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Advanced Materials for Neural Surface Electrodes

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Abstract

Designing electrodes for neural interfacing applications requires deep consideration of a multitude of materials factors. These factors include, but are not limited to, the stiffness, biocompatibility, biostability, dielectric, and conductivity properties of the materials involved. The combination of materials properties chosen not only determines the ability of the device to perform its intended function, but also the extent to which the body reacts to the presence of the device after implantation. Advances in the field of materials science continue to yield new and improved materials with properties well-suited for neural applications. Although many of these materials have been well-established for non-biological applications, their use in medical devices is still relatively novel. The intention of this review is to outline new material advances for neural electrode arrays, in particular those that interface with the surface of the nervous tissue, as well as to propose future directions for neural surface electrode development.

Introduction

Great strides have been made over the past decade in the field of neuroscience, leading to ground-breaking technologies, such as optogenetics, for the study of neural circuits and mechanisms (Deisseroth, 2011). These novel methods not only have revolutionized neural research, but have also opened up new opportunities for neural interface technology. These opportunities, however, come with new specific requirements and challenges. The ability to use optogentics to stimulate neurons with light allows for precise, controlled activation of specific cell groups (Cardin et al., 2010). However, exploitation of this technique to its fullest potential, particularly for biomedical applications, requires devices that can be implanted into 3D tissue and animal models. To ensure that the devices can function well for optogenetic application there are several fundamental elements needed, such as incorporation of both light stimulation and transparent recording electrodes, through which

light be transmitted. In addition to electrophysiological research, neural interfaces are also useful for a variety of therapeutic applications, including epilepsy mapping, neural prosthetics, deep brain stimulation, pain management, and brain-computer interfacing (Berger et al., 1989; Schwartz, 2004; Perlmutter and Mink, 2006; North et al., 2002; Felton et al., 2007). As the medical understanding of neurological disorders continues to expand, newer and better therapeutic devices must be fabricated for symptom management. Thankfully, advancements in materials science and thin film technology have kept pace with those in the medical field and allowed for the development of smaller, more transparent and more biocompatible neural electrode arrays (Kotov et al., 2009).

Several different types of electrode arrays can be used for neural interfacing, ranging from invasive devices which penetrate into nervous tissue to completely non-invasive electrode caps worn over the skin (Hopkins et al., 1988; Maynard et al., 1997). Although the most invasive devices, such as traditional silicon intracortical probes, provide the highest signal resolution due to their proximity to nerve cell bodies, there is a large trade-off between recorded signal quality and device biocompatibility (Schwartz et al., 2006) (Fattahi et al., 2014). The primary drawback to these types of devices is that the significant scar tissue formation around the implants often renders them unusable within a short time period after implantation (Polikov et al., 2005). On the other hand, the most minimally invasive electrode arrays are those that do not penetrate the body at all, such as electroencephalography (EEG) grids worn over the scalp. These devices do not cause any tissue trauma, but the information contained within the recorded signals is significantly degraded by the amount of bone and skin tissue through which the signals have to travel (Leuthardt et al., 2004). To develop an implant that will ultimately be acceptable for long-term human use, it is necessary to strike a balance between the invasiveness of the device and the quality of the recorded signals. For this reason, surface electrode arrays, which are implanted within the body but rest atop the neural tissue rather than penetrating into it, have been developed. Examples of these types of devices include electrocorticography grids for recording from and stimulation of the cerebral cortex, as well as nerve cuff electrodes, which wrap around peripheral nerves (Leuthardt et al., 2004; Loeb and Peck, 1996; Rodríguez et al., 2000; Thongpang et al., 2011).

In order to conform to the non-uniform, curvilinear exterior of neural tissues, such as the cerebral cortex and peripheral nerves, surface electrode arrays must be composed of flexible materials. This means that the substrates of these devices are generally polymeric in nature, due to the intrinsic dielectric and mechanical compliance properties of these materials (Hassler et al., 2011). Traditional intracortical electrode arrays require rigid substrates, such as silicon, for insertion into neural tissues, but the mechanical impedance mismatch between the soft brain tissue and the stiff devices can cause a large amount of the tissue trauma contributing to glial scar formation (Polikov et al., 2005; Rousche et al., 2001) (Fattahi et al., 2014). Therefore, an added benefit of the flexible substrates required for surface electrode arrays that conform to neural structures is that they also allow these devices to move and bend with the soft surrounding tissues, rather than slicing through them. Thus these flexible devices are often more biocompatible in terms of both invasiveness and rigidity.

As previously mentioned, the proximity of neural interfaces to the structures from which they are recording is a crucial factor contributing to the quality and resolution of the acquired signals (Schwartz et al., 2006) (Fattahi et al., 2014). However, in order to obtain a more biocompatible interface with nervous tissue, which will lead to more stable signal recordings over the long-term, less invasive implants are required. Since neural cell bodies primarily lie in the deeper layers of the cortex and peripheral nerve axons are contained within several layers of connective tissue sheaths, there is an inevitable sacrifice of signal information when shifting to a surface neural recording or stimulating modality. Although this loss of signal resolution is unavoidable, it does not prohibit the use of surface electrode arrays for tasks which require high-information signals to decode user intent, such as brain-computer interfacing and neural prosthetic control (Navarro et al., 2005; Wilson et al., 2006). In fact, several studies have been performed which validate the employment of micro-electrocorticography (micro-ECoG) surface arrays for such applications (Humayun et al., 2003; Leuthardt et al., 2009; Rouse et al., 2013).

The validation of surface electrode arrays for neural interfacing tasks has triggered a sea of investigation into developing more advanced, but minimally invasive devices to match the new requirements of the field. This review aims to outline these cutting edge technologies as well as to look forward and propose future directions for the advancement of neural interfaces as tools for research and medical therapy.

Current State of the Art

State of the art neural surface electrodes aim to incorporate increased biocompatibility with the tools necessary for performing electrophysiological experiments using modern research techniques. Here, we discuss examples of new technologies for enhancing device biocompatibility and function in terms of the novel design modifications employed.

Open Architecture and Dissolvable Device Substrates

One method for reducing the tissue response to implanted medical devices is to minimize the amount of foreign material present. This has been demonstrated in the neural field with histological studies of the cellular response to open-architecture intracortical devices (Seymour and Kipke, 2007). Through these studies, it has been discovered that not only does the presence of holes through implanted micro-electrode arrays allow for tissue integration, but also for diffusion of neural chemicals from one side of the device to the other, another crucial factor for maintaining normal signal transduction and cell health (Polikov et al., 2005; Richardson-Burns et al., 2007b; Roitbak and Syková, 1999).

Recently, researchers have begun to adopt more open substrate geometries for neural surface electrodes as well. Schendel et al have developed a 'mesh' micro-electrocorticography (micro-ECoG) grid with individually insulated electrode sites and traces to allow for maximum tissue integration (Schendel et al., In Press). A comparison of the tissue response to the mesh micro-ECoG array and a standard micro-ECoG array with a single solid Parylene substrate encapsulating all of the electrode sites revealed that a collagen scar tissue formed around both arrays (Figure 1), but the distribution of the scar tissue around the devices varied. In the case of the mesh device, the tissue grew thinly beneath the array,

between the device and the brain, but thickened on top of the array, between the device and the cranial window (used for *in vivo* imaging of the tissue response). Conversely, in the case of the solid device, the tissue grew thick between the device and the brain, but thinly, or sometimes not at all, on top of the device. The dispersion of tissue growth found around the mesh devices was more favorable for neural interfacing applications, since minimization of the amount of material between the electrode sites and the brain is vital to attain maximum recorded signal quality. The results of this study demonstrated that, as has been reported for intracortical devices, open-architecture substrate geometries, similar to the mesh array, are more favorable than traditional solid designs.

Kim et al have also recognized the benefits of a mesh-like neural surface electrode array, but have taken the idea a step further by not only minimizing the surface area of the substrate material, but also its thickness (Kim et al., 2010). As in the case of penetrating electrode arrays, surface devices require a sufficient degree of structural integrity for handling during processing and implantation. However, this mechanical stiffness is not necessary for the function of the device *in vivo*, and in fact can be disadvantageous, causing an increased amount of pressure on neural tissue, which can have harmful effects. Additionally, the increased structural integrity required for device handling results in a decrease in flexibility, diminishing the ability of these devices to conform to non-uniform tissue surfaces. To create a device with adequate mechanical stability to withstand the required processing and implantation procedures, but maximum flexibility to enhance conformity with neural structures, Kim et al employed the use of a dissolvable silk matrix. This matrix was adhered to a mesh-type micro-ECoG array with a very thin (~2.5 μm) polyimide (PI) layer insulating the traces. The silk matrix was robust enough to permit precise implantation of the electrode arrays over the feline visual cortex, but dissolved away within 1 hour after implantation, allowing the array to conform to the gyri and sulci of the brain and enhancing the quality of the recorded signals by increasing connectivity of the electrodes with the cortical tissue (Figure 2). Although there are many other biodegradable polymeric materials that could be employed, the transparency, robustness, and flexibility of silk, combined with its tunable dissolution properties make it an ideal candidate for neural interfacing applications.

In addition to bio-resorbable substrate materials, dissolvable conductive materials, such as the melanin semiconducting films created by Bettinger et al, are also desirable for some neural applications (Bettinger et al., 2009). While these types of devices may not be relevant for long-term neural implants, they are extremely beneficial for neural regeneration purposes, in which electrical stimulation has been shown to promote axonal growth. In these applications, it is desired to stimulate nerves over the short term to promote re-growth, but removal of devices after tissue regeneration would cause undesirable trauma. Thus, completely dissolvable electronic devices would be ideal. Although Bettinger et al have laid down the groundwork for these types of neural regenerative systems, much investigation is still required into making these types of devices completely functional.

Hwang et al have not only successfully fabricated dissolvable conductors, but have made complete circuits with active and passive components that dissolve over time when implanted in the body (Hwang et al., 2012). These circuits take advantage of silicon nanomembranes for the active electronics, in addition to dissolvable dielectric materials

such as silk. There is much potential for these devices for medical applications as transient electronic systems, sensors, actuators, and power supplies. This technology would allow for implantation of devices for short-term monitoring of data such as temperature and neural activity, without the requirement for an additional surgery to remove the devices post data collection.

Conductive Polymers

The use of conductive polymers in neural interfaces has sky-rocketed over the past several years, as it has been discovered that these materials increase device flexibility, biocompatibility, and recording/stimulation capabilities (Cui and Martin, 2003; Fattahi et al., 2014; Kim et al., 2008; Kotov et al., 2009; Widge et al., 2007). The previously mentioned bio-degradable melanin is just one example of a conductive polymeric material, with polypyrrole (PPy), polythiopene (PTh), and polythiopene derivatives, such as poly(3,4-ethlyene dioxythiopene) (PEDOT) being the most popular non-resorbable alternatives (Green et al., 2008). The conducting capabilities of these materials are a result of conjugated double bonds present in the polymeric backbone as well as dopant ions introduced into the molecular structure (Green et al., 2008). When they are incorporated into neural interfacing devices, the flexibility and high surface area of these materials help improve the conformity of the devices to neural surfaces, as well as to increase tissue integration, which leads to enhanced recording and stimulation parameters, and ultimately an extended device lifetime (Kim et al., 2008; Owens and Malliaras, 2010; Richardson-Burns et al., 2007a; Widge et al., 2007).

Khodagholy et al have demonstrated the use of poly(3,4-ethlyene dioxythiopene) poly(styrenesulfonate) (PEDOT:PSS) as a conductive coating for electrocorticographic recordings in rats (Khodagholy et al., 2011). This particular co-polymer was chosen for its biocompatibility, chemical stability, and commercial availability. Devices were fabricated on a Parylene C substrate, which was also selected for its superior performance *in vivo*. The performance of arrays of gold electrodes coated with PEDOT:PSS was compared to that of bare gold electrode arrays, with the finding that the PEDOT:PSS coating enhanced signal resolution in the 1-10 Hz and 30 Hz bands.

Castagnola et al have also shown the use of PEDOT-carbon nanotube (CNT) coated micro-electrodes for us in micro-electrocorticography arrays (Castagnola et al., 2013). These devices were patterned onto a polyimide substrate and their viability was verified by recording of sensory evoked potentials in the rat cerebral cortex. The PEDOT-CNT coating was found to reduce the electrochemical impedance of the recording electrodes by about four orders of magnitude in comparison to un-coated gold electrode sites (Figure 3).

Although long-term studies are required to assess the bio-stability of conductive polymer coatings, these materials have shown great promise for increasing the recording and stimulation capabilities of neural electrodes. The majority of conductive polymer investigations have been directed at their use with intracortical devices (Ludwig et al., 2006; Xiao et al., 2004; Yang et al., 2005), however the two studies reported above outline their benefits for neural surface electrode arrays. In particular, the flexibility of these materials allow for the creation of increasingly conformal devices, which will enhance

biocompatibility, improve recorded signal quality and longevity, and decrease the stimulation currents required to elicit behavioral responses.

Transparent Electronics

The invention of optogenetics has revolutionized the way scientists study neural circuitry, while increasingly more sophisticated *in vivo* imaging modalities provide the tools necessary to understand the behavior of the multitude of cell and tissue types regulating neuronal behavior and the *in vivo* stability of neural interfaces. Whereas the transparency of penetrating probes is usually irrelevant since these devices are most often embedded deep within the tissue, the use of surface electrode arrays for optogenetic or imaging studies requires light transmission through the devices, to or from the underlying nervous tissue. This necessity has ignited a wave of research into developing thin-film, transparent electrodes for neural interfacing.

Being that the use of transparent polymeric substrates, such as Parylene C and silicone, has been well established for medical devices (Grill and Mortimer, 1998; Hassler et al., 2011; Ledochowitsch et al., 2011; Schendel et al., 2013), the main challenge in the development of completely transparent neural electrode arrays is finding a suitable conductor material. Although conductive polymers, such as PEDOT, can be formulated to have transparent properties, fundamental materials chemistry issues make synthesis of polymers with both conductive and transparent properties difficult. Furthermore, development of conductive polymers that are transparent across a broad spectrum of wavelengths is almost impossible (Pringle et al., 2010). Therefore, these materials are more often used as coatings rather than solitary transparent conductors. However, the ability of these materials to be switched from one oxidation state to the other makes them useful for other interesting applications, such as electrochromic windows (Argun et al., 2003). So, although conductive polymers may not be the ideal choice for neural interfacing applications requiring broad-spectrum transparency, they may have utility in other applications where it is desired to filter out specific wavelengths of light.

The most commonly used transparent conductive film to date is indium-tin oxide (ITO).Transparent ITO-based micro-ECoG devices have been fabricated by Ledochowitz et al and Kwon et al, however, due to the brittleness of ITO and its limited transparency in the UV and IR spectral ranges, researchers have been making an effort to find alternative transparent conductors to ITO. To create electrodes that are transparent over a broad light spectrum, deeper exploration into the materials chemistry of electrode materials will be necessary.

What's Next?

Despite the advancements in neural surface electrode technology over the past several years in terms of both device biocompatibility and function, there is always room for further technology development. In particular, future directions may include the incorporation of drug delivery modalities into implantable surface arrays, as well as hybrid devices that integrate optogenetic capabilities with minimal invasiveness and the potential to deliver drugs or other factors to the cerebral cortex. Additional research could also involve the use

of shape memory polymers and energy harvesting materials to enhance the function of surface electrode arrays. Finally, consideration of the steps necessary to obtain approval for use of these types of devices in human patients is a crucial next step for making these devices clinically available. In this section, we outline several future directions for neural surface electrode array research.

Drug Delivery

Delivery of drugs and other substances to neural tissue can not only be employed to help mitigate scarring around implanted devices, but also to study the contributions of different cell and tissue types to neural network function (Bodor et al., 1991; Cadotte and DeMarse, 2005; Shain et al., 2003; Willerth and Sakiyama-Elbert, 2007). Modifications have been made to intracortical MEAs to enable drug delivery via micro-channels incorporated into the probe shanks, as well as adherence of soluble factors onto the device surfaces (Chen et al., 1997; Kim and Martin, 2006; Retterer et al., 2004; Williams et al., 2005). Incorporation of drug delivery modalities with surface electrode technology, however, remains unaccomplished. Methods for printing liquid substances in controlled patterns have been achieved using specialized ultrasonic equipment, and could be useful for future research studies involving the application of drugs to neural device surfaces (Larson et al., 2006). This method would allow for direct delivery of substances to the implant site, and could aid with the transmission of particles across the blood-brain barrier. Furthermore, printing of substances onto the surfaces of electrode arrays could be used as a method of performing test-tube-like experiments, in which different drug titrations and patterns can be studied *in vivo* in a single animal. For example, one could print different concentrations of substances such as oxygen scavengers onto the surface of thin-film electrode array and create local areas of hypoxia to correlate the effects of hypoxia on neural signaling. Table 1 outlines some biological problems which could be studied using surface electrode technology, and the potential approaches and necessary materials considerations involved.

Additional drug delivery methods for surface electrode applications could include the incorporation of microfluidic channels through the flexible polymer substrates of these devices. Ziegler et al and Takeuchi et al have reported two different methods for fabricating Parylene micro-channels (Takeuchi et al., 2005; Ziegler et al., 2006). Although both of these studies focused on penetrating probe applications, the same concepts could be applied to micro-fluidic surface electrode array development.

Electro-spun polymer nanotubes have also been employed to deliver drugs around intracortical neural electrodes (Abidian et al., 2006).This modality is particularly intriguing, since the conducting polymer nanotubes not only intrinsically decrease the impedance of the electrode sites onto which they are deposited, but also allow for controlled release of the drug by application of electrical stimulation, which dilates the tubes, causing the drug to diffuse out. This approach could also be an interesting next step for targeted drug delivery from neural surface electrodes.

Shape Memory Polymers

Although shape memory metal alloys have been around for quite some time, the development of shape memory polymers has been relatively recent. These materials, which have temperature-sensitive elastic moduli, could be extremely useful substrates for neural interfacing devices. Ware et al have developed intracortical neural electrode arrays on shape-memory polymer substrates (Ware et al., 2012). These devices are stiff at room temperature for easy insertion into the brain, but become flexible at body temperature, to minimize tissue damage as a result of mechanical impedance mismatch. One could imagine a similar application of these materials for neural surface arrays, as a modification of the dissolvable silk substrate method employed by Kim et al for easy implantation of ultra-thin, flexible micro-ECoG devices.

Additionally, polymers that change shape at different temperatures could be useful for a variety of neural surface electrode applications, including implantation of such devices through small burr holes, to reduce surgery-induced trauma. This could be accomplished by setting the shape of the device at room temperature to fit into a small catheter tube, and once the device reaches body temperature have it expand to its desired *in vivo* configuration, similar to the method used to implant nitinol stents into arteries. One could also imagine the ability to apply some chilled saline to the device, causing it to curl back up for easy removal or replacement. Shape memory polymers could also be used to create high surface-area electrode sites to maximize signal ecording capabilities. This would require the use of a flexible, stretchable, conductor material, such as graphene, but could be accomplished by shape setting the regions of the polymer around the electrode sites to be flat at room temperature, and then crumple once they reach body temperature, causing the electrode sites themselves to crumple, and increasing their surface area.

Hybrid Devices

This review has discussed many cutting-edge enhancements applied to neural surface electrodes, including improvements to make these devices more biocompatible, flexible, and amenable to use in optogenetic and imaging experiments. Ideally, however, there would be one device with all of the capabilities necessary for ideal performance in any neural electrophysiology application. To achieve this goal, researchers must now focus on the creation of hybrid devices, which incorporate two or more of the features and functions described above. Kwon et al have already begun to achieve this goal, by the integration of transparent electrode sites with LEDs to create a device capable of both optogenetic stimulation and recording. Next steps should include incorporation of drug delivery modalities into these types of optrode devices, to allow for research studies involving the impact of cortically delivered factors on neural excitability. Additionally, future hybrid devices should include wireless technology, which would enable improved *in vivo* behavioral studies, as well as bring us one step closer to a clinically available brain-computer interface technology. These wireless devices could also incorporate thermocouple temperature sensors to monitor tissue heating and shut down the wireless capabilities if the device gets too hot. Many recent research efforts have focused on the development of wireless platforms which can achieve the necessary signal transmission with minimal tissue heating effects (Ha et al., 2013; Irazoqui-Pastor et al., 2003; Kim et al., 2013).

Energy Harvesting

Incorporation of wireless technology with implantable neural interfaces requires the use of an implantable power supply. Many types of implantable medical devices require electrical power to operate, such as pace makers, neural stimulators, and drug pumps. These devices generally use some sort of lithium ion battery. These batteries, however, have a finite lifetime and must be recharged or replaced after a certain period of time. If one could harvest energy from the body to power a device, the problem of battery recharging or replacement could be avoided. Piezoelectric materials, such as zinc oxide, can convert mechanical energy into electrical signals and vice versa, due to the layout of their crystal structures. These materials could be used to harvest mechanical energy, such as the pulsing of a cortical blood vessel, and convert it to electrical energy to generate power for a wireless neural interface platform, or for a neural drug delivery or stimulation device. Want et al have used zinc oxide nanowire arrays to fabricate nano-generators which could be used to power small-scale devices of this nature (Wang and Song, 2006). The application of these types of power sources with neural interfaces could solve some of the problems inhibiting clinical application of these types of devices by minimizing the chances of more than one neural surgery during the patient's lifetime.

Clinical Considerations

In addition to the obvious need for the incorporation of wireless technology into neural microelectrode arrays for clinical applications, there are several other considerations that need to be taken into account. First and foremost is the previously mentioned necessity to mitigate scar tissue formation, in order to make these types of devices reliable over the long term. Although many efforts are underway, more research is still required to gain a complete understanding of the tissue response to surface electrode arrays, as well as to decipher whether the less-invasive benefits of epidural implantation of ECoG arrays outweigh the loss of signal information which occurs as a result of the presence of the dura-mater (Bundy et al., 2014). Another extremely important factor that must be considered before these devices can be used clinically is the types of materials used, and whether they are currently or are capable of becoming FDA approved.

At the moment, polyimide is one of the main polymers used for surface electrode array substrates. Although this material has an ideal set of properties for thin film neural device applications, it is difficult to find a vendor willing to sell this material for use in human implants (Hassler et al., 2011). Parylene C, on the other hand, is currently approved by the FDA for unlimited use in medical devices. This material has also proven to be a successful candidate for surface electrode substrates, and so researchers may be well-advised to transition to a Parylene substrate material if clinical applications are on the horizon. Furthermore, first steps to clinical implementation of these devices should include taking into account implantation procedures for current clinical grids, and adapting thin-film arrays to fit these procedures. This will make it easier for doctors to transition from macro-devices to micro-sized thin-film arrays by not requiring any changes in the implantation surgery.

Overall, thin-film surface electrode technology appears to have considerable future potential for neural interfacing applications, due to its minimal impact on surrounding tissue combined with its amenability to a multitude of research methodologies.

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- Brain surface electrodes are an optimal tradeoff between invasiveness and signal quality.
- Brain surface electrodes have numerous materials considerations.
- Materials determine both the device function and the brains reactive response.
- Advances in the field of materials science continue to yield new and improved materials with properties well-suited for neural applications.
- This review outlines new materials advances for neural electrode arrays.

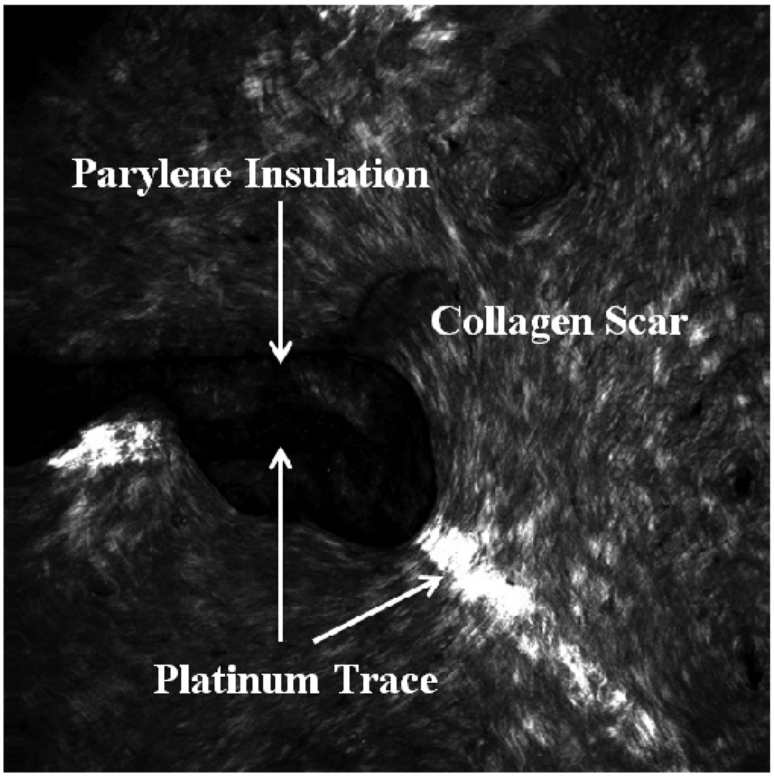

Figure 1.
Second harmonic generation (SHG) image of collagen scar tissue surrounding the trace of a "mesh" micro-ECoG device.

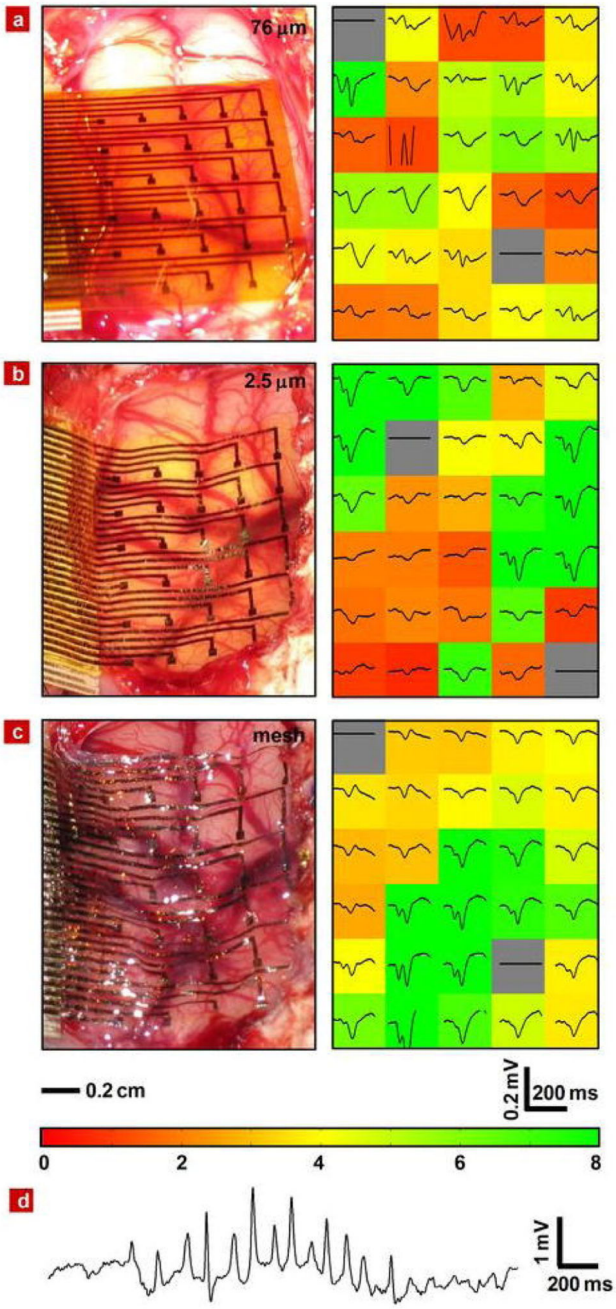

Figure 2. Photographs and data from animal validation experiments

Image of electrode array on feline brain (left) and average evoked response from each electrode (right) with the color showing the ratio of the RMS amplitude of each average electrode response in the 200 ms window (plotted) immediately after the presentation of the visual stimulus to the RMS amplitude of the average 1.5 second window (not shown) immediately preceding the stimulus presentation for 76 μm a, 2.5 μm b and 2.5 μm mesh c electrode array. The stimulus presentation occurs at the left edge of the plotted window. In all 3 images, the occipital pole is at the bottom of the frame and medial is at the right. The scale bars at the bottom of c indicate the spatial scale for the left frames and the voltage and

time scales for the right frames of a,b and c. The color bar at the bottom of c provides the scale utilized in the right frames of a,b, and c to indicate the RMS amplitude ratios. d, Representative voltage data from a single electrode in a 2.5 μm mesh electrode array showing a sleep spindle. (Kim et al., 2010)

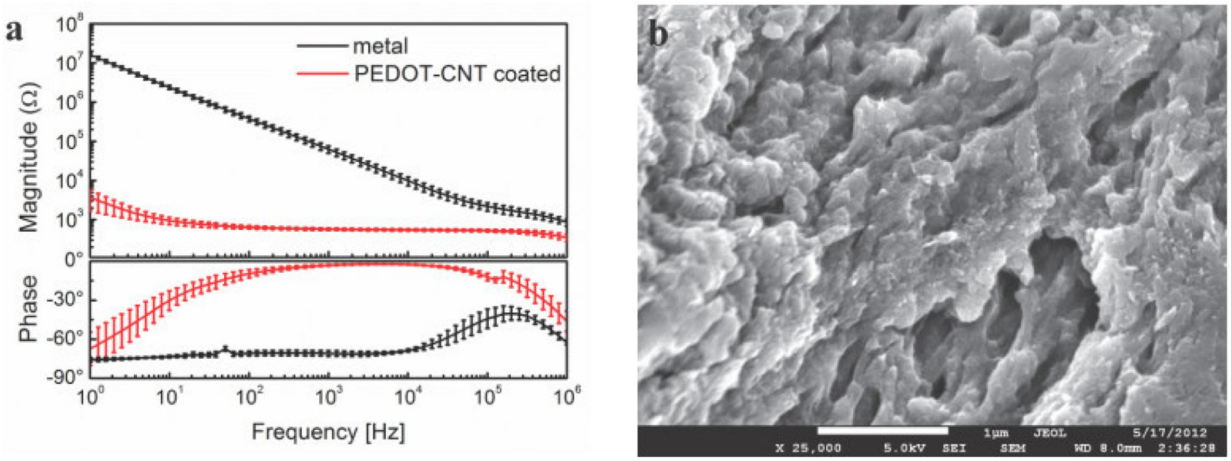

Figure 3.

(a) Impedance spectra of a sub-group of microelectrodes (200×200 μm) of the ECoG (mean and standard deviation of 8 recording sites) before (black) and after (red) PEDOT-CNT electro-coating. **(b)** Scanning electron micrograph of the surface of PEDOT-CNT coated microelectrodes. (Castagnola et al., 2013)

Table 1

Examples of biological problems that could be assessed using surface electrode technologies.

Biological Problem	Possible Approach	Example Technology	Materials Considerations
Angiogenesis	Study VEGF	Drug delivery of Avastin	Delivery schemes including microchannels, biodegradable polymers
Wound Healing	Image immune response for example collagen	Image collagen scarring via Second Harmonic Generation	Transparency, geometry, material biocompatibility
Neural Signaling	Relate blood flow to neural signaling	Optogenetics	Transparency Conductivity Photoelectric effect
Metabolism	Image intrinsic fluorescence to the electrode	Multiphoton imaging of NADH and FAD and delivery of metabolic factors	Transparency, delivery schemes
Therapeutic application	Surface recording Surface stimulation	Micro-ECoG, ECoG	Conductivity Charge carrying capacity Dieletric properties Substrate materials