We have successfully fabricated and demonstrated 32-channel and 64-channel electrical dura (Fig. 1) for initial demonstration with electrode diameters of 40 µm and 20 µm respectively. The electrical dura was packaged with flexible polyimide adaptor printed circuit boards (PCBs) using zero-insertion-force (ZIF) connectors through a bondpad array defined on the two "arms" of the device that extend out of the circular patch in the center (Fig. 1B). The flexible PCBs are then connected to a custom rigid PCB where the trace signals are routed to an OMNETICS connector to interface with commercial headstage amplifiers (Grapevine, Ripple Neuro).

2) PEDOT:PSS Coating

After the fabrication and release of the electrical dura devices, we modified the electrode surfaces by electrodepositing PEDOT:PSS using an Autolab system (PGSTAT204, Metrohm, Switzerland) to reduce the electrochemical impedance. Electroplating was performed in potentiostatic mode with a three-electrode configuration and the electrical dura as the working electrode, an Ag/Ag-Cl reference electrode and a tungsten counter electrode. A constant voltage was applied to the counter electrode and the electrodeposition was finalized after a charge density of 100 mC/cm^2 was reached, indicating sufficient amount of full coverage of PEDOT:PSS coated on the electrode surface to reduce electrode impedance. The solution used for electrodeposition consisted of a mixture of 1.2 wt% Poly-sodium-4-styrenesulfonate (PSS) and 0.01 M 3,4-Ethylenedioxythiophene (EDOT). PEDOT is polymerized by injecting current through the electrode-solution interface.

3) Electrochemical Impedance Spectroscopy

Prior to *in vivo* validation, we performed electrochemical impedance spectroscopy (EIS) to characterize the performance of the electrodes on the electrical dura, using a standard method [9]. For the EIS measurements, we prepared a 1x phosphate-buffered-saline (PBS) solution with a similar conductivity to the cerebrospinal fluid (CSF) in the brain [10]. We used a three-electrode configuration with the electrical dura as the working electrode, an Ag/Ag-Cl reference electrode and a tungsten counter electrode. The reference voltage from the Ag/Ag-Cl electrode and the current through the tungsten electrode were used to measure

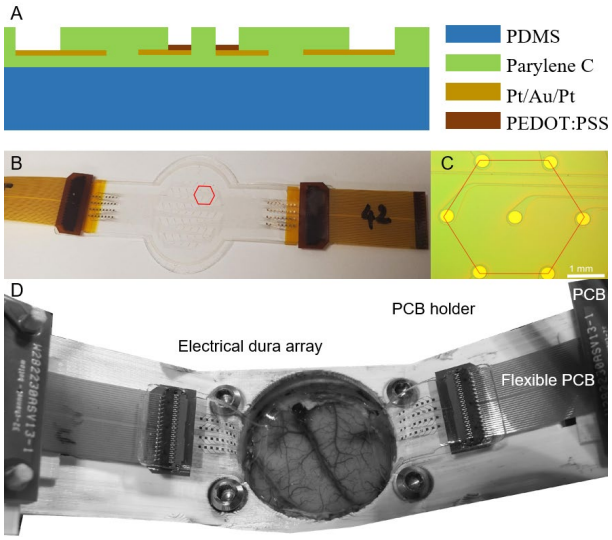

Figure 1. Electrical dura array. (A) Schematic of the electric dura material stack. (B) Packaged 64-channel electrical dura. (C) Micrograph showing 40-µm electrodes exposed in a honeycomb lattice. (D) Base holder affixed to the skull and supporting the electrical dura array and connectors during experiments.

the electrochemical impedance through the electrode-electrolyte interface.

4) *Recording and Tactile Stimulation Components*

We custom designed a stack-up of parts to collect electrophysiological recordings from the electrical dura. It includes a base holder that can be affixed to the skull with four titanium screws, as well as additional supporting parts that can be easily attached to and detached from the holder arms to support the electrical dura PCBs during electrophysiology recordings (Fig. 1D). Both the base holder and the adjustable PCB holders were made of polylactic acid (PLA) using a 3D printing process. We used a custom-made tactile stimulator on the monkey's left hand fingertips.

5) *Surgical Procedure and Data Acquisition*

The electrical dura was validated *in vivo* in monkey M during anesthesia under urethane (0.52 g/L). We performed tactile stimulation of fingertips with simultaneous neural recording from sensorimotor cortex bilaterally. The details of our surgical procedure is described here [11]. We controlled electrophysiology data collection and tactile stimulation with a Grapevine Nomad (Ripple Neuro) and a custom code implemented in MATLAB (The MathWorks Inc).

C. *Optical Dura*

1) *Design and Fabrication*

The optical dura is designed based on a high-density of light emitting diode (LED) arrays integrated in a flexible multilayer polyimide material platform (Fig. 2). The optical dura is compact, lightweight, and relatively easy to fabricate and assemble, since compact LEDs (APHHS1005 Series from Kingbright) are commercially available and the optical dura device can be implemented using a standard flexible PCB manufacturing process at a low cost. Our optical dura interfaces with a custom-designed controller board to generate arbitrary spatiotemporal patterns of light illumination on the surface of the brain to provide the desired stimulation pattern. In our current design up to 64 LEDs can be turned on simultaneously.

2) *Controller Board*

The controller board uses high speed USB communication to interface with the LEDs on one side and with a computer on the other side. The controller board features an Arduino Nano board which includes an 8-bit ATmega328a microcontroller. The LED driver IC is a linear LED driver (STP16 series from STMicroelectronics), which supports high speed serial peripheral interface (SPI) communication up to 30 MHz.

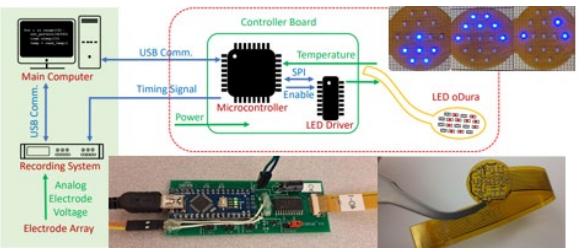

Figure 2. Optical dura system, featuring the controller board and the optical dura device. Different spatiotemporal illumination patterns can be generated.

3) *Recording and Stimulation Components*

To test and validate the first generation Smart Dura, we used our electrical dura alone to demonstrate the feasibility of electrophysiology recording while providing optical access to the surface of the brain tissue for imaging. We also stacked the optical dura with one of our previous MMAD devices [4],[12] to demonstrate the feasibility of optogenetic stimulation and evoking activity in the brain.

4) *Data Acquisition*

To demonstrate the optical dura, we collected data from an awake behaving monkey. We had previously implanted a titanium headpost (6-FHP-X2F, Crist Instruments co., Hagerstown, MD, USA) as well as a custom-made titanium chamber providing optical and electrophysiological access to the left posterior parietal cortex (PPC) of the animal. We had also infused an optogenetic viral vector (AAV8-hSyn-Jaws-GFP, UNC Vector Core, NC, USA) at eight locations throughout the PPC using CED. More details about surgical procedures for this animal can be found elsewhere [11]. We controlled electrophysiological recordings and optical dura stimulation with a Grapevine Nomad (Ripple Neuro) and custom code implemented in MATLAB (The MathWorks Inc.).

III. Results

A. *Electrical Dura*

1) *Electrochemical Impedance Spectroscopy*

Electroplating of PEDOT:PSS on Pt electrodes was performed to reduce the electrochemical impedance of the electrical-dura electrodes by ~30 fold. The impedance at 1 kHz decreased from 971 ± 183 kΩ to 30.4 ± 2.4 kΩ on electrodes with a diameter of 20 µm (Fig. 3) and from 365 ± 46.8 kΩ to 13.4 ± 0.48 kΩ for 40 µm diameter electrodes.

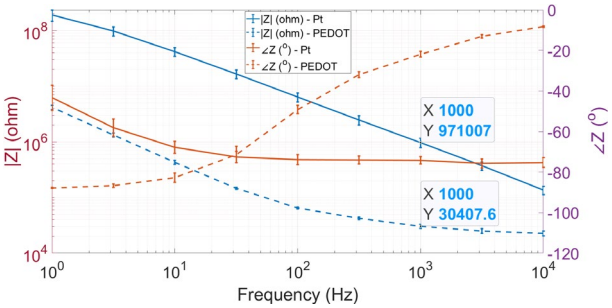

Figure 3. Electrochemical Impedance Magnitude and phase spectrum of native Pt and modified PEDOT:PSS electrode.

2) *In vivo Electrophysiology Recordings*

In vivo validation was performed to show proof of concept demonstration on the performance of electrical dura. We were able to acutely collect spontaneous activity as well as tactile stimulation-induced evoked electrophysiological signals from the somatosensory cortex of monkey M. Spontaneous activity was recorded using a 64-channel electrical dura array with 20-µm diameter electrodes. The multichannel raw data was band pass filtered in the frequency range of 500-7500 Hz. Using a Mountainsort based neural signal processing pipeline, we have identified putative multi-unit (Fig. 4A, left) from the detected threshold crossing events [13]. The spike band activity appears to be localized

to an individual channel as can be seen from the high pass filtered multichannel recording traces shown in Fig. 4A (right). In previous work, Khodagholy et al. showed detection of spikes on µECoG array with an electrode surface area of 10×10 µm^2 and 30-µm interelectrode spacing [14]. In this electrical dura design, the electrode surface area was ~300 µm^2 with an electrode pitch of 1.8 mm, suggesting that the recorded putative multi-unit activity is spatially localized very well.

We recorded LFPs using a 32 channel, 40 µm-diameter electrode electrical dura from the right hemisphere of the sensorimotor cortex while stimulating the monkey's left hand fingertips using our tactile stimulation device. We observed significant increase of the recorded activity in the low frequency range (4-12 Hz) only, in 2 of the 32 channels during stimulation in comparison to baseline (Fig. 4B).

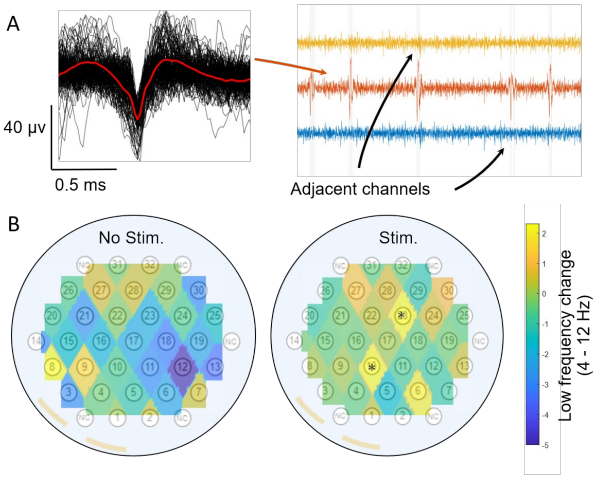

Figure 4. Electrophysiological signals recorded from the electrical dura. (A) Spike waveforms for a putative isolated multi-unit on a specific channel (left), band-pass filtered time traces of the same channel and adjacent channels (right). (B) Spatial mapping of the change in LFP power at 4-12 Hz for control (left) and tactile stimulation (right) sessions. Channels indicated with "*" show significant increase ($p<0.05$) in activity during tactile stimulation.

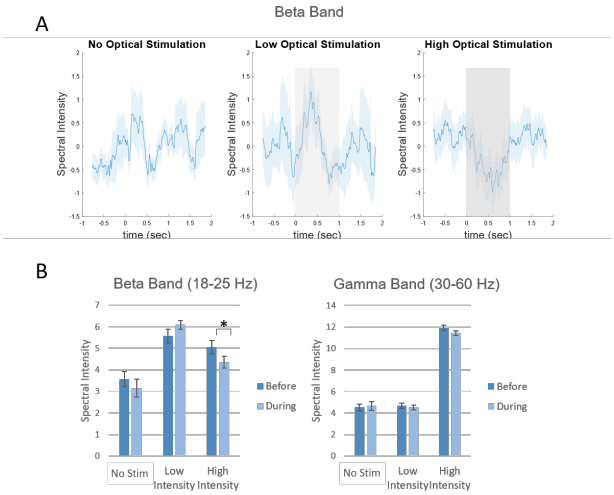

Figure 5. Optogenetic modulation of neural activity using optical dura. (A) Beta band spectral intensity averaged across 30 trials when the LEDs were OFF (left), when all LEDs were ON with a low optical intensity (0.001 mW/mm^2) (middle), and when all LEDs were turned ON with a high optical intensity (0.107 mW/mm^2) (right) in comparison with the baseline. Stimulation times are shown in gray. (B) Comparison of the spectral intensity before and during optical dura illumination for the control, low intensity and high intensity parameters in the beta and gamma bands.

B. *Optical Dura*

14 weeks after injection of the inhibitory opsin Jaws, we tested our optical dura with red LEDs, emitting at a wavelength of 635 nm by illuminating the PPC using the LED array with different illumination parameters, while recording the evoked changes with the previously implanted MMAD. We compared the spectral power intensity of neural recordings in the beta band (18-25 Hz) when the LEDs were OFF, when all LEDs were ON at a low optical intensity (0.001 mW/mm^2), and when all LEDs were ON at a high optical intensity (0.107 mmW/mm^2) with baseline (Fig. 5A). We observed a significant decrease ($p<0.05$) in the spectral intensity during high optical illumination in the beta band (Fig. 5B, left). This change wasn't significant at higher frequencies.

IV. Discussion

Electrical recordings were acquired acutely in the macaque sensorimotor cortex using arrays with 20 and 40 µm-diameter electrodes. These experiments show that the electrical dura is capable of recording electrophysiological signals, while maintaining optical access over large regions of the NHP cortex. Tactile stimulation-induced evoked response in the recorded neural activity shows the first proof of concept that the electrical-dura can link a sensory function to the corresponding circuit activity. In parallel, we have implemented a high density LED array and demonstrated its use for optical stimulation of large cortical areas. The design of our optical dura is flexible. Any arrangement of LEDs can be integrated on the flexible substrate and the versatile controller enables precise spatiotemporal control of LEDs to generate arbitrary spatiotemporal patterns of light illumination. The optical dura can be stacked with our transparent electrical dura to provide a bidirectional interface (i.e., Smart Dura) with the brain for adaptive recording and stimulation of neural activity.

V. Conclusion

Here we have demonstrated the fabrication, benchtop characterization and in-vivo validation of the first generation Smart Dura, which improves the capabilities of current state of the art optogenetic surface interfaces. The customizable design and scalable fabrication process of our first generation electro-optical interface shows the potential for the ultimate Smart Dura to integrate higher density of recording electrodes and optical channels. Our work paves the way towards long-term, large-scale bidirectional interfaces and offers possibilities to study brain circuits and connectivity in large animal models such as NHPs. Our results show a wired connection between the electrical and optical dura to external recording and control devices, but in future the implementation of wireless communication devices integrated onto the Smart Dura platform will obviate the need for wired connection for experimentation and animal care. We believe that developing such an advanced multimodal interface in models that are close to humans will provide significant insight and opportunities for the development of stimulation-based therapies for neurological disorders.

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