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Next generation material interfaces for neural engineering

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Neural implant technology is rapidly progressing, and gaining broad interest in research fields such as electrical engineering, materials science, neurobiology, and data science. As the potential applications of neural devices have increased, new technologies to make neural intervention longer-lasting and less invasive have brought attention to neural interface engineering. This review will focus on recent developments in materials for neural implants, highlighting new technologies in the fields of soft electrodes, mechanical and chemical engineering of interface coatings, and remotely powered devices. In this context, novel implantation strategies, manufacturing methods, and combinatorial device functions will also be discussed.

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Introduction

Neural devices have clinical applications in neurodegenerative disease, spinal cord injury, and in the restoration of sensory functions. While non-invasive stimulation and recording methods are well researched and clinically available (e.g. transcranial magnetic stimulation, electroencephalography), they are not applicable to all neurointerventions. The complex signaling required for many neural stimulation or recording applications require deeper implantation, often under the skin, skull, or deep into neural tissue. The foreign body response induced by implanted devices often results in encapsulation by cells and fibrous tissue [1]. This eventually hinders communication between the device and surrounding neural tissue, thus limiting longevity. As such, mitigating host responses to implants has led to new efforts to modify implant biological interfaces, and brought materials science to the forefront of neural engineering research.

Stiffness mismatches between electrodes and neural tissue are a strong modulator of the host response [2]. As such, soft electrodes dominate the field of neural interface engineering, and recent advances will be discussed. We will highlight new materials used in conductive layers, as well as novel manufacturing methods that can be used with conventional soft electrode materials. While many new technologies in the field of soft electrodes are focused on skin-mounted devices, similar concepts can be applied to devices mounted on the surface of the brain or spinal cord. However, deeper insertion of soft materials is challenging, and we will therefore highlight new strategies for their implantation.

Modification of device interfaces can also modulate foreign body responses when the device itself is stiff or otherwise less biocompatible. We will discuss methods to modify surfaces such that the host response is lessened, including soft material coating. Chemical interface engineering will also be discussed, with a focus on sensors of ionic electrical signals.

Transdermal and transmeningeal device components also contribute to a stronger host immune response [3,4]. As such, recent strategies to wirelessly power devices have arisen that would avoid wires protruding through the skin or meninges. We will highlight new devices that enable remote powering, and discuss the materials used in each case. Implant geometry is also a determining factor in the tissue response, with feature sizes below the ~10 μm size scale often showing reduced encapsulation [5–9]. We will therefore highlight the small but growing field of nanoscale neurostimulators that also employ remote powering. Materials that enable additional functions beyond sensing and stimulation, such as drug delivery, will also be discussed.

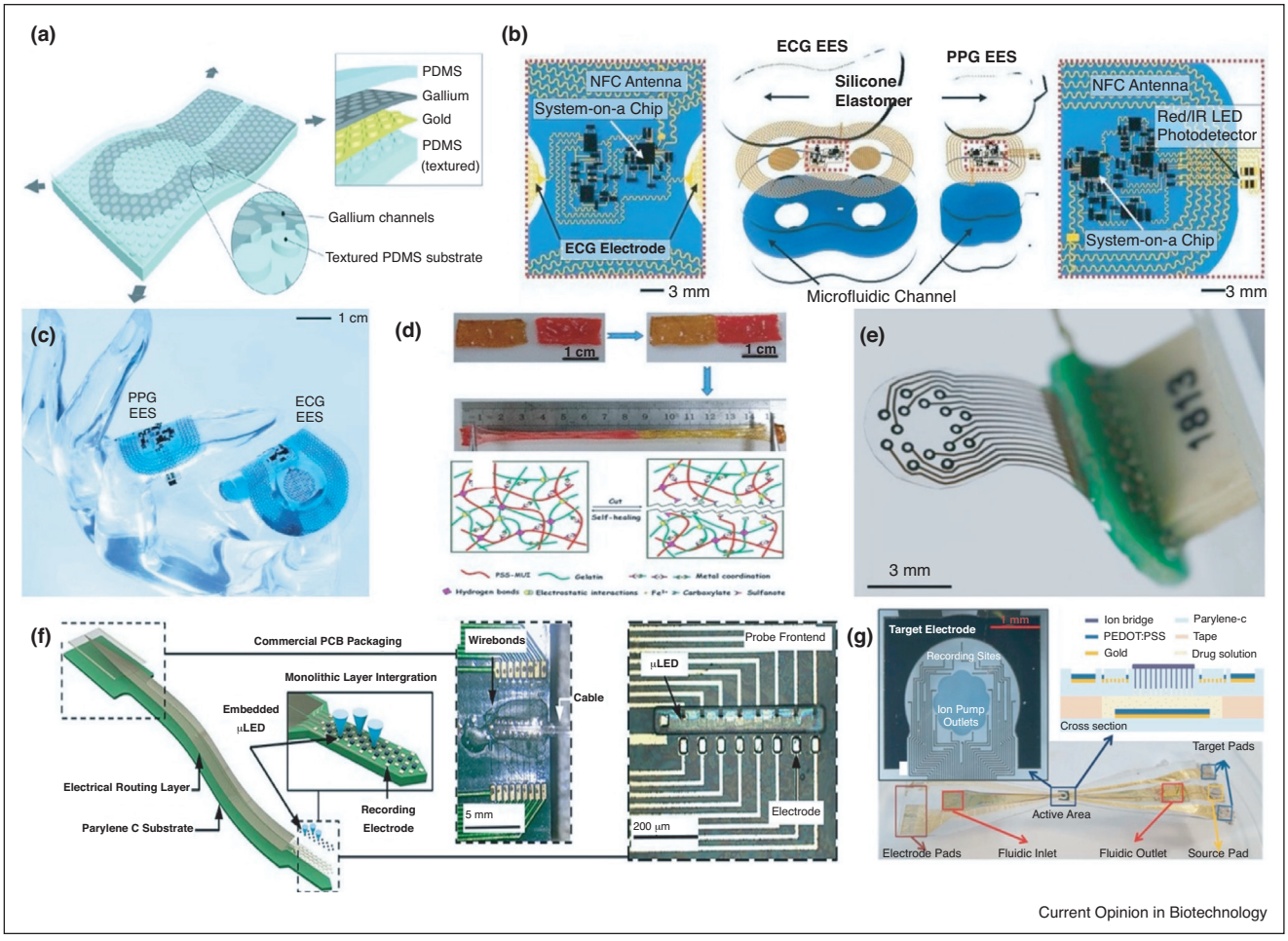
The technologies examined below represent the most recent advances in materials for neural interfaces. Future neural devices will likely incorporate combinations of these technologies, such as remote powering of soft electrodes, or soluble implantation strategies for soft ionic sensors. Herein, we will examine the current state of neural interface engineering, and highlight these technologies as essential to optimizing neural devices in the future.

Soft electrodes

A primary challenge in soft electronics is manufacturing the conductive component such that the implant maintains overall flexibility. Liquid metals based on gallium as either thin films [10••] or within microfluidic channels [11] provide a conductive layer that is liquid at room and body temperature, and is nontoxic (Figure 1a). Gallium based hydrogel electrodes using layers of poly(2-hydroxyethyl methacrylate) (pHEMA) and poly(dimethylsiloxane) (PDMS) recently demonstrated tolerance of repeated swelling/deswelling cycles, used for hydrogel reshaping, or long-term (months) storage [10••].

Strategies to circumvent the lower flexibility of common conductive layers have recently been demonstrated using geometric patterning or mechanical isolation. Y-shaped cut-outs in the Pt layer of a poly(imide) (PI)–Pt–PI thin film increased the failure tensile strain value to 80%, versus 3% with no patterning. Furthermore, when the thin films were encased within a PDMS carrier, the elastic modulus and fracture strain of PDMS were only minimally affected [12••]. An additional strategy to maintain electrode flexibility using low flexibility conductive layers is to minimize the strain that the conductive layer undergoes. Chung *et al.* designed skin-adhesive PDMS soft electrodes with copper conductive layers that where mechanically separated from the source of strain (i.e. the skin) with a nontoxic ionic liquid encased in the PDMS [13] (Figure 1b,c). The sigmoidal geometry of the copper layer also contributed to electrode flexibility,

Figure 1



Recent advances in soft electrode technology. **(a)** A gallium-based stretchable conductor in schematic view embedded in PDMS. **(b)** Schematic of the skin-adhesive PDMS soft electrodes with conductive copper layer for recording electrocardiogram (ECG) data (left), and for photoplethysmogram (PPG) data (right). **(c)** Demonstration of the size and flexibility of these modules. **(d)** A self-healing PSS-MUI/gelatin-based hydrogel, and a schematic showing the self-healing reaction**. (e)** Photograph of a transparent and stretchable ECoG-array 'Opto-E-Dura' based on PDMS. **(f)** Illustration of a flexible optoelectronic device, with zoomed images of the external component and probe shaft that contains the recording electrodes and the μLEDs. **(g)** Photographic representation of a microfluidic ion pumping system inside a recording electrode. Reproduced with permission from Refs. [11,13,16•,18••,64•,69].

and could be designed to avoid closed loops and thereby enable MRI compatibility [14].

A plant-based composite material was recently demonstrated, with the goal of making transcranial electrostimulation (TES) electrodes more biocompatible, while maintaining high charge capacity [15••]. TES electrodes were fabricated using a combination of conducting polymers, such as poly(3,4-ethylenedioxythiophene):poly (styrenesulfonate) (PEDOT:PSS), and a hydrophilic gel derived from aloe vera. These showed lower electrochemical impedance and higher charge capacity than previous TES electrodes. The efficacy of this material was demonstrated *in vivo* in rats, in which focal seizures were simultaneously induced and neural activity was recorded [15••].

Soft electrodes with combinatorial or new functionalities have also been demonstrated in recent years. Figure 1d shows a self-healing flexible electronic using ferric ion crosslinkers in a poly(4-styrene sulfonate-co-methyl-uracil-imidazolium) chloride (PSS-MUI)/gelatin based hydrogel. As the same noncovalent crosslinking binds the bulk hydrogel and heals the fracture, the healed interface becomes mechanically and electrically indistinguishable from the original hydrogel after two hours of contact [16•]. A similar self-healing and conductive hydrogel was recently validated as a strain sensor on human skin [17].

'Opto-E-Dura', an optically transparent, stretchable, 16-channel electrocorticography (ECoG) array was recently presented that combines different measurement modalities [18••] (Figure 1e). Previously, a soft, stretchable multielectrode array (MEA) called 'E-Dura' was presented by Minev *et al.* for spinal cord injury [19]. As fabrication techniques were improved by subsequent work [20–23], chronic stability for long-term electrical measurements was demonstrated for up to three months [24]. Based on this work, PDMS was chosen as the base material for Opto-E-Dura due to its optical transparency and flexibility [25–27]. *In vivo* studies in mice demonstrated the functionality of Opto-E-Dura in combination with wide-field calcium imaging, 2-photon calcium imaging, and recordings from inserted MEAs [18••].

Advances in manufacturing

While the materials in soft electrodes most commonly rely on the same polymers (i.e. PEDOT, PSS, PDMS), new manufacturing methods have led to novel geometries and capabilities. Additive manufacturing was used to build organic electrochemical transistors (OECTs), with 3D printing used to write the conducting and insulating layers, and inkjet printing to deposit the PEDOT:PSS semiconducting thin film [28]. A new additive manufacturing technique used printing of Ag or PEDOT:PSS fibers within a layer of high molecular weight (4 million Da) poly(ethylene glycol) (PEG). This method does not require post-processing, and can make controllably small (1–3 μm) fibers with good conductivity (10^6 S/m). This technique also enables layering of fibers and control of junction formation between layers to make 3D and connectable fiber architectures [29]. For other bottom-up manufacturing techniques, a recent study has shown that 3,4-ethylenedioxythiophene (EDOT) oligomers can incorporate the advantages of PEDOT, but enable new material processing methods. In block copolymers with poly(caprolactone) (PCL), they showed they could write OligoEDOT-PCL fibers via solvent and melt electrospinning, and OligoEDOT hydrogels via block copolymerization with PEG [30].

A top-down method was recently shown using laser cutting to achieve patterning of PEDOT:PSS and other active materials. By laser cutting into the insulating material and drop-casting the polymer solution, controlled, micron-scale patterns can be achieved [31]. This could replace comparable photolithographic techniques for OECT patterning, which simplifies fabrication and eliminates waste of the active material.

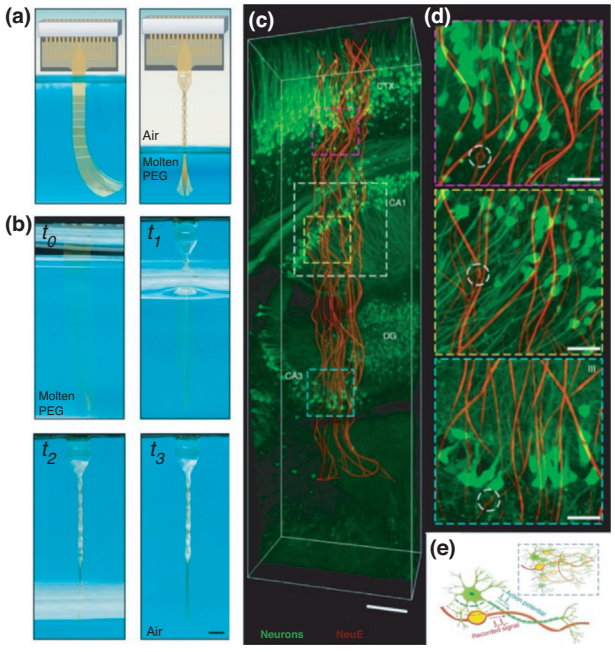
Yan *et al.* recently demonstrated fabrication of ultrathin (40–100 nm) metallic glass electrodes via repetitions of thermal co-drawing within a polymer. The size and cross-sectional interface of the two materials is tunable, and enables fabrication of up to meter length scales. Co-drawing of metallic glass with flexible polyetherimide (PEI) was used to make flexible electrodes for stimulation and recording in the brainstem of rats [32••]. For 3D polymer architectures, conductive, porous scaffolds with no insulating matrix were fabricated by Jayaram *et al.* by mixing PEDOT:PSS with multi-walled carbon nanotubes (CNTs) and freeze-drying [33].

Implantation strategies

The use of soft electrodes superficially provides fewer barriers to implantation. However, applications that require the electrode to reach into tissue, rather than to remain on its surface, require strategies to temporarily stiffen soft electrodes during implantation. A polyimide-Pt-polyimide (PI–Pt–PI)/PDMS soft electrode was recently implanted into the auditory brainstem in mice using a dissolvable poly(vinyl alcohol) (PVA) guide. This guide was large enough to be held by forceps (1 mm thick), temporarily added stiffness, and allowed for 35 min of handling before becoming soft and eventually dissolving [12••].

A soluble polymer coating was also used to enable soft electrode injection. An array of up to 1024 individual soft electrodes were adhered together and stiffened by immersing them in molten PEG (Figure 2a,b). This enabled injection of the soft electrodes, with the PEG coating dissolving within seconds after tissue contact [34].

Figure 2



Strategies for insertion of soft electrodes into brain tissue. **(a)** Schematic and **(b)** photographic representation of a neurotassel to illustrate elastocapillary self-assembly (Scale bar, 1 mm.) **(c)** 3D reconstructed image six weeks post implantation of Neuron-like electronic (NeuE) probes (red) and neurons (green) (Scale bar, 200 μm). **(d)** shows the magnified images from cortex (top), CA1 (middle), and CA3 (bottom) regions (Scale bars, 50 μm). **(e)** Schematic showing the biomimetic structure of NeuE (red: polymer layer, yellow: interconnectors) relative to neurons (green). Reproduced with permission from Refs. [34,36].

Similarly, a soluble PEG coating was used for implantation of liquid crystal elastomer (LCE) based microelectrodes. The electrodes were fabricated and held in a 2D conformation with the PEG coating, and then released to a predetermined 3D conformation after implantation [35]. For soft electrodes with dimensions that allow needle insertion, injection can also be carried out by coordinating injection and needle retraction [36] (Figure 2c–e).

To reduce inflammation and damage to the brain, a new system of inserting electrodes was introduced, called the 'sewing machine'. This device includes fine, flexible thin-film polymer probes, a thin and stiff insertion needle, and an insertion robot [37••]. After the dura mater is exposed through a craniotomy, an image of the surface of the brain is captured by a camera on the surgical robot, and custom software selects target sites. Laser ablation creates micro-durotomies at the insertion sites, and the insertion needle captures a small loop located at the end of each electrode. The robot then inserts the electrode into the brain, the needle is removed, and the process is repeated until all electrodes are inserted. This system allows a fast and precise implantation of a large number of electrodes.

Device surface modification

Chemical interface engineering

The bulk of chemical interface research in neural engineering focuses on OECTs. These devices transduce biological, ionic electric signals into electronic signals that can be carried via conductors, and are therefore a key component in biosensors. In addition, OECTs are typically soft, operate well within aqueous environments, and can be integrated into microfluidics or larger neural devices.

Electrolyte interfaces with ion selective membranes typically rely on a liquid electrolyte layer between the membrane and transistor in order to optimize the membrane's selectivity and sensitivity. This internal fluidic compartment adds bulk and reduces flexibility, due to the plastic or glass chamber that encases it. In order to address this, Han *et al.* recently demonstrated a polymeric replacement for the liquid electrolyte using poly(sodium 4-styrenesulfonate) (PSSNa) that yielded 1 s response times, superNernstian sensitivity (85 mV/dec), and high current sensitivity (224 μA/dec) [38]. This group also showed that PSSNa blended with PEDOT:PSS in an OECT led to faster response times [39].

P-type, or hole-transporting, polymers dominate OECT literature due to the poor performance of n-type, or electron transporting, polymers in aqueous conditions. Recent work, however, has demonstrated an n-type conductive polymer, poly(*N*,*N*′-bis(7- glycol)-naphthalene-1,4,5,8-bis(dicarboximide)-co-2,2′-bithiophene-co-*N*,N′-bis(2-octyldo-decyl)-naphthalene-1,4,5,8-bis(dicarboximide) (P-90) with nearly comparable performance to current p-type polymers [40]. As n-type polymers are better suited to sensing cation fluxes, this new polymer has important implications for future biological sensors.

While OECTs optimize sensing functions of neural interfaces, recent work in chemical modification of neural implants has also focused on biocompatibility. Implant surface modification with zwitterionic polymer poly(sulfobetaine methacrylate) (PSB) codeposited with polydopamine (PDA) on silicon neural probes reduced reactive astrocytes and microglia, and promoted better blood–brain barrier (BBB) integrity around the implant [41].

Mechanical interface engineering

Similarly to soft electrodes, modification of stiff neural devices with soft interfaces is a common strategy to reduce inflammation and foreign body responses in the host tissue [2]. Choi *et al.* demonstrated a transient soft surface coating using polyanhydride-based encapsulation layers. They were able to demonstrate controlled

degradation rates, and biocompatibility of both the coating and its degradation products [42].

Carnicer-Lombarte *et al.* recently validated a mechanotransduction link between interface stiffness and foreign body response. By coating implants with PDMS or polyacrylamide substrates with elastic moduli ranging from 0.1 to 50 kPa, they demonstrated that tissue stiffness matching of the interface (1 kPa and below) reduced the foreign body response to a subcutaneous implant after three months in rats. They then showed a correlation between stronger foreign body reactions with nuclear localization of the mechanotransducer yes-associated protein (YAP) [43].

In addition to mechanical stiffness, implant size can also modulate tissue responses. Recently, a carbon fiber microwire array with 32 electrodes was presented for neural recording [44•]. The individual carbon fibers have a diameter of 4.8–5.4 μm, which is below the threshold for fibrous capsule formation [5–9,45]. These were spaced 38 μm apart in an array, which is a markedly smaller electrode spacing compared to similar carbon fiber arrays [7,45]. This allowed for full-volume scanning while minimizing adverse biological effects. Thus, this array is reported as having the highest density and the finest electrode diameter versus all previous microwire arrays.

Wireless neural devices

Wireless and small scale neural devices are less well studied than soft electrodes or interface engineering as a method to modulate biological responses to implants. However, remote powering can eliminate wires going through the dura, skull, and/or skin. Small size, as discussed above, changes the tissue response such that fibrous capsule formation can be prevented [5–9,45]. As there is not yet a convention for use of the term 'wireless' in neural devices, herein, we will focus only on devices which are remotely powered.

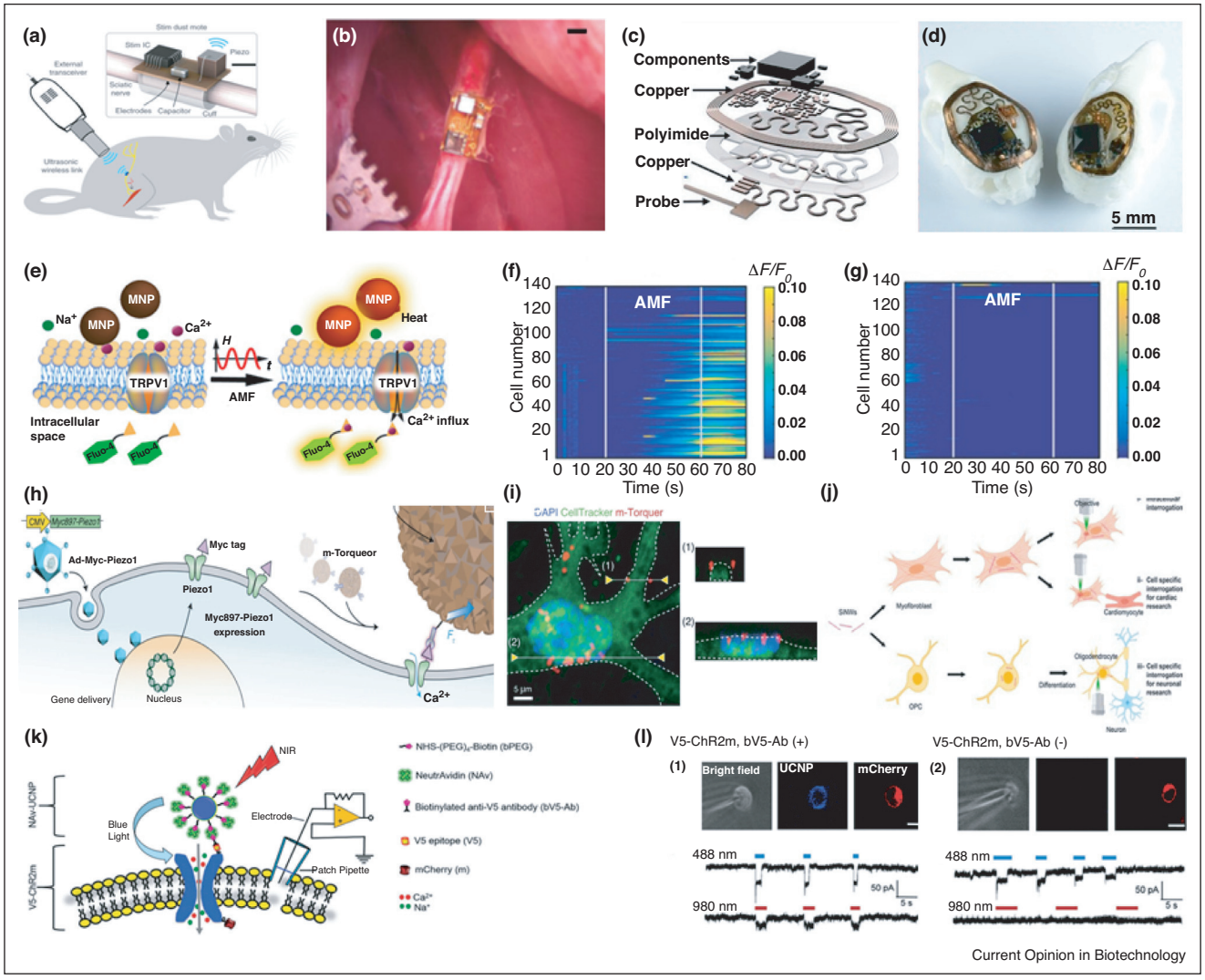
Several new devices using remote powering of piezoelectric transducers via acoustic signaling have recently been demonstrated. Ghanbari *et al.* showed recording from multiple implants simultaneously, and verified operation through 5 cm of a tissue phantom material [46•]. Stimulation and recording was demonstrated in the sciatic nerve of anesthetized rats (Figure 3a,b) [47]. Acoustic powering of piezoelectric nanoparticles has also been shown in rat hippocampal and cortical slices [48]. In addition, a new approach for the treatment of glioblastoma by ultrasound-mediated piezoelectric stimulation was developed *in vitro*. In this approach, glioblastoma cells were electrically stimulated at low intensity, which reduced the proliferation of these cells and showed an apoptotic effect in combination with temozolomide [49].

Magnetic powering schemes may be advantageous over acoustic schemes depending on the application, as acoustic powering requires contact between tissue and the external transducer. A magnetoelectric thin film, which converts magnetic to electric signals, was used as a transducer to remotely power a biphasic stimulator in freely moving rats. The mm-scale device could be implanted underneath the skin, with an electrode wired into the deep brain. Importantly, this device stimulated the deep brain within a therapeutic frequency range for Parkinson's disease (150–200 Hz), and thereby treated symptoms [50••]. On a similar size scale, magnetic resonant coupling of antennae was used to remotely power a subdermal, skull-mounted soft electrode photometer in rats [51] (Figure 3c,d).

Magnetic actuation of magnetic nanoparticles can stimulate neuronal activity using unconventional methods such as magnetothermal [52,53] and magnetomechanical [54,55] transduction. While magnetothermal stimulation often requires transgenesis of heat-responsive ion channels such as transient receptor potential (TRPV-1) [52], stimulation of native TRPV-1 was recently demonstrated in the adrenal gland (Figure 3e–g) [53]. Magnetomechanical stimulation was recently demonstrated *in vivo* in the cortex of mice, albeit by first genetically introducing a mechanosensitive ion channel [55] (Figure 3h,i), as well as *in vitro* using native mechanosensitive ion channels [54]. Conversely, magnetic stimulation of magnetoelectric nanoparticles provides transduction of magnetic signals directly to electrical stimulation, and has recently been used for deep brain stimulation in mice [56].

Materials that transduce light have also emerged as neurostimulators. Nanoparticles made of photosensitive semiconductor poly(3-hexylthiophene) (P3HT) were used for retinal stimulation via optical input in a rat retinal dystrophy model. The nanoparticles were injected into the subretina and used to stimulate inner retinal neurons to recover visual cortical activity and percepts. This technology is very promising for chronic and progressive diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP), in which rods and cones are damaged, but inner retinal neurons remain intact [57••]. Photosensitive nanoparticles have also demonstrated visual detection of near-infrared light (NIR) via nanoparticle upconversion of the light frequency [58]. Yadav *et al.* developed a technique to bind upconversion nanoparticles closer and more specifically to channelrhodopsin-2, thereby reducing NIR power (Figure 3k,l). For this purpose, the upconversion nanoparticles were modified with NeutrAvidin and a biotinylated antibody marked channelrhodopsin-2, resulting in a strong biotin–avidin interaction [59]. Compared to other implantable optogenetic devices where light is unable to penetrate deep into tissue, upconversion nanoparticles have the advantage of being able to stimulate deeper tissue

Figure 3



Remotely powered neural implants. **(a)** Schematic and **(b)** photograph of StimDust for stimulation of the rat sciatic nerve using a remotely powered piezoelectric transducer. (Scale bar, 1 mm). **(c)** Illustration of the individual layers of a photometry device consisting of the implant and the injectable photometry probe. **(d)** shows the two photometry variants on 3D printed mouse skull models. **(e)** Schematic representation of the functionality of magnetothermal nanoparticles. **(f)–(g)** show the normalized Fluo-4 intensity in rat adrenal cell cultures after an external alternating magnetic field was applied, with (f) magnetic nanoparticles and (g) the control of wüstite nanoparticles. **(h)** Schematic of transgenesis of mechanosensitive ion channel Piezo1 with Myc tag, and magnetomechanical control by m-Torquer with an anti-Myc antibody. **(i)** shows confocal images of a neuron expressing Piezo1 tagged with m-Torquer (red). (1) and (2) each show a cross-sectional view. **(j)** Schematic representation of spontaneous internalization of silicon nanowires (SiNW) from myofibroblasts (top) and oligodendrocyte progenitor cells (bottom) for localized and cell-specific photostimulation. **(k)** Illustration of the specific binding of the NeutrAvidin-modified upconversion nanoparticles to channelrhodopsin-2. **(l)** shows the efficacy of the nanoparticles bound to (1) channelrhodopsin-2 and the (2) control without biotinylated antibody, preventing the nanoparticles from binding. Scale 20 μm. Reproduced with permission from Refs. [47,51,53,55,59,60•].

structures. Figure 3j shows a new silicon nanowire (SiNW)-based tool for *in vitro* intracellular electrical interrogation presented by Rotenberg *et al.* [60•]. Previously, SiNWs have been used for extracellular light modulation of excitable cells such as neurons or cardiomyocytes [61,62]. Because SiNWs are often spontaneously taken up by many cell types, the idea of a nongenetic intracellular optoelectronic living system emerged [63]. Rotenberg *et al.* demonstrated local and cell-specific photostimulation using SiNWs in myofibroblasts cocultured with cardiomyocytes. It was also shown that this system can be extended to neuronal networks, using oligodendrocytes containing SiNWs co-cultured with dorsal root ganglion neurons.

Combinatorial interface functions

Devices with capabilities beyond electrical communication enable simultaneous functions such as drug delivery, optogenetic stimulation, and electrophysiological recording. To minimize damage to brain tissue when implanting optical neural probes, a new approach to fabricate flexible optoelectronic neural interfaces was recently presented [64•]. Previously, micro-light-emitting diodes (μLEDs) were fabricated mainly on rigid silicon and sapphire substrates [65–67]. Here, gallium nitride (GaN) μLEDs and recording electrodes were combined on a flexible polymer substrate of Parylene C (Figure 1f). The GaN-μLEDs are around 22×22 μm in size, and in arrays of up to 32 μLEDs per probe. Both the GaN-μLEDs and electrodes are cofabricated on the front and back sides, and thus can optically stimulate and electrophysiologically record neuronal activity on both sides.

A battery-free, wireless optofluidic cuff system, which can be fully implanted, has recently been introduced for modulation of the peripheral nervous system [68••]. This system can be used for local drug delivery as well as optogenetic stimulation through co-integrated microscale inorganic light-emitting diodes (μILEDs). Activity in the sciatic nerve could then be upregulated using optogenetic stimulation, and downregulated by administration of the drug bupivacaine.

Proctor *et al.* recently demonstrated a microfluidic ion pump system within a flexible recording electrode that can simultaneously record activity in the mouse brain and deliver cationic drugs such as H^+, K^+, acetylcholine, and gamma amino butyric acid (GABA) [69] (Figure 1g). This system pumps ions electrophoretically across a PSS-based ion bridge without also pumping solvent. This adds negligible pressure following delivery, and was also demonstrated to sense and control seizures on-demand via GABA delivery [70].

An electronic ion pump controlled by an ionic diode with fast (5 ms) delivery times has also recently shown delivery of ions and neurotransmitters [71••]. Externally controlled drug release has also recently been shown at the nanoscale, using magnetothermal heating of magnetic nanoparticles coated with a thermosensitive lipid bilayer to deliver small molecules [72].

Conclusions and future perspectives

Implanted neural devices are in use with a limited patient population, as implantation risk can currently only be balanced by the need to treat severe disease such as drug-resistant Parkinson's disease [73] or spinal cord injury [74]. Making neural devices that are safer and less invasive requires materials engineering to change the stiffness, chemistry, and/or geometry of the device interface with neural tissue.

In line with these efforts, soft electrode technologies are the clear leaders in terms of reducing foreign body response while maintaining similar recording and stimulation capabilities as conventional electrodes. They can easily be combined with ionic sensor interfaces, such as OECTs, and can be remotely powered. Recent developments in implantation strategies of soft electrodes have also enabled their use in deeper tissue sites, as opposed to just brain or dural surfaces.

Conversely, remote powering technologies for neural devices is a much newer and less researched field, although shows great promise for modulating the body's response to a device. Eliminating battery changes and transdermal or transdural wiring can reduce the risk of implantation, and thereby enable device use in applications with lower disease severity. Because of the breadth of different wireless powering strategies currently being explored, more than one ideal method may arise in the future, depending on the specific application. While an even less established field, injectable nanoscale neurostimulators may one day enable nonsurgical device implantation. However, as many of these technologies are currently dependent on transgenesis, their translation to clinical use must either circumvent or depend on genetic engineering in humans.

In order to accelerate development towards clinical use, the field of neuroengineering can take cues from medical fields that have successfully implemented electrical devices clinically (e.g. cardiology, gastroenterology, urology, audiology). Such systems most commonly use electrodes at the site of action, wired to an enclosed, centimeter-scale container which houses the power source. In neuroengineering, deep brain stimulation (DBS) devices are clinically available, and follow this design scheme, with the pacemaker component implanted subcutaneously on the chest. As clinical application of new technologies is often conservative, surface modification to make conventional electrodes softer or less immunogenic may be among the earliest of neural interface technologies to reach wide clinical use. Similarly, soft electrodes wired to a subcutaneous power source may be the earliest to reach clinical use, especially given recent advances that enable implantation into (rather than only onto) neural tissue. While still a nascent technology, wireless and remotely powered medical devices may overcome the challenges that such devices face, which are often due to wire failure and infection [3,75]. Different considerations exist for wireless devices, however, such as the method and device that provides external powering, as well as how to extract and/or degrade wireless materials that are too small to be removed manually.

Neural devices of the future will likely include a combination of the technologies discussed herein. Certainly, specific applications will be suitable to different devices

and materials. However, it is clear that all new neural device development will need to consider the materials used at biological interfaces. Continued development of new materials, and an analysis of their interaction with the nervous system, are both critical components in the design of neural implants of the future.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Hannah Wunderlich: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Kristen L Kozielski:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

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