COMMUNICATION

Highly Conformable Conducting Polymer Electrodes for In Vivo Recordings

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Electronic devices that interface with living tissue have become a necessity in clinics to improve diagnosis and treatments. Devices such as cardiac pacemakers and cochlear implants stimulate and monitor electrically active cells, restoring lost function and improving quality of life. On a more fundamental level, most breakthroughs in our understanding of the basic mechanisms of information processing in the brain have been obtained by means of recordings from implantable electrodes.[1–3] Materials science is playing a pivotal role in this field. For example, state-of-the-art implantable electrodes are microfabricated devices that contain high-density arrays of metal sites on a silicon shank (silicon probes).[4] Still, as neuroscience continues to advance and more options for electrical intervention become a reality for patients (ocular implants, deep-brain stimulation for epilepsy and Parkinson's disease),[5] there is a tremendous need for developing advanced materials solutions for the biotic/abiotic interface. One such example is the necessity to develop electrodes that can conform to the curvilinear shapes of organs (e.g., the surface of the brain or its sulci) and form high-quality electrical contacts. Such surface electrodes are needed for electrocorticography (ECoG), which is increasingly used for functional mapping of cognitive processes before certain types of brain surgery (e.g., tumors) or for diagnosis purposes (e.g., epilepsy).[6] Placed on the somatosensory cortex, surface electrode arrays are also being used in brain-machine interfaces, an assistive technology for people with severe motor disabilities.[7] In contrary to silicon probes that penetrate the brain and cause tissue damage, these arrays are placed on the surface of the brain and are hence less invasive.

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Not surprisingly, there has been a lot of interest within the materials science community to develop conformable electrodes. As bending rigidity decreases with thickness, thin sheets of polymeric materials, including polyimide,[8,9] polydimethylsiloxane,[10,11] and parylene[12–14] are being used as substrates and insulation layers for the fabrication of such surface arrays, typically in conjunction with Au, Ir, or Pt electrodes. To ensure that these arrays are sufficiently self-supporting and can be handled during surgery, they are built to a total thickness exceeding 10 μm (and in some cases 100 μm), which, however, limits their conformability. A creative solution involving the use of bioresorbable substrates was recently reported by the Rogers and co-workers:[15] Ultrathin electrode arrays (which were not self-supporting on their own) were fabricated by sandwiching Au electrodes between two 1.2 μm thick layers of polyimide. They were transferred onto films of silk, which made handling possible and dissolved after flushing with saline.

In a parallel effort, conducting polymers have emerged as ideal electrode materials for interfacing with neurons and are being used to overcoat metal electrodes and improve the performance of silicon probes.[16–18] Conducting polymer electrodes were shown to reduce the foreign body response of the brain to the probe and to enable the recording of electrical activity for longer time intervals. Moreover, they were shown to lower the electrical impedance at the interface with tissue, improving the quality of recordings.[19] Although this is not understood in a quantitative manner, it is often attributed to a decreased impedance at the biotic/abiotic interface, due to the ability of polymers to conduct ions.[16] Furthermore, conducting polymers have been used to release drugs such as neurotrophins, enabling combined electrical/biochemical stimulation.[18,20] Finally, conducting polymer electrodes were used to detect transmitter molecule release from single cells,[21] creating the tantalizing potential for combined electrical/biochemical recording at a single cell level.

Given the high demand for the development of biocompatible and conformable electrodes for in vivo applications and given the advantages provided by conducting polymers for neuronal interfacing, it is essential to develop general procedures for integrating conducting polymers with flexible substrates. This demand has remained largely unanswered. Actual solutions available rely almost exclusively on electrochemically grown conducting polymers on pre-patterned metal electrodes,[16] which dramatically limits the range of polymers that can be utilized. One exception involves a rather exotic patterning technique based on microfluidics

and results in thick arrays with limited conformability.[22] Here, we provide a generic solution to this challenge and demonstrate highly conformable electrode arrays that consist of a 4-μm-thick parylene C film that contains photolithographically defined microelectrodes based on poly(3,4-ethylenedioxythiophene) doped with poly(styrene sulfonate) (PEDOT:PSS). PEDOT:PSS is an obvious choice as electrode material, given its state-of-the-art conductivity, its biocompatibility,[23] its chemical stability,[18] and the fact that it is commercially available. Similarly obvious is the choice of parylene as a substrate and an insulator, given its combination of biocompatibility[24] and good mechanical (flexibility) and electrical (insulation) properties. We demonstrate the use of these electrode arrays for in vivo electrocorticography (ECoG) in rats, in which sharp-wave events mimicking epileptic spikes were successfully recorded. We also show that the arrays provide high spatial resolution and that PEDOT:PSS electrodes outperform Au ones during in vivo evaluation of devices of similar geometry.

The fabrication process and the resulting layout of the conducting polymer electrodes are shown in **Figure 1**. The fabrication started by depositing a 2-μm-thick parylene film, which became the substrate of the array, on a quartz wafer. Au contact pads and interconnects were subsequently patterned using a standard lift-off process. The sample was then coated for a second time with a 2-μm-thick parylene film, which became the insulator of the array, and a window was opened over part of the Au film via photolithography and etching. The PEDOT:PSS film was deposited from solution, and the sample was coated for a third time with a sacrificial parylene film whose purpose was to protect the conducting polymer electrode from the subsequent processing steps. Final photolithography and etching steps defined the structure of the PEDOT:PSS electrodes. The fabrication ended with immersion in deionized water, which removed the parylene film overlying the PEDOT:PSS and exposed the electrodes. Finally, the arrays were peeled-off the quartz wafer before use. This process is fairly generic and relies on the better adhesion of the conducting polymer on the metal electrode than on the overlying parylene film. As the latter is hydrophobic, it is expected to work with most conducting polymers, which obtain some hydrophilic character due to their doping. It should be noted that, in separate tests, it was established that the deposition and removal of a parylene film from a PEDOT:PSS film did not affect the conductivity of the latter.

The process described above yielded electrode arrays with a total thickness of 4 μm, with the Au interconnects and the PEDOT:PSS located at the neutral mechanical plane. The layout of an array is shown in Figure 1b. The arrays had a hole in the middle (through the parylene film), in order to allow the simultaneous insertion of a silicon probe (see below). Two sets of 32 electrodes each were placed on either side of this hole. Each set consisted of two subsets of 16 electrodes each, placed on a hexagonal lattice, with individual electrodes having an area of 20 μm × 20 μm and a center-to-center distance of 60 μm. This particular design provides a fine surface map of the electrical activity of a brain region of interest, while at the same time it allows depth-recordings from a silicon probe to be performed. Despite their thinness, the electrode arrays had adequate mechanical strength to be self-supporting and to be manipulated by a surgeon. Figure 1c shows a partially peeled array (Au contact pads are visible) supporting not only its own weight, but also the weight of a 100 mm quartz wafer (1 mm thick). At the same time, the arrays were able to conform to surfaces with a small radius of curvature. Figure 1d shows a microscopy image of an array conforming to a cylinder with a radius of 2.2 mm, a conformability which is adequate for most in vivo applications.

In order to validate the PEDOT:PSS array and show that it can record signals of biological origin, the following experiment was performed: An array was attached to a printed circuit board (with its recording end extending into free space), which provided connections to the recording electronics and helped place the array on the brain of an anesthetized rat. A small craniotomy was performed above the somatosensory cortex, the dura was removed, and the array was placed on the surface of the brain (**Figure 2**). At the same time, a silicon probe (Neuronexus) attached to a stereotaxic frame was implanted through the hole in the center of the array. The silicon probe had a single shank with 16 Ir electrodes (177 μm^2 area each) arranged in a linear configuration with a center-to-center distance of 100 μm. Simultaneous recordings from PEDOT:PSS electrodes placed on the surface of the brain and from Ir electrodes on the silicon probe implanted in the cortex are shown in Figure 2c. The recordings were carried out after the addition of 100 μM of bicuculline, a $GABA_A$ receptor antagonist that enables the

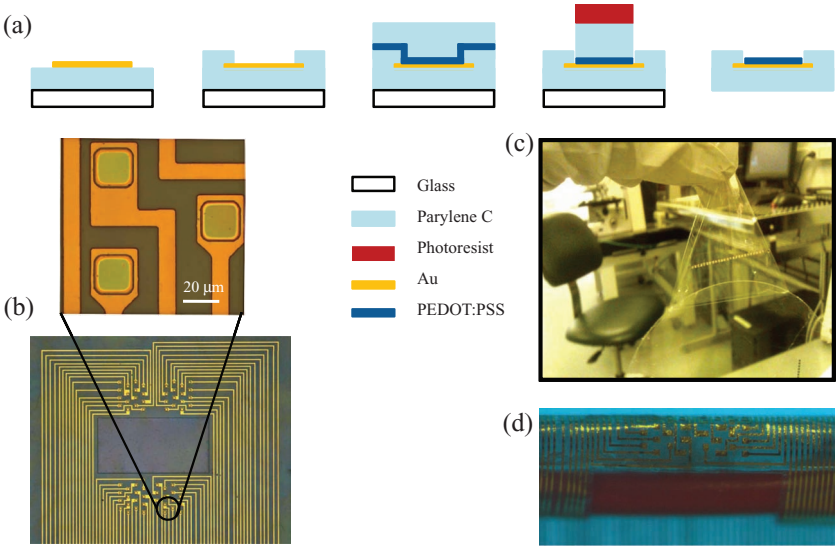

Figure 1. a) Schematic representation of the fabrication process indicating the cross-section of an electrode (not to scale). b) Microscopy images of the array showing the hole through which a silicon probe was inserted and a detailed view of three electrodes. The electrode array is shown to support the weight of a quartz wafer (c), and to conform to a cylinder with a radius of 2.2 mm (d).

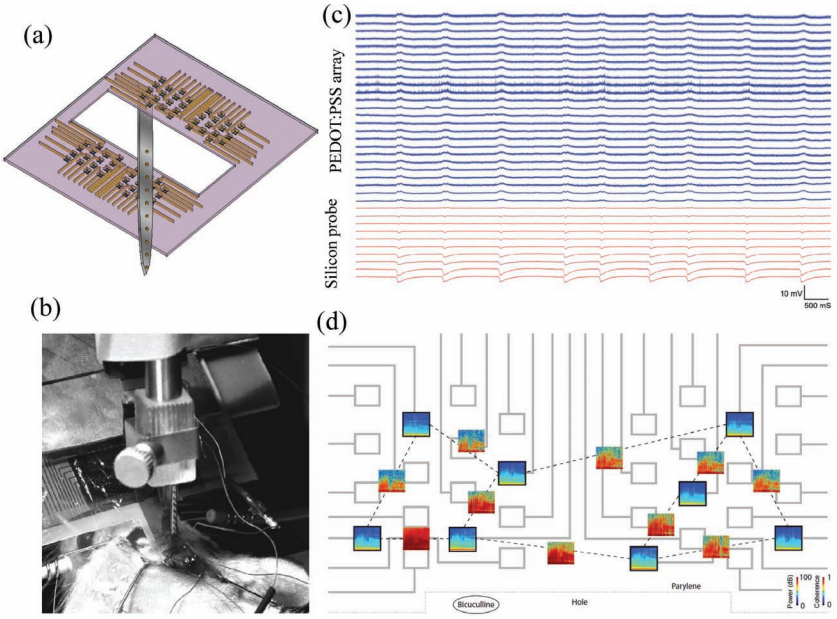

Figure 2. Schematic of the experiment used for the validation of the PEDOT:PSS array with a silicon probe viewed from inside the brain (a) and photograph showing the implantation (b). Recordings from 25 electrodes in the PEDOT:PSS array, and from 10 electrodes in the silicon probe, ordered from superficial to deeper in the cortex (c). d) Time-frequency (TF) analysis of the signals recorded by a few electrodes (black frames, X-axis: time, 10 min; y-axis: frequency, 0.1–50 Hz; color coding: power, dB) and their cross-spectrum coherences (open boxes, same axes as TF plots, color coding: coherence).

genesis of sharp-wave events, which mimic epileptic spikes.[25] This typical activity is recorded by the silicon probe in the different cortical layers. As the recordings were taken after sufficient time was elapsed for the effects of bicuculline to diffuse in the cortical layers (20 min), a stronger activity is measured by the silicon probe at the deepest layers of the cortex. At the same time, the PEDOT:PSS electrodes were also able to record the same sharp-wave events as a depth/volume summation. The coincidence of the peaks recorded by the PEDOT:PSS electrodes and the silicon probe provides validation for the former and shows that the measured signals are indeed of biological origin. It should be noted that the polarity of the ECoG signal is inverted, due to the fact that the electrical dipoles that generate the bicuculline-triggered sharp-wave activity are located deep in the cortex.[26]

In order to assess the spatial resolution of the PEDOT:PSS array, we evaluated correlations in the signals recorded by a few electrodes, located at different distances from the position of bicuculline injection. A time–frequency (TF) analysis (0.1 to 50 Hz over 10 min) of signals recorded by these electrodes is shown in Figure 2d. Each TF plot shows a high power in the 1–2 Hz band and an elevated power in the 30 Hz, corresponding to the epileptiform sharp-wave activity triggered by the bicuculline. Also shown in Figure 2d are the computed cross-spectrum coherences between these electrodes. For the two electrodes close to the site of bicuculline injection (the ones at the bottom left of the Figure), similarities are seen in all the frequency spectra of the recorded signals. On the other hand, as the distance between two electrodes increases, significant coherence (red color) is only seen in the 1–2 Hz and 30 Hz band, while a low coherence (blue color) is seen in the rest of the spectrum. This indicates that, even if all the sites do record synchronously the sharp-wave events (as seen through the 1–2 and 30 Hz bands), each ECoG signal is specific to the particular location of the electrode, meaning that the spatial resolution of the array is of the order of the interelectrode spacing.

As seen in Figure 1a, the addition of PEDOT:PSS electrodes adds to the complexity of fabrication. The question, therefore, arises as to how these electrodes compare to plain Au ones. To address this issue, arrays with similar geometry consisting of plain Au electrodes were fabricated by terminating the fabrication after the deposition and etching of the second parylene layer. An array with Au electrodes was placed on the brain of an anesthetized rat and recordings were performed for a period of 30 min, after which time an array with PEDOT:PSS electrodes was placed on the same spot and recorded for the same amount of time. **Figure 3** shows the power spectra of recordings from five representative channels from Au and from PEDOT:PSS electrodes. Both show the typical 1/f property of the ECoG spectrum.[26] The power spectra of the PEDOT:PSS electrodes, however, show a better definition of the 1–10 Hz and the 30 Hz (gamma) bands, which are indicated by arrows in the first panel of Figure 3b. These frequency bands, as shown in Figure 2d, are the dominant ones during bicuculline-triggered sharp-wave events. Thus, PEDOT:PSS electrodes record the electrophysiological signal with a higher accuracy, which highlights the importance of incorporating conducting polymers in a highly conformable electrode array format.

In conclusion, we developed a generic process for incorporating conducting polymer electrodes on highly conformable substrates. Contrary to previously reported methods such as electrochemical growth off of patterned metal electrodes, the process described here involves the direct patterning of the polymer layer and thereby enables the use of "champion" materials such as PEDOT:PSS. Arrays of PEDOT:PSS electrodes were fabricated on parylene substrates, and their total thickness of 4 μm endowed them with high conformability. Their use in electrocorticography was demonstrated and validated against a silicon probe, and they were shown to outperform Au electrodes of similar geometry. In addition to their application in ECoG, highly conformable electrode arrays can find a host of other applications in Neuroscience. They can be folded on themselves, creating arrays with electrodes on both sides. Such arrays provide a means of recording ECoG signals inside sulci in the human brain, which will further diagnostic capabilities. Moreover, with the aid of an appropriate insertion shuttle, they can be implanted deep in the brain, where, owing to their high mechanical flexibility, they might be less invasive than traditional electrode arrays made from hard materials.

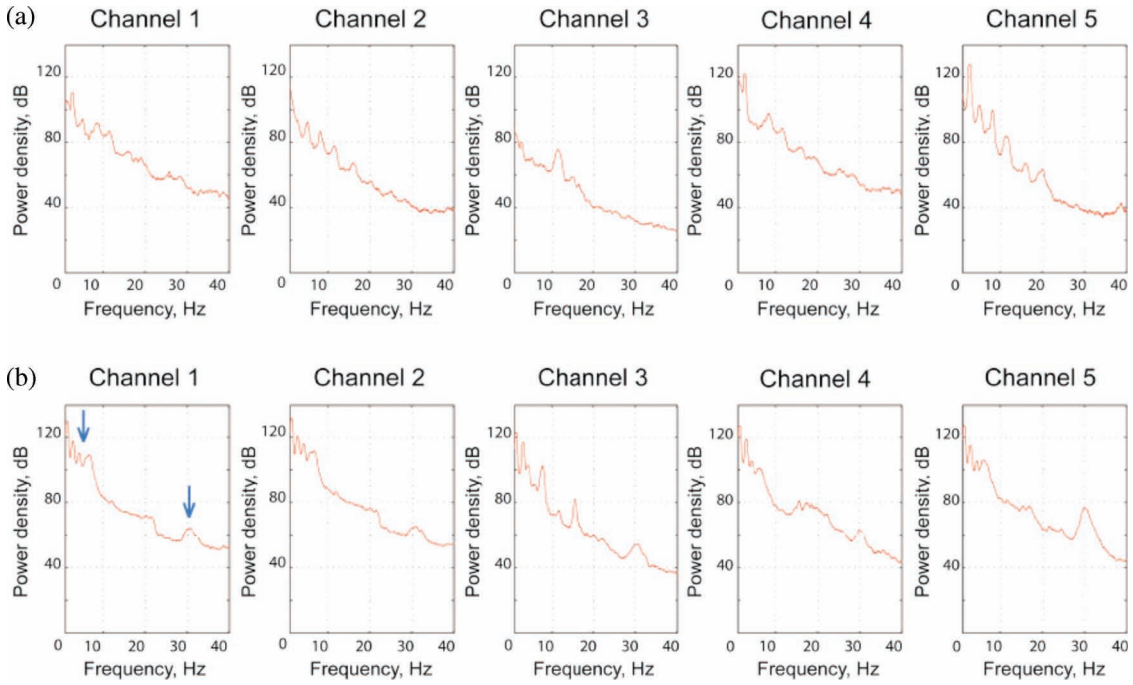

Figure 3. Power spectra of representative recordings with Au (a) and PEDOT:PSS (b) electrodes. The arrows indicate the 1–10 Hz and the 30 Hz (gamma) bands.

Experimental Section

Array Fabrication: The fabrication process, outlined in Figure 1a, included the deposition and patterning of parylene, metal and PEDOT:PSS. These steps were performed as follows: Parylene C was deposited using a SCS Labcoater 2 to a thickness of 2 µm (at which thickness parylene films are pinhole-free). These films were patterned with the aid of a 4.6 µm thick layer of AZ9260 photoresist and reactive ion etching by an O_2 plasma using an Oxford 80 plus. Metal pads and interconnects were patterned by a lift-off process. A bilayer photoresist, LOR 5A and S1813, was spin coated on the parylene film and exposed to UV light using a SUSS MBJ4 contact aligner, then developed using MF-26 developer. This was followed by the deposition of 5 nm of titanium and 100 nm of gold using a metal evaporator. Lift-off was performed using 1165 stripper. For the preparation of the PEDOT:PSS films, 20 mL of aqueous dispersion (PH-500 from H.C. Stark) was mixed with 5 mL of ethylene glycol, 50 µL of dodecyl benzene sulfonic acid (DBSA), and 1 wt% of 3-glycidoxypropyltrimethoxysilane (GOPS, as a cross-linker), and the resulting dispersion was spin-coated at 650 rpm. The films were subsequently baked at 140 C for 1 h and were immersed in phosphate buffered saline (PBS) to remove any excess low molecular weight compounds.

In Vivo Evaluation: All the protocols have been approved by the Institutional Animal Care and Use Committee of INSERM. Male Wistar rats (Charles River, MA, weight of 400-500 g) were anesthetized with a ketamine/xylazine mixture [35 and 1 mg kg^{-1}, intramuscular (i.m.)]. Additional doses of ketamine/xylazine (7 and 0.3 mg kg^{-1}, i.m.) were given as needed. Other rats, used for the implantation of both a deep-brain probe and an ECoG, were anesthetized with urethane (1.5 g kg^{-1}, intraperitoneal) and ketamine/xylazine (80 and 2 mg kg^{-1}, i.m.). The animals were restrained and their skulls were immobilized in a stereotaxic apparatus. Their body temperature was monitored and kept constant with a heating pad. A 5 mm × 3 mm craniotomy was performed in the right hemisphere above the somatosensory cortex (centered at –3 mm in the anterio-posterior axis and –2 mm in the medio-lateral axis relative to Bregma). The dura matter was removed and the PEDOT:PSS electrode array was slowly lowered on the surface of the brain. Two miniature stainless steel screws were driven into the skull above the cerebellum and served as ground and reference electrodes respectively. The electrodes were connected to a HST headstage (Plexon), which was connected to a multi-channel Digital Lynx 10S system (Neuralynx). The neurophysiological signals were amplified (1000×), band pass-filtered (1 Hz–5 kHz) and acquired continuously at 32 kHz on the 64-channel Neuralynx system (16-bit resolution). To validate the PEDOT:PSS electrodes, an implantable probe (Neuronexus A1 × 16–3 mm–100–177, with a single, 3 mm long shank, and a linear array of 16 electrodes with 100 µm spacing and 177 μm^2 area/electrode) was inserted through the center of the PEDOT:PSS array in the cortex to reach a final depth of 2 mm. All analysis was performed using custom-written tools in Matlab (Mathworks). The signal was firstly whitened to reduce the dyna leakage of low frequencies in the higher frequency bins during spectrum estimation.[27] Spectral analysis were performed using fast Fourier transform of the ECoG signal between 0.1 and 50 Hz and coherence was computed using direct multitaper estimates.[27–28] Typically, window sizes of 2–4 s and three to five tapers were used.

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