Development of polyimide electrodes for high-resolution intracranial EEG recordings

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Abstract (450 words):

Object: Resective surgery remains the most effective, yet underutilized treatment for drug resistant focal epilepsy. The high cost and patient discomfort associated with prolonged intracranial EEG monitoring likely contributes significantly to the underutilization of resective surgery. Current intracranial electrodes are largely handmade, bulky, costly, and pose several risks to patients. Furthermore, recent research supports that biomarkers of the epileptic networks occur on sub-millimeter spatial scales that are not probed by standard clinical subdural and depth electrodes. Here we describe thin, flexible, polyimide substrate electrodes, that can be easily manufactured that show promise for improving human brain mapping .

Methods: To examine biological impact on mammalian brain, polyimide substrate electrodes were implanted into the subdural space alongside standard clinical subdural electrodes in pigs for one week. The tissue underlying the two types of electrodes was removed, fixed, stained, and examined for immunological responses. Electrophysiological properties were examined by acute recordings in pigs and from tissue to be resected in patients undergoing surgery. To examine the electrophysiology of thin film electrodes and compare to clinical electrodes acute intra-operative recordings where obtained in an acute seizure model in procine cortex and in 5 patients undergoing resection for drug resistant epilepsy.

Results: Histological analysis showed reduced immunological reaction to prolonged polyimide substrate implants compared to standard silicone substrate, clinical electrodes. Electrophysiological recordings showed data obtained from polyimide electrodes showed feasibility of high fidelity multi-scale electrophysiology, and for standard macroelectrode the EEG was comparable to standard clinical electrodes, while also displaying easier deployment of polyimide electrodes through burr holes and underneath the dura.

Conclusions: Thin, flexible polyimide substrate electrodes with lithographic deposition of metallic contacts provide multi-scale electrophysiological data and for macroeletrodes recordings similar to standard clinical electrodes with markedly reduced immunological response. In addition, the flexibility and reduced volume of polyimide electrodes should reduce pain and edema associated with subdural grid implantation, and the increased number of channels per grid with a single electrode tail exiting the brain should provide reduced infection risk by reducing the number of tails. Combined, these properties suggest that the replacement of current silicone electrodes with polyimide substrate electrodes for the acquisition of intracranial EEG could provide enhanced clinical electrophysiological value with reduced cost, infection risk, and patient discomfort..

Introduction:

Intracranial EEG (iEEG) allows electrophysiology recordings directly human brain {Staba, 2014; Bower, 2012; Navarro Hasboun, 2010; Worrell Gardner, 2008}, and is often required for localization of epileptogenic tissue prior to epilepsy surgery {Engel, 2013}. Currently, available electrodes for iEEG include subdural strips, grids and penetrating depth. Historically, clinical electrode manufacturers primarily provided electrode arrays that sampled brain tissue at approximately centimeter spatial scales for localizing epileptogenic brain, e.g. 6 cm^2 contacts and 10 cm spacing (Adtech, Inc.; PMT, Inc.; Integra, Inc.; Dixi Medical, Inc.). However, recent studies have demonstrated that unique and potentially clinically relevant electrophysiology is obtained by recording iEEG at sub-millimeter spatial scales {Stead, 2010; Schevon, 2010} {Chang 2015} and thousand Hz sampling rates {Worrell 2012}. In addition, advances in digital EEG acquisition have made large-scale recordings from 100s of electrodes possible {Brinkmann Stengel, 2009}.

Despite these advances, high-spatial-resolution iEEG has been slow to impact clinical practice. One of the primary reasons is the challenge and cost of producing high-density, sub-millimeter resolution electrode grids and depth electrodes. Clinical electrodes are composed of platinum-iridium contacts embedded in a silicone substrate and are manufactured largely by hand, which is labor intensive and limits the size and number of electrodes{Wyler 1984} {Myllymaa 2009}. The technology for lithographic deposition of thin metal films, in contrast, has matured and is widely available on a range of polymer substrates {Myllymaa 2009}. (Figure 1). While not currently available for clinical use, multiple groups have fabricated and tested polyimide (PI) substrate multi-contact electrode arrays {Gonz Rodr, 1997; Rousche, 2001; Bossi, 2009; Chen Lai Lin, 2009; Patrick, 2010}. Here we describe a series of experiments in animals and humans using high-resolution polyimide subdural grid and penetrating depth electrode arrays to record local field potentials and single neuron activity. We show: 1) high fidelity LFPs can be recorded from subdural and depth electrodes intraoperative pig and human, 2) single neuron activity from penetrating depth electrodes in pig and human, 3) deployment of polyimide electrode via burr hole, and 4) histological response to prolonged implantation of polyimide electrodes and a silicone substrate clinical strip electrode.

Methods

Development of the polyimide electrode and headstage

Polyimide electrodes were designed by the the Mayo Clinic Division of Engineering and fabricated with 25-µm thick polyimide (Metrigraphics, Lowell, MA). The 64 gold microcontacts, each 40 µm in diameter, and the gold connecting traces, which varied in width from 10 µm to 20 µm, were deposited by photolithographic methods. To connect the electrodes to recording equipment, the tail of the polyimide electrode array was attached to a custom printed circuit board (PCB) by means of a pressure contact interface. An array of 0.5-mm diameter solder bumps on the PCB, also designed by the Mayo Clinic Division of Engineering, aligned with a matching array on the polyimide

electrode tail, which was held in place and under pressure by a hinged transparent clamp. Proper alignment was confirmed visually, by peering through the transparent clamp and the translucent PCB. Traces on the PCB connected the array of solder bumps to two 32-channel Omnetics connectors (Omnetics, Inc., Minneapolis, MN), each accommodating a Neuralynx HS-36 multichannel headstage amplifier. Each headstage was connected by a shielded Litz-wire tether to a Digital Lynx recording system (Neuralynx, Inc., Bozeman, MT) that sampled each channel at 32 kHz.

Figure 1 near here.

Development of the depth electrode

A customized clinical depth electrode incorporating 40-µm diameter electrodes has been developed for research purposes by the Mayo Clinic Division of Engineering. The 25-µm thick polyimide electrode array (Metrigraphics, Lowell, MA) was rolled into a cylinder and adhesively attached to a 1.6-mm diameter ceramic rod (Accuratus, Phillipsburg, NJ) with 0.002-inch thick acrylic adhesive transfer tape (3M, Maplewood, MN). ~~The stylus was withdrawn after insertion~~. The 64 electrodes were connected to the Digital Lynx recording system by the previously described pressure-contact interface PCB, HS-36 headstages and tether cables, and were sampled at 32 kHz.

Figure 2 near here.

Acute subdural recordings in porcine epilepsy model

All pig experiments were approved by the Mayo Clinic Institutional Animal Care and Use Committee. Animals were housed and cared for, and anesthesia administered, under the supervision of licensed staff veterinarians. As described previously {Van Gompel, 2011}, we employed an acute swine model of epilepsy to demonstrate the recording capability of the polyimide electrode. Juvenile male pigs (20-40 kg) were placed under general anesthesia and positioned prone. In the first set of experiments, a large bilateral craniotomy was made. The dura was carefully opened and removed over the brain bilaterally, taking care to leave the superior sagittal sinus intact. A standard, 16-contact (4x4) clinical silicone grid electrode (PMT, Inc.) was placed onto the brain, and 30 minutes of recording data were obtained. The grid was then removed, the polyimide strip electrode was placed onto the brain, and another 30 minutes of recording data were obtained. A polyimide depth electrode containing microcontacts along the length of the shaft was then inserted into the brain and advanced stereotaxically to hippocampus. Recordings obtained from microcontacts were filtered for single neuron activity (600-6,000 Hz) and action potentials detected offline through a semi-automated process described previously {Bower, 2012}.

Safety of chronically implanted polyimide versus silicone electrodes

To demonstrate the superior safety profile of the polyimide strip electrodes compared with the standard silicone strip electrodes, prolonged subdural placement experiments were conducted in pigs. Each pig was placed under general anesthesia and positioned prone. Under sterile technique, the scalp was incised open, and two 1-cm burr holes were placed posteriorly in the skull on either side of the midline. The dura was carefully

incised through each. A standard, 4-contact (1x4) clinical silicone strip electrode (Adtech Inc.) was slid subdurally through one burr hole and a polyimide electrode through the other. They were both cut, and tacked to the pericranium adjacent to the burr hole with silk sutures, to simulate the tacking in place of subdural grids and strips in human patients during chronic recording. The scalp was then closed in layers and the pig recovered from anesthesia. A period of four days of prolonged placement was set, based on the observation of our neuropathologist (JEP) that histopathological changes in brain tissue underlying silicone grids and strips can be seen after three days of chronic placement in humans. Pigs were monitored closely during this four-day period for any adverse effects. Following this period, the pigs were sacrificed and, using careful surgical technique, the scalp and skull were removed and the dura elevated to demonstrate the correct subdural placement of both electrodes. The side with the polyimide electrode was marked with a suture, and the brain was carefully removed from the skull and placed in formalin for fixation. After a period of at least six days in formalin, the brains were sectioned and sent for histological processing. They were stained with hemotoxylin and eosin (H&E) stain and examined under the microscope.

Acute subdural and hippocampal depth recordings in humans
After approval by the Mayo Clinic Institutional Review Board, five patients were recruited to undergo placement of the polyimide strip electrode for acute recording. All five patients were diagnosed with drug resistant temporal lobe epilepsy, and were undergoing temporal lobectomy and amygdalohippocampectomy, with electrocorticography preceding resection, as part of a standard clinical protocol {Burkholder 2014}. At the time of resection, and prior to electrocorticography, the polyimide strip was placed on the brain tissue identified for resection, and five minutes of recording was done. The polyimide strip was then removed, and the underlying brain examined for any changes.

Results

Porcine Electrophysiology
PI electrodes were inserted through a burr hole (Fig 3A) and advanced subdurally (Fig 3B) towards a small burr hole containing an epileptiform focus produced by cortical injection of penicillin {Van Gompel, 2011} (Fig 3C). Using real-time recordings, the electrode was advanced until a maximum-amplitude epileptiform spike was observed , providing evidence that PI strip electrodes possess sufficient flexibility, maneuverability and recording fidelity to localize regions of clinical interest based on electrophysiological signals obtainable in an operative setting. The PI strip electrode was removed and the PI depth electrode was inserted through the large burr hole. Recordings were obtained after the depth electrode was advanced stereotaxically to the hippocampus (Fig 3D). The highest density of detections occurred in two clusters which, when compared to the CT-MRI reconstruction, corresponded to cell layers CA3 and Dentate Gyrus (DG) of hippocampus (Fig 3D-F), providing evidence that PI electrodes posses sufficient recording fidelity to identify deep brain structures from single neuron recordings.

Porcine Histology

Three pigs were implanted subdurally with both standard silicone electrodes and polyimide electrodes and allowed to recover for one week (Fig 1A). When electrode sites were examined (Fig 1B), significantly less immunological response was observed under the polyimide recording sites than under the silicone recording sites, in both cases at the macroscopic level (Fig 1C). Under histological stain and microscopy, a larger immunological response to silicone electrodes (Fig 1D & F) compared to the polyimide electrodes (Fig 1E & G). At 100X (Fig 1D & E) and significant leptomeningeal inflammation was observed. At 400X, the increased presence of lymphocytes and, interestingly, eosinophils was observed.

Figure 3 near here

Human Intraoperative Electrophysiology

Intraoperative recordings were obtained from five human patients undergoing intra-cranial monitoring for the treatment of epilepsy: four using a thin film PI grid electrode and one using a PI depth electrode. Intraoperative recordings from PI grid electrodes (Fig 5 A-C) provided sufficiently low noise (~10 µV RMS) and high fidelity to record localized epileptiform activity (Fig 5 D-F) with noise levels similar to that of standard silicone grid electrodes for recording microseizures in patients {Stead Van Gompel, 2010}. The intraoperative depth recording from the patient (Fig 6A) produced similar low-noise high-fidelity recordings that permitted distinguishing single neuron activity that is characteristic of the different neuronal layers, as was also the case for porcine depth electrode recordings (Fig 6B). Because intraoperative MRI was not clinically relevant in this particular case, it was not possible to co-localize the electrode locations to specific temporal lobe structures.

Figure 4 near here

Figure 5 near here

Discussion

Thin polyimide sheets containing lithographically deposited electrodes provide a safe and reliable alternative to current silicone electrodes, and also provide several benefits. PI electrodes produce comparable electrophysiological recordings, including fine scale LFPs on subdural grids and single neurons on penetrating electrodes, and reduced immunological response as evidenced by reduced histological response, possibly due to less immunoreactivity of PI film, less mechanical injury, or both{Prodanov 2016}. The use of lithographic techniques could reduce electrode costs, overcome the technical challenge of making electrodes capable of sub-millimeter spatial sampling of electrical activity and allow for high density of connections, reducing the number of electrode tails, which are known to increase infection risk. The known complications of iEEG monitoring include: 1) Intracranial hemorrhage, 2) subdural hematoma, 3) infection, 4) brain edema {Hamer, 2002; Van Gompel Bell, 2008; Gonzalez-Martinez Jehi Bulacio, 2013}. These complications are related directly to increased number of electrodes, possibly due to the increased mass within a closed volume and the greater number of electrode tails crossing the skin and thereby providing more avenues for infection.

The increased flexibility of thin polymer films has been exploited to allow high-density, high-fidelity recordings from animals and patients, emphasizing temporal and spatial resolution {Viventi Avrin, 2011; Viventi Avrin, 2014; Khodagholy, 2015}. While these devices provide substantial advances in the state of thin-film recording technology, they are still expensive and so do not provide an immediate alternative to silicone electrodes for clinical use. Polyimide-based lithographic electrode technology provides a low-cost, low-risk avenue for the immediate replacement of silicone based electrodes for intracranial recording in patients, that should provide lower cost and lower patient risk than current, silicone-based electrode grids and depth electrodes.

FIGURES

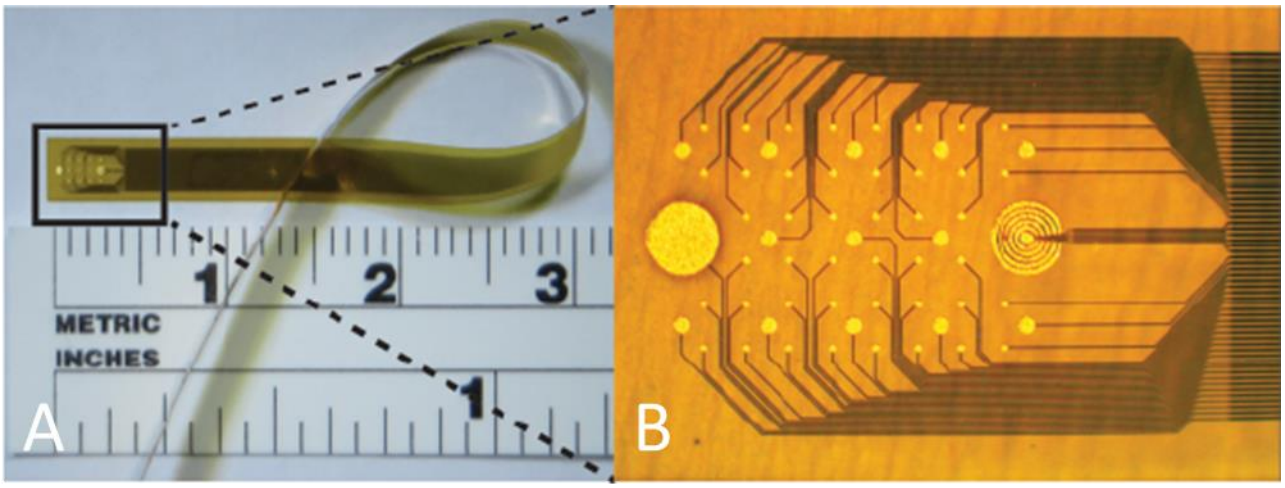


Figure 1. Micropatch electrode array used in porcine and human recordings and studies. A. Flexible polyimide thin-film electrode array. B. Enlarged view of the 64-contact multi-scale recording array (designed in collaboration with the Mayo Clinic Division of Engineering).

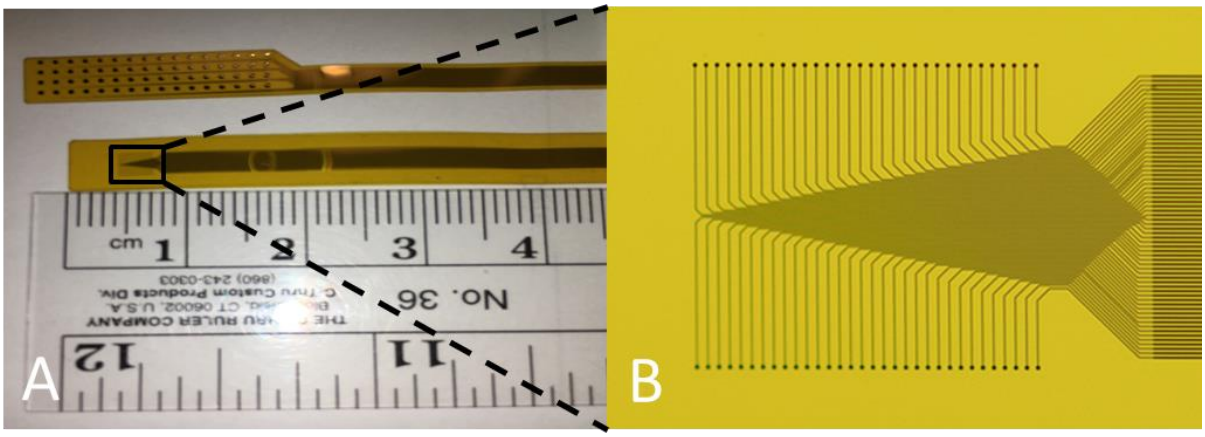


Figure 2. Depth electrode array used in porcine and human recordings and studies. A. Flexible polyimide thin-film electrode array prior to be wrapped around a ceramic stylus. B. Enlarged view of the 64-contact ~~multi-scale~~ recording array deposited on film (designed in collaboration with the Mayo Clinic Division of Engineering).

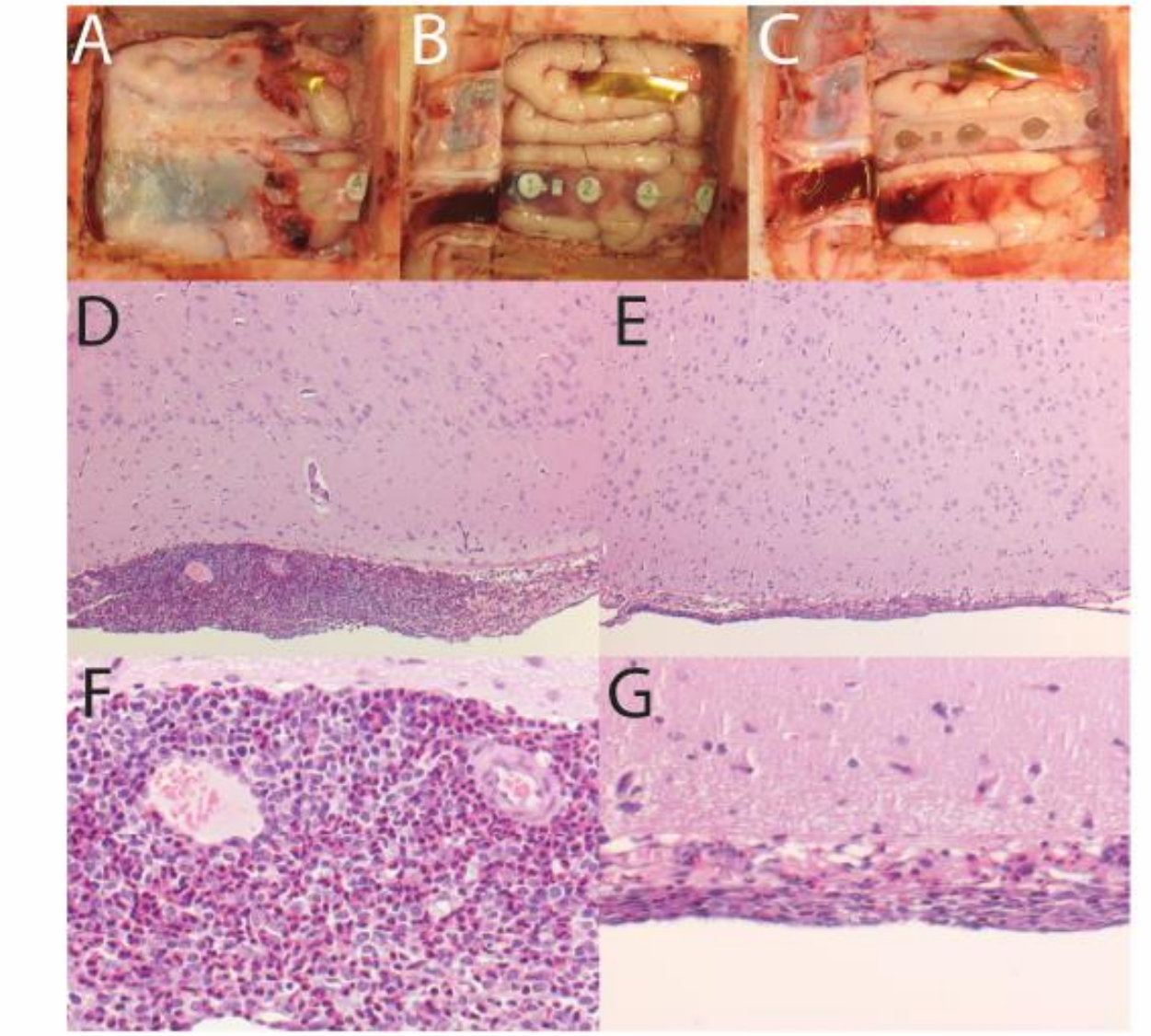
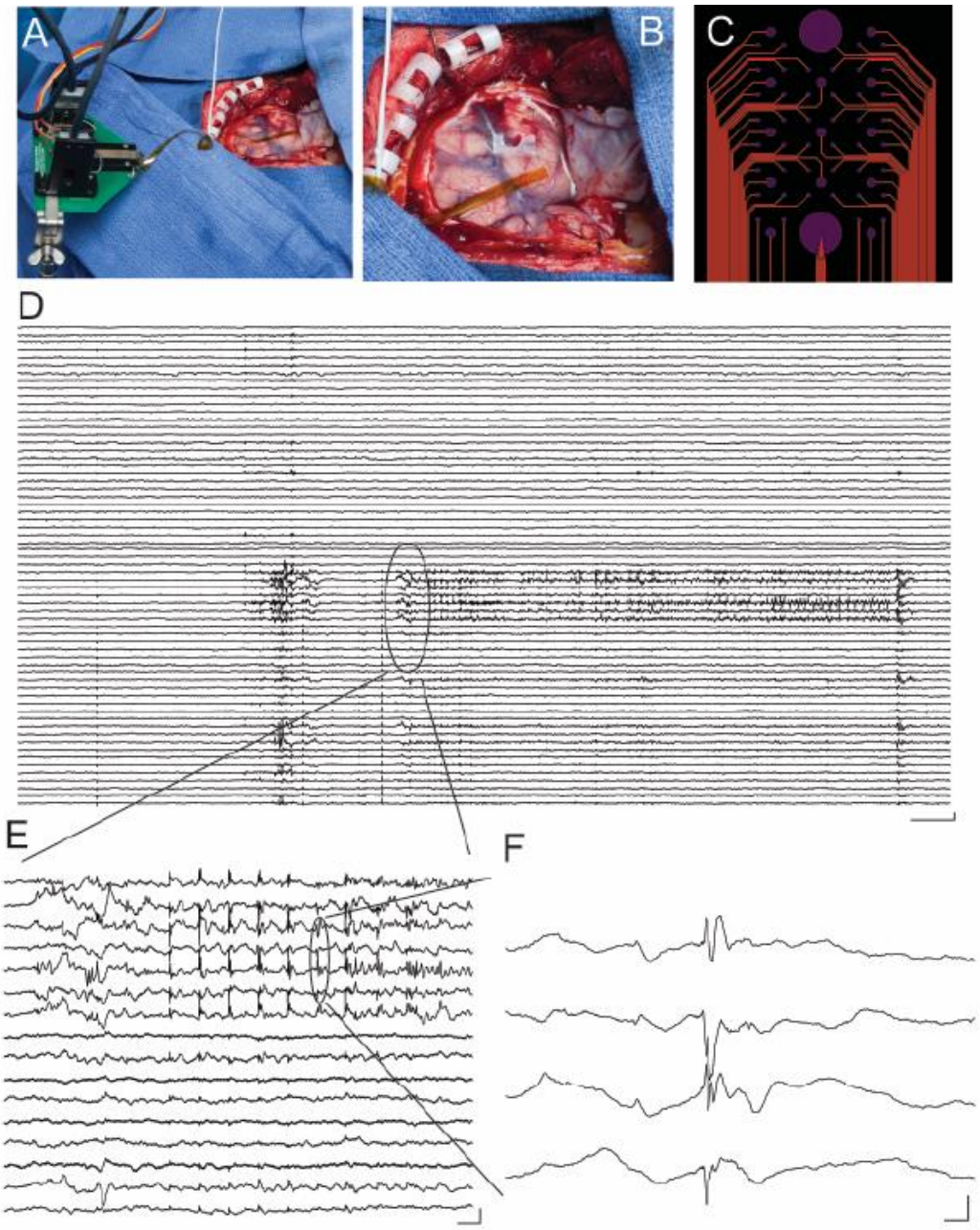


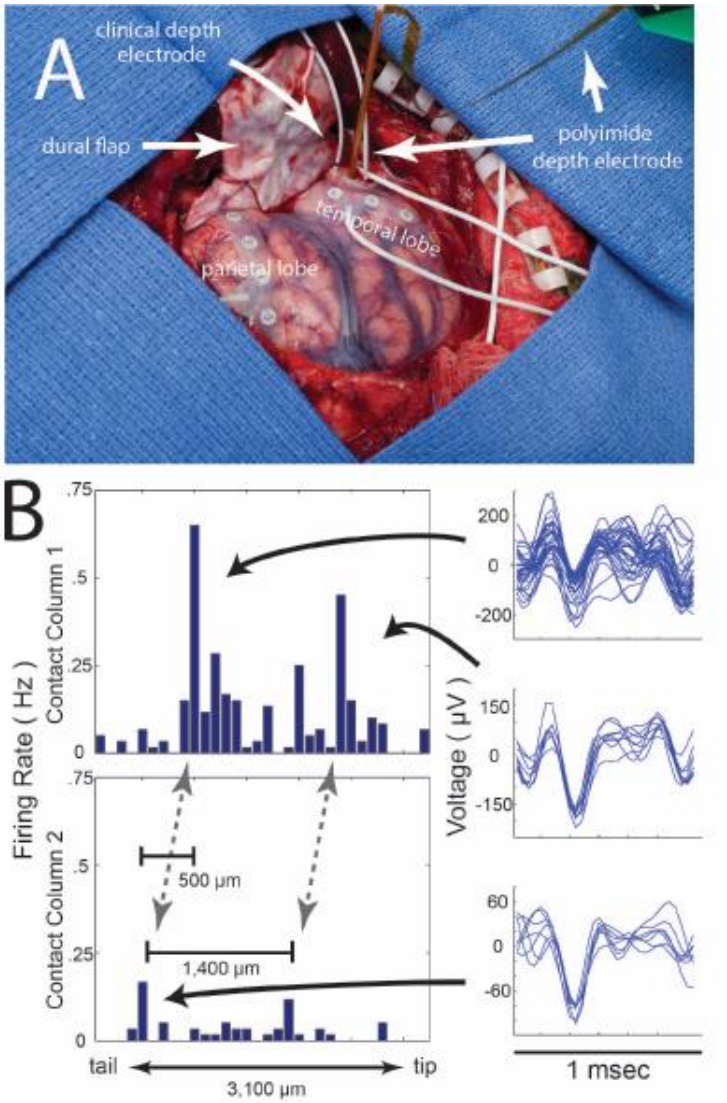
Figure 3. Porcine polyimide acute electrophysiology. A. Example of burr hole through which subdural thin film polyimide strip is placed into the subdural space, with smaller burr hole through which the penicillin focus is placed. B. Craniotomy demonstrating ease of placement of the thin film polyimide strip electrode subdurally (strip can be seen through the dura in the subdural space). C. Another example of polyimide strip (cut) placed through burr hole, demonstrating size of both burr holes. D-F. Polyimide microelectrodes with 100µm spacing resolve cell layers in a pig. D. MRI scan shows the electrode passed through hippocampus (inset shows actual polyimide depth electrode). E. Firing rates for detected units cluster in two groups that are presumably cell layers. F. Example waveforms taken from active regions.

Figure 4. Porcine electrode safety studies. A. Brain at necropsy, dura still in place, demonstrating polyimide (small arrow) and silicone (large arrow) strip electrodes in the subdural space. A hemorrhage overlying the silicone strip can be seen even through the dura. B. Same brain with dura reflected anteriorly. Minimal hemorrhage seen about the polyimide electrode, but clear hemorrhage seen both overlying and underlying the



silicone strip. C. Same brain with the electrodes displaced to show the underlying brain. D-G. Cortex and leptomeninges underlying strip electrodes in the same pig, stained with hematoxylin and eosin: D. Silicone strip, 100X. E. Polyimide strip, 100X. F. Silicone strip, 400X. G. Polyimide strip, 400X. Significant leptomeningeal inflammation, with presence of lymphocytes and, interestingly, eosinophils is noted underlying the silicone strip, with less inflammation noted underlying the polyimide strip.

Figure 5. Human intraoperative electrophysiology using polyimide electrodes. A. Experimental setup. B. Expanded view showing polyimide electrode lying on the brain surface. C. Polyimide electrode grid showing electrodes (40 µm) and connections (scale bar: 500 µm). D. Signals from all 64 channels showing a transient burst of epileptiform spiking on a sub-region of the grid (scale bar: 2 mV; 200 msec). E. Expanded view of epileptiform



activity showing 4 sec of data containing temporal and spatial variations of the waveforms. (scale bar: 1 mV; 100 msec). F. Expanded view showing 400 msec containing inter-ictal spikes. (scale bar: 50 mV; 50 msec).

Figure 6. Human polyimide depth electrode containing 64 microcontacts arranged in two rows of 32 contacts on opposite sides of the depth electrode. A. Polyimide depth electrode placed between two clinical depth electrodes during intraoperative recordings. B. Detections of action potentials from single neurons as a function of depth along the electrode, which has two axial columns of 32 microcontacts opposed to each other by 180º across the ceramic rod. Note the increased detection counts at two points on both sides of the depth electrode. Example waveforms are shown at right.

References

{Bibliography}