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# Recent progress of electroactive interface in neural engineering

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## Abstract

Neural tissue is an electrical responsible organ. The electricity plays a vital role in the growth and development of nerve tissue, as well as the repairing after diseases. The interface between the nervous system and external device for information transmission is called neural electroactive interface. With the development of new materials and fabrication technologies, more and more new types of neural interfaces are developed and the interfaces can play crucial roles in treating many debilitating diseases such as paralysis, blindness, deafness, epilepsy, and Parkinson's disease. Neural interfaces are developing toward flexibility, miniaturization, biocompatibility, and multifunctionality. This review presents the development of neural electrodes in terms of different materials for constructing electroactive neural interfaces, especially focus on the piezoelectric materials-based indirect neuromodulation due to their features of wireless control, excellent effect, and good biocompatibility. We discussed the challenges we need to consider before the application of these new interfaces in clinical practice. The perspectives about future directions for developing more practical electroactive interface in neural engineering are also discussed in this review.

This article is categorized under:

Implantable Materials and Surgical Technologies > Nanomaterials and Implants

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**KEYWORDS**

electroactive interface, nerve electrode, neural engineering, piezoelectric material

## 1 | INTRODUCTION

Neuroscience research is the most challenging subject in the 21st century. Nerve system is a relatively complex electronic system with billions of neurons. The communication between neurons relies on the electrical signals to transfer information to other neurons and muscles. To understand the neural activity and connection, people record neural

  

signals and/or stimulate certain parts of nerve system (Hatsopoulos & Donoghue, 2009). The neural electroactive interface is the interface between the nervous system and external devices for information transmission. Ever since the 1960s, neural electroactive interfaces have been applied to record neural signals and stimulate neural tissue in both experimental animals and humans (Evarts, 1966; Marg & Adams, 1967). With the development of new materials and advanced fabrication technologies, more and more new-type neural interfaces are developed and the interfaces can play a crucial role in treating many debilitating diseases like paralysis, blindness, deafness, epilepsy, and Parkinson's disease (Fattahi et al., 2014; C. Liang et al., 2022). Deep brain stimulation is a typical example of the neural electroactive interfaces. The electrodes implanted in the brain can send high-frequency electrical stimulation to the relevant nerve nuclei that control movement (globus pallidus, subthalamic nucleus, etc.). The electrical signals can interface with abnormal nerve electrical activity and restore motor control loops or disturbed neurotransmitters to a relatively normal functional state, thus alleviating the symptoms of movement disorders and improving the life quality of patients (Vissani et al., 2020).

The neural electroactive interfaces can communicate with nerve tissue through the electrodes by transmit electrical signals to and from biological signals, so the performances of the electrodes determined the quality of the communication at the interface (Cogan, 2008). The performance is related to many factors, including the physical and chemical properties of the neural interface. Some key surface-interface structures exist in neural interfaces, including neural electrodes contact points, substrates, and heterogeneous interfaces formed by biological environmental media. These key interfaces greatly affect the performance of neural interfaces, including ion-electronic signal conversion and biocompatibility, so the precise construction and regulation of these surface-interface structures is crucial. In recent years, nanotechnology, micro-nanoelectronic technology and biotechnology develop rapidly, a series of important progresses have been made in the construction and regulation of neural interfaces. For example, surface modification based on nanomaterials and conductive polymer (CP) materials improves the ion-electron conversion efficiency of the interface; flexible electronic technology improves the mechanical matching between implanted devices and brain nerve interfaces and increases the biocompatibility of the device. Furthermore, the model of piezoelectric materials-based indirect neuromodulation shows great potential due to the features of wireless control, excellent effect and good biocompatibility. Many researchers have reviewed the area of neural electrode, mostly focus on the using of new materials and technologies (Ferro & Melosh, 2018; Green & Abidian, 2015; S. Lee & Lee, 2018; S. Liu, Zhao, et al., 2020; Scaini & Ballerini, 2018; Shin et al., 2021). Scaini et al. reviewed the nanomaterials used at the neural interface. Liu et al. focused on the microtechnology and nanotechnology for neural electrode–tissue interfaces. In this review, we illustrated the physical and biological mechanism underlying the interactions at the interface and then introduced the recent progresses of all kinds of electrodes based on different materials, especially, hybrid nanomaterials and piezoelectric materials.

## 2 | THE INTERFACE OF ELECTRODE AND NERVOUS TISSUE

The neural interfaces can provide long-lasting functional nervous tissue electrical stimulation and recording efficiently. When an electrode is placed inside a biological tissue, an interface is formed at the interface of electrode and nervous tissue. It is essential to understand the physical and biological mechanism underlying the interactions between electrodes and neurons.

### 2.1 | Physical basis of the electrical/electrochemical interface

During the electrical stimulation period, the charge is loaded mainly in two ways. Charge is transferred by means of electrons in the electrode and related electrical circuits. In the physiological environment (electrolyte), charge is transferred through ions like potassium, sodium, and chloride. The processes that take place at the interface are mainly the conversion between electrons in the electrodes and ions in the electrolyte.

When the current flows through the electrode, the electrical potential change occurs from the electrode to the electrolyte, thus forming an electric field at the interface. If the equilibrium condition of the electrical potential profile is broken, the electrochemical reactions may occur. The electron transfer mechanisms at the interface are usually divided into two types (Figure 1a,b). The first one is a non-Faradaic reaction with no electrons transferred between the electrode and electrolyte. The ions accumulate in a double layer through charging and discharging at the interface. The

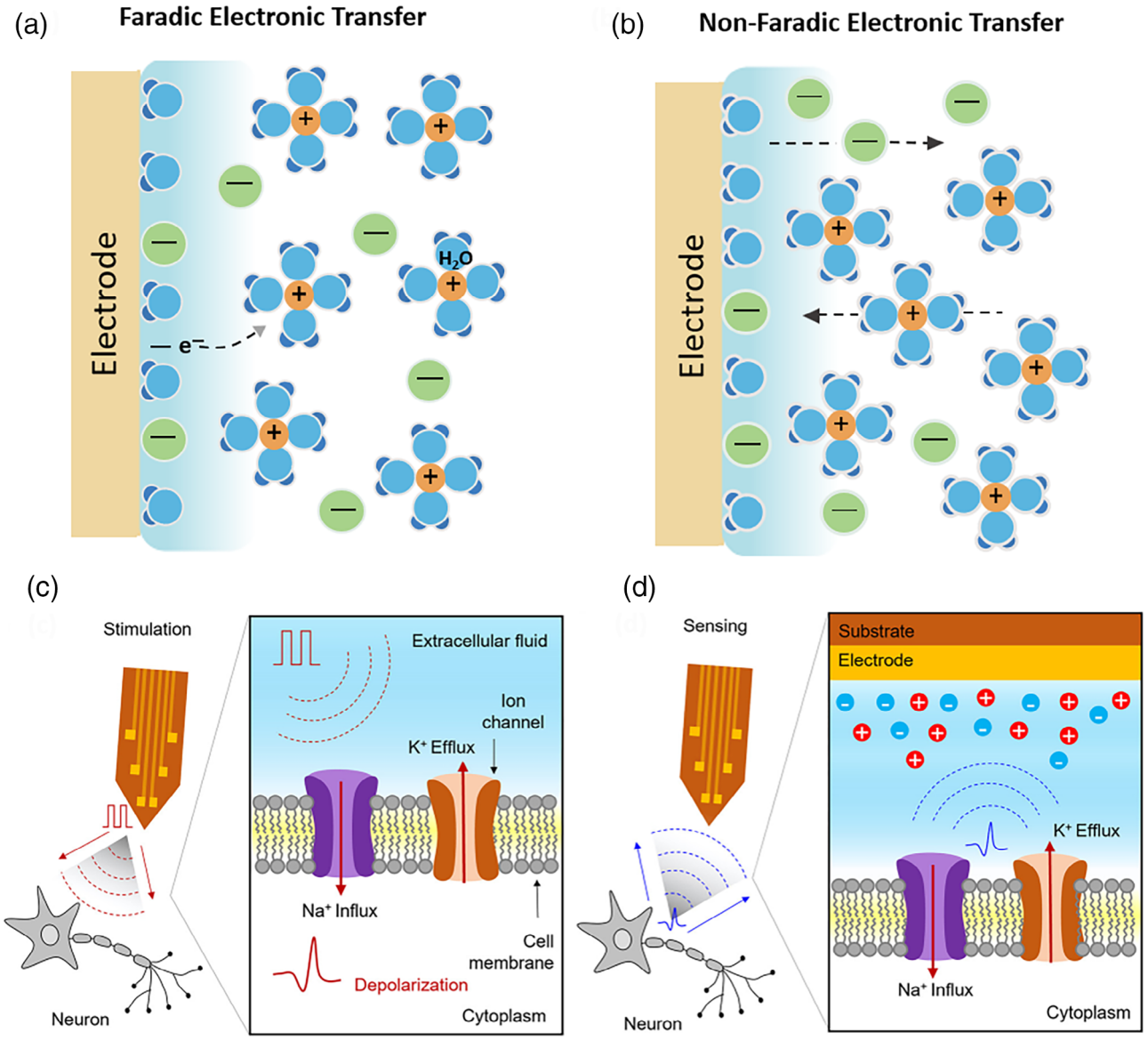


**FIGURE 1** Simple illustration of the electrical/electrochemical and electrophysiological interface. (a) Faradaic charge injection mechanism. (b) Capacitive charge injection mechanism. (c) Electrophysiological process at the cell membrane when neural stimulation. The extracellular stimulation can induce $K^+$ efflux and $Na^+$ influx which could cause the depolarization of neuron cell membrane. (d) Electrophysiological process at the cell membrane when neural sensing and recording. Neural activity can induce $Na^+$ efflux and $K^+$ influx that can produce action potential.

second mechanism is a Faradaic reaction which relies on electrochemical reactions occurred at the interface (Merrill et al., 2005).

As for non-Faradaic reaction, a double-layer capacitor model forms between the electrode and electrolyte, which includes the charges at the surface of the electrode and the opposite charge in the electrolyte. There is no charge transfer between the electrode–electrolyte interface during resting state, but as the potential changes, due to the occurrence of the adsorption and desorption process and the charging and discharging of the electric double layer, the structure of the electrode–electrolyte interface changes and causes the flow of the current. This process does not follow Faraday's law (Grahame, 1947).

The transmission of charges from the electrode to the electrolyte can also happen by means of the processes of reduction and oxidation. The number of chemical reaction due to current is proportional to the amount of electricity transferred. This kind of process is called Faradaic charge transfer (Randles, 1947). Faradaic reaction is different from the capacitive mechanism (non-Faradaic reaction). The result of charge injection in the electrolyte is the production of new products, which leads to the fact that the direction of the current cannot be reversed.

## 2.2 | The simple electrophysiology of neuron stimulation at the interface

The transaction of electrons in the electronic circuits and the ions in the biological matrixes of the neurons occur at the interface of electrode and electrolyte (Figure 1c,d). Under the resting conditions, the neuron cell membrane is in a polarized state, potassium ions inside the membrane are higher than those outside the membrane while it is opposite for sodium ions. At this moment, the cell membrane is highly permeable to potassium ions, and the outflow of potassium ions forms a resting potential. When the cell is effectively stimulated, the sodium channel of the cell membrane opens, and a large amount of sodium ions flow in, generating an action potential, and it spreads rapidly to the entire cell, producing the bioelectricity to excite the neuron. When the action potential arrives at the synapse, the presynaptic axon releases neurotransmitters to the postsynaptic neuron. The receptors of downstream dendrites combine with these neurotransmitters and convert the chemical signals into electrical signals.

## 2.3 | Biological response at the interface of electrode and nerve tissue

Except for the electrical interactions, tissue–electrode interfaces also include many biomechanical interactions (Biran et al., 2005) (Figure 2). There are mainly two kinds of reactions occur at the interface of electrode and tissue (Fattahi et al., 2014). The first is acute response owing to the mismatch of the mechanical properties and implanted devices. The electrode may push aside the nearby matrix as it inserts deeper into tissue, thus causing the area between the electrode and tissue under high pressure (Leach et al., 2010). This kind of mechanical trauma initiates the nervous system inflammatory and wound healing response that follow. During the acute inflammation period, erythrocytes, platelets, and clotting factors present from the disrupted blood vessels. Inflammation can also activate astrocytes, microglia, and infiltrate nearby macrophages (Whitney et al., 2009). Activated microglia will proliferate around the injured site as early as 1-day post-implantation (Polikov et al., 2005).

After the acute reaction, the chronic reaction initiates. It is a complex chain of reactions. The first is the attachment and clustering of microglia on the electrodes because of the persistent existence of the foreign bodies for the tissue (Kao et al., 1999; Stensaas & Stensaas, 1976). The function of this kind of cells is similar to that of the peripherally derived macrophages in the removal of foreign objects (Stensaas & Stensaas, 1976). Except for the microglia, astrocyte can also proliferate and secrete inhibitory factors. The factors like chondroitin sulfate proteoglycans are an vital component in the formation of glial scar (Fawcett & Asher, 1999). This kind of dense and thick structure could push the nerve away

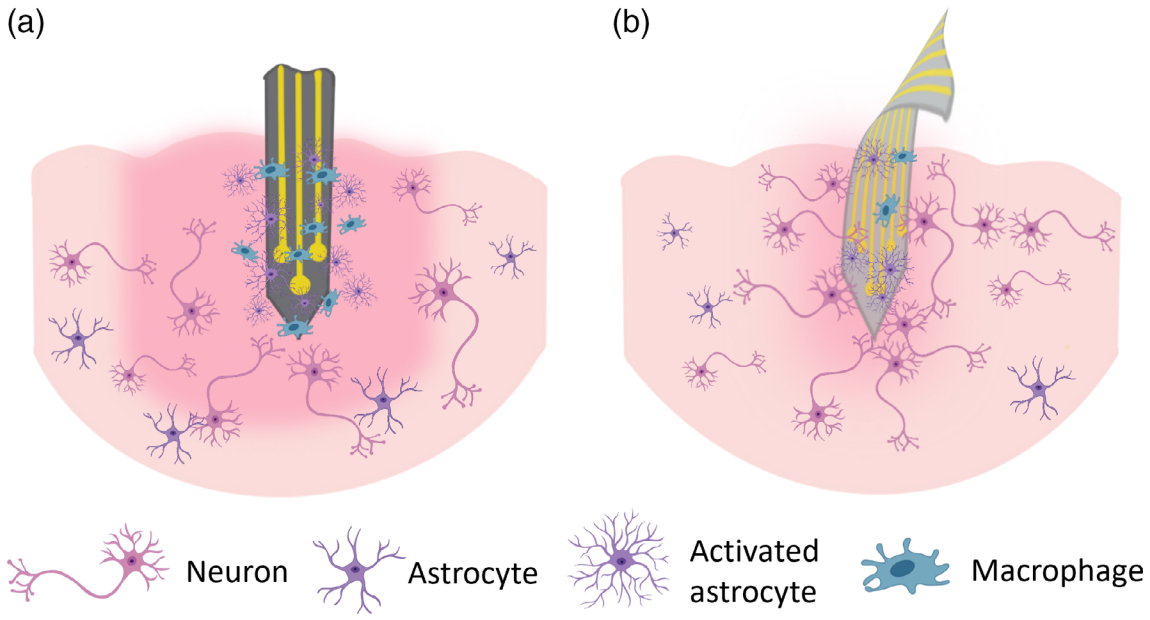


FIGURE 2 Tissue reactivity around the tissue-electrode interface. (a) An inflammation area forms when a no complaint electrode inserted into the neural tissue. A large number of reactive astrocytes appears and a activated microglia shield presents around the probe (in red); (b) By contrast, less proliferation of glia cells and lower level of neurodegeneration happen when insert a soft and flexible electrode.

from the electrode, thus increasing the impedance of the interface and weaken the electrical stimulation effect. Some researches indicates that fibroblasts can further aggravate the extent of encapsulation of electrode by cellular and extracellular matrix substances (Carbonell & Boya, 1988).

# 3 | MATERIALS FOR NEURAL ENGINEERING INTERFACE

## 3.1 | Conductive materials-based direct electrical stimulation

Conductive materials are the direct choice for fabricate the neural interface. Metal electrodes were the first developed neural interface for nerve record and stimulation, then microfabrication technology promotes the birth of micro-array silicon electrodes. The most common commercial devices are this kind of electrodes like the Michigan-style probes and Utah arrays. The modulus of the above electrodes and nerve tissue limited their development. Advances in nanomaterials can help increase the biocompatibility of the interface; reasonable design of the nanomaterial-based electroactive interface can realize composite functions.

### 3.1.1 | Metal electrodes

Early neural electrodes were single- or multi-microwires made of metals such as tungsten, stainless steel, gold, and platinum because of their high electrical conductivity and chemical stability in physiological environments. Neural recording and stimulation occur through the coating of noncytotoxic insulator material on the noninsulating tip of the wires and their circuits. This kind of microwire can be fabricated into arrays ranging from 4 to over 164 with spacing of 100–300 μm. Many reseachers have attempted a lot to obtain long-term single-neural recordings with arrays of microwires from behaving animals (Hatsopoulos et al., 1998; Maynard et al., 1999; Rousche & Normann, 1998; Yuen & Agnew, 1995). By using the implanted microwires, a group recorded 247 cortical neurons individually from 384 within 704 arrays in monkey's brain during 18 months after implantation (Hatsopoulos et al., 1998). But the mechanical properties of metal microwires are mismatch with the tissue that may stimulate tissue adverse responses (Edell et al., 1992).

### 3.1.2 | Silicon-based electrodes

With the development of the microfabrication technology, people have begun to use heavily doped semiconductors to fabricate the electrodes. One of the most represenative electrode is the silicon electrode array using microelectromechanical system processing technology (Cui et al., 2001; Vetter et al., 2004). This high-throughput neural interface technology can collect more neuronal signals in a smaller size to facilitate the overall decoding of the function of the neuronal network in vivo, while providing a greater number of control degrees of freedom and robustness for brain-computer interface technology (Kipke et al., 2008; Wise & Najafi, 1991). Two most representative silicon microelectrode arrays are the Utah array and the Michigan electrode. The Utah electrode is a two-dimensional (2D) electrode array with recording points only at the tip (Figure 3a) (Hochberg et al., 2006; House et al., 2006). The processing method is to fabricate the needle body on the bulk silicon material by mechanical cutting combined with chemical etching. The insulation between the needle body is achieved by semiconductor PN junctions or glass (Campbell et al., 1991; Normann et al., 1999). The Michigan electrode is fabricated by a silicon planar process. Its width is usually 10 to more than 100 microns, and its thickness is only tens or even ten microns. The needle body is made by boron diffusion and selective etching. The structural feature of the Michigan electrode is that many recording points are arranged on the same electrode needle, which is very beneficial to achieve high-density and high-throughput recording and stimulation (Figure 3b). Through assembly, the number of channels of this electrode array can reach 256 or even 1024, and the channel density can reach 12/mm$^3$ (Branner & Normann, 2000; Kipke et al., 2008; Qing et al., 2000). Zhang et al. fabricated the highly P-doped single crystal silicon electrodes on a silicon probe through complementary metal-oxide-semiconductor-compatible processes. Multi-walled carbon nanotubes (MWCNTs) and Au nanoparticles are selectively coated onto the electrode site with only a minimum enlargement in physical diameter of electrode (<10%) and the typical impedance is reduced to 21 $\pm$ 3 kΩ (S. Zhang et al., 2014).

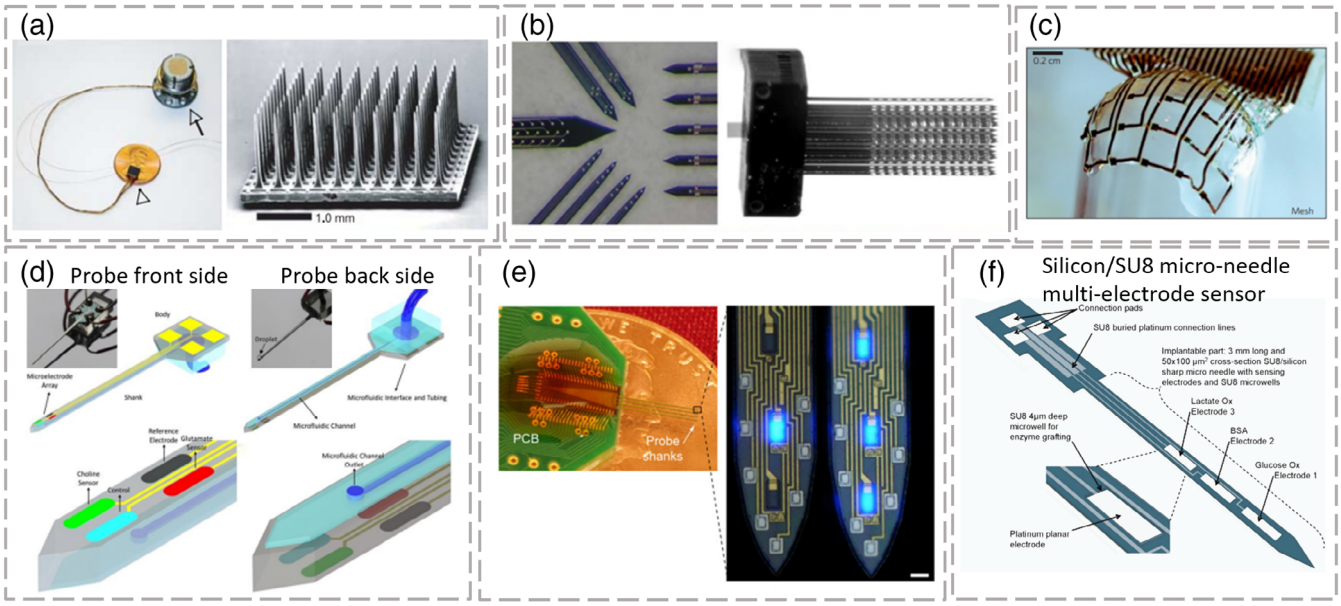


**FIGURE 3** Silicon-based electrodes and their functionalized applications. (a) The BrainGate sensor (Utah array) and the scanning electron micrograph of the 100-electrode sensor, 96 of which are available for neural recording. (b) High-magnification photographs illustrating four different types of sites layouts for specialized interfaces (Michigen electrode) and the 128-site array made from several multi-shank planar electrodes. (c) Photograph of the soft electrode wrapped onto a glass hemisphere. (d) Schematic diagram of the multi-functional neural probe with chemical delivery and multi-sensing functions. (e) Photograph of an implantation-ready micro-LED probe on a penny and magnificated images of the illuminated mLEDs. (f) Silicon/SU8 micro-needle multi-electrode sensor for monitoring glucose and lactate. mLEDs, microscopic light-emitting diodes; μLED, micro-light emitting diode

To overcome the mechanical mismatch between the hard and 2D silicon electrodes and the soft and three-dimensional (3D) nerve tissue, researchers started to fabricate soft and flexible electrodes. Kim et al. used a series bio-resorbable silk film to make a kind of extremely thin polyimide (PI) electrodes (<10 μm) (Figure 3c). They decreased the bending hardness of the electrode through decreasing the substrate thickness, thereby improving the conformal contact. By implanting three different surface electrodes in cats for visual cortex neural recording, Kim et al. proved that the 2.5-μm mesh electrode performed best with good contact and higher signal to noise ratio (SNR). What is more important is that the immune response after 4 weeks of implantation was barely observed (D.-H. Kim, Wiler, et al., 2010). However, too soft electrode may make the insertion of the electrode become difficult. It is important to find a balance of the rigidity of the electrode. Xiang et al. fabricated an ultra-thin flexible PI neural probes coated with the maltose on the neural probe surface. This coated maltose layer transforms the flexible neural probe into a stiff micro-needle for successful penetration. It can be dissolved by body fluids several seconds after implantation (Xiang et al., 2014).

With the gradual improvement of the biocompatibility of silicon-based neural electrodes, people have begun to further functionalize silicon-based electrodes for their application in different medical scenarios (Fekete, 2015). The use of convection-enhanced diffusion (CED) is a kind of method to allow drugs diffuse through the blood–brain barrier (BBB). Briefly, an injection pump that contains drugs is placed parallel to a transcranial catheter to make the pressure driven flow producing high drug levels in the brain. Silicon electrodes have many advantages that can help to realize CED, like relative position of microfluidic channels, recording sites and outlet ports with micron-scale accuracy. Some studies have proved the feasibility of microfluidic (Pongrácz et al., 2013) and recording (Márton et al., 2013; B. Wang et al., 2020) features in ultra-long (near 70 mm) probes (Figure 3d).

Silicon-based microelectrode can also combine with the optogenetic tools to achieve higher spatial and temporal resolution. In central neural system studies, optogenetics usually can be realized through combining optical fibers and silicon microelectrodes. To modify the manufacturing scheme to wafer-scale level, people integrated dielectric waveguides such as SU-8 on top of silicon-based microarrays (Wu et al., 2013; Zorzos et al., 2010). With the decreasing of the electrode size, the problems like the signal crosstalk between electric and optical lines and thermal management have been raised. A possible way to solve these problems is to integrate micro-light emitting diode (μLED) arrays into the

electrodes (T. I. Kim et al., 2013; McAlinden et al., 2013; McAlinden et al., 2015). Wu et al. monolithically integrated the microscopic LEDs (mLEDs) and recording electrodes on silicon probe shanks (Figure 3e). The size of each mLED and recording site is similar as a pyramidal neuron soma, and all dimensions are defined at resolution of <1 mm. After implanting the probes into the CA1 pyramidal layer of anesthetized and freely moving mice, they achieved independent control of distinct cells and of differential somato-dendritic parts of single neurons (Wu et al., 2015).

Another function that can integrate with silicon-based electrode is the in vivo monitoring of neurotransmitters which can help neurochemical data extracted at the time scale that is similar as electrode stimulation and recording (J. Wang et al., 2016; Y. Zhang, Jiang, et al., 2021). Johnson et al. developed the first silicon-based electrode that can realize both the electrical and chemical measurements (Johnson et al., 2008). Since then dopamine, choline (Frey et al., 2011) and glutamate sensors (Frey et al., 2010) have been integrated on silicon-based electrodes successfully. Some complex functional electrodes that can monitor the glucose and lactate at the same time in the brain were also reported (Figure 3f) (Frey et al., 2010).

### 3.1.3 | Carbon-based electrodes

Carbon materials, mainly including graphene and carbon nanotubes (CNTs), stand out among many materials due to their unique physical and chemical properties, and become important materials for constructing neural electrodes or regulating neural interfaces (Y. Liu & Duan, 2020; A. Zhang & Lieber, 2016). Graphene sheets can be obtained by exfoliation method, and the graphene fiber (GF) electrodes can be made by using graphene sheet suspension (X.-Y. Wang et al., 2017). The high porosity and roughness of GFs are conducive to realizing low electrical impedance and high charge injection capability. In terms of CNTs, vertically aligned CNT arrays can be grown by chemical vapor deposition, and then CNT fibers with high electrical conductivity and tensile strength can be obtained through drawing and spinning processes, which can be used to fabricate the deep brain stimulation (DBS) electrode (Q. W. Li et al., 2006).

*Graphene*

Graphene is a material in which carbon atoms connected by $sp^2$ hybridization are tightly packed into a single-layer 2D honeycomb lattice structure. The features of this material are cheap and easy to fabricate. Many studies have proved the biocompatibility of graphene, it can promote the adhesion and proliferation of neural cells without inducing cell stress (Rastogi et al., 2017). Graphene is easy to be functionalized which can make it suitable for biomedical applications. Mouse hippocampal neurons could grow and sprout well on the polylysine-coated graphene films during early developmental phases (N. Li et al., 2011). People also cultured the neural stem cells (NSCs) in graphene and they observed the NSCs proliferated into neurons and astrocytes broadly and cell adhered within the 3D graphene foams (Figure 4a) (N. Li et al., 2013).

Researchers have also devoted to improve the mechanical mismatch between graphene-based electrode and biological tissue and improve the conductivity. A group fabricated a soft, hydrophilic graphene microelectrode and they successfully measured the action potentials from the axons of abdominal nerve in crayfish (Hess et al., 2011). Heo et al. developed a flexible, noncytotoxic, and transparent graphene and poly(ethylene terephthalate) stimulating electrode to stimulate the human neuroblastoma cells and optical observe the cells' morphological changes in real time. The results showed that the cell coupling can generate under a weak electric field (4.5 mV $mm^{-1}$) due to the field enhancement factor of graphene layer (C. Heo et al., 2011). To realize DBS, the flexible and free-standing GF-based microelectrode arrays were fabricated by Wang et al. successfully (K. Wang et al., 2019). Because of the ordered and separated structure of graphene, this kind of GF micro-arrays has higher geometrical area, charge injection capacity (CIC), and specific impedance (Figure 4b). Graphene-based electrodes can also integrate well with functional magnetic resonance imaging (fMRI) without artifacts caused by metal electrodes (Figure 4c) (S. Zhao, Li, et al., 2020).

As for the biocompatibility of graphene, many studies have investigated the direct cell-to-graphene interfaces (Y. Lu et al., 2018). The cellular survival rates and cell activities were tested and compared to other commonly used materials. Park et al. found in one of their studies that compared to the cells on glass, human NSCs adhered and proliferated more on the graphene substrate. And they demonstrated that the graphene substrate promoted human NSC differentiated into neurons by specific immunofluorescence staining of glial fibrillary acidic protein (GFAP) and neuron-specific class III beta-tubulin (Tuj1) after 1-month differentiation (S. Y. Park et al., 2011). Except for one-dimensional (1D) culture substrates, 3D scaffolds used for nerve tissue and other area of tissue engineering based on graphene were developed (Hu et al., 2018; N. Li et al., 2013; Martín et al., 2017). Martin et al. presented a new class of graphene-based hydrogels and

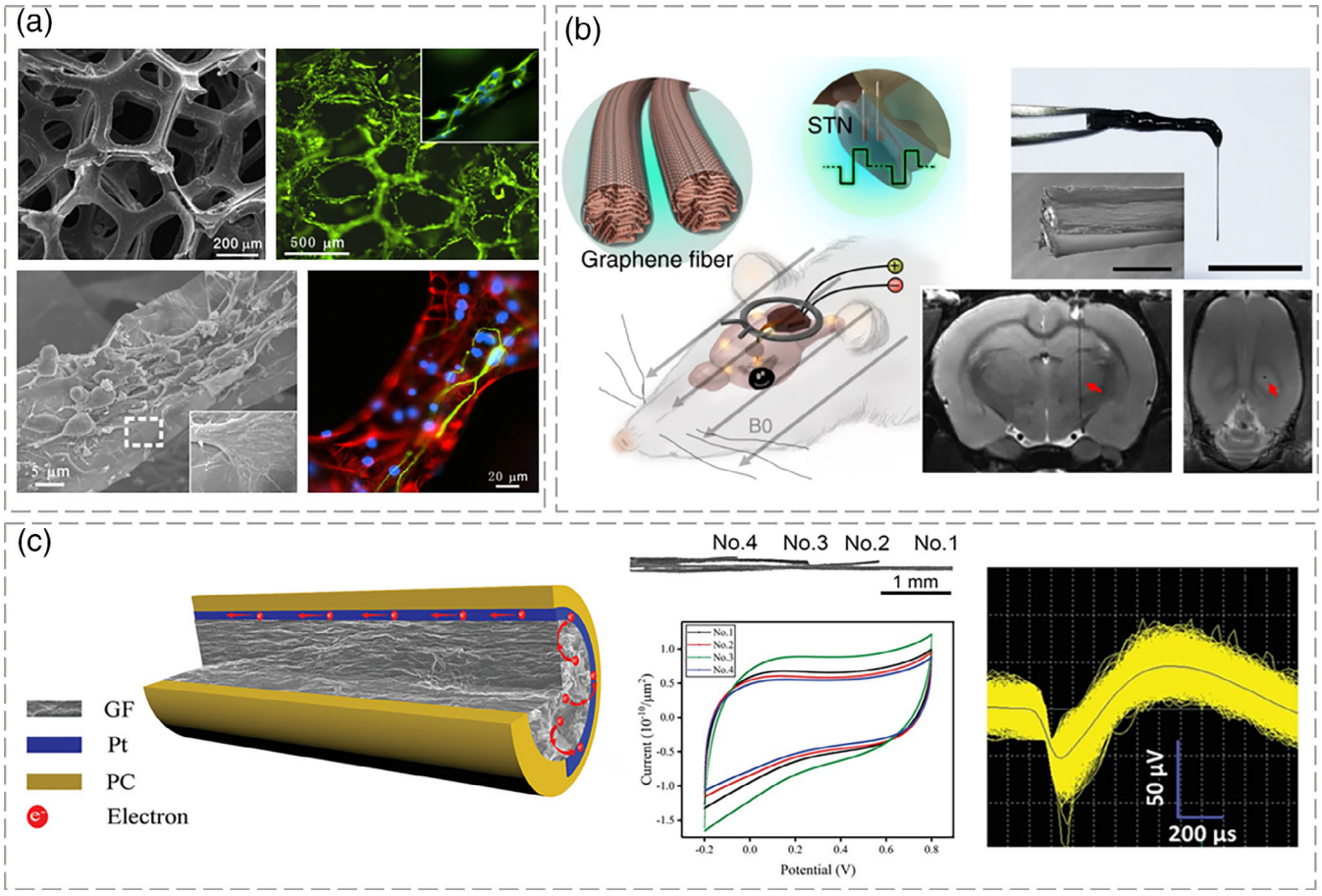


**FIGURE 4** Graphene-based electrodes for neural engineering. (a) SEM micrographs of three-dimensional graphene foam and NSCs cultured on the foams. The picture showed that the NSCs lined well on the foam. The fluorescence images showed the proliferation of NSCs under differentiation conditions, the cells were immunostained with Tuj-1 for neuron (green, a), GFAP for astrocyte (red), O4 for oligodendrocyte (green) and DAPI (2-(4-Amidinophenyl)-6-indolecarbamidine dihydrochloride) for nuclei (blue). (b) The picture illustrated the graphene fiber electrode could realize simultaneous deep brain stimulation and fMRI. Representative coronal (left) and horizontal (right) sections of the T2 MRI images of rat brains implanted with a GF bipolar microelectrode, through the position of the implants. (c) The structure of the graphene-Pt microelectrode and the electrochemical stability of the electrode. The electrode showed good signal noise ratio. DAPI, xxxxx; fMRI, functional magnetic resonance imaging; GFAP, glial fibrillary acidic protein; NSCs, neural stem cells; SEM, scanning electron microscopy.

they found that hippocampal neurons and astrocytes developed efficiently only in the graphene-doped hydrogels. Through $Ca^{2+}$ imaging experiments, active synaptic networks were observed in these materials (Martín et al., 2017).

### *Carbon nanotubes*

According to the different layers of the tube, CNTs can be divided into single-walled CNTs (SWCNTs) and MWCNTs (Iijima, 1991). CNTs have many advantages for preparing neural electrodes like mechanical flexibility (J. P. Lu, 1997), high-mass-specific surface area (Peigney et al., 2001), electrical conductivity (Tans et al., 1997; Voge & Stegemann, 2011), and biological stability (L. Lu et al., 2019). CNTs have been fabricated into 3D scaffolds for neural activity recording and the brain and spinal cord regeneration (Gheith et al., 2006; Harrison & Atala, 2007; Jan & Kotov, 2007). In addition, researchers use different polymers or bioactive molecules to functionalize the CNT surface and improve their biocompatibility and bioactivity (Angelini et al., 2007; Schipper et al., 2008). CNTs can be used to promote synaptogenesis and neurite elongation while increase synaptic efficacy at the functional level (Figure 5a) (Baughman Ray et al., 2002; Bianco et al., 2011).

Many studies have proved that the soft CNT electrode can record the neural signal and stimulate nerve tissue at high spatial resolution. Voge et al. developed flexible and MRI compatible CNT fiber-based neural interfaces for long-term and chronic electrophysiological recording by using the features of high flexibility and near magnetic susceptibility

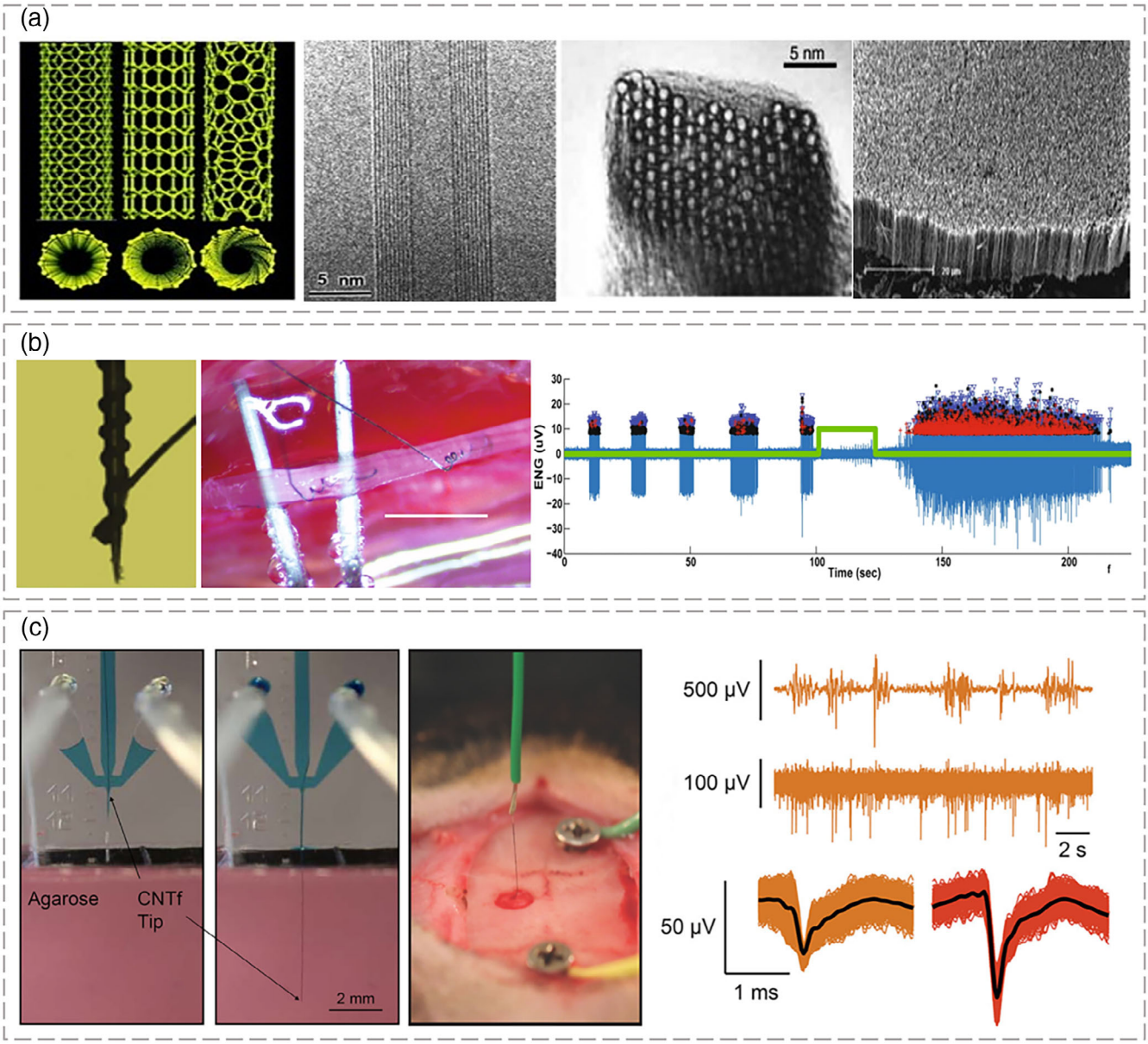


**FIGURE 5** Carbon nanotube-based electrodes for neural engineering. (a) Schematic illustrations of the structure of SWCNTs and tunneling electron microscope image of the helical structure of a 1.3-nm-diameter chiral SWCNT. Scanning electron microscope showed the array of MWCNTs grown as a nanotube forest. (b) CNT yarns were wound around the tip of a tungsten microneedle to help implant the electrode into the nerve. The CNT yarns could record the spontaneous neural activity and indicated the hypoxia event from the vagus nerve 16 weeks post-implantation. (c) Photograph of microfluidic-assisted insertion of 12-μm microelectrode into a rat brain. Orange traces were collected from the electrode. CNT, carbon nanotube; MWCNTs, multi-walled carbon nanotubes; SWCNTs, single-walled carbon nanotubes.

of CNT microfibers (Voge & Stegemann, 2011). Although flexible electrodes have good mechanical matching with nerve tissue, they also bring challenges to their implantation process. Durand et al. prepared flexible CNT fiber electrodes for recording peripheral nerve activity (McCallum et al., 2017). They obtained CNT fiber electrodes (10–20 μm in diameter) by high-speed spinning of vertically aligned MWCNT arrays for electrical recordings of the glossopharyngeal and vagus nerves in rats. One end of the electrode is wrapped around a tungsten wire for auxiliary implantation, and then the tungsten wire is removed (Figure 5b). The mechanical properties of the electrode are compliance to the surrounding nerve tissue, thus reducing nerve damage and inflammatory response. Long-term neural recordings can be performed using this electrode, with an impedance of 18 ± 8 kΩ at 1 kHz maintained over a 10-week period and the signal-to-noise ratio exceeds 10 dB (Yu et al., 2019). Vitale et al. proposed a method of using a bilayer polydimethylsiloxane microfluidic device to assist in implanting CNT fiber electrodes into biological tissues (Figure 5c) (Vitale et al., 2018).

The studies about the toxicity of CNTs have explored the phenomenon and mechanism of the influence of CNTs on biological tissues (Dubin et al., 2008; Smart et al., 2006; Y. Zhang et al., 2010). Zhang et al. synthesized a series of graphene layers and SWCNT and explored their cellular toxicity by using methyl thiazolyl tetrazolium (MTT) assay (Y. Zhang et al., 2010). They found the shape of these materials was directly related to their induced cellular biocompatibility, and the effect of the materials on cells was concentration and shape dependent. Graphene showed better metabolic activity than SWCNT at low concentrations but this reversed at higher concentrations. The authors illustrated that the tubular shape of SWCNTs is expected to promote penetration of membranes, uptake by cells, and stronger interactions with various protein systems.

### 3.1.4 | Conducting polymers

CPs have great potential to make neural electrodes. Fast charge transfer of the ions from biological tissue and electrons in the electrode can happen at the interface (Berggren & Richter-Dahlfors, 2007). CPs could be made into totally soft electrode interface, which could realize the conformal contact with the nerve tissue. Typically, CPs are synthesized by means of chemical and electrochemical approaches. Electrochemical polymerization is easy to fabricate and frequently used (Roncali, 1992). The CP film can be fabricated by electrochemical polymerization and formed in one step, and the properties of CP films like thickness, surface properties, and conductivity can be prepared in demand (Heeger, 2001).

There are mainly three reasons for the widely use of CPs (Green & Abidian, 2015): (1) the biocompatibility of CPs can be easily improved by adding proteins to functionalize them and CPs can target specific cellular through functionalization (George et al., 2006). (2) The ionic and electronic conductivities of CPs can facilitate efficient charge transduction from ions to electrons (MacDiarmid, 2001). (3) CPs can combine drugs and biomolecules by trapping them within the polymer backbone or reservoirs. When the redox reaction occurs, drugs and biomolecules can be precisely released (Abidian et al., 2006; Simon et al., 2009; Thompson et al., 2010). Among CPs, poly(pyrrole) (PPy), poly(aniline), polythiophene, and its derivatives including poly(3,4-ethylene dioxythiophene) (PEDOT) have been applied to neural electrodes.

The pyrrole monomer is a nitrogen-containing five-membered ring with a pair of conjugated double bonds and a lone pair of electrons on the nitrogen atom. When the pyrrole monomer is oxidized, it loses an electron to form a cationic radical first, which collides with each other to form a dimer, and finally a polymer. Polypyrroles are usually prepared by electrochemical methods and have good physical and chemical properties, such as electrical conductivity, controllable surface properties, biocompatibility, stability, easy preparation, good flexibility, and strength (Chougule et al., 2011). Its conductivity and biocompatibility are related to the types and properties of the doped anions. Guo et al. fabricated a stretchable polymeric multielectrode array that combined PPy with hydrophobic diol (polycaprolactone-block-polytetrahydrofuran-block-polycaprolactone, PCTC, CL$x$-THF$y$-CL$z$, $x + z \approx 11$, $y \approx 17$) (Figure 6a). The impedance of the electrode was very low and the charge storage/injection ability is admirable. This electrode showed good electrical conductivity and it can be used to capture action potential of model rat. The impedance of the electrode was very low and the charge storage/injection ability is admirable (Guo et al., 2014). For nerve regeneration, Zhao et al. developed a polypyrrole/silk fibroin (PPy/SF) conductive scaffold by electrospinning and 3D bioprinting. Constructed PPy/SF conductive nerve scaffolds combined with electrical stimulation could promote axon regeneration and remyelination in vivo effectively (Y. Zhao, Liang, et al., 2020).

But PPy is easy to be irreversible oxidized and interfered by chemical conditions, which inhibits PPy-based electrodes develop further. The most common CPs used for making neural electrodes is PEDOT:polystyrene sulfonate (PEDOT:PSS). PEDOT has poor solubility in either pristine or doped forms due to the thiophene ring on the main chain, so researchers developed PEDOT:PSS. This kind of polyelectrolyte complex consists of positively charged p-doped PEDOT and negatively charged water-soluble PSS (Kayser & Lipomi, 2019). Completely oxidized PEDOT chains under ideal conditions possess one charge carrier per three monomers. Negatively charged PSS serves as a counterion to balance the positive charges of PEDOT, and together with the PEDOT matrix, forms a homogenous and stable aqueous dispersion. The capacitance of PEDOT:PSS scales with film volume which is different from traditional metal electrode. A capacitive model proposed by Proctor et al. may explain these phenomena (Proctor et al., 2016). In this model, the ions could diffuse into the materials and "charge" the materials through polymer fibers. And the fibers can be understood as capacitors in parallel. This character of PEDOT:PSS is beneficial to making electrodes that need small size and low impedance. Due to the properties of PEDOT:PSS such as excellent film-forming ability, optical transparency, electrical conductivity and good physical and chemical stability, it has been widely used in making biomedical devices (H. Shi et al., 2015).

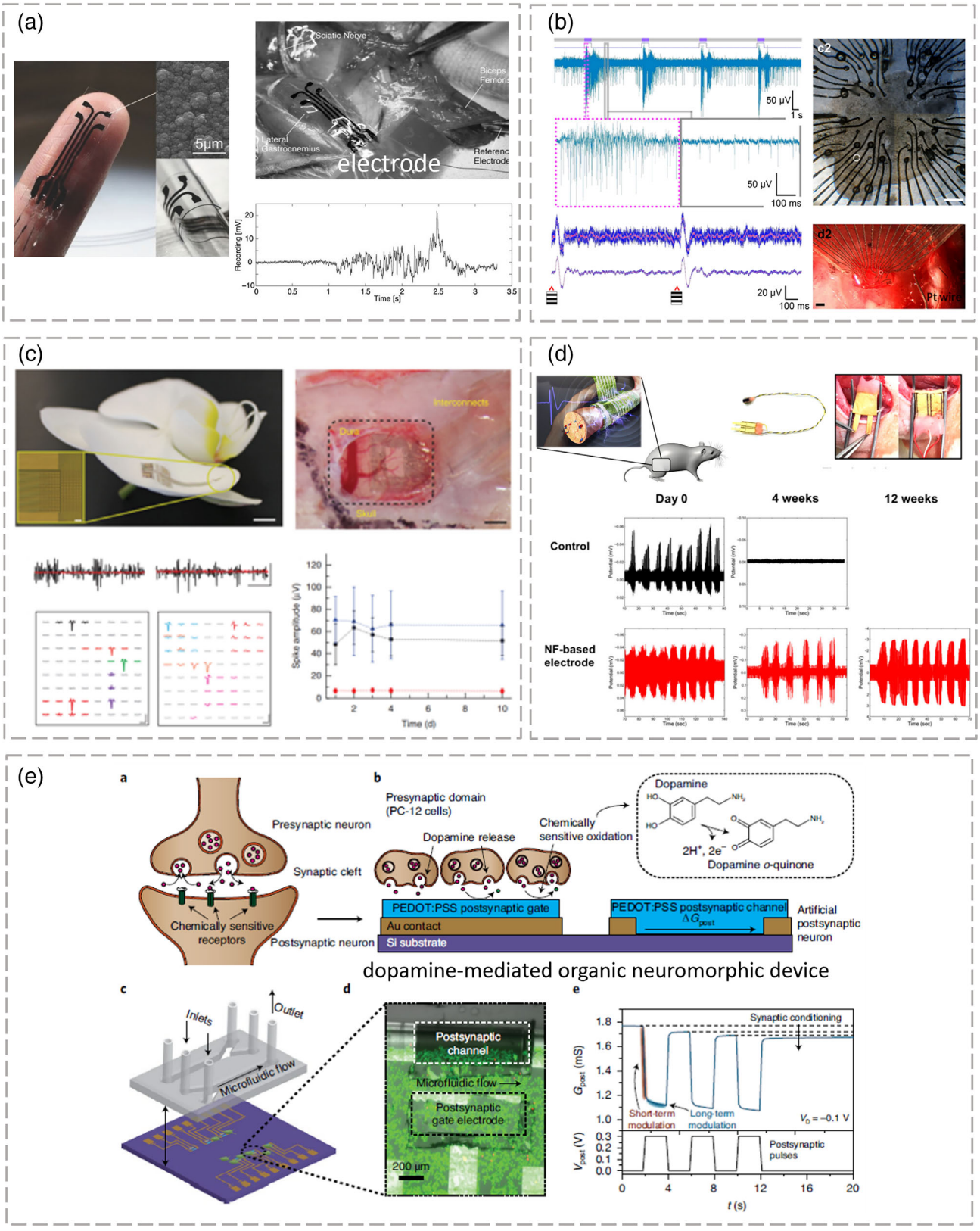


FIGURE 6 Legend on next page.

Many studies developed electrode based on PEDOT:PSS. Neurons can attach and grow well on the PEDOT:PSS electrode that added nerve growth factors (NGFs) and peptides (D. H. Kim et al., 2007). Based on PEDOT:PSS, Blau's team fabricated a soft and non-cytotoxic all-polymer electrode array that can capture cardiac and cortico-hippocampal action potential steadily (Figure 6b) (Blau et al., 2011). To increase the flexibility of CPs, Green et al. dispersed PEDOT:PSS into a soft elastomer (polyurethane) to make a soft electrode (Cuttaz et al., 2019). Another study used this material build a device that can deliver neurotransmitters by electrophoretic transport (Leung et al., 2008). This electronic device could deliver neurotransmitters, such as aspartic acid and glutamate to simulate synapses. By the auditory brainstem response, the controlled delivery of glutamate was verified. Many electrodes may induce serious adverse reactions such as inflammation, blood vessel compression, and neurological atrophy. Researchers coated the electrode with conducting polymers like PEDOT:PSS to improve this problem (Y. Liang et al., 2021). Khodagholy et al. fabricated a neural interface array (NeuroGrid) that combined PEDOT:PSS and parylene C. This electrode showed stable recordings of local field potential and action potentials from superficial cortical neurons in 1 week (Figure 6c) (Khodagholy et al., 2015). Another group developed a cuff electrode that coated with PEDOT:PSS, a polyethylene glycol hydrogel and poly(lactic-co-glycolic) acid microspheres loaded with drugs (D. N. Heo et al., 2016). The electrodes showed a sustained drug release and high-quality nerve signal recording and the coated surface exhibited significantly decrease of the fibrous tissue deposition. This team also developed a PI nanofiber-based nerve interface which use PEDOT:PSS as conductive layer (Figure 6d). The PEDOT:PSS layer could significantly increase the CIC of the cuff electrode and help to record higher signal amplitudes than electrodes without PEDOT:PSS. This coated layer also showed reduced immune responses of neural tissue (D. N. Heo et al., 2017). PEDOT:PSS-based device can also be used for the electrochemical detection of neurotransmitters because of their redox activity (Gualandi et al., 2016). Keene et al. reported a functional biohybrid synapse which combined a dopaminergic presynaptic domain of PC-12 cells coupled to an PEDOT:PSS neuromorphic device as the postsynaptic domain (Keene et al., 2020). It is similar as the transport of neurotransmitter molecules in the synaptic that the transport of electrons from dopamine to the postsynaptic gate was only in one direction (Figure 6e).

The biocompatibility of the CPs depends on the ionic species integrated into the polymer structures. Wan et al. studied the cytocompatibility of the conducting polymer—PEDOT:PSS (Wan et al., 2012). They focused on the influence of the material to fibronectin (Fn) which is a prominent extracellular matrix (ECM) glycoprotein that regulates cell adhesion, migration, differentiation and growth. Förster resonance energy transfer imaging was used in this research to assess Fn conformation on the surface of the conducting polymer. They found that the electrical stimulation would change the conformation of Fn which could provide guidance to the building of precisely controlled physiologically relevant 3D platform. Some researchers have also probed the biocompatibility of PPy-based neural electrode (Feron et al., 2018; George et al., 2005; X. Wang et al., 2004). George et al. examined the biocompatibility of PPy, they cultured primary cerebral cortical cells on PPy samples that had been doped with PSS or sodium dodecylbenzenesulfonate. Neural networks grew well on all of the PPy surfaces. PPy-based electrodes were also implanted into the cerebral cortex of the rat, and the gliosis level of the area around the electrode in experimental groups was almost the same as Teflon (George et al., 2005).

Many new ways have been used to improve the biocompatibility of CPs interfaces. The most widely mentioned in the recent research is to combine biomolecules and therapeutic agents on the surface of the electrodes (Z. J. Du et al., 2018; R. Kim & Nam, 2019; X. Liu et al., 2011; Richardson et al., 2007; Wadhwa et al., 2006). Many dopants were used to combine with the electrodes like NGF (D. H. Kim et al., 2007), neurochemical 6,7-dinitroquinoxaline-2,3-dione (Z. J. Du et al., 2018), fibrillar collagen (X. Liu et al., 2011), dexamethasone (Wadhwa et al., 2006), neurotrophin-3, and

**FIGURE 6** Conducting polymer-based electrodes and their functionalized applications. (a) The photograph showed the stretchable polymeric multielectrode array (SPMEA) and representative recording trace following a mechanical movement of the sciatic nerve. (b) The recording characteristics of the all-polymer microelectrode arrays (polyMEAs) in an exemplary in vitro recording from a co-cultured cortico-hippocampal neural network, and the epidural in vivo recording from the visual cortex of an anesthetized rat. (c) The structure of NeuroGrid and neural activity recordings in freely moving rats. The electrode can conform to the surface of the rat somatosensory cortex and successfully detect the action potentials in hippocampus (right) and cortex (left). (d) The polyimide (PI) nanofiber and poly (3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS)-based electrode was implanted to the rat sciatic nerve and the neural signals were collected by the electrode from sciatic nerve tissue over 12 weeks. (e) The picture illustrated the design and performance of dopamine-mediated organic neuromorphic device.

so on. Integration of brain-derived NGF (BDNF) into the Ppy film significantly increased neurite elongation of dorsal root ganglion explants and PC12 cells (Evans et al., 2009; D. H. Kim et al., 2007).

#### 3.1.5 | Hybrid nanomaterials

Except for using a single electroactive material, people are exploring the composite materials to increase the stability and biocompatibility and maintain the functionality of the neural interface. It is a good way to combine the merits of different kinds of materials by developing hybrid nanomaterials (S. Lee, Peh, et al., 2017; J. Wang et al., 2018; Xiang, Sheshadri, et al., 2016). The most common polymeric material used to fabricate the composite materials is hydrogel. Hydrogels are a kind of hydrophilic, cross-linked and water-swollen polymeric network (Yuk et al., 2019), and they have excellent ionic conductivity. Hydrogels can generate ion current through dissolving the ions that were adsorbed in the polymer network of the hydrogel into water. Particularly worth mentioning is the porous structure of hydrogels can provide sufficient space for the doping of other conductive materials, thus further improved the electrochemical properties of the networks without sacrificing hydrogels' biological characteristics (Fu et al., 2020; C. Liang et al., 2022). The Young's modulus of hydrogels is very low that can minimize the mismatch of chemical components between the electronic devices and the biological tissue. The hydrophilicity of the hydrogel matrix can also restrain the proinflammatory proteins move onto the surface of the electrode (Kozai et al., 2015). Many researches have proved that hydrogel is a good choice to make tissue engineering and drug delivery scaffolds and carriers due to their water containing and soft mechanical properties (Athukorala et al., 2021; Green, 2019; Jia & Rolandi, 2020; Sunwoo et al., 2020; C. Wang et al., 2022; Yuk et al., 2019). Kim et al. investigated the effect of HG coatings with various thicknesses on the nerve tissue. They implanted the electrode in the auditory cortex of guinea pigs and evaluated the long-term performance of the neural electrodes. The results showed the coating not only improved the electrode biocompatibility but also facilitated more efficient signal transmission (D. H. Kim, Viventi, et al., 2010).

Green et al. proposed a concept of the biohybrid electrode. The structure of the biohybrid electrode was a Pt electrode coated with conducting hydrogel and such electrode can support the growth of neural progenitor and glia cell. The Pt electrodes were coated with a layer of PVA, and then they were electropolymerized with the PEDOT. At last, a macromonomer solution containing neural cells or glia cells was deposited on top of the conductive hydrogel. The modulus of the electrode can decrease as time goes by, from 140 to 1.5 kPa (Goding et al., 2017). With the further development of the biohybrid electrode, Cullen et al. developed an axon-based electrode that was consisted of columnar microstructures. The hydrogel lumen array with local host neurons can be injected to the brain through microinjection and the axonal segment penetrates to prescribed depth for synaptic integration with local host neurons (Figure 7a) (Serruya et al., 2018). This kind of approach can enhance neuromodulation through the long-term integrated bioactive interface (Struzyna et al., 2015). The soft hybrid nanomaterials-based electrodes could also be implanted into the peripheral nerve to realize neuromodulation. Bao et al. developed a conductive-hydrogel-based electrode by mixing PEDOT:PSS with the hydrogel (Figure 7b). The electrode showed high current-injection density and high conductivity due to its low electrical impedance ($\sim$1k$\Omega$). It can stimulate the sciatic nerve of mice under anesthesia at a relatively high current density of 10 mA $cm^{-2}$ and a low voltage of 50 mV. Owning to the low modulus and high flexibility of the electrode, close contact between sciatic nerve and the electrode still existed during the repetitive leg movement in rats (Y. Liu et al., 2019). The local drug-delivery systems can realize through the hybrid electrode. In a study, a PEDOT:PSS-based hydrogel implantable electrode can play a role in a neuropathic pain model. When the PEDOT:PSS electrode was overoxidized, a salt bridge formed through the cation-selective channel which enabled the unidirectional transportation of drugs (Figure 7c). They implanted the electrode onto the spinal cord of nerve-injured rats and locally delivered the inhibitory neurotransmitter g-aminobutyric acid (GABA). The results showed the highly localized treatment resulted in a significantly lower pain response at low doses and no significant side effects were observed (Jonsson et al., 2015). Wang et al. fabricated an artificial nerve fiber by mimicking the structure and functions of the myelinated axon, exhibiting the property of fast and potential-gated signal transmission (C. Wang et al., 2022).

### 3.2 | Piezoelectric-based materials for indirect electrical stimulation

Piezoelectric nanomaterials are a specific class of all the materials that can show electromechanical property by converting mechanical energy into electrical polarization without applying an external power source. The piezoelectric effect

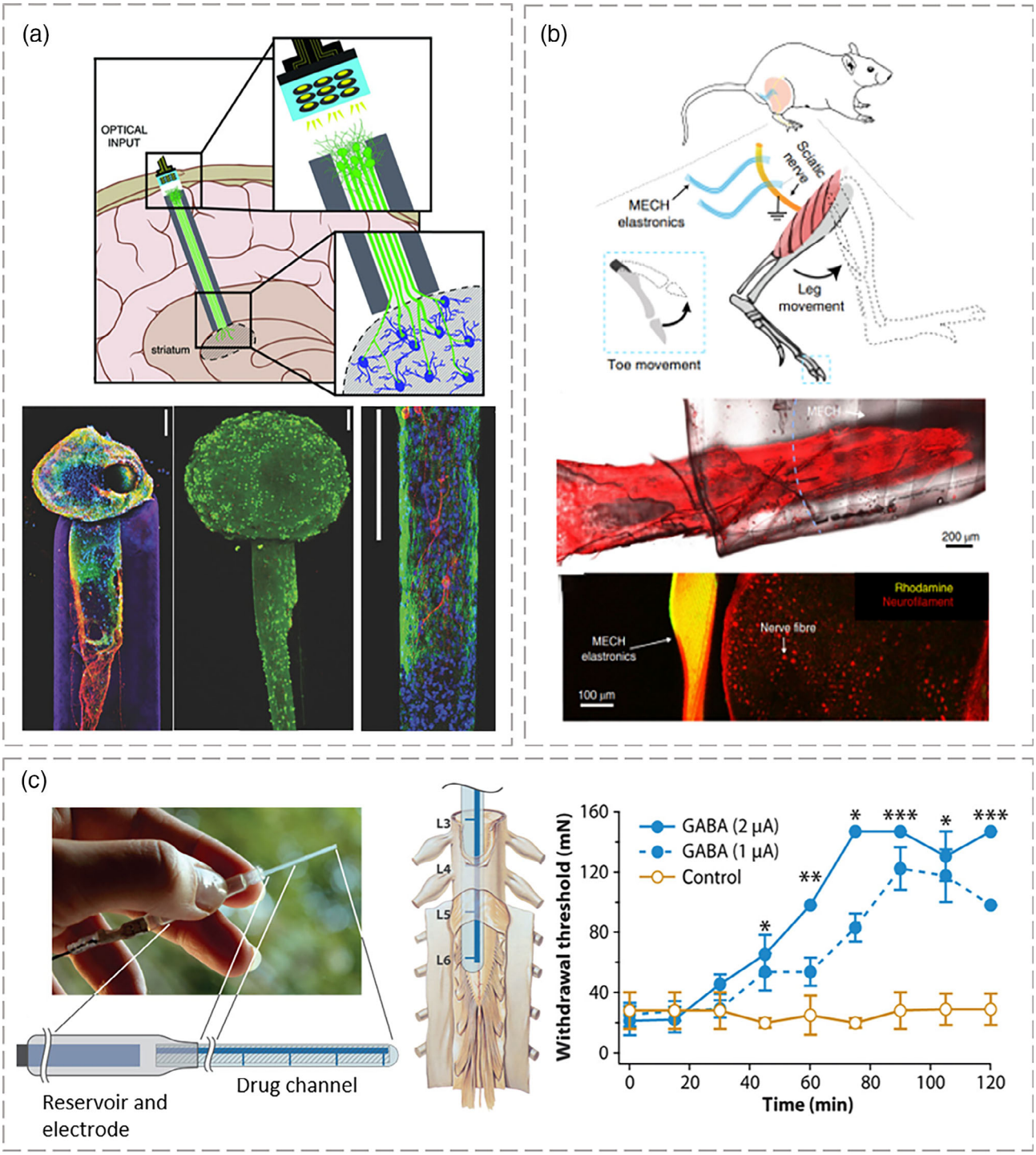


**FIGURE 7** Hybrid nanomaterials electrodes and their functionalized applications. (a) A biohybrid "living" electrode in which a neuronal axon electrode is cultured in columnar hydrogel in vitro with the potential to be injected into the brain and connected to a neuromodulation device. The immunofluorescence staining image of the cerebral cortical neuronal living interface after 11 days in vitro (below). (b) The picture illustrated the micropatterned electrically conductive hydrogels implanted into the mouse sciatic nerve to conduct peripheral nerve stimulation. Leg swing was stimulated by an electrode with a size of 0.2 mm × 3 mm, and the individual toe movement was achieved by localized stimulation with a microelectrode. (c) The poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS)-based hydrogel electronics that can transport drugs to the spinal cord precisely and reduce pain. Depiction of the four outlets aligned with the sites where the sciatic nerve bundles enter the spinal cord. The data showed the therapeutic effect of g-aminobutyric acid (GABA) delivery in vivo.

can be divided into direct piezoelectric effect and reverse piezoelectric effect. Piezoelectric material deformation could induce charges transfer asymmetrically and results in electric polarization and in a consequent electricity generation. This phenomenon is known as direct piezoelectric effect. The reverse piezoelectric effect is that the piezoelectric materials undergo a strain in response to the application of an electric field (Curie & Curie, 1880). Piezoelectric effect is a molecular phenomenon that generates a macroscopic potential, the piezoelectric potential, through the continuous superposition of dipole polarizations (Z. L. Wang, 2010; Wang Zhong & Song, 2006). The inorganic piezoelectric materials generally refer to the piezoelectric crystal grown in a long-range order according to the crystal space lattice. This crystal structure has no center of symmetry and the displacement of positive and negative ions inside the crystal produces a dipole moment that could not be canceled out by other dipoles, and that is what piezoelectricity produces (Espinosa et al., 2012). Piezoelectricity in organic materials originates from the orientation and alignment of molecular dipoles.

The piezoelectric biomaterials possess a built-in capacity for electrical stimulation which could easily transduce electricity to organisms. The drive of these piezoelectric materials does not need to connect with any wired external power supply, they can be activated by mechanical forces of the body like compressions and vibrations or the sources of mechanical stimulation that can penetrate tissues like ultrasound (US) (Jianqing et al., 1997). Small charge changes on the surface of piezoelectric materials can act on biological interfaces that directly contact the material, and these small potential differences can affect nerve activity. These features of piezoelectrical stimulation can avoid the complexity and inconvenience to patients of the traditional wired electrical stimulation mode (Marino et al., 2017). Piezoelectric materials show great potential in indirect or remote electrical stimulation of many tissues, such as bone (Danti et al., 2013; Khare et al., 2020), nervous (Zaszczynska et al., 2020), and muscles (Danti et al., 2013).

In recent years, many biocompatible piezoelectric materials have been exploited for the fabrication of novel electroactive biological interfaces (Kapat et al., 2020). The piezoelectric inorganic materials, such as lead zirconate titanate (PZT), zinc oxide (ZnO), boron nitride (BN), and barium titanate (BT), were the earliest and most widely used piezoelectric materials due to their extremely high piezoelectric coefficients and stability (Chorsi et al., 2019). Piezopolymers are another important piezoelectric material used in biomedical engineering. Kawai first discovered the piezoelectricity of polyvinylidene fluoride (PVDF) and the flexibility and nontoxicity of PVDF making it a substitute for PZT (Foster et al., 2000; Kawai, 1969). Other piezopolymers like poly(L-lactic acid) and poly(vinylidene fluoride-trifluoro ethylene) (P(VDF-TrFE)) are often used in many biomedical applications (Ribeiro et al., 2015). People also explored many new-type piezoelectric materials like lithium niobate, gallium nitride, polyhydroxybutyrate, bismuth sodium titanate, diphenylalanine, and peptide nanotubes (Kholkin et al., 2010; Yuan et al., 2019). And they attempted to synthesis many hybrid piezoelectric materials for improving properties and functions (Rajabi et al., 2015; Tandon et al., 2018).

For the in vitro use, it is possible to deliver electrical signals to excitable cells like neurons remotely and safely by taking the advantage of US-responsive piezoelectric nanomaterials (either in the form of nanoparticles and films) (Table 1). The size of piezoelectric nanoparticles is very small so that they can integrate well with cells. Ciofani et al. first combined US with BN nanotubes and they found that this kind of treatment can enhance the differentiation of the neural-like cells (PC-12) compared to that in the control cultures (Figure 8a) (Ciofani et al., 2010; Marino et al., 2015). This work provided a new thinking and method for the further exploration of the effect of other neural cells and stem/progenitor cells. One of the subsequent groups synthesized BT nanoparticles (BTNPs) and added them into the cultured medium of SHSY5Y cells (Figure 8b). After incubating for 24 hours, most of the NPs distributed on the membranes of the cells. Neural activation was observed due to US stimulation and piezoactivity (Rojas et al., 2018). Zhao et al. developed the US-activated BTNPs with a carbon shell and they verified in PC-12 neuron-like cells that BTNPs under US stimulation can increase $Ca^{2+}$ influx and upregulate synaptophysin and tyrosine hydroxylase, they also found that BTNPs under US can ameliorate the neural behavioral disorders in zebrafish (Figure 8c) (D. Zhao, Feng, et al., 2020). For the use of piezoelectric films, Royo-Gascon tested the possibility of the electrical activity from the vibration of PVDF substrate. After mechano-electrical stimulation of rat spinal cord neurons for 4 days, neurons grew more neurites compared to neurons grown on non-stimulated substrates and further induce changes of plasticity in neurons of central nervous system. Genchi et al. prepared P(VDF-TrFE)/BTNP films for neuronal stimulation through direct piezoelectric effect. This piezoelectric film can significantly improve the differentiation of SH-SY5Y and elicit $Ca^{2+}$ transients (Genchi et al., 2016). Except for the external induction ways of piezoelectricity of piezoelectric materials like exerting US or acoustic vibration, researchers found that the piezoelectric potential generated by the cell movement and traction living on the piezoelectric films can also influence stem cell differentiation. They found the piezoelectricity and nanotopography of PVDF films together rather than nanotopography alone can promote rat bone marrow-derived mesenchymal stem cells (rbMSCs) differentiate into neuron-like cells (X. Zhang et al., 2019). Du et al. also found that the

**TABLE 1** The in vitro use of piezoelectric materials to stimulate neuronal cells

| Materials | Way to generate piezoelectricity | Piezoelectric constants | Cell type | Outcome | References |
|---|---|---|---|---|---|
| Boron nitride (BN) nanotubes with glycol chitosan coating | Ultrasound<br>$f = 40$ kHz, $P = 20$ W, $t = 5$ s<br>4 times a day for 9 days | — | Rat neuronal-like cells (PC-12)<br>Human neuroblastoma cells (SH-SY5Y) | Increase neurite elongation | Ciofani et al., (2010)_ |
| Barium titanate (BT) nanopatricles (NPs)<br>with gum Arabic coating | Ultrasound<br>$f = 1$ MHz, $I = 0.8$ W/cm$^2$, $t = 5$ s<br>4 times a day for 9 days | — | SH-SY5Y | Activate of volatage-gated $Ca^{2+}$ channels and $Na^{+}$ channels | Marino et al. (2015) |
| BTNPs in poly(vinylidene fluoride-trifluoro ethylene) (P(VDF-TrFE)) | Ultrasound<br>$f = 1$ MHz, $I = 1$ W/cm$^2$, $t = 5$ s | $d_{31} = 53.5$ pm/V<br>$g_{31} = 0.24$ mV/N | SH-SY5Y | Enhance $Ca^{2+}$ transients and neurite lengths | Genchi et al. (2016) |
| BTNPs with carbon shell | Ultrasound<br>$f = 1$ MHz, $I = 0.64$ W/cm$^2$, $t = 5$ min, for 7 days | — | PC-12 and wild-type zebrafish | Increase $Ca^{2+}$ influx; up-regulate synaptophysin and tyrosine hydroxylase | D. Zhao, Feng, et al. (2020) |
| BTNPs with gum Arabic coating and embedded in *Spirulina platensis* micromotor | Ultrasound<br>$f = 1$ MHz, $I = 1$ W/cm$^2$ | — | PC-12 | Increase neurite elongation; activate voltage-dependent $Ca^{2+}$ channels and adenylyl cyclase pathway | L. Liu, Chen, et al. (2020) |
| BTNPs with gum Arabic coating | Ultrasound<br>$f = 1$ MHz, $I = 1$ W/cm$^2$, $t = 3$ min | — | Primary rat cultures of cortical and hippocampal neurons | Increase the neural network activity | Rojas et al. (2018) |
| BTNPs with DSPE-PEG-5000 coating | Ultrasound<br>$f = 500$ kHz, $P = 2$ kPa, $t = 10$s | — | Primary rat cortex neurons | Increase $Ca^{2+}$ concentration and neuron network response | Y.-C. Chen, Li, et al. (2019) |
| BiFeO3 (BFO)@CFO/GelMA | Magnetic fields | — | SHSY5Y cells | Promote SHSY5Y into neuron-like cells | Dong et al. (2020) |
| Polyvinylidene fluoride (PVDF) films | Acoustic vibration (50 Hz, 0.3 g) | $d^{R}_{31} = 22.6 \pm 1.23$pC/N | Spinal cord neurons | Promote the growth of more neurites | Royo-Gascon et al. (2013) |
| PVDF films | Ultrasound<br>$f = 132$ kHz, $P = 80$ W, $t = 10$ min, 5 times a day | $d_{33} = -30 \pm 2$pC/N | PC-12 cells | Promote the differentiation of PC-12 cells | Hoop et al. (2017) |
| PVDF electrospun fiber | — | — | Neural stem cells (NSCs) | Promote NSCs differentiate into neurons | Lins et al. (2017) |
| PVDF electrospun fiber | Cell traction | — | | Promote rbMSCs into neuron-like cells | |

TABLE 1 (Continued)

| Materials | Way to generate piezoelectricity | Piezoelectric constants | Cell type | Outcome | References |
|---|---|---|---|---|---|
| | | | Rat bone marrow-derived mesenchymal stem cells (rbMSCs) | | X. Zhang et al. (2019) |
| PVDF/polycaprolactone(PCL) scaffold | — | $d_{33} = 13.2$ pm/V | Rat Schwann cells (SCs) | Promote SCs to neurons | Y. Cheng et al. (2020) |
| FeOOH/PVDF nanofibrous hybrid membrane | Ultrasound $P = 400$ W, $t = 8$ min, twice a day | $d_{33} = 27.2$pC/N | rbMSCs | Promote rbMSCs into neuron-like cells | R. Zhang, Han, et al. (2021) |
| P(VDF/TrFE) films | Cell movement and traction | — | Human neural stem/progenitor cells (hNSCs/NPCs) | Promote the differentiation of hNSCs/NPCs | Y.-S. Lee and Arinzeh (2012) |
| P(VDF/TrFE)/$CoFe_2O_4$ (CFO) magnetic NPs | Ultrasound | — | PC-12 cells | Promote the differentiation of PC-12 cells | X.-Z. Chen, Liu, et al. (2019) |
| P(VDF/TrFE) nanofiber | Hydro-acoustic actuation | — | NSCs | Promote NSCs differentiate into neurons | Tai et al. (2021) |
| poly (3,4-ethylenedioxythiophene) (PEDOT)/chitosan (CS) nanofibers | Cell traction | Output voltage = 0.93 V/$cm^3$ | Brain neuroglioma cells (BNCs) | Promote the adhesion, proliferation and growth of BNCs | L. Du et al. (2020) |

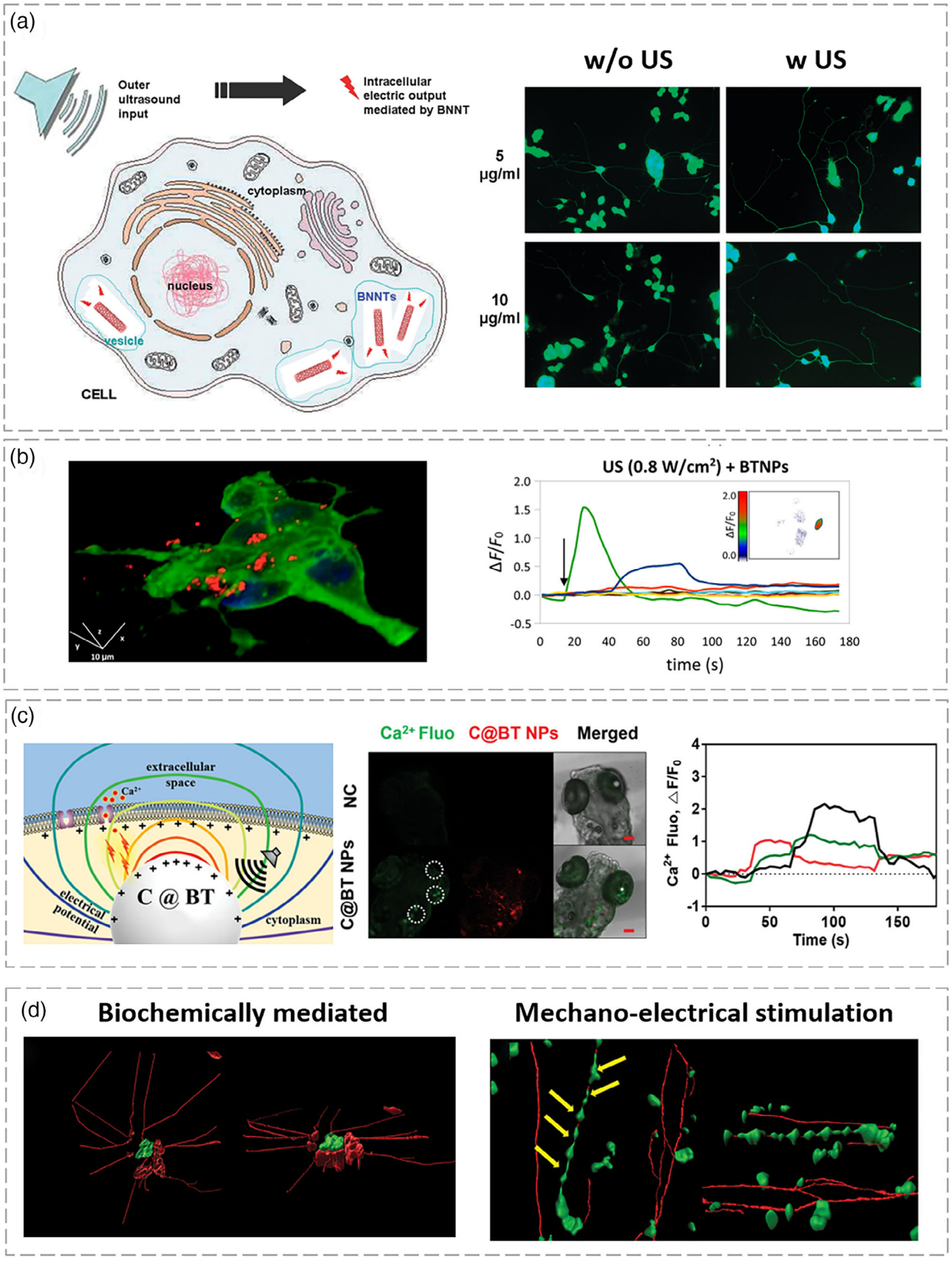


FIGURE 8 Legend on next page.

piezoelectric effect produced by cell traction on PEDOT/chitosan (CS) nanofibers can promote the adhesion, proliferation and growth of brain neuroglioma cells (BNCs) (L. Du et al., 2020). Tai et al. developed a mechano-electrical stimulation in vitro neural model. The P(VDF-TrFE) scaffolds can generate electric charges under hydro-acoustic actuation and this mechano-electrical stimulation can enhance the interactions of the 3D neuron–glial interface (Figure 8d) (Tai et al., 2021).

Piezoelectric materials can also be used in vivo in many different biomedical scenes (Kapat et al., 2020). They can deliver drugs to specific tissue through the polarization-depolarization effect (Mushtaq et al., 2019) and materials like ZnO, BT, and BFO could be used in theranostic therapeutic methods because these nanoparticles could be loaded with contrast agents and other drug molecules (Curry et al., 2020; Ye et al., 2016). For tissue engineering, piezoelectric materials are good choices as they can provide in situ electrical stimulation of tissues and promote the tissue repair and regeneration. We can see many studies around this area and piezoelectric materials can apply in the regeneration of bone (Timin et al., 2018), cartilage (Y. Liu et al., 2022), nerves, skin (Bhang et al., 2017), and muscles (Yoon et al., 2017).

In the field of neural electroactive interfaces, piezoelectric materials mostly applied for building nerve scaffolds. Autologous nerve transplantation was thought to be the "gold standard" for nerve repair, but this is unrealistic in clinical practice. Implanting nerve scaffolds are considered as a replaceable and effective way to help enhance nerve regeneration after nerve injury especially for sciatic nerve injury and spinal cord injury (Vijayavenkataraman, 2020; Xue et al., 2021). Conventional nerve scaffolds are passive that they only provide physical support and guidance for nerves in damaged areas, people started to develop "active" scaffolds which can adjust the microenvironment of the injured site dynamically and accelerate the repair process. Many conductive materials have shown good potential for neural engineering and nerve regeneration such as polypyrrole, polyaniline, polythiophene, and conductive hydrogels (J. Park et al., 2020). But in fact, the intrinsic electrical conductivity of these materials may disturb the nerve signal transduction as the tissue regenerates.

Considering the above problems, piezoelectric materials can provide a method to transmit electrical signals to the cells attached to the electroactive interface without interfering the innate electrical signal transduction (Tai et al., 2021). Moreover, applying piezoelectric materials as tissue engineering scaffolds can realize wireless electrical stimulation that do not need electrodes, external power source or implanting batteries. Aebischer et al. first proposed using piezoelectric materials to build nerve scaffolds (Aebischer et al., 1987). Compared to unpoled PVDF scaffolds group, animals in poled PVDF scaffolds showed a higher number of myelinated axons. PVDF-TrFE-based piezoelectric fibrous materials have higher piezoelectric performance and are more suitable for neural repair (Fine et al., 1991). Lee et al. demonstrated the dorsal root ganglion on the scaffold with aligned PVDF-TrFE fibers showed the longest neurite outgrowth. This result showed that the scaffold with aligned fibers had the greatest application value in neural engineering (Y.-S. Lee et al., 2011). In recent years, many groups did many researches based on the concept of piezoelectric nanogenerator proposed by Zhonglin Wang (Wang Zhong & Song, 2006) and they fabricated combined piezoelectric materials with excellent piezoelectric performance to build nerve scaffolds. Qian et al. developed a piezoelectric ZnO nanogenerator scaffold by 3D-injectable multilayer biofabrication. Animal experiment showed that the scaffold can accelerate nerve conducting velocity, promote axonal remyelination and restore motor function (Y. Qian et al., 2020). Yuan's group implanted the PVDF/PCL composite nerve tissue engineering scaffold into the 15-mm defect rat sciatic nerve model for 4 months, they found the scaffold group exhibit significant electrophysiological, morphological and functional nerve restoration (Cheng et al., 2020). Chen et al. fabricated an ultrasound-active thin film nanogenerator with excellent output performance based on piezoelectric composite films containing $0.5Ba(Zr_{0.2}Ti_{0.8})O_3$-$0.5(Ba_{0.7}Ca_{0.3})TiO_3$ nanowires

**FIGURE 8** Piezoelectric materials-based electroactive interface for neural engineering. (a) Promotion of neurite elongation in PC-12 cells internalized boron nitride nanotubes (BNNTs) and stimulated with US. (b) The immunofluorescence photograph of barium titanate nanoparticles (BTNPs) distributed within SH-SY5Y-derived neurons. When applied with US, an obviously higher calcium flux is detected. (c) The potential distribution of C@BT NPs and the mechanism of the intracellular electromagnetization of nanoparticles. The right picture showed the confocal images of zebrafish brain of the experimental groups and the control group after injecting nanoparticles labeled with Fluo3 AM and DiI into the brain. The nanoparticles in red, Ca2+ probe in green. Ca2+ intensity increased after US stimulation in zebrafish with the injected nanoparticles. (d) The confocal images of cell–cell interactions in the neuron-glial interface derived from a single neural stem cell source in situ by piezoelectric P(VDF-TrFE) scaffold mediated mechano-electrical stimulation. BTNPs, barium titanate nanoparticles; P(VDF-TrFE), poly(vinylidene fluoride-trifluoro ethylene); US, ultrasound

and PVDF polymer. By implanting the piezoelectric thin film nanogenerators subcutaneously, it is possible to electrical activate the sciatic nerve.

## 4 | CONCLUSION

Understanding the function and connection of the nerve system is prominent for correcting disease and disabilities. Only electroactive interfaces with excellent performance could realize good communication with nerve system. Traditional commercial electrodes like Utah arrays and Michigan probes are being replaced by the more flexible interfaces with better properties. These interfaces have excellent electrical properties like low impedance, signal stabilization, and low SNR, and they also have good mechanical properties that can match with the nerve tissue and avoid adverse reaction.

Despite the development of neural engineering interfaces, we still need to note that most of the new neural interfaces are far from clinical translation, and we should be cautious before implanting them into patients. First, the chronic stability and toxicity of the majority of the new technologies and new materials above still need to be validated. The delamination of multilayer electrodes, exudation of by-products of processing and decomposition products may all affect the long-term implantation of electrodes. Scientific standards and experimental procedures need to be established to verify the biocompatibility of these new interfaces. Second, the modulus of the electrodes requires careful design. For better fitting with the brain surface, the electrodes need to be soft enough. And they should be rigid enough to allow precise insertion and convenient placement during surgery. And it is better to add some structure consideration to the design of the electrode to better fit the nerve (S. Lee et al., 2016; Xiang, Yen, et al., 2016). Third, the flexible and bioabsorbable transient devices can degrade in the implanted site at a controlled rate and integrate with the course of treatment (Y. Shi et al., 2020). Implanting them into the body for electrical stimulation treatment will eliminate the need for additional surgery to remove the device. This characteristic is very advantageous for the treatment of neurological diseases with complex tissues and high surgical (Shan et al., 2020). Fourth, the mechanism of the electrical stimulation and recording still need to be studied. The problems such as whether the neurons recorded next to the probe are representative, whether the electronic transmission at the interface could interfere chemical signaling, and oxygen supply and so on are important for fully understanding the process happen at the interface and providing guidance on electrode design. Fifth, we need to develop an integrated neural interface that can make a close-loop system including the power supply, electric circuits, and electrodes. The self-powered system seems to be a good choice to build this complex system which has been proved to be efficient in many biomedical applications of electrical stimulation such as cardiac pacing (Ouyang et al., 2019; Zheng et al., 2021), bone repair (Y. Zhang, Jiang, & Yetisen, 2021; Y. Zhang, Lingling et al., 2021), neural stimulation (Lee, Wang et al., 2017; Lee et al., 2018; Xiang, Liu, & Lee, 2016), and so on. Finally, as the requirements for neural interfaces become more complex, we need to develop multifunctional electrodes including integrate electrical stimulating, recording, optogenetic, and pharmacological modulation.

Totally, electroactive interfaces show tremendous potential for neural engineering. For the future success of clinical translation of the neural interfaces, further studies are required to test the suitability and capabilities of these electrodes. With the challenges ahead, future research could combine sustained efforts across many disciplines, including neuroscience, material science, electronics, and mechanical engineering.

### AUTHOR CONTRIBUTIONS

**Yizhu Shan:** Conceptualization (lead); data curation (lead); writing – original draft (lead); writing – review and editing (lead). **Xi Cui:** Data curation (lead); writing – review and editing (supporting). **Xun Chen:** Funding acquisition (lead); supervision (lead); writing – review and editing (equal). **Zhou Li:** Conceptualization (lead); funding acquisition (lead); supervision (lead); writing – review and editing (lead).

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### CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## RELATED WIREs ARTICLE

Electrically active nanomaterials as improved neural tissue regeneration scaffolds

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