Introduction

Progress in neuroscience is limited by the lack of proper tools available to biologists and neuroscientists to study neural circuits with high spatial resolution and cell type specificity. One area of neuroscience that is particularly affected by this absence is the study of somatosensory and motor control systems. Currently available tools used to study these systems and mimic their functions consist of electrode arrays, such as the polymer cuff electrode, attached to the peripheral nervous system[1] or the Utah electrode array implanted directly into the motor cortex[2]. These electrode arrays, however, lack the ability to induce or record neural activation with cell specificity.

Herein, I propose the development of a novel class of miniaturized, battery-free, wireless, soft, implantable neural machine interfaces (NMIs) utilizing optogenetics to study the somatosensory system in non-human primate (NHP) models via the peripheral nervous system (PNS). This proposal considers the recent advancements within the fields of optogenetics and photometry, advanced micro- and nano-fabrication methods, and the necessary collaborations to bring this project to fruition within a three-year period.

Background

Optogenetics is a growing neuroscience tool which utilizes viral injections to genetically modify neuron populations to express light-sensitive ion channels. The targeted neurons can be selectively stimulated among other tissues by selecting viral vectors and opsins with preferential tropisms. In NHPs, initial research in optogenetic stimulation of the peripheral nervous system shows channelrhodopsin-2 (ChR2) and Chronos delivered via adeno-associated virus and stimulating muscle injection to be successful[3]. Once the opsins are virally delivered, these neuron populations can be excited or silenced by targeting them with varying wavelengths and stimulation frequencies from light-emitting diodes. Recent papers have shown the success of optogenetics in stimulating the central nervous system via the brain and the spinal cord[4,5]. Similarly, genetically-encoded calcium indicators (GECI's) and photometry can be used to visualize neural activation of defined cellular populations *in-vivo*[6]. These tools have significant advantages over electrical probes which lack the stimulation and recording specificity required for high resolution research into light touch information propagation through the low-threshold mechanoreceptor afferent neurons in the dorsal root ganglia (DRG). Neuron populations of particular interest for this study are the low-threshold mechanoreceptor afferent neurons within the DRG located in cord segments C6, C7, and C8, which are responsible for light touch information propagation from the lower forelimb and hand[7].

Aim 1: Optical Recording and Stimulation of Low-Threshold Mechanoreceptor Afferent Neurons

The primary functions of the proposed device are to optically record the neural activity of low-threshold mechanoreceptor afferent neurons in a healthy NHP's DRG, and to stimulate those neurons to replicate light touch information being transmitted through the neural circuit up A-β and A-δ fibers. The cells will be targeted following the methods outlined by Williams et al. using ChR2 and Chronos, and with GECI's. To enable both recording and stimulation, the device will employ a collocated microscale inorganic light-emitting diode (μ-LED) and photodetector (μ-IPD), both interfaced with a microcontroller for stimulation control and data processing respectively.

Additional functional requirements to ensure device reliability are highly deformable mechanics and a usable lifetime of 10 years or longer. To ensure the device function for applications lateral the spinal column serpentine geometries, polymer substrate and encapsulations, and thin annealed metal traces will be employed to keep local strains under fatigue limits even under high bending and linear loads. To extend the usable lifetime of these devices, dielectric interlayers of thermally grown Silicon Dioxide and Hafnium Oxide will be used. These interlayers, employed in a total thickness up to 100μm, work to extend usable lifetime by retarding the ingress of ions and water vapor and disrupting pin-hole defects while remaining translucent[8].

Device encapsulation and fatigue mechanics will be tested using accelerated life testing (ALT) in an 87°C phosphate buffered saline bath with complex mechanical loading conditions for 4 months, simulating an implanted lifetime of 10 years and 8 months. While ALT is being performed, the long-term reliability of the stimulating and recording capabilities will be assessed by measuring the irradiance of the μ-LED and the recorded signal of an external light source via the μ-IPD over time. Device electronics and wireless power harvesting will be assessed via continuous data logging.

Aim 2: *In-Vivo* Testing in Non-Human Primates

The final aim of the proposed research is to implant the proposed device into NHPs to conduct research on light touch propagation via low-threshold mechanoreceptor afferent neurons in the DRG. The anatomical similarities of mechanoreception between NHPs and humans allows for the study of light touch perception in the forelimbs that could not be studied in small animal models. This work will be done with collaborators who conduct NHP behavioral studies, external to the Yoon Lab at the University of Michigan where I propose to do my PhD. One study of interest includes training the NHPs to perform two-alternative forced choice tasks involving the differentiation of textures on their fingertips or palms and studying the neural activity for each of the presented textures. After the behavior is learned with accuracy of 95% or greater and the neural activity has been recorded and decoded, the NHP will perform the task again. However, this time the NHP will receive light touch information from the device via optogenetic stimulation of the mechanoreceptor afferent neurons in the C6 C7 and C8 DRG without any textures presented.

Future Directions

Upon completion of this work, the goal is to transition from the study of the peripheral nervous system's role in light touch perception to implantation within a NHP amputee. Once implanted, this device will interface with an upper-limb prosthetic via near field communication and used to replace the lost light touch perception abilities of the amputated limb. If shown to be successful, the next step is to use this device in conjunction with functional magnetic resonance imaging to study the long-range neural circuits of the somatosensory system, a study never before possible.

Intellectual Merit

The development of this device will utilize recent advances in materials science, fabrication, and optogenetics to advance neuroscience tools. The design process and *in-vivo* testing will also require collaboration with the departments of Biology and Neuroscience as well as external collaborators to inform the selection of virus, opsin, μ-LED, and μ-IPD. Once developed, these devices would directly promote an advancement in the understanding of the peripheral nervous system's role in somatosensory processing and propagation and introduce a platform of devices for the targeted study of the somatosensory system and other short- and long- range neural circuits *in-vivo*.

Broader Impacts

These devices would be applicable not only in the study of light touch information but any neuron type and thus have broad impacts in neuroscience, neurotherapies, and limb rehabilitation or replacement for paralyzed or amputated individuals. Outside of the medical field, the ability to transmit somatosensory from an external input to the peripheral nervous system could also be used to advance entertainment systems and virtual reality to include touch perception.

References

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