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Chronic intracortical neural recordings using microelectrode arrays coated with PEDOT–TFB

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ABSTRACT

Microelectrode arrays have been extensively utilized to record extracellular neuronal activity for brain–machine interface applications. Modifying the microelectrodes with conductive polymers such as poly(3,4-ethylenedioxythiophene) (PEDOT) has been reported to be advantageous because it increases the effective surface area of the microelectrodes, thereby decreasing impedance and enhancing charge transfer capacity. However, the long term stability and integrity of such coatings for chronic recordings remains unclear. Previously, our group has demonstrated that use of the smaller counter ion tetrafluoroborate (TFB) during electrodeposition increased the stability of the PEDOT coatings *in vitro* compared to the commonly used counter ion poly(styrenesulfonate) (PSS). In the current work, we examined the long-term *in vivo* performance of PEDOT–TFB coated microelectrodes. To do so, we selectively modified half of the microelectrodes on NeuroNexus single shank probes with PEDOT–TFB while the other half of the microelectrodes were modified with gold as a control. The modified probes were then implanted into the primary motor cortex of rats. Single unit recordings were observed on both PEDOT–TFB and gold control microelectrodes for more than 12 weeks. Compared to the gold-coated microelectrodes, the PEDOT–TFB coated microelectrodes exhibited an overall significantly lower impedance and higher number of units per microelectrode specifically for the first four weeks. The majority of PEDOT–TFB microelectrodes with activity had an impedance magnitude lower than 400 kΩ at 1 kHz. Our equivalent circuit modeling of the impedance data suggests stability in the polymer-related parameters for the duration of the study. In addition, when comparing PEDOT–TFB microelectrodes with and without long-term activity, we observed a distinction in certain circuit parameters for these microelectrodes derived from equivalent circuit modeling prior to implantation. This observation may prove useful in qualifying PEDOT–TFB microelectrodes with a greater likelihood of registering long-term activity. Overall, our findings confirm that PEDOT–TFB is a chronically stable coating for microelectrodes to enable neural recording.

Statement of significance

Microelectrode arrays have been extensively utilized to record extracellular neuronal activity for brain–machine interface applications. Poly(3,4-ethylenedioxythiophene) (PEDOT) has gained interest because of its unique electrochemical characteristics and its excellent intrinsic electrical conductivity. However, the long-term stability of the PEDOT film, especially for chronic neural applications, is unclear. In this manuscript, we report for the first time the use of highly stable PEDOT doped with tetrafluoroborate (TFB) for long-term neural recordings. We show that PEDOT–TFB coated microelectrodes on average register more units compared to control gold microelectrodes for at least first four weeks post implantation. We collected the *in vivo* impedance data over a wide frequency spectrum and developed an equivalent circuit model which helped us determine certain parameters to distinguish between PEDOT–TFB

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microelectrodes with and without long-term activity. Our findings suggest that PEDOT–TFB is a chronically stable coating for neural recording microelectrodes. As such, PEDOT–TFB could facilitate chronic recordings with ultra-small and high-density neural arrays.

1. Introduction

Implantable microelectrode arrays (MEAs) are miniature devices that record electrical activity of single or multiple neurons in the brain. Compared to other modalities such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), implantable MEAs enable neural recordings that have higher temporal and spatial resolution, which make them suitable candidates for applications such as brain–machine interfaces [1–3]. Although MEAs are fabricated in different shapes and designs, small microelectrodes facilitate spatial selectivity and high microelectrode density on a probe. However, reduced microelectrode size is associated with an increase in impedance, which elevates thermal noise levels [4,5] and contributes to poor electrical coupling between the microelectrode and tissue [6]. As a result, high impedance microelectrodes can lead to low signal-to-noise ratio (SNR) and loss of neuronal signals at the interface. Therefore, it is desirable to increase the effective surface area of the microelectrodes while maintaining their geometrical surface area.

Conductive polymers (CPs) such as poly(3,4-ethylenedioxythiophene) (PEDOT) and polypyrrole (PPy) have frequently been utilized over the last decade as coatings for neural probes [7–10]. CPs can be readily electrodeposited on microelectrodes to create a porous and large electrochemical surface area resulting in coatings with excellent intrinsic electrical conductivity [11–13]. Among the CPs, PEDOT in particular has gained interest because of its unique electrochemical characteristics including a low oxidation voltage for the monomer [14] and high electrical conductivity due to the conjugated double bonds in the polymer backbone [15]. However, the long-term stability of the PEDOT film, especially for chronic neural applications, is elusive. Ludwig et al. [16] reported that PEDOT-coated microelectrodes on silicon shank probes were able to register activity only up to 8 days, whereas, latter work with PEDOT doped with carbon nanotubes demonstrated more than 12 weeks recording of the evoked potentials in visual cortex [17]. Based on the prior studies, it is difficult to ascertain the longevity of neuronal recordings with PEDOT coated microelectrodes. While prior work does not directly point out any major stability issues with PEDOT–PSS, the recent work show longer lifetimes with alternative PEDOT formulations [17]. Therefore it is necessary to examine the long-term utility of any PEDOT-coated probes for neural applications.

Electrochemical polymerization of EDOT requires a supporting counter ion, which is incorporated into the polymer film and plays an important role in the stability, electrical characteristics, and macroscopic features of the deposited polymer [18,19]. The most common counter ion for PEDOT electrochemical polymerization is poly(styrenesulfonate) (PSS) [4,13,20,21]. However, recent reports suggest that replacing PSS with a smaller molecule could enhance the electrical properties of the PEDOT as well as its long term stability [19,22]. Prior work has shown that neural probes coated with PEDOT polymers doped with perchlorate ions, which are smaller than PSS and monoanionic, showed unit activity up to six weeks post implant [9]. Recently, our group demonstrated improvements in the *in vitro* long-term PEDOT stability through use of an alternative smaller counter ion, tetrafluoroborate (TFB) [23]. PEDOT–TFB microelectrodes exhibited smaller impedance and longer lifetime in accelerated aging studies when compared with PEDOT–PSS or PEDOT–PSS blended with carbon nanotubes [23,24].

Here, we report for the first time the use of highly stable PEDOT–TFB coated microelectrodes for long-term neural recordings. We show that PEDOT–TFB microelectrodes on average register more units compared to control gold (Au) microelectrodes for at least first four weeks post implantation. In addition, we demonstrate that the impedance of PEDOT–TFB microelectrodes remains lower than Au microelectrodes over at least 12 weeks. Moreover, our equivalent circuit model of the *in vivo* EIS data suggests that the polymer-related components of the circuit model remained stable for the duration of the study. In addition, we observed that coated microelectrodes that appeared more likely to yield long term recordings were associated with increased double layer capacitance assessed by equivalent circuit modelling of the electrochemical impedance spectra prior to implantation.

2. Material and methods

2.1. Electrochemical modification of neural probes

Single-shank silicon-based chronic probes were purchased from NeuroNexus (NeuroNexus Inc., Ann Arbor, MI). Each probe was 5 mm long with the thickness of 15 μm. It consisted of 16 iridium microelectrodes with surface area of 177 μm^2 and 100 μm inter-microelectrode distance. Electrochemical modification and characterization was carried out using a CHI 660D electrochemical workstation (CH Instruments Inc., Austin, TX). Similar to the process described in earlier reports [24], initial impedance profiles of the microelectrodes were measured by running electrochemical impedance spectroscopy (EIS) in Phosphate Buffered Saline (PBS) over the frequency range 0.1 Hz to 100 kHz using a 20 mV sine wave. A thin layer of Au was electrochemically deposited on the microelectrodes using an aqueous solution of 5 mM chloroauric acid ($HAuCl_4$) in 0.1 M $NaClO_4$ as the supporting electrolyte. Chloroauric acid was employed to avoid use of the highly toxic $HAu(CN)_2$ reagent and possible incorporation of cyanide in the Au layer. The deposition was performed by running fast voltage sweeps between −1.5 and 0 V at a rate of 1 V/s for ~6 cycles. Subsequently, PEDOT–TFB was deposited on alternating blocks of 4 consecutive microelectrodes in each probe (8 total), the order of which was counterbalanced across probes to control for the position of PEDOT–TFB modified microelectrodes within the cortical layers of the brain. The scheme for the probe modification and an optical image of a modified probe are shown in Fig. 1A and B. The solution for the conductive polymer deposition contained 10 mM EDOT, the PEDOT monomer, in 0.1 M tetrabutylammonium tetrafluoroborate in acetonitrile. The deposition process was performed by cyclic voltammetry between 0 to 1.2 V with a scan rate of 1 V/s for 50 cycles. The total deposition charge was 390 mC/cm^2 and the polymer thickness was around 1.7 μm. To maintain consistency, the deposition parameters such as voltage window, number of cycles, and the deposition solution were kept consistent for all the microelectrodes. The microelectrodes were then cycled between 0 and 0.5 V in PBS to exchange the loosely attached TFB anions. Although there is little information available on the toxicological effects of TFB other than a general study

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