Perspectives: Neural Interfaces – Materials Chemistry to Clinical Translation

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Abstract

Neural interfaces serve as a cornerstone technology to better understand the nervous system and treat debilitating neurological disorders. The ideal implantable neural interface can be integrated with tissue using minimally invasive procedures and can record high fidelity neuronal activity for long periods in vivo. Chronically stable neural implants can serve as scientific tools and broaden the clinical and therapeutic impact of many neurotechnologies. However, formidable technical and design challenges remain. At present, many of these challenges are related to the materials, mechanics, and form factors of implantable neural interfaces. This perspective highlights recent progress and challenges related to arguably two of the most common failure modes for implantable neural interfaces: (1) compromised barrier layers and packaging leading to failure of electronic components; (2) encapsulation and rejection of the implant due to injurious tissue-biomaterials interactions, which erodes signal quality and bandwidth. Novel materials and device design concepts could address these failure modes thus improving the performance and translational prospects of neural interfaces. This perspectives article provides a brief overview of contemporary neural interfaces, highlights recent progress in chemistry, materials, and fabrication techniques to improve reliability of these implantable devices. Topics include novel barrier materials and harmonizing the various incongruences of the tissue-device interface. Challenges and opportunities related to the development and clinical translation of these devices will also be presented.

1. Introduction

1.1 Motivation and Brief Overview of Contemporary Neural Interfaces

Neural interfaces are important tools for neuroscience and compelling medical devices for potential applications in clinical rehabilitation. Implantable microdevices for neural recording have increased in both complexity and recording capability in recent decades. Brain-penetrating microelectrode technologies for recording and stimulation have been made commercially available to researchers for a decade or more[1]. Many early iterations of neural recording technologies used microwires. Individual microwires can record single channels whilst bundling many wires together could be used for multichannel recording[2]. Three common microwire technologies include metal microwire arrays (e.g. from Microprobes, TDT, and Plexon), single channel silicon microwire arrays (e.g. from Blackrock Microsystems), and silicon multi-electrode probe arrays (e.g. from NeuroNexus, Atlas Neuroengineering, Cambridge NeuroTech, and Neuropixel). Advances in neural recording technology have leveraged new materials and microfabrication technology to improve the performance and channel count.

Silicon-based micro-technologies have advanced neural recording capabilities primarily by facilitating insertion, simplifying cabling and connectors, and increasing channel count. The invention, commercialization, and deployment of the Utah and Michigan arrays are perhaps the two most prominent examples of applying silicon-based microdevices to applications in neural recording. The bandwidth of multichannel recording capabilities has further increased. Leveraging silicon manufacturing techniques from the microelectronics industry can produce neural recording implants with >1000 channels and on-chip amplification greatly improving the bandwidth and quality of data. For example, the Neuropixel uses CMOS circuitry for signal condition and digitization which allows it to fit 960 recording sites within a 10 mm long, 70 mm wide shank and select 384 of these for simultaneous recording[3]. The Neuropixel device has been used to great effect for in vivo recording from animal subjects[4–5].

Although there are many types of devices, chronic recording capabilities are often limited by the glial response and subsequent fouling and encapsulation of recording sites by proteins and cells. This widely conserved phenomenon is associated with acute damage to the vasculature of the brain during insertion along with the downstream immune response that is generated from the continuous presence of rigid implants comprised of foreign materials[6–7]. This fundamental challenge in interfacing silicon-based microdevices with excitable tissue in the brain has motivated the investigation of flexible implants to reduce the modulus mismatch at the tissue-device interface and miniaturized form factors to minimize vascular damage and tissue loss altogether[8]. Recent examples of polymer-based devices include individual carbon fibers[9] and polymers [10–14]. Polymer-based devices are now available from companies such as Qualia, NeuroNexus, and Modular Bionics. At present, these devices typically lack integrated CMOS circuitry and have comparatively low channel counts to silicon-based counterparts. However, the gap between polymer- and silicon-based neural interfaces continues to shrink.

While most brain-machine interfaces are designed for scientific or preclinical research in animal models, there is great interest in development of more sophisticated electrode-based brain interfaces for use in human subjects. The Utah Array from Blackrock Microsystems has been the only intracortical microelectrode array approved for human use by the US Food and Drug Administration[15]. Neuralink which is backed by tech entrepreneur Elon Musk, is developing new technology for eventual clinical use. Recently, the company shared details of its system, including its thread-like thin film polymer electrode array technology and the use of robotics to assist in their implantation[16]. This technology will be described in more detail later (see Emerging Concepts for Tissue Integration).

1.2 Electrical coupling between neural interfaces and excitable tissues

Voltage-mediated signals between neurons and implanted electrical sensors remains the gold standard for bi-directional communication between the nervous system and neural interfaces. However, there are now numerous possible alternative modes of communication between neurons and synthetic recording/stimulation devices. Neurons can be manipulated using many exogenous signals including external electric fields, ultrasound, light, or even magnetic fields. Devices can be classified as invasive, minimally invasive, minutely invasive, non-invasive, or anywhere in between. However, at present, voltage-mediated communication between neurons and human-made electronics using implantable devices is the most likely candidate for widespread clinical adoption. There are many reasons for this widely held tenet. Neuromodulation using electric fields has a well-documented history of both safety and efficacy. Modulating neural activity using electronic fields can trace back its roots to deep brain stimulation (DBS), an approach clinically approved since 1997[17]. Electric fields and the flow of ions are the intrinsic information currency of excitable tissues such as neurons in the brain. Therefore, no genetic manipulation is required for signal transduction across these sub-systems. Implantable neural interfaces must strike the appropriate balance between invasiveness, specificity, and information density. Implantable neural interfaces often require invasive procedures and carry potential infection risk. However, anatomically precise positioning of devices in the body also confers target specificity.

1.3 Defining Materials-Related Challenges to Improving the Performance of Neural Interfaces

Neuroscientists, neural engineers, and clinical practitioners largely agree that there is significant merit in the ability to measure neural activity for years, if not decades, in awake behaving subjects including humans. The ultimate vision of the ideal neural interface varies according to intended application and even the specific experiment. The utility of a generalized neural interface can broadly be improved by addressing one or more of the following: increasing bandwidth, reducing the invasive of implantation or integration, expanding the recording volume, improving signal quality, and extending the in vivo lifetime of the device. Essentially, the design of the ideal neural interface is guided by the desire to extract as much spatiotemporal information throughout the usable lifetime of the device.

Many of these parameters are inter-dependent and inextricably linked by fundamental tradeoffs in performance. Increasing bandwidth, reducing invasiveness, and expanding the recording volume are compelling and meritorious pursuits that can be addressed in part by exploring new recording paradigms, implementing new device architectures, or and exploring novel form factors. While the aforementioned technical challenges are formidable, improving the signal quality and extending the in vivo lifetime of the device are of interest to the neural interface community at-large. For example, several research programs funded by agencies such as the Defense Advanced Research Projects Agency (DARPA) are focused on maintaining in vivo device performance to improve prospects of clinical translation. There are two commonly observed failure modes in implanted neural interfaces: (1) compromised packaging leading to failure of electronic components; (2) deterioration of recording quality at the tissue-device interface. These canonical failure modes underscore two important technical challenges to improve the scientific and clinical utility of implanted neural interfaces: (1) improving barrier layers and packing to increase the lifetime of in vivo devices (2) improving implant biocompatibility and supporting neuronal health. These challenges are governed by limitations in materials properties and, as a corollary, can be addressed by discovering and implementing new materials into device architectures.

2. Materials to Improve Hermeticity in Neural Interfaces

Designing barrier layers for neural interfaces is challenging because these implantable medical devices have delicate miniaturized electronic components that operate in complex biological environments. The ideal barrier layer for neural interfaces would be electrically insulating, impermeable to liquid water and ions, chemically stable, processable into thin conformal films with low defect densities, and adhesive to any substrate material. This wish-list of properties, while challenging to achieve in total, contextualize performance limitations of existing materials and provide guidance for designing new barrier materials. While the ideal barrier layers is application specific, the foundational challenges of designing barrier layers that are impermeable, chemically robust, thin, and conformal are common. High performance barrier layers also play important roles established industries such as food packaging and storage, consumer electronics, and other types of implantable medical devices. Materials advances in other domains can be translated to the field of neural interfaces.

Mature industries also provide standardized testing methods and establish key figures of merit that can help compare the performance of barrier layers. Water vapor transmission rate (WVTR), while not the only measure of device hermeticity, is perhaps the most important and informative parameter that can predict the in vivo performance of a barrier layer. The WVTR is an extensive property that measures the steady state flux of water vapor through a film with a certain thickness. WVTR is also easily measured and therefore able to be compared across various materials and form factors. Benchmarking WVTR values can be informed (in part) by other industries. For example, visual displays that use organic light emitting diodes (OLED) are highly sensitive to moisture and therefore provide a convenient benchmark for barrier layer performance. To achieve a device lifetime of ~10 yr, barrier layers for OLED much achieve an extensive WVTR of no more than ~10^{-6} g m^{-2} day^{-1} [18]. Other potentially useful figures of merit include gravimetric water sorption and, in the case of hydrolytically labile materials, etch rates due to hydrolysis.

2.1 Inorganic barrier layers

Silicon-based packaging materials

Silicon-based ceramics are workhorse packaging materials and dielectrics for the microelectronics industry. Silicon oxide is an attractive material for neural interfaces as well because of the availability of robust manufacturing capabilities and a vast foundational knowledge of physical and chemical properties. Silicon oxide is a compelling choice as a barrier layer owing to excellent dielectric properties, electronic insulation, near-zero water vapor transmission rates, and relatively low ionic permeability. However, conformal SiO_2 films produced by plasma enhanced chemical vapor deposition (PECVD) or thermal evaporation have relatively high defect densities. SiO_2 films with high defect densities are susceptible to hydrolysis, producing water-soluble silicic acid at rates that can impact the function of chronic implants[19]. SiO_2 films are also permeable to sodium and potassium ions, which accumulate at interfaces and ultimately limit the in vivo lifetime of implanted electronic devices. Thermally grown silicon oxides have minimal defects and are more resistant to hydrolysis but are difficult to integrate with flexible electronics. A recently described fabrication technique can integrate 1 μm thick films of thermally grown oxide with flexible electronic structures[20]. Hydrolysis rates of ~10^{-2} nm day^{-1} at 37 ^{o}C suggest that these films have a projected lifetime of >70 years.

Other Ceramics and Carbon-Based Barrier Layers

Ceramics are attractive barrier layers because they are electronically insulating, resist water sorption, and can be deposited as thin conformal films using reliable manufacturing processes. For example, aluminum oxide (Al_2O_3) is an attractive barrier layer since it can be deposited into thin conformal films by atomic layer deposition (ALD) using commercially available equipment. Al_2O_3 films produced by ALD are chemically stable in aqueous conditions and can achieve a WVTR of approximately ~10^{-10} g mm m^{-2} day^{-1}, making them attractive options as barrier layers. Like silicon oxide, aluminum oxide surfaces can be easily modified to bind self-assembled monolayers, peptides, proteins, or other polymers to improve in vivo biocompatibility.

Pin-hole free silicon oxide films can restrict the transport of water vapor, but are relatively permeable to cations in body fluid such as sodium and calcium. Silicon oxides films can be combined with ion diffusion barriers composed of silicon nitride, for example[21]. Devices packaged with SiO_2/SiN_x bilayers exhibit dramatically extended lifetimes when incubated in PBS. Furthermore, silicon nitride[22] and silicon carbide[23] have been used as packaging materials in neural interfaces.

Combining silicon oxide with hafnium oxide can also produce thin film composites that resist hydrolysis and reduce ionic diffusion. Thin films of hafnium oxide have been used as gate dielectric layers in high performance silicon-based microelectronics. HfO_2 films can be processed using ALD and have exceptional electronic properties such high electric constants and low leakage currents[24]. HfO_2 films on the order of 100 nm in thickness were recently incorporated into SiO_2/HfO_2 bilayers to encapsulate flexible electronic implants[25]. SiO_2/HfO_2 bilayers exhibit hydrolysis rates that are significantly smaller compared to SiO_2 monolayer counterparts. Specifically, devices encapsulated using HfO_2/SiO_2 bilayers versus SiO_2 monofilms incubated in phosphate buffered saline (PBS) at 37 °C have a projected lifetime of over 40 yr and 30 h, respectively[20].

Similarly, devices encapsulated with SiO_2/HfO_2 bilayers and incubated in aqueous solutions of Na^+ or Ca^{2+} exhibit lifetimes >10x longer compared to devices encapsulated in SiO_2 monolayers. Barrier films composed of SiO_2/HfO_2 bilayers can therefore greatly address the two most common failure modes of silicon-based films: hydrolysis and ionic diffusion. Composite barrier layers have been combined with thin-film processing techniques to create a high-resolution multiplexed electrode arrays for in vivo recording called the NeuroMatrix[26]. The efficacy of the barrier layers is evident by long-term in vivo recordings in various animal models (including non-human primates) for up to 1 year with predicted operational lifetimes of up to 6 years. This impressive technological demonstration represents a confluence of materials research and development combined with non-conventional thin-film processing strategies to greatly improve the longevity of in vivo recording thus addressing one of the foremost challenges in neural interfaces.

Diamond-based coatings are compelling alternatives to ceramic films because they are mechanically robust, chemically inert, and have enjoyed recent improvements in manufacturability and processing for use in biomedical devices[27]. The properties of polycrystalline diamond can be controlled through doping, which allows the same base material to be used for multiple components thus greatly improving the prospects of hermeticity for the overall device[28]. For example, boron-doped nanocrystalline diamond coatings have been used successfully as an electrode material for implantable neural interfaces[29].

2.2 Polymer-based barrier layers

Parylene-based materials

Parylenes are hydrophobic films prepared by the chemical vapor deposition of aromatic precursors to produce poly(*p*-xylene). Parylene has many different compositions that are defined by the substituents on precursors. Parylene-C is formed from a chlorinated precursor, which confers exceptional performance as a barrier layer. Parylene-C is the gold standard of polymeric encapsulation layers for neural interfaces owing to its and long history as a coating material for medical implants[30]. Conformal films of parylene-C can be prepared using chemical vapor deposition and etched using oxygen plasma to create photolithographically-defined structures. Film thicknesses vary widely from as low as <100 nm up to >50 μm. The WVTR of parylene-C varies with film thickness and processing conditions. However, typical values for normalized WVTR are on the order of 15 g m^{-2} day^{-1} 25 μm^{-1}. The WVTR for a 25 μm thickn parylene-C film is orders of magnitude larger than inorganic counterparts such as Al_2O_3. Diverse manufacturing capabilities have motivated the use of parylene-C as a barrier layer for flexible electronic implants including neural interfaces. Polymer-based encapsulation layers such as parylene-C are attractive for mechanically compliant implants. Parylene-C is an intrinsically non-toxic material and resists moisture uptake with equilibrium water sorption of <2 wt% for films >40 nm in thickness[31]. Neural interfaces with parylene-C encapsulation layers can therefore preserve suitable signal-to-noise ratios of in vivo recordings for long periods of time[32]. While certainly a promising material, there are consistent technical challenges that limit long-term performance such high defect density and low crystallinity in thin films, challenges with cohesive bonding, and poor interfacial adhesion to many substrate materials[33].

Polyimides

Polyimides are commodity polymers that has been used extensively in flexible microelectronics for decades. Polyimides are most often used as substrates for flex-circuits because of the robust chemical and thermal stability. The size of polyimide-based structures can be controlled by spin coating and photolithography. Polyimide films can also be etched and patterned using laser ablation, oxygen plasma or deep reactive ion etching (DRIE). Most types of polyimides require high-temperature post-bake processes, which typically restricts their use to substrates and other structural materials[11–34]. The Young's modulus of polyimides is in the range of 1—10 GPa.

Therefore polyimide films with typical thicknesses of 10—50 μm exhibit low flexural rigidity compared to many ceramics and metals[35]. While attractive from a potential tissue-biocompatibility standpoint, the low flexural rigidity complicates probe insertion. Thus polyimide-based probes often employ a rigid implantation shuttle, which eases insertion but may also cause excess local damage to the tissue.

Polyimides offer significant advantages as an encapsulation material for neural interfaces. Some of the first demonstrations of flexible neural interfaces fabricated microelectrodes arrays on a specific types of polyimide (PYRALIN PI 2611) by optimizing metallization procedures and interconnect design[36]. Since these early demonstrations, flexible polyimide neural interfaces with have been multiplexed into arrays that can record brain activity in a freely moving rodent model[37]. However, polyimides have challenges for chronic applications owing to large equilibrium water sorption (0.4—4 wt%)[38–39].

Dielectric Elastomers

Dielectric elastomers are compelling for packing flexible electronic implants because this class of materials combines mechanical compliance, extensibility, and electronic insulation. Many of these elastomers are commercially available, used widely in various mature industries, and their properties are well characterized. Perhaps the most common class of dielectric elastomers are silicones including polydimethylsiloxane (PDMS). Silicones are widely used as structural materials in medical devices including recent demonstrations as flexible neural interfaces[40]. PDMS and other siliconcontaining polymer networks are suitable for both packaging materials and substrates because they are electronically insulating, hydrophobic, and therefore resistant to liquid water. However, silicones are highly permeable to water vapor, which is problematic for achieving hermeticity in chronic implants. The WVTR of silicones varies widely across precursor composition, processing, and form factor, however a typical range of normalized WVTR is 100—2000 15 g m^{-2} day^{-1} 25 μm^{-1}. Silicone alkyds have WVTR closer to 100 g m^{-2} day^{-1} 25 μm^{-1} while silicone RTV have WVTR closer to 2000 g m^{-2} day^{-1} 25 μm^{-1}. In general, silicones have a WVTR that is up to 1000X larger than parylene-C films of comparable thickness. Other widely available dielectric elastomers that have potential as packaging materials include styrene-ethylene-butylene-styrene copolymer (SEBS) and polyisobutylene (PIB)[41–42], though they have been used sparingly in neural interfaces to date.

One of the persistent challenges with using dielectric elastomers as encapsulation materials for chronic implants is the relatively high permeability to water vapor compared to their inorganic counterparts. The critical challenge in advancing dielectric elastomers as encapsulation materials for implantable neural interfaces is the strong correlation between extensibility and permeability. Elastomeric properties are achieved by creating networks of amorphous polymers while superior barrier properties are achieved by forming polymer layers with large crystalline domains and low defect densities. These properties are fundamentally anticorrelated at the molecular level, which makes it difficult to employ engineering solutions to achieve both extensibility and superior barrier properties. Breakthroughs in the performance of dielectric elastomers for applications in flexible neural interfaces will likely have to originate from advanced polymers that engineered at the macromolecular level. The materials design challenge is further confounded by application-specific needs with multiple figures of merit and establish trade-offs in performance. For example, neural interfaces recording from dynamic environments for short periods of time may value extensibility over barrier properties. These are open questions that require a continuous dialogue between end-users and materials scientists.

2.3 Multi-layer and Composite Strategies

Composite barrier layers may consider multi-layers that can combine orthogonal properties including the following: high dielectric constant; low water vapor transport; low water sorption; and low permeabilities for ions found in biological fluids. Barrier layers composed of multi-layer composites are advantageous for two principle reasons. First, stacks of multi-layers can mitigate the negative impact of high defect densities of a single layer. Defects are critical to barrier performance because they can potentially short-circuit the transport of water, gases, and ions directly across the film. However, stacking multiple thin film barrier layers can reduce the likelihood that defects overlap thereby improving overall barrier performance relative to a single film of equal overall thickness to the multilayer. Second, each material of the composite can contain orthogonal chemistries that provide a specific function. Multi-layer composites can therefore combine the barrier properties of each individual layer. Utah arrays have been encapsulated in multilayer composites of aluminum oxide and parylene-C. Al_2O_3 films on the order of ~50 nm in thickness deposited by ALD are combined with parylene-C films 6 μm in thickness deposited by chemical vapor deposition (CVD). Devices coated with Al_2O_3/parylene-C bilayers retained critical device function when incubated in vitro for >1000 days. Al_2O_3/parylene-C bilayers outperformed films composed of parylene-C only, which preserved device function for ~100 days. This dramatic improvement is attributed to the much improved WVTR of Al_2O_3 compared to that of parylene-C ($WVTR_{Al2O3}$ ~10^{-10} g mm m^{-2} day^{-1}; $WVTR_{parylene\text{-}C}$ ~0.2 g mm m^{-2} day^{-1}. Al_2O_3 films have been recently fashioned into composite barrier layers with polymers such as the perfluoropolymer CYTOP[43], PDMS, and photoresists such as SU-8[18]. Al_2O_3/polymer thin film composites achieve WVTR of 1.23×10^{-6} g m^{-2} day^{-1} and 1.05×10^{-6} g m^{-2} day^{-1} when combining with PDMS and CYTOP, respectively. The performance of these composite multilayers is significantly improved compared to both Al_2O_3/SU-8 composite films (7.94×10^{-4} g m^{-2} day^{-1}) and control films without polymers (5.43×10^{-5} g m^{-2} day^{-1}).

2.3 Opportunities to Improve Barrier Layer Performance

The ideal encapsulation material for implantable neural interfaces would be easily processable into thin films with low defect densities, have exceptional barrier properties, and can accommodate large cyclic strains without degradation in performance. In general, it is advantageous to combine the moisture barrier and electrical insulation properties of ceramics with other encapsulation materials that impart chemical resistance to reactions such as hydrolysis. While sufficiently thin ceramic-based barrier layers can accommodate some degree of out-of-plan bending, these brittle materials have poor in-plane extensibility. Therefore, any barrier layer strategy using ceramics cannot support certain deformation modes. Novel ceramics or ceramic hybrids, possibly engineered at the molecular level, that can serve as an extensible high-performance barrier layer would be of broad interest to the neural interface community.

Another opportunity in barrier layer design is the intrinsic trade-off between flexural rigidity and barrier layer thickness. As previously mentioned, the design of neural interfaces is application specific and full of trade-offs between device design, manufacturing, performance, and reliability. Yet another compelling trade-off is choosing the ideal film thickness to both minimize flexural rigidity thereby preserving biocompatibility while also maintaining suitable barrier properties. The flexural rigidity D of a film of thickness t scales as $D \sim t^3$ while the steady state flux of species through a film Φ_i scales with film thickness as $\Phi_i \sim t^{-1}$. Assuming the dimensions of the implant are dictated by the structural materials and barrier layers, as opposed to the microelectronics and metallization, there is an implicit tradeoff between these critical device properties. The optimization exercise should ideally be informed by many considerations including the anticipated tissue reaction of the implant site, recording volume, and intended device lifetime.

Experiments to determine key figures of merit (e.g. water vapor transmission rate and water sorption) for barrier layer properties use idealized test structures. However, implantable devices that use these materials often fail much more rapidly than their theoretical predictions. Oftentimes the barrier layers do not fail within the continuum film construct but rather they are compromised at materials interfaces such as recording/stimulation windows or coating for packaging and connectors. Total encapsulation of the device across all components is critical to translating fundamental discoveries in barrier layer design to practical improvements for improving in vivo device lifetime. Complex geometries complicate material deposition processes and can lead to poor uniformity across the entire device. Also, the components of the device that are most susceptible to failure from permeable species may not be the front-end multielectrode arrays, but rather the back-end connectors, flex circuits, and cabling. Comprehensive packaging solutions are therefore critical when using devices in "real world" application such as recording neural activity in freely behaving animals.

3. Materials Strategies to Improve Implant Biocompatibility and Supporting Neuronal Health

3.1 Biomaterials Challenges at the Tissue-Device Interface

High spatiotemporal resolution electrical, optical, and chemical signals rapidly fall off in the body with increasing distance from the source[44–46]. In turn, this necessitates that the sensing components of brain-machine interfaces (BMI) must be implanted close to the target sources (typically neurons) and maintain this close proximity throughout the intended lifetime of the implant. This has historically been true because neuronal activity generally elicits membrane depolarizing action potentials that can be detected by a nearby microelectrode as an electrical signal. As a consequence, neuroscience research and neuromodulation applications have largely assumed that neurocomputation is a purely neuronal process governing by electrically excitable cells. However, non-neuronal cells make up the majority of cells in the brain and are responsible for modulating signal transduction across the biotic-abiotic interface [47].

Early biocompatibility studies used post-mortem histology to examine neurons together with astrocytes and microglia since these two glial cells could form insularly scar tissue around the implanted interface[48]. This led to the dogma that any non-neuronal cell activity negatively affected neuronal activity and compromised BMI function in vivo. The assumption was that “inactive” glial cells “activated” in response to implantation injury, and this “activation” lead to an upregulation of proinflammatory cytokine release, and ultimately neurodegeneration. When BMI failed to record action potentials, it was assumed that the glial activation led to the apoptosis of nearby neurons around the electrode within the recording radius. However, recent advances in subcellular level resolution in vivo high-speed two-photon microscopy (TPM) and the development of new transgenic approaches have enabled researchers to examine non-neuronal cell activity in real-time[49–51]. In turn, this has enabled new studies that challenge old assumptions.

A recent study showed examples of an intracortical microelectrode with good material integrity, electrical impedance, neuronal density, and lack of a glial scar that was unable to recording any single unit activity[49]. Other studies confirmed that histological outcomes remain poor predictors of actual recording performance[52–53]. In vivo TPM and mesoscale calcium imaging and blood-oxygenation level dependent optical intrinsic imaging (BOLD-OIS) further elucidated the nature of this unexpected outcome. Following intracortical microelectrode insertion, tissue around the probe can receive less blood supply based on the degree of vascular injury during implantation[51]. In turn, this leads to decreased oxygen and nutrient supply to the nearby tissue[49]. Ultimately, this leads to decreased metabolic support, increased metabolic stress, upregulation of pro-inflammatory cytokines by nearby glia, loss of nearby oligodendrocytes, decrease in neurotrophic support by glia, and ultimately the silencing of nearby neurons [47–49–54]. However, restoring metabolic support during the critical period may allow for recovery of nearby neurons[49].

Taken together, these early results highlight unexplored dimensions to biocompatibility and new avenues to materials-based strategy for improving the integration of the brain and technology. For BMI, it is particularly important to consider that compatibility of the tissue (not producing a toxic or immunological response) is an insufficient definition of biocompatibility[55]. Instead, BMIs biocompatibility needs to also consider the fidelity in which signals from nearby cells can be detected by the BMI or the ability of the BMI to modulate the activity of nearby cells in the desired manner. As such, it is important to explore novel materials to improve the integration of the tissue and interface technology[56] including novel coatings and form factors[57]. Lastly, as technology improves, sizes of the interfaces decrease, and channel counts increase, it is important to weigh the tradeoffs of multiple material property during material selection and design. In turn, recent studies have highlighted that these non-neuronal cells are normally active and play crucial roles in homeostasis. Following implantation injury, the activity of the cells changes to upregulation of pro-inflammatory cytokines and downregulation of some resting-state activity. Therefore, materials and interface designs need to consider minimally impacting non-neuronal cell activity or restoring the original activity rather than using pharmaceuticals that completely suspend non-neuronal cell activity.

3.2 Dynamically Softening Polymers

The merits of using implant with mechanical flexibility have been etched into the cannon of the BMI community in recent decades. However, soft or flexible penetrating probes must be initially mechanically resilient to facilitate insertion and tissue integration. One strategy to resolve this inherent dilemma is the use of self-softening polymeric as substrates for neural interfaces. These polymers are initially mechanically robust to withstand insertion forces during the implantation, but then soften upon hydration to reduce the modulus mismatch at the tissue-device interface[58–64]. The compliance to tissue is expected to reduce foreign body responses and therefore to improve the long-term recording capabilities of devices due to minimized scar tissue formation. The first generation of softening polymeric substrates was comprised of thiol-ene and thiol-ene /acrylate polymers that contain ester groups in their backbone and are therefore susceptible to hydrolytic degradation. In order to reliably record neural signals over decades however, softening polymers must also be chemically stable at physiological conditions. Next-generation dynamically softening polymers are ester-free to limit hydrolysis and exhibit greatly improved durability over first-generation polymers[65]. Neural interfaces can benefit by designing systems that employ non-degradable self-softening polymers as substrates.

3.3 Transient Substrate Materials

It is advisable to design neural interfaces with materials and form factors that limit implant micromotion and reduce the mechanical mismatch at the tissue-device interface. This guidance is most often cited in the context of cortical interface which often uses high-density silicon-based multielectrode arrays implanted into highly compliant tissue. Recent studies suggest a limit to the efficacy of mechanical matching between the implant and the resident tissue[66]. At least in the context of tissue response, the marginal benefits of reducing the mechanical modulus becomes vanishingly small for implants with an effective Young's modulus of E~1 MPa. These data combined with previous findings[48] suggest that the persistent presence of a material is largely responsible for degradation of signal transduction across the biotic-abiotic interface.

Transient substrate materials with elastomeric properties could therefore serve as an emerging approach to neural interface design[67–68]. Biodegradable elastomers have been explored in the context of regenerative medicine[69–71], but may also have applications as transient substrates. This class of materials may facilitate device implantation and then erode in a controllable way to allow tissue to integrate with the underlying electronics. Biodegradable elastomers offer significant advantages including tunable mechanical properties, controllable and well-characterized degradation mechanisms[72], intrinsic biocompatibility[73], and unique properties such as shape-memory[74]. Biodegradable elastomers can be processed into diverse form factors using widely available manufacturing processes such as laser cutting[75], photolithography[76], and replica-molding[77–79]. Therefore, there may be new opportunities to integrate electronics with transient support materials that can facilitate tissue integration and then biodegrade into benign components that can be metabolized by cells near the implant site.

4. Emerging Concepts for Tissue Integration

The material requirements to maintain the biotic-abiotic interface and device packaging of multielectrode arrays are depend on the device form factor, implantation site, and procedure for tissue integration. Tissue-penetrating monolithic probes with multiple recording sides inserted into excitable tissue remains the gold-standard for neural interfaces. Prominent examples include Utah and Michigan multielectrode arrays. However, there have been many exciting innovations in device architecture in recent years. This section briefly highlights some emerging concepts for tissue integration that could dictate future materials requirements for maintaining chronic device biocompatibility and hermeticity in vivo.

4.1 Highly Parallelized Implantable Fiber Arrays

Recording over large tissue volumes can provide great value for both neuroscientists and clinicians. Increasing the recording volume often requires increased device size and subsequently more damage to tissue upon device integration. Individual recording microwires can reduce tissue damage, but often scale poorly since it is difficult to bundle microwires into larger arrays. A novel concept by Melosh et al. and Paradromics fabricates and packages large microwire arrays into easy-to-handle systems that enable bidirectional recording in large tissue volumes[80]. Briefly, the device uses techniques from the textile industry to bundle as many as ~10,000 insulated microwires in a collet to create a multielectrode arrays[81]. The microwires are trimmed and sacrificial layers are removed to define the device dimensions and electrode spacing. Finally, the microwire arrays are bonded to a CMOS pixel arrays stochastically fusing microwires with recording elements. This clever design affords numerous advantages including modular device dimensions that are defined by choosing the microwire length, sacrificial layer thickness (inter-wire spacing), and the total number of microwires in the array. Furthermore, highly parallelized microwire arrays have the potential for long-term high density recording because of the miniaturization of each individual recording site. The device lifetime is therefore likely governed by the tissue biocompatibility and barrier properties of the insulation material on the individual microwires[82]. These microwire arrays also simplify packaging challenges because the packaging, connectors, and back-end electronics can be safely positioned far from the recording site.

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4.2 Robotic-Assisted Insertion of High Bandwidth Devices: "Neural Lace"

Another iteration of highly parallelized microscale recording devices is the "neural lace" developed by Neuralink[16]. The recording device in this concept consists of multiple polyimide fibers that are ~20 mm long, between 4-6 μm thick, and between 5-50 μm wide. Each fiber contains up to 32 independent passive electrodes with coatings to improve charge injection and metallized traces. Each array contains up to 96 threads and the overall device contains ~3000 individual recording electrodes. The device contains the following on-board electronics: individually programmable amplifiers, on-chip analog-to-digital converters, and peripheral control circuitry for serializing the digitized outputs. Critically, the back-end hardware also ultimately interfaces flexible polyimide arrays to a USB-C connector, which could accelerate broad adoption by a diverse user base. While the device fabrication and hardware are impressive, perhaps the most innovative aspect of the "neural lace" concept is not the device itself, but the tissue integration strategy. Specifically, a robotic system uses optical tracking and precise movements to rapidly and reliably insert threads into the surface of excitable tissue such as the cortex. Light modules combined with software predetermine insertion sites to avoid rupturing the neuro-vasculature and thus maximizing the likelihood for chronic high-fidelity recordings. Devices with over 3000 independent electrodes have recorded neural activity in freely moving rats. The clinical prospects of this device are bolstered using well-characterized materials such as gold and polyimide. Future challenges include ensuring barrier layer integrity long-term and reducing the effect of micromotion artifacts. Nevertheless, the "neural lace" is a compelling concept that could help usher in the era of high-bandwidth devices.

4.3 Minimally Invasive Neural Interfaces: Stentrode

Tissue-penetrating implants can provide access to high quality electrophysiological recordings of unitary activities and local field potentials when placed within the brain. However, insertional probes require highly invasive craniotomies, risk damage to the brain regions and vasculature along the implantation track and have well-documented challenges with long-term in vivo biocompatibility. This limitation motivated the use of vasculature as an alternative minimally invasive route to accessing inner brain regions[83]. A recent example is the Stentrode led by Oxley et al. along with partners at Synchron. This bidirectional interface is essentially an endovascular stent with ~10 electrode discs 750 um in diameter that are oriented on the external radial surface[84]. The device can be introduced into blood vessels measuring approximately 3 mm in diameter[85]. Multielectrode arrays on these devices can record local field potentials (LFP), which may have compelling applications in decoding of speech. Stentrodes have been implanted into both sheep (>180 days) and more recently in humans[85–86]. Devices are eventually incorporated into the neointima and deliver stable recordings while preserving vessel patency during the testing period. Avoiding costly and invasive surgeries by routing neural interfaces through the vascular is compelling. Although the number of recording sites and the possible use cases will likely increase with time, the set of potential recording sites is ultimately dictated by the anatomy of the neuro-vasculature. Furthermore, there are potential biocompatibility concerns not with the device, but with the blood-contacting catheter that is necessary for transmitting recording data extracorporeally. Nevertheless, this creative approach and impressive demonstration could inspire new types of minimally invasive approaches to integrate neural interfaces with the body.

5. Conclusions and Future Directions

5.1 Challenges to Clinical Translation of Neural Interfaces

The developments described above highlight the fact that there is a concerted and significant effort in leveraging materials research to improving the performance and utility of BMI. The same conclusion can be drawn by the increasing number of bioelectronics-themed talks symposia at MRS and other meetings. A large amount of work, for example, concentrates on the development of new materials for neural electrodes. This effort, however, seems to be disproportionate to the number of new materials introduced in implantable electronic medical devices (IEMD), which is very limited. Indeed, there has been little innovation and adoption of new materials in these devices: The electrode array of the cochlear implant, for example, has changed little since the device was first developed in the late sixties. This raises the question as to why the efforts of a large research community are not valorised, when they can potentially lead to improvements in healthcare and quality of life for many patients. The answer lies in the high costs and high risks associated with the introduction of new materials in medical devices. When a new material is introduced, device biocompatibility must be re-evaluated. While the device may pass biocompatibility tests, it can fail after several years in the human body, leading to very costly lawsuits. This makes chemical industry reticent to supply new materials to implant manufacturers. Finally, the cost associated with the introduction of new materials is borne disproportionately by the first manufacturer who innovates and ends up lowering the regulatory barrier for their competitors. As a result, there must be *compelling advantages* arising from the use of new materials to make a sound business case. A new electrode coating that significantly lowers electrode impedance leading to longer battery life, might be such an example. When it comes to more disruptive concepts, such as devices with novel form factors that enable less invasive surgery, or devices employing novel transduction/actuation mechanisms, the path to the clinic would, in general, be even longer. Perhaps a SEMATECH (Semiconductor Manufacturing Technology)-style consortium[87], bringing together industry and government with academia and healthcare providers, would help develop a model that allows to share the risks and benefits of innovations in invasive BCI. Still, a great deal of progress can be achieved within academia by collaborations between technology-based and clinical groups. An example is the NeuroGrid[88], a flexible microelectrode array for electrocorticography (ECoG). The electrodes are coated with the conducting polymer PEDOT:PSS that lowers impedance[89], allowing the fabrication of electrodes with diameters down to tens of micrometres. They are placed on a thin plastic foil that ensures conformal contact to the brain[90]. The combination of small electrodes and conformal contact leads to high resolution corticograms that capture single neuron signals without penetrating the brain. This is compelling advantage compared to traditional ECoGs, and the device was translated to the clinic where it is used to explore the human brain at unprecedented spatial resolution[91].

5.2 Future Materials Challenges and Opportunities

Materials innovations will fundamentally drive advances in the performance of implantable neural interfaces in the coming decades. Two prominent materials challenges highlighted here including reliable device packaging and managing the tissue-device interface. For designing and testing of novel packaging materials, our collective scientific understanding of the problem is likely sufficient, the technical challenges are properly framed, the figures of merit to define performance are well defined, and the testing platforms are standardized across laboratories. Therefore, creative engineering solutions, bounded only by fundamental limits on materials performance, will forge the path to improved barrier layer performance in neural interfaces. Materials innovations to better manage the tissue-device interface have a potentially more tortuous path because many scientific questions remain. The community of BMI and biomaterials scientists have advanced our knowledge of the biological mechanisms that underpin the tissue response to implants. However, critical knowledge gaps remain and must be first addressed with additional detailed fundamental studies. Furthermore, it is difficult, but not impossible to make global comparisons of results related to in vivo device performance conducted by different laboratories. Heterogeneity in animal models, data acquisition, data analysis, insertion methods, and post-operative care make it difficult to compare results across various studies. Challenges and opportunities for improving materials for implantable neural interfaces are currently by defined de facto roadmaps. It is very possible that the neural interface of the future may avoid implantation altogether or may use alternative signal transduction mechanisms without the need for genetic manipulation. For now, however, materials limitations establish device criticalities that must be addressed with the mindset of >10X improvement to realize the full potential of implantable neural interfaces.

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Figures

Figure 1

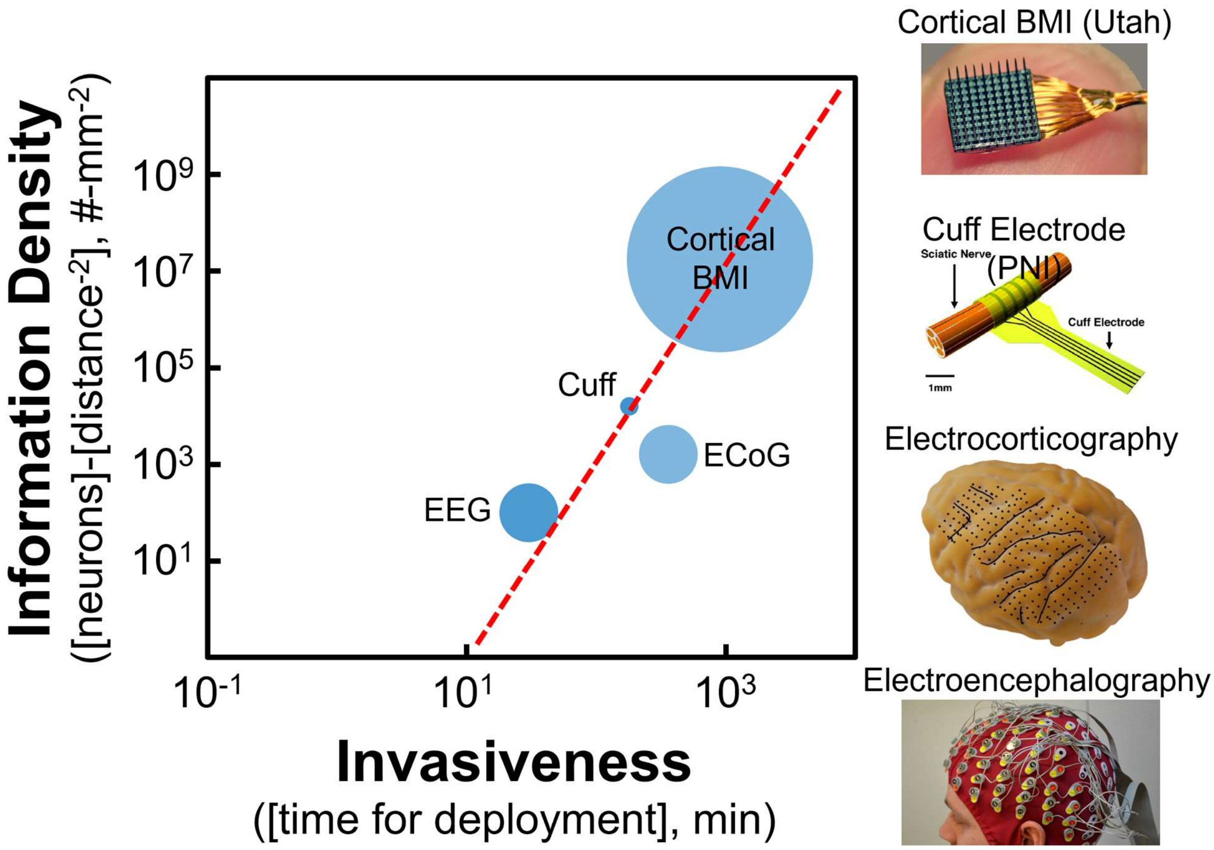

Fig. 1 *Log-log plot of information density vs. invasiveness for various classes of brain-machine interfaces. Information density is an estimate of neurons that can be accessed using the approach normalized by the square of the approximate distance between the neuron and the sensor owing to the r^{-2} decay in electric fields. Invasiveness is quantified by the approximate number of minutes to integrate the device with the intended target. The approximate total number of neurons accessible is represented by the radius of the circle. The trade-off between information density and invasiveness becomes apparent.*

Figure 2

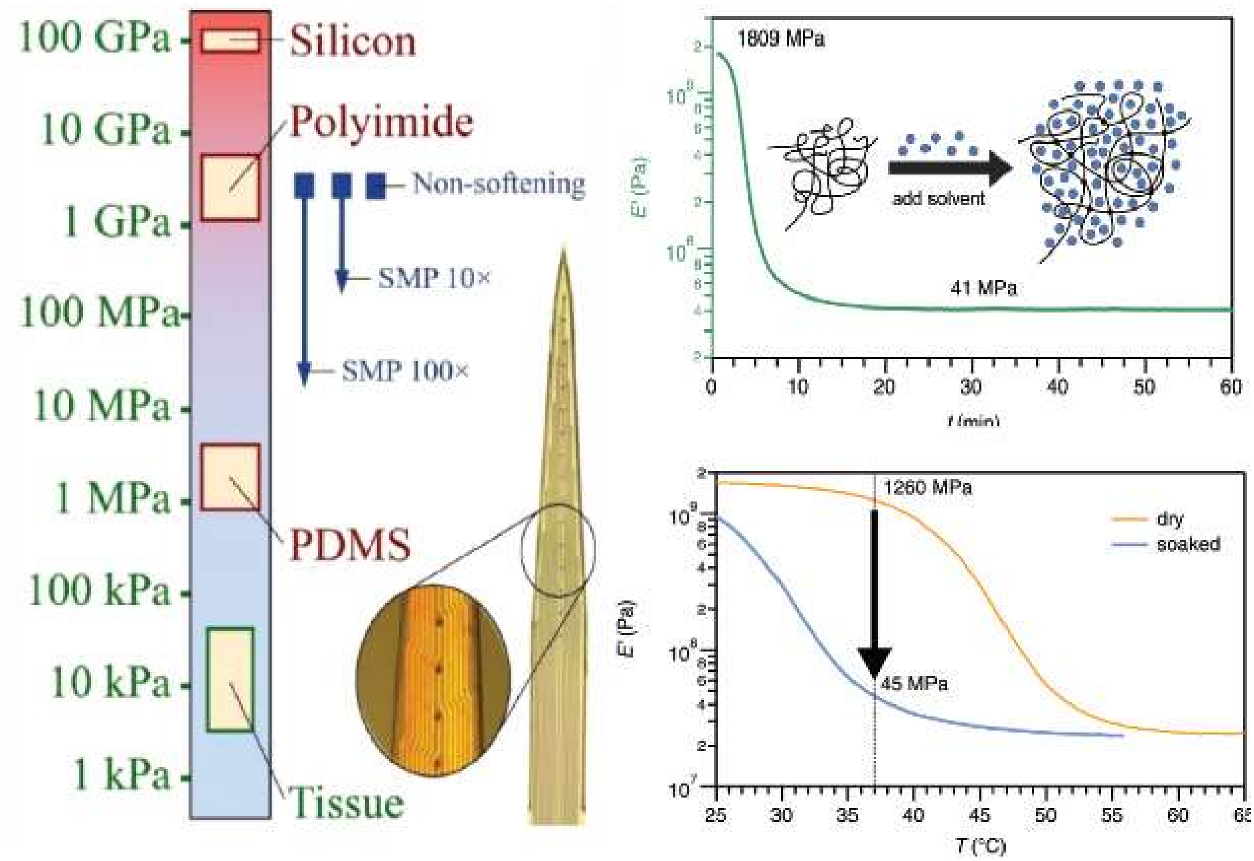

***Fig. 2** Schematic displays the stiffness of various materials as compared to tissue (left) and the softening of polymers under physiological conditions due to plasticization as measured by dynamic mechanical analysis (right)*[58].

Figure 3

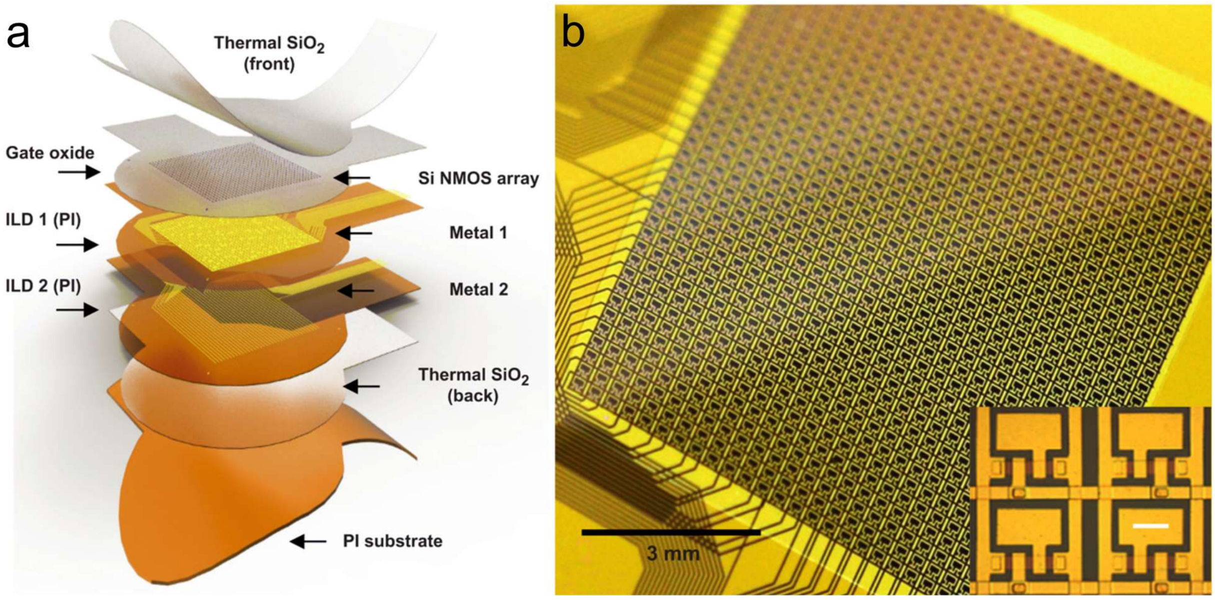

Fig. 3 *(a) Schematic of packaging stack and (b) macroscopic image of flexible recording arrays termed the NeuroMatrix*[26]*. This device can produce stable in vivo recordings for up to 1 year with predicted operational lifetimes of up to 6 years. Scale bar in (b) inset is 100 μm.*

Figure 4

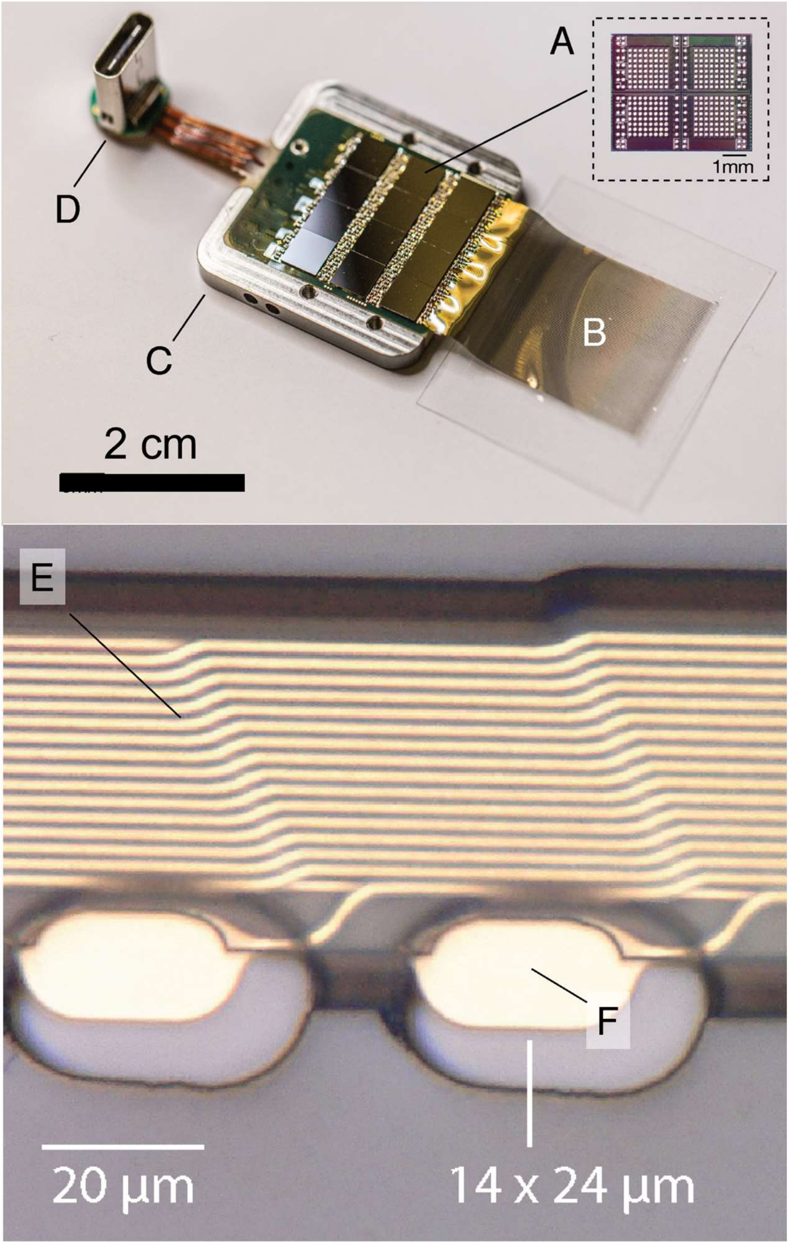

Fig. 4 *(top) Macroscopic photograph of the neural lace technology*[16]*. This device features the following components: (A) 12 application specific integrated circuits for processing; (B) arrays of electrode arrays on polymer threads on a parylene-c*

handling layer; (C) titanium enclosure with lid removed; (D) USB-C connector; (bottom, E) close up of two recording sites with gold traces.

Figure 5

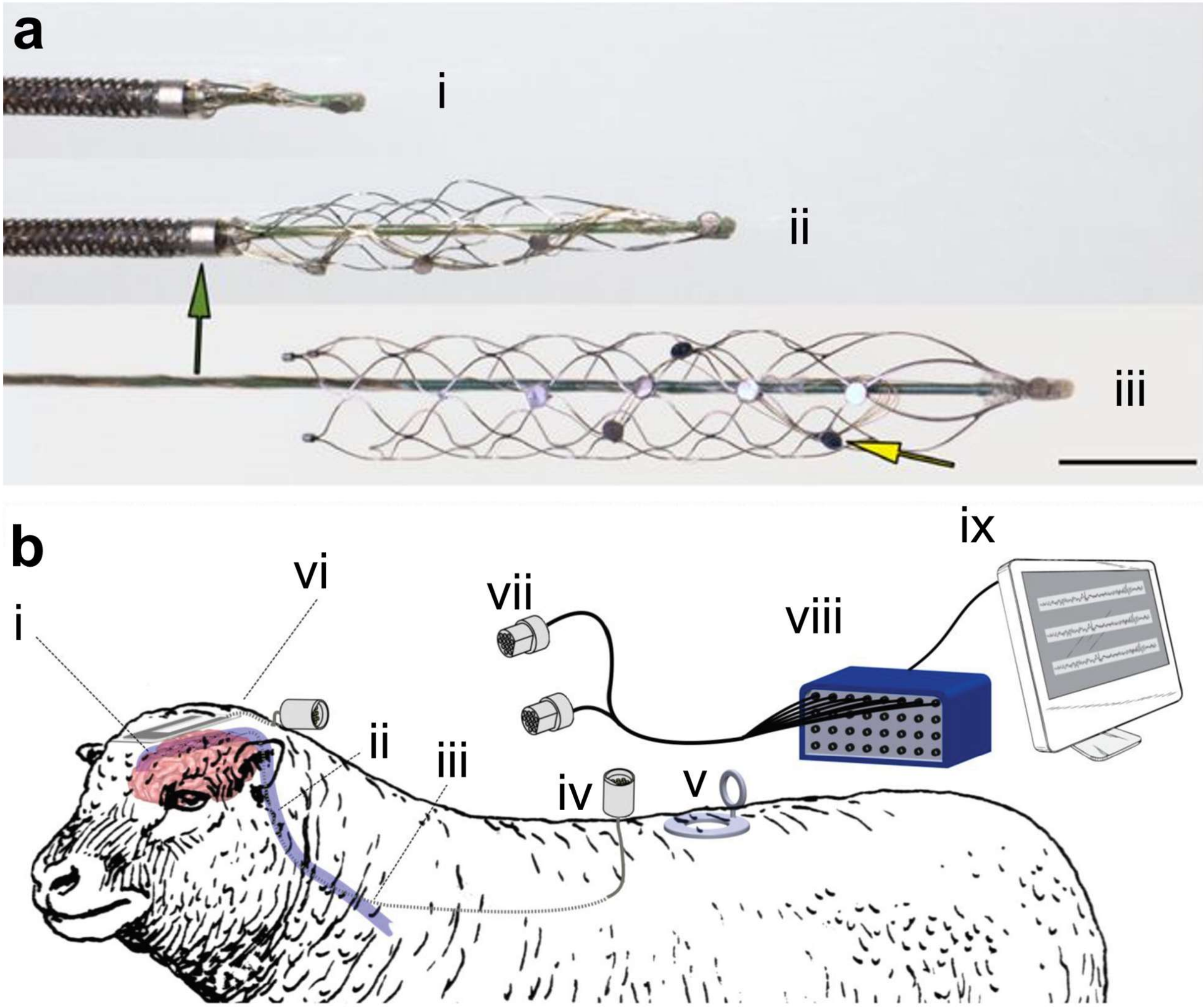

Fig. 5 *(a) Stentrode with 8 × 750 μm electrode discs (yellow arrow) self-expanding during deployment from a 4 French (4F) catheter (green arrow); (i) retracted device; (ii) partially deployed device; (iii) fully deployed device. Scale bar is 3 mm. (b) Schematic of recording setup for the endovascular stentrode (i) implanted in the brain of sheep. (ii) Leads exit the brain via internal jugular vein and (iii) protrudes through the wall of the common jugular vein tunneling subcutaneously to (iv) custom-made connectors secured*

to a muscle. (v, vi) stainless steel and platinum ground electrodes. (vi) Electrode lead wires and ground electrodes are connected to omnetics connectors (vii) that are connected to a (viii) data acquisition system (ix) and computer for recording.

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