Smart Materials in Medicine 1 (2020) 131–147

HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

Smart Materials in Medicine

journal homepage: www.keaipublishing.com/en/journals/smart-materials-in-medicine/

Recent development of implantable and flexible nerve electrodes

Yue Shi [a,1], Ruping Liu [a,1], Liang He [c], Hongqing Feng [b], Ye Li [a,**], Zhou Li [b,*]

[a] Beijing Institute of Graphic Communication, Beijing, 102600, China
[b] CAS Center for Excellence in Nanoscience, Beijing Key Laboratory of Micro-Nano Energy and Sensor, Beijing Institute of Nanoenergy and Nanosystems, Chinese Academy of Sciences, Beijing, 100083, China
[c] State Key Laboratory of Advanced Technology for Materials Synthesis and Processing, Wuhan University of Technology, Wuhan, 430070, China

ARTICLE INFO

Keywords:
Implantable flexible nerve electrode
Smart materials
Neural chronic recording
Neural prosthesis

ABSTRACT

Implantable electrical devices offer a variety of potential diagnostic options and treatments in different medical fields. Especially in the absence of specific drugs, the implantable nerve electrodes (INEs) are one of the main treatments for neurological diseases such as epilepsy, Parkinson's disease, Alzheimer's disease, etc. INEs are helpful in studying and regulating nervous system *via* recording nerve electrical signals or stimulating nerve tissue, but the mechanical mismatch between rigid electrode and soft biological tissue is a critical challenge for long-term implantation. The advances in micromachining technologies and materials have greatly promoted the development of INEs, such as enhanced biocompatibility, reduced foreign body reactions, and structural innovation. In particular, the mechanical performances of flexible implantable electrode and soft biological tissue matched better with less tissue damage. In this review, the implantable flexible nerve electrodes (IFNEs) based on functionalized substrates, intelligent electrodes, and innovative structures are elaborated and discussed. We summarized their various applications in neural prosthesis and neural signal recording. We also discussed the questions and possible methods for developing future IFNEs in the perspective.

1. Introduction

As the most complex organ of the human body, the brain contains a large number of neurons and glial cells [1]. These neurons and cells complete the transmission of information by electrical signals in the forms of action potentials and chemical signals through neurotransmitters [2,3]. At present, the research on the brain and nervous system is still in its infancy, and there are still a lot of unknowns to be revealed. Therefore, exploring the activity of a large number of neurons in brain tissue is an important way to increase the understanding of the brain [4]. The extracellular electrical recordings of the brain are mainly divided into four main modes: electroencephalogram (EEG), electrocorticogram (ECoG), local field potentials (LFPs), and single neuron action potential recording [5]. Among them, the spatial and temporal resolution of implanted monitoring (ECoG, LFPs, single neuron action potential recording) is higher than that of non-implanted (EEG), and the implanted monitoring is more conducive to obtain reliable electrical signal [6]. The implantable nerve electrode (INE) that completes the electronic communication between the nervous system and external equipment is a key interfacial device for information fusion between the human body and external machine, which is convenient for monitoring and affecting the activity of nerves [7]. Early INEs are mostly composed of metal and semiconductor [8]. Although they have superior electrical conductivity, the mechanical mismatch between rigid material and soft brain or neural tissue leads to the destruction of local nervous environment, inflammation and formation of scar [9]. It can only be monitored for a short period of time and will cause a great damage to the implant [10]. Therefore, it is a great challenge to solve the mismatch of mechanical and electrical performances between INE and biological tissue. In recent years, the emergence of implantable flexible nerve electrodes (IFNEs) with the similar elastic modulus as that of brain tissue opened up the new research directions for INEs [11]. Therefore, current researches on INEs are mostly based on flexible implantation. It combines functional materials, micro-processing technologies and neural engineering, showing characteristics superior to other INEs. As shown in Fig. 1, we sort the elastic modulus of the materials applied in INEs. In order to intuitively illustrate the contrast between the materials and human tissues, we take some typical human organs as representatives to display the elastic modulus of

* Corresponding author.
** Corresponding author.
E-mail addresses: liye@bigc.edu.cn (Y. Li), zli@binn.cas.cn (Z. Li).
[1] The authors contributed equally to this work.

https://doi.org/10.1016/j.smaim.2020.08.002
Received 22 June 2020; Received in revised form 3 August 2020; Accepted 9 August 2020
Available online 18 August 2020

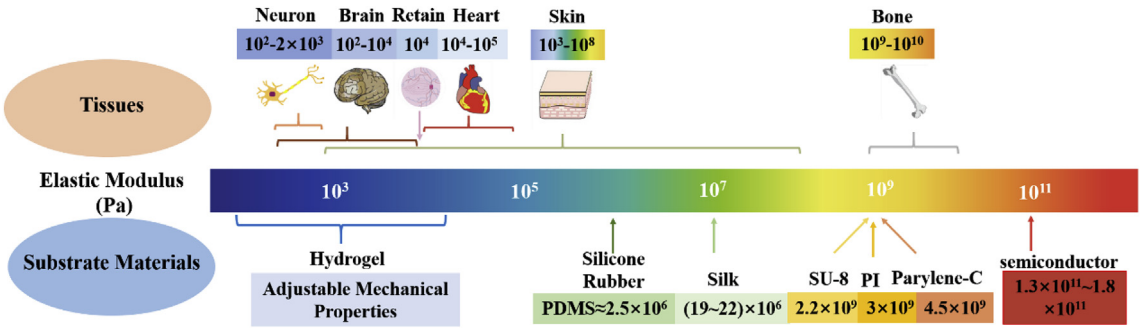

Fig. 1. Elastic modulus matching between substrate material and biological tissue can guide the design of IFNEs. The elastic modulus of the human organ (top) and of the IFNEs manufacturing material (bottom) are plotted on a logarithmic spectrum of the elastic modulus [12–23].

the materials [12–23].

The requirements in IFNEs for long-term stability monitoring are high biocompatibility, low elastic modulus, high corrosion resistance, excellent sealing and stability [24]. Classified by specific function, IFNEs are mainly divided into recording electrodes [25] and stimulating electrodes [26]. Recording electrodes with excellent performance also need to be sensitive to detect low-level signals, especially the signals required for recording and low impedance. In addition, an IFNE with a stimulating function should have a high charge injection limit (CIL), a high charge storage capability (CSC), and a low impedance [27]. The purpose is to inject sufficient electric charge in the selected material and electrode area to achieve the expected physiological response, and doesn't cause the electrode to produce excessive irreversible Faraday reactions and damage the tissue or electrode [28]. In order to enable microelectrodes to meet the different requirements of recording and stimulation, it is necessary to combine biomedical, electrical, mechanical engineering and chemical disciplines to optimize and solve various problems. Therefore, the current research mainly focuses on the continuous improvement of IFNEs and the expansion of their applications.

In this review, we provide an overview of the latest research in this field, focusing on those innovative results that have important basis and research direction for future study. This review is mainly divided into the following three aspects: 1) materials for IFNEs, including substrate materials (biodegradable materials, stretchable materials, etc.), electrode materials, encapsulation materials, and materials for modification; 2) new structures of IFNEs, we reviewed the new structures of IFNEs emerged in recent years. We also introduced the research progress of IFNEs in miniaturization, high density, and implantation methods; 3) applications of IFNEs, we investigated and elaborated the various applications of IFNEs, including neural prostheses, neural signal recording, and neural modulation. In the conclusion and prospection, we summarized the issues in the future development of IFNEs, and introduced the future research directions of IFNEs. When IFNEs are combined with functional magnetic resonance imaging (FMRI), magnetoencephalography (MEG), microfluidics, and self-powered devices, etc., they have the possibility to develop multifunctional neural interfaces.

2. Materials for IFNEs

The IFNE is mainly composed of a substrate, an electrode, and a package, each of which plays a crucial role in the performance of the IFNE. This section reviews various functional substrates, electrode materials, materials for encapsulation and surface modification applied in IFNEs, etc.

2.1. Materials for substrate

Currently IFNEs related common substrates include polyimide (PI), polydimethylsiloxane (PDMS), parylene C, etc [29,30]. Among them, PI film is a kind of high-temperature resistant polymer film. Although it served as a medical implantable material has a long history, it has great limitations in terms of tensile strength and Young's modulus [31]. Another common substrate, parylene C, has excellent sealing, biocompatibility and stability [32]. However, the high sealing and stability after implantation in the body are not conducive to the coexistence of the electrode and human tissue, and it is difficult to degrade in human body [33]. Therefore, in recent years, the development of functionalized substrates becomes a new research direction and is attracting widespread attentions.

2.1.1. Degradable material

Micromotion between the soft biological tissue and the implanted electrode will cause inflammation and form an insulating sheath around the electrode, leading to the insulation and even failure of the device [34]. As indicated in reported results, the severe foreign body reactions can be limited *via* flexible and/or soft implants, namely flexible electrodes [35]. However, there are two main problems in flexible electrodes, one is that the flexible electrode with a small elastic modulus does not have sufficient mechanical strength to withstand the high-speed insertion process, which brings a great challenge to the implantation [36]. The second is that the flexible electrode needs to be taken out again after the implantation or treatment, which causes secondary harm to the patient while facing a series of complications [37].

The applications of degradable materials in flexible electrodes will solve the above problems to a certain extent. Leber et al. [38] proposed a self-dissolving 10 × 10 and 4 × 4 Utah microelectrode array (UEA). To facilitate implantation, the multi-electrode array remained together with the help of biocompatibility and the soluble material, polyethylene glycol (PEG). Once implanted, the PEG is dissolved in the biological fluid, causing all electrodes to float freely in the neural tissue, greatly reducing the micromotion between the device and the brain tissue. In addition, PEG can also be employed as a drug carrier to promote neuron growth, etc. Degradable PEG as the electrode substrate not only enhances the mechanical strength during implantation, but also reduces the micromotion between the electrode and the tissue after the degradation of the implant. However, after the silicon-based probe invades the tissue, it causes certain damage to the tissue. Compared with silicon, the carbon fiber has a small diameter and lower mechanical strength, so it has less damage to the tissue [39]. However, carbon fiber microelectrodes have the limitations of low hardness and small insertion depth [40]. Silk fibroin is a material with super softness, biocompatibility, and programmable water solubility [41]. Lee et al. [42] made use of embedded degradable silk fibroin as a mechanical support to enable the electrodes to penetrate the brain while reducing immune rejection. According to immunohistochemical staining, silk fibroin scaffolds cause less glial cells. Additionally, one month after implantation in the hippocampus of the rat, the impedance of electrode remained the same, and the ratio of active electrodes was above 70%, which had a good recording function [42].

Compared with invasive electrodes, non-invasive electrodes will further achieve long-term stability monitoring, so they have close contact

with the soft curved surface of biological tissues, providing long-term implant stability [43]. Kim et al. [44] proposed a soluble substrate using silk fibroin. In comparison with the 2.5 μm PI film, the ECoG electrode based on silk soluble substrate has good common contact on the brain surface and the quality of signal is improved [44]. In addition to monitoring EEG signals, the measurement of intracranial pressure is very important during the diagnosis and treatment of doctors, because an increase in intracranial pressure often causes further brain damage. At present, through brain scans and clinical characteristics, doctors cannot reliably judge patients' intracranial pressure [45]. Kang et al. [46] proposed an implantable intracranial pressure monitoring sensor including poly (lactic-*co*-glycolic acid) (PLGA) and silicone, which could transmit accurate pressure, temperature and other parameters. The most important thing is that when the device is immersed in aqueous solution (including cerebrospinal fluid and other biological fluids), it could be completely dissolved into a biocompatible final product, eliminating the risks and costs associated with surgical removal of implanted devices [46]. Curry et al. [47] used the biodegradable polymer poly (L-lactic acid) (PLLA) to spin nanofibers that have a width of only 200 nm and a length of tens to hundreds μm, and woven them into a web. The arrangement of the fibers enhanced their piezoelectric response, making the PLLA nanofiber use less electricity to vibrate more forcefully than ordinary polymer films. The researchers used these highly piezoelectric nanofibers to create a sensitive biodegradable implant sensor that can wirelessly measure the pressure in the organ, as shown in Fig. 2a [47]. And the device functioned well in its predefined lifetime and eventually self-degraded (Fig. 2b).

2.1.2. Stretchable material

The brain is not thoroughly understood, and the volume of brain will constantly change within a day, that is, swelling and deflation. However, current electronic implant cannot follow the brain to expand and contract accordingly, which makes the seamless connection between electronic implant and the brain complicated [48]. Therefore, the flexible device is required to have the important feature of stretchability. Flexible devices mainly obtain stretchability from two directions, one is that the material itself has stretchability [49], and the other is that the structure is constructed onto a stretchable structure [50].

In order to obtain materials with stretchable performances, the first is to modify the materials. For example, Bao et al. [48] prepared a polythiophene (PEDOT) film with high cycling stability, high stretchability, and high electrical conductivity through doping ionic additives-assisted stretchability and electrical conductivity (STEC) enhancers, and the stretchability and electrical conductivity are enhanced. This film has an electrical conductivity higher than 4100 S/cm under a strain of 100%. The schematic diagram representing the morphology is shown in Fig. 2c [48]. Second, the inherently stretchable electrode materials, such as carbon nanotube (CNT), graphene, etc are widely applied [51,52]. Zhang et al. [53] constructed a stretchable transparent electrode array composed of PDMS/mesh CNT/SU-8, which had a transmission of up to 85% over a wide wavelength range (400 nm-2.5 μm), low impedance (0.20 ± 0.03 MΩ, 10^4 μm^2 size), high CSC, and resistance to multiple mechanical stretching. The effectiveness of the CNT electrode array in the electro-optical neural interface is verified by simultaneous optical stimulation and electrical recording imaging of cortical activity in rats [53]. Third, the elastic materials are utilized as the substrates, including PDMS, silicone, and rubber [54]. For instance, Tybrandt et al. [55] prepared a stretchable electrode *via* transferring Au–TiO_2 nanowires (NWs) pattern to the semi-cured PDMS substrate and rotating the top coating PDMS layer as the encapsulation layer. The tensile test results of this

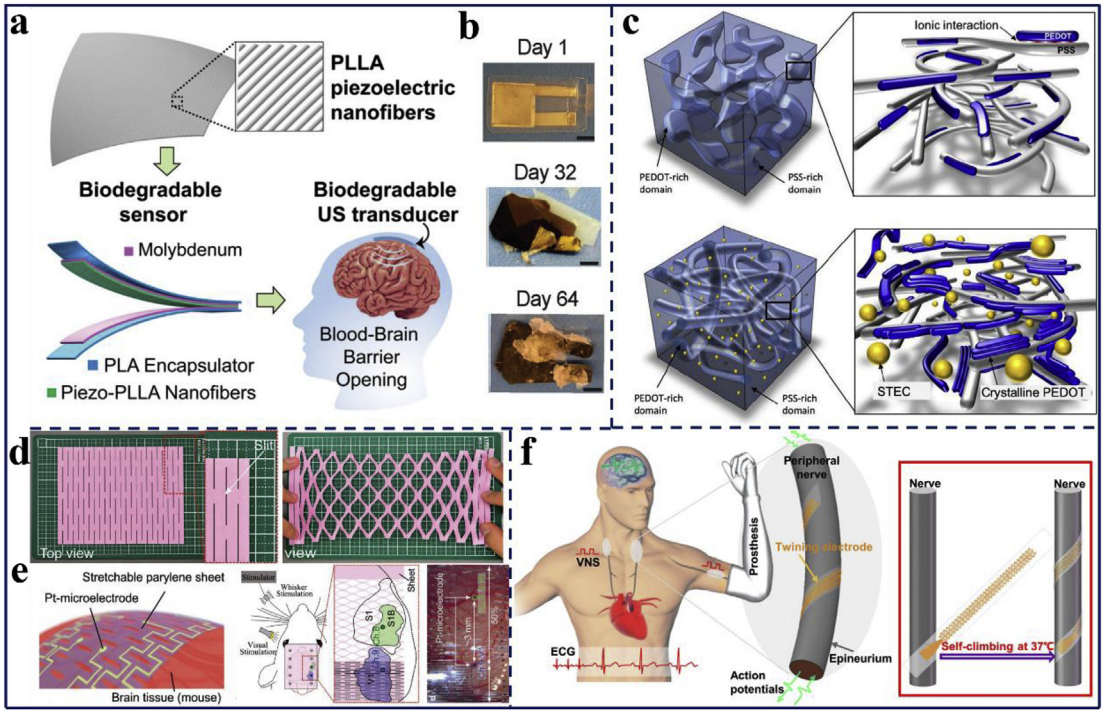

Fig. 2. Functionalized flexible substrates. (a) PLLA nanofibers with highly controllable and excellent piezoelectric performance for biodegradable implanted piezoelectric devices. (b) The optical images of a typical biodegradable ultrasound transducer at different days in the buffered solution under an accelerated-degradation temperature of 70 °C, (Scale bars, 5 mm), reproduced with permission [47]. Copyright 2020, Proc. Natl. Acad. Sci. (c) Schematic diagram representing the morphology of a typical PEDOT: PSS film (upper) versus that of a stretchable PEDOT film with STEC enhancers (bottom), reproduced with permission [48]. Copyright 2017, Sci. Adv. (d) Photographs and schematics of stretching of a "kirigami" paper (120 mm × 160 mm) with a slit pattern formed by scissors. (e) Illustration of the animal experiment and the positions of the Pt electrodes, reproduced with permission [57]. Copyright 2018, Adv. Healthcare Mater. (f) Schematic diagram of the conceptual peripheral nervous system (PNS) neuromodulation for restoring the motor and physiological functions (left), the electrode-nerve interface (middle) and concept of the self-climbing process from the flattened state driven by body temperature (right), reproduced with permission [60]. Copyright 2019, Sci. Adv.

stretchable electrode showed that the composite exhibited an excellent stability of strain cycling when stretched at 20%, 50% and 100% strain for 1000 times. This stretchable electrode was able to detect high spatiotemporal neural signals from the surface of the cortex in free-moving rats, and maintained the consistency of the electrode signals within 3 months after implantation.

In addition to the material that can be stretched by means of itself, through the design of the geometric structure, the rigid material can be stretched structurally. Kirigami refers to cutting a sheet of paper/film into a large number of two-dimensional (2D) and/or three-dimensional (3D) structures through cutting, folding and gluing [56]. Kawano et al. [57] utilized kirigami to construct an electrode with a highly stretchable structure consisting of parylene and platinum (Pt)/titanium (Ti) layers of unstretchable material. The electrodes array with 3 × 91 slits had a strain of up to 840% under a stress of 0.53 MPa. Moreover, when the film is stretched <50%, the deformation only requires a force of <3.3 mN. Using this device to record the biological signals of brain tissue and heart of mouse often associated with the reduced stress on the device, which further proved the superiority of the device [57]. A drawing photo and schematic diagram of kirigami paper with slit pattern formed through scissors and a schematic of the kirigami device placed over the brain tissue of mouse are shown in Fig. 2d and e, respectively.

2.1.3. Shape memory material

The special geometric shapes and sizes of some biological tissues or nerves caused extreme mismatches in the mechanical performances and geometrical structures between the electrodes and the nerves or soft tissues. Shape memory material is a kind of intelligent material. After sensing the change of the environment, such material can adjust its shape, position, strain and other mechanical parameters, and finally it can recover to its original state [58]. Using these shape memory materials, the flexible electrodes and the tissues or nerves can be well matched and connected [59].

Zhang et al. [60] proposed a 3D imitation climbing wound electrode to solve the interface mismatch between electrode and nerve bundle. The complex IFNE was prepared on a 2D plane. The shape of the peripheral nerve bundle [61–66] was employed to design the permanent shape of the IFNE using the reconfigurable function of shape memory polymer (SMP), polyurethane, to form a 3D wound electrode. Before implantation, the 3D wound electrode was flattened to facilitate surgical operation. During implantation, the electrode was automatically restored to the designed 3D spiral shape with the help of using 37 °C physiological saline, as shown in Fig. 2f. The natural adhesion formed a good electrode-nerve bundle interface without additional surgical fixation. The low elastic modulus and reasonable mechanical design (network-like serpentine structure) of this intelligent material decreased the tensile and bending stiffness of the IFNE, ensuring that the IFNE could deform with the dynamic deformation of the nerve bundle without causing too much pressure on the nerve bundle. In order to verify the application potential of wound electrodes in peripheral nerve electrical stimulation and signal acquisition, they also achieved specific applications of wound electrodes in electrical stimulation of vagus nerve and sciatic nerve. This kind of electrode, which matches the geometry of the peripheral nerve bundle, is beneficial to the treatment of some current drug-refractory diseases, and has distinctive research significance [60].

In addition, Du et al. [67] developed a flexible microelectrode arrays (fMEAs) with a large area (100 mm^2) and high-density electrode sites (126 channels) on the PI substrate, and added a SMP layer (PDLLA-g-PAA (10 wt%)/PEG (10 wt%) blend). Due to the excellent shape memory characteristics of the SMP layer, the contradiction between minimally invasive implantation and large-area electrodes was eliminated. The temporary tubular shape of fMEA with a diameter of 2 mm was retained at room temperature. And, in the air at 37 °C, fMEA realized self-unfolding from temporary tubular shape to a permanently flat shape in just 20 s. This novel SMP-based fMEAs had an effective stimulation area of 4.0–9.1 mm^2, and is expected to obtain a field of view of 13.4 × 30.15°. It had superior image resolution, which can further improve the performance of retinal repair equipment [67].

In order to understand these functional substrate materials more clearly, we sorted them through Table 1, including their evaluation criteria, application scenarios, etc.

2.2. Materials for electrode

As neural interfaces, microelectrodes have the following requirements. Firstly, the IFNE is biologically compatible with biological tissues and nerves. The main manifestation is the long-term implant stability. The shape and mechanical matching between implanted electrode and soft biological tissue are required. Under this situation, some intelligent metallic materials are emerged, which are functionalized while adapting to the mechanical requirements of the corresponding biological organisms.

Secondly, the electrical performances of microelectrodes should be tuned within a certain range to stabilize neuron signal recording and stimulation. Specifically, low impedance, high CSC and high CIL are required. So far, noble metals (Au, Pt, Ir, Ti) and their alloys are the most common electrode materials due to their superior biocompatibility, chemical stability, and good electrical performance in the biological environment [68]. However, the higher impedance, lower CIL and limited CSC of these materials are not suitable for small-area microelectrodes, so it is difficult to realize the purpose of improving spatial resolution [69]. Among them, the common Pt microelectrode has an impedance of 36.67 kΩ cm^2, the limited CSC of 3.56 mC/cm^2 (measured at 1 KHz) [70], and the Pt microelectrode appears to delaminate after 1 million pulses [71]. Its high impedance and low CSC make it difficult to achieve long-term stability monitoring and stimulation. As an

Table 1
Evaluation and application scenarios of functional substrate materials.

Functional Substrate Materials	Substrate Materials	Evaluation Criterion	Applications	References
Degradable Material	PEG; Silk; PLGA; PLLA; … …	Degradable rate; Degradable temperature	Biological scaffolds; Biodegradable implanted sensor for intra-organ pressure measurement; Enhanced device/tissue conformal; Drug carrier; Increase the elastic modulus of electrode for easy implantation	38, 42, 44, 46
Stretchable Material	PDMS; Silicone; … …	Tensile strain; Stretching load; Cycles	New wearable electronics; Implantable medical devices	53–55
Shape Memory Material	Polyurethane; PDLLA-g-PAA (10 wt%)/PEG (10 wt %); … …	Phase transition temperature; Shape memory cycles; Shape fixity; Shape recovery ratios	Twining electrodes; Peripheral neuromodulation; Retinal prosthesis	60,67

improvement, Pt gray has a rougher fractal morphology, and the CSC increasing to 5.3 mC/cm^2 and CIL to 1 mC/cm^2 [70,72], but its CSC is still not ideal in high-density microelectrodes array. In addition, iridium oxide (IrO_x) is one of the most famous stimulation electrode materials. Although its CIL is 4 mC/cm^2, higher than Pt gray, it is also easy to delaminate under long-term stimulation [73]. In this case, increasing the effective surface area of the material will reduce the electrochemical impedance and improve CIL, so some nanostructured noble metals, carbon-based materials and conductive polymers (CPs) are attracting research interests, and they become the hotspots in the development of IFNEs.

2.2.1. Smart metal material

The noble metal used for the electrode has the disadvantages of high elastic modulus, low CSC and CIL mentioned above. After being subjected to external force, it will first undergo elastic deformation, and when it reaches the yield point, its plastic deformation will occur [74]. These disadvantages make it difficult to adapt to the complex, soft environment of the living body. In order to achieve functionalization while matching the mechanical requirements of corresponding biological organisms, the intelligent metal materials are emerged.

2.2.1.1. Shape memory alloy. As the most complex part of the human body, the brain will inevitably experience inflammatory reactions of the immune system when exploring the nerves in the brain, which makes it difficult to achieve long-term stability recording. Flexible devices could reduce the inflammatory response to a certain extent, however, their low elastic modulus makes the implantation difficult. If the flexible nerve probes array can be reliably inserted into the brain and can be evenly distributed in the brain area without damage after implantation, it will be beneficial to achieving long-term large-scale recording [75]. Shape memory alloys (SMAs) are one kind of smart materials with unique functions and intelligent performances, attracting much attention. SMAs have the advantages of high mechanical performance, high power-to-weight ratio, resistance of large deformation, and biocompatibility, providing highly promising solutions for microdevices [76]. Shull et al. [77] synthesized woven neural probes (WNPs) by means of interweaving a linear array of 32 flexible insulated microwires with SMA wires. The experimental results successfully verified that the contracted SMA WNPs could be reliable when inserted into the brain. Furthermore, the *in-vitro* experimental results showed that the SMA in WNP could act as a driver, which drove WNPs to unfold slowly under thermal induction [77]. Part of the foreign body response when exploring the nerves of the brain comes from the damage of the cerebral vascular system, that is, the damage of the blood-brain barrier and the bleeding caused by the rupture of cerebral blood vessels when the electrodes are inserted. It is especially harmful, not only causing extensive nerve damage, but also making the electrode lose its ability to record nerve activity over time. Zhao et al. [78] prepared a 3D expandable nitinol microwave electrode array. With the help of programming the SMA to conform to the shape of the cerebral vascular system, it reduced the damage of cerebral blood vessels to a greater extent after implantation. In addition, nitinol microarrays were tested in live animal experiments, and it was successfully demonstrated that this electrode could detect single spikes and LFPs with minimal damage to tissues and blood vessels.

2.2.1.2. Liquid metal. Liquid metals have high ductility and electrical conductivity, and show the advantages of both inorganic electronic materials and organic electronic materials [79]. Currently in neural interface applications, the most common liquid metal is GaIn alloy. At room temperature, due to its fluidity, GaIn alloy (weight percent: 75.5% Ga and 24.5% In) shows zero stiffness and almost infinite ductility, and is well adapted to the soft structure in the body [80]. Guo et al. [80] fabricated a flexible neural microelectrodes array based on GaIn alloy by embedding four liquid metal electrodes and stretchable interconnects into PDMS membrane, as shown in Fig. 3a. The flexible neural

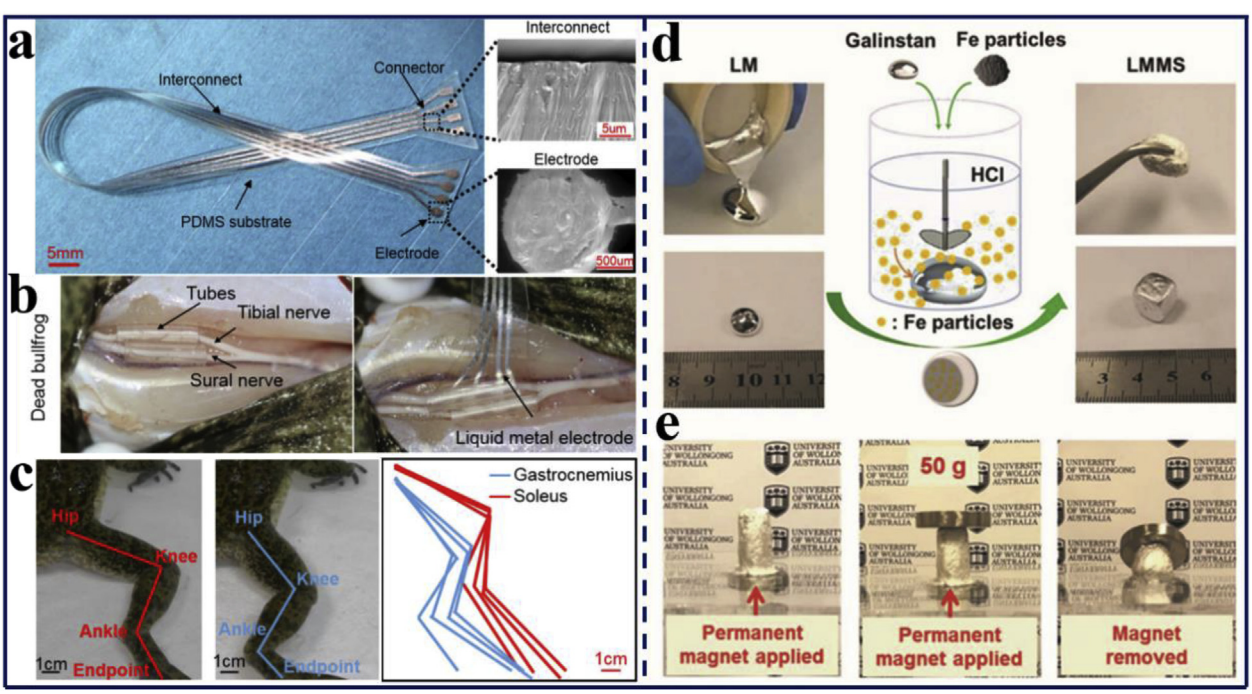

Fig. 3. Smart metal materials-liquid metal. (a) Optical image of the liquid metal electrodes, and scanning electron micrographs of the electrode and the interconnect. (b) Optical images of the implanted liquid metal electrodes for the bullfrog sural nerve and tibial nerve. (c) The hind limb kinematics of a dead bullfrog after implantation, reproduced with permission [80]. Copyright 2017, J. Micromech. Microeng. (d) Schematic illustration and photographs demonstrating the preparation of LMMS. (e) In addition to the viscosity that appears after suspending Fe in the LM, the stiffness of the LMMS sample could be further enhanced by applying an external magnetic field. The cylinder molded under the field from a permanent magnet shows no deformation with a 50 g weight on the top. The high cylinder toppled over immediately, however, after the magnet was removed. Reproduced with permission [83]. Copyright 2018, Adv. Mater.

microelectrodes array has the similar elastic modulus as neural tissue, low impedance and biocompatibility. Through implanting liquid metal electrodes on the sural and tibial nerves of the bullfrog (Fig. 3b) and applying electrical stimulation, the dead bullfrog's hind limbs were found to flex under electrical stimulation (Fig. 3c) [80].

For complex and dynamic biological systems, soft electrode materials can't meet all functional requirements [81]. More ideally, the Young's modulus of the electrode materials can be freely tuned, and they can be adapted to the mechanical requirements of corresponding biological tissues while achieving functionalization. Stimuli-responsive materials are a class of materials with "smart" behavior that can produce corresponding response signals to the external environment, such as magnetism, light, heat, humidity, etc [82]. Ren et al. [83] utilized the principle of magnetic response to prepare liquid metal based on magnetic response. This liquid metal magnetically responsive material was synthesized through dispersion of magnetic Fe (iron) particles in a Ga-In-Sn liquid metal. When iron particles contact with a Ga-based liquid metal, Ga atoms would diffuse into the iron. An alloy layer was slowly formed at the solid-liquid interface at room temperature, so that the solid iron particles were well combined into the liquid matrix. Due to the excellent liquid flow properties of liquid metal at room temperature, the iron particles moved freely inside the liquid metal and affected the viscosity of the fluid, forming a series of liquid-metal-based magnetoactive slurries (LMMS). The preparation process is shown in Fig. 3d. Under magnetic field stimulation, the mechanical performance and viscosity of LMMS are quickly and reversibly changed and be finely controlled in a wide range, as shown in Fig. 3e. The Young's modulus of LMMS was adjusted within 1000 times of the Young's modulus from KPa to MPa, even reaching GPa, through controlling the strength of magnetic field and content of iron particle. And the current response was clearly recorded *via* inserting the electrode into the bioelectrolyte and applying the stimulation voltage, confirming the high electrical conductivity of the LM matrix. Furthermore, the resistance measurement results by the four-probe method proved that the transition from rigid to soft LMMS electrodes had little effect on the electrical conductivity of the prepared electrodes. In summary, the LMMS electrode can be used as a soft implantable electrode or a penetrating electrode in biological systems, which not only overcomes the difficulty of flexible electrode implantation, but also provides a new mechanical adaptive biological electrode system for multi-function implanted electrode in biological system [83].

2.2.2. CP hydrogels

CPs have the potential to promote better tissue integration *via* immobilizing biomolecules on their surfaces or releasing drugs from their matrix through electrochemical conversion [84]. However, the CP coating has a poor mechanical stability, and is prone to problems such as peeling and breaking [85]. Based on this, CP hydrogels (CPHs) form a substance network composed of CPs in the hydrogel matrix, where the hydrogel component provides a highly hydrophilic porous network, and the CPs are filled to increase its electrical conductivity. Moreover, due to the soft structure of the hydrogel, the mechanical mismatch between the tissue and the electrode can be reduced, and the originally fragile CP can be stabilized to extend the service life [86,87]. Therefore, in order to obtain the full benefits of the combination of CP and hydrogel, the two polymer systems should be truly integrated to form an interpenetrating network (IPN). However, forming a true IPN also faces challenges, the most important of which is how to achieve good miscibility between CP and hydrogel. The efficient miscibility of the two is reflected in two aspects: (1) the hydrogel is a highly hydrophilic system, but CP is hydrophilic or hydrophobic depending on the composition. The two components can be better mixed by adjusting the hydrophilicity and hydrophobicity of CP [88]; (2) the hydrogel as a porous network structure provides channels and convenience for the integration of CP, but on the other hand, the large mesh of the hydrogel will cause CP to migrate out of it. Then, the CP layer is formed on the surface or bottom of the hydrogel, so controlling the pore size of the hydrogel is also a key factor in achieving miscibility. Therefore, in order to constitute IPN, researchers have made various attempts [89]. Kleber et al. [89] attached the dopant sodium 4-styrene sulfonate (SSNa) to the hydrogel backbone, forcing PEDOT to grow along the hydrogel network, realizing the true integration of CP and hydrogel, forming an IPN composed of synthetic hydrogel (P (DMAA-co-5% MABP-co-2, 5% SSNa)) and PEDOT. The hydrogel composite not only formed a covalent connection with a surface electrode to achieve stable adhesion, but also modified the positions of selected electrode *via* photolithographic process. Compared with bare hydrogel, the CPH had higher CSC, lower impedance, excellent electrochemical stability and good biocompatibility [90]. Goding et al. [91] covalently linked sulfonate-doped groups to polyvinyl alcohol (PVA) macromolecules, and controlled the growth of PEDOT by changing the spacing and density of dopant in the hydrogel grid. Finally, they constituted a new type of CPH system. The study found that the smaller the distance between dopants, the larger the CSC of the CPH and the lower the impedance, which are the key factors for the formation of IPN.

In CPH, in addition to the synthetic hydrogels mentioned above, natural polymer hydrogels, such as chitosan (CS) [92], sodium alginate (SA) [93], etc., have good biocompatibility, large surface area and porous structure, which are conducive to cell adhesion and proliferation. Sun et al. [94] prepared a myo-inositol hexakisphosphate gelated polyaniline (PANI) hydrogel with good cell compatibility, which enhanced neural cell adhesion and increase cell proliferation rate. In the implantation experiment, the PANI hydrogel modified electrode had a milder inflammatory response, and had a wide application prospect in the field of medical electronics. Wang et al. [95] uniformly dispersed the PEDOT:PSS-coated CNT solution into the alginate solution, and formed a hydrogel IPN on the IFNE through electrochemical deposition. The CPH had higher CSC and lower electrochemical impedance, which are helpful for stimulation and recording performance.

2.2.3. CPs

Microelectrodes have been widely used in the detection and regulation of neural networks, and various materials have been widely applied in the preparation of microelectrodes. Among them, CPs are one of the hot topics in current research. CPs have high electrical conductivity, high specific surface area, and good environmental stability. In addition, the properties of CPs vary greatly with different materials, and in particular, the adjustment of electrical performance from insulator to conductor can be achieved. The use of CPs to increase the specific surface area at the electrode-tissue interface reduces the impedance of the electrode site, thereby enhancing the signal strength of the IFNE when recording or stimulating, which is an ideal implantable IFNE coating [96]. At present, more CPs have been studied, such as polypyrrole (PPy), PANI and PEDOT and these CPs are further functionalized *via* doping different materials [97–99].

2.2.3.1. PPy. PPy has the advantages of high stability, high electrical conductivity and wide variation range, diverse synthetic methods and good biocompatibility [100]. It has broad application prospects, so it has attracted widespread attentions from researchers. Qi et al. [101] successfully polymerized a patterned PPy conductive film *via* electrochemical polymerization, and further synthesized PPy NWs. PPy NWs were used to enhance the adhesion between PPy film and stretchable substrate (PDMS), and a stretchable polymer material with 100% tensile strain and good electrode-substrate adhesion (1.9 MPa) was prepared. A series of high tensile electrodes with enhanced substrate adhesion are shown in Fig. 4a. In addition, microelectrode arrays (MEAs) with low Young's modulus (450 KPa), good cycling stability and high electrical conductivity up to 820 S/cm were achieved. In addition, the researchers employed PPy MEAs to record electrical signals from normal and epilepsy rats, and successfully stimulated the sciatic nerve of rats *in-vivo* under the high CSC of PPy MEAs (67 mC/cm^2) [101].

Although PPy has good biocompatibility as a coating material, after

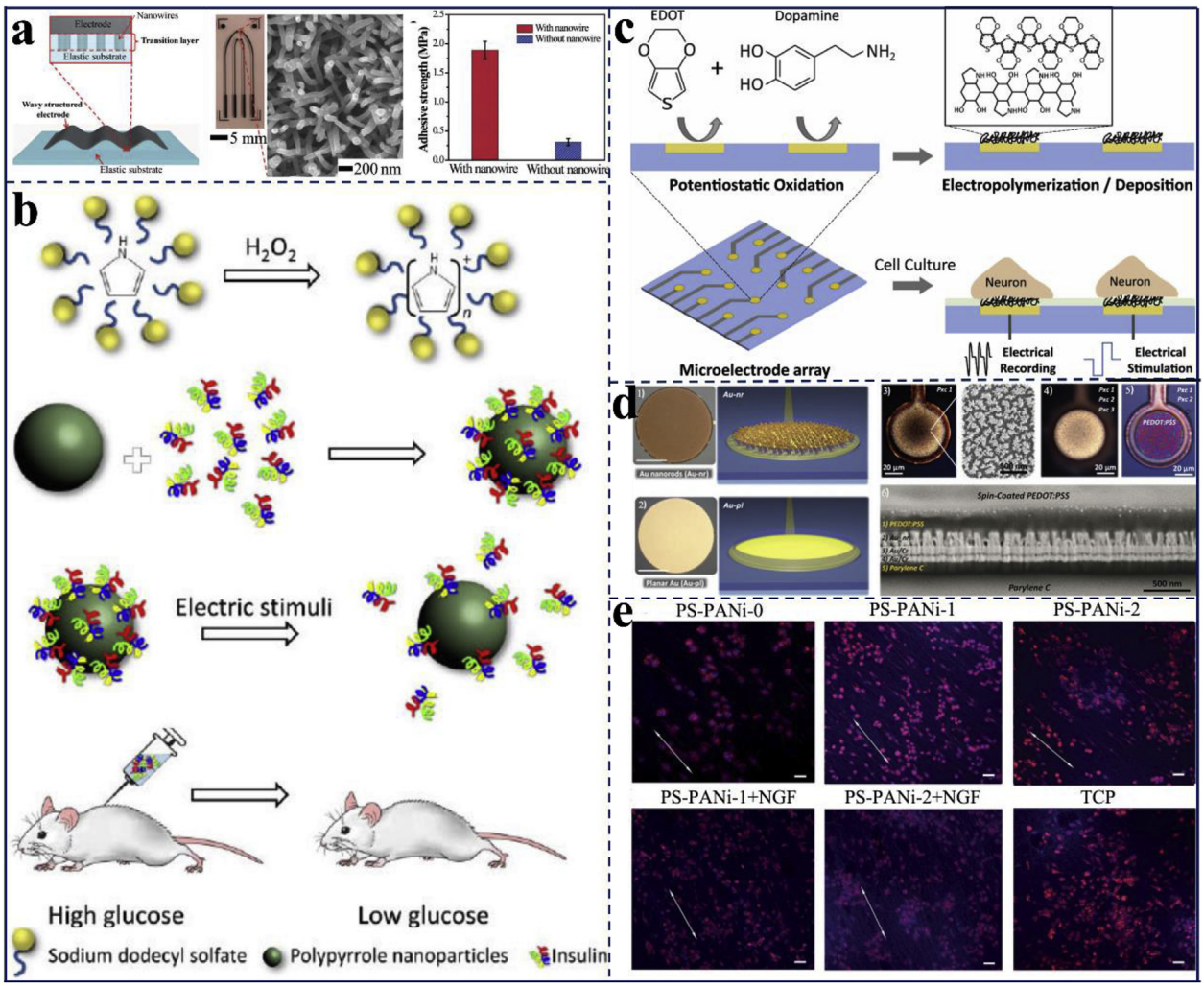

Fig. 4. The role of CPs in nerve stimulation, drug delivery, and biocompatibility, as well as reliable solutions to improve the stability between metal electrodes and CPs. (a) A drawing of the inspired highly stretchable electrode with enhanced substrate adhesion. Here, the wavy structures provide stretchability, and transition layer (nanowire and substrate materials) enhanced the adhesion between the electrode and substrate (left). Optical images of the multielectrode array on ITO glass and scanning electron microscopy (SEM) image of the PPy NWs synthesized on the PPy electrode surface (middle). And adhesion comparison of the PPy films with NWs modification and without NWs modification (right), reproduced with permission [101]. Copyright 2017, Adv. Mater. (b) Schematic representation of INS delivery using PPy NPs, reproduced with permission [104]. Copyright 2017, Nanoscale. (c) Schematic illustration of PEDOT/PDA deposited microelectrodes, reproduced with permission [111]. Copyright 2019, J. Neurosci. Methods. (d) 1) and 2) Au NRs versus Au planar (PL) electrodes. Top-view optical image and corresponding cross-sectional schematic of Au-NR and Au-PL macroelectrodes with a diameter of 500 μm (scale bar, 200 μm), 3) Au-NR adhesion layer definition on sensing site (adjacent top-view SEM image shows morphology of the nanostructures of Au-NR film), 4) selective etching of the parylene C layers on top of the metal contact, and 5) deposition of the PEDOT: PSS layer using spin-coating/peeling-off technique, 6) tilted-view SEM image showing the cross-section of the stacked layers highlighting the intimate contact between different layers of the device, and sandwiched in between the parylene C and PEDOT: PSS films are the only electrochemical interfaces, reproduced with permission [114]. Copyright 2018, Adv. Healthcare Mater. (e) Representative confocal laser micrograph images of Schwann cells cultured on the aligned electrospun PS/PANi fibers with and without NGF loading at day-5 (scale bar, 10 mm) and TCPs were used as control, reproduced with permission [121]. Copyright 2014, J. Mater. Chem. B.

implantation of the whole nerve electrode, foreign body reactions will inevitably occur in long-term records. Electrochemical reduction of polymer *via* voltage pulse and release of loaded anti-inflammatory drugs is a more useful solution [102]. Kojabad et al. [103] loaded PPy nanotubes with anti-inflammatory biological factor dexamethasone (Dex) to eliminate the unwanted immune rejection and maintain the quality and stability of signal transmission as much as possible, and proved that PPy nanotubes can achieve a drug encapsulation rate of 93%. Then, Au nanoparticles (NPs) were synthesized *via* anodic electrophoretic deposition (EPD) method on the surface of PPy nanotubes. The modification of Au NPs can effectively increase the specific surface area of PPy nanotubes. The impedance of the modified microelectrode decreased to one tenth of that of the bare electrode. *In-vitro* studies on U87MG cells showed that the release of Dex from the coating controlled by electrical stimulation could effectively decrease the number of reactive astrocytes without any toxic side effects on SK-NMC and PC12 neuron cells [103]. At present, some small molecule drugs such as Dex mentioned above have been successfully released from CP films, however, releasing large molecule drugs such as peptides and nucleic acids is still a major challenge. Niloufar et al. [104] proposed that CP nanoskeleton could be used to control the release of high-molecular-weight peptides, such as insulin (INS). By means of changing the ratio of the number of NPs to the amount of INS, an estimated drug loading rate of up to 51 wt% was obtained. The schematic representation of INS delivery using PPy NPs is demonstrated in Fig. 4b. *In-vivo* experiment results in mice confirmed that INS released after electrical stimulation was still biologically active. It provided a passing model for the development of other polymer drugs delivery [104].

2.2.3.2. PEDOT. In recent years, PEDOT is one of the most commonly used nerve interface CPs. The performances of CPs vary greatly with the composition of the materials. The current common combination types are PEDOT: sodium polystyrene sulfonate (PSS) [105], PEDOT: *p*-toluenesulfonate (pTS) [106], PEDOT: CNT [107], and PEDOT: graphene oxide (GO) [108], etc. The main role of doping is to obtain the improved electrical conductivity. What's more, Mandal et al. [109] indicated that the PEDOT coatings obtained with the smaller counter ion tetrafluoroborate (TFB) were more stable *in-vitro* than the commonly used counter ion PSS during electrodeposition. Charkhkar et al. [110] further studied the long-term performance of PEDOT-coated microelectrodes in vivo, compared with the Au-plated microelectrodes, the PEDOT -TFB-coated microelectrodes exhibited lower impedance and higher unit charge numbers of the electrodes. The electrode coating had greater application potential. Furthermore, polydopamine (PDA), a biomolecule inspired through mussels, provides unique chemical and mechanical properties to biological interfaces and is a promising material for neuron interface manufacturing. Kim et al. [111] obtained a PEDOT/PDA film *via* electrochemical polymerization, and obtained CSCs as high as 166 ± 51.8 mC/cm^2 and CILs as high as 5.97 ± 0.28 mC/cm^2 (mean ± standard deviation, n = 5). Therefore, PEDOT/PDA microelectrodes will provide highly stable electrical stimulation. The schematic illustration of PEDOT/PDA deposited microelectrodes is shown in Fig. 4c [111]. Wang et al. [112] prepared a neural electrode based on reduced GO (rGO) and PEDOT: PSS. This composite neural electrode had low impedance, high CSC and high signal-to-noise ratio (SNR) advantage. It is worth mentioning that the composite film deposited on the microelectrode will contain L-ascorbic acid (LAA) component, which was slowly released after implantation and improved neural activity [112]. In addition to the partially doped substances described above, there are more and more materials doped with PEDOT to obtain improved performance.

Although PEDOT has many advantages, the problem of poor adhesion of CPs to metal electrodes is still a major challenge in specific applications. Pranti et al. [113] utilized selective iodine etching of the Au electrode to produce a rough and porous surface, thereby improving the stability. Compared with an unetched electrode, the coating on an iodine-etched Au electrode showed 100% stability under a strong ultrasonic stability test. A long-term continuous *in-vitro* stimulation was performed for 7 days to evaluate the stability of the coating. The 1 μm-thick PEDOT: PSS coating on the iodine-etched Au electrode was completely retained under 604 million continuous current pulses [113]. Additionally, Ganji et al. [114] formed an alloy *via* co-depositing Au–Ag and then formed Au nanorods (NRs) with the help of a dealloying method to improve the mechanical stability between the metal electrode and the PEDOT: PSS coating (Fig. 4d). Compared with the PEDOT: PSS film on the flat Au electrode, the Au-NR adhesion layer allowed the coated PEDOT: PSS film to show no delamination after 10,000 cyclic voltammetry (CV) cycles and didn't significantly change the electrochemical impedance [114].

Aside from improving electrical conductivity, biomolecules sometimes are employed as the dopants of CPs. For example, peptide drugs can induce strong interactions between neurons and electrodes [84]. Extracellular matrix (ECM) proteins [115] or nerve growth factors (NGF) [116] promote the growth of neurites. Dex can reduce the inflammation of biological tissues. The release of these drugs or macromolecular substances will undoubtedly make CPs coated electrodes not only enhance the detection and conduction of neural electrical signals, but also have anti-immunity, promoting nerve growth and rehabilitation functions. Boehler et al. [117] synthesized a CP coating PEDOT/Dex and applied a CV signal with a three-electrode configuration in fully awake animals. Dex-functionalized probes not only provided stable records and impedance characteristics, and the overall degree of inflammation around all flexible probes was low after 12 weeks of implantation. The pharmacological regulation of tissue response in the acute inflammatory phase alone is not enough. Continuous delivery technology with actively controlled release is needed to address the chronic immune response.

2.2.3.3. PANI. PANI has some outstanding characteristics, such as facile synthesis, low cost, high thermal stability, excellent redox sensitivity, excellent electrical conductivity and excellent electrical stimulation function [118]. Recently, Wang et al. [119] found that a complete CP coating can play a better role than a broken CP coating, however, once the coating is broken, it would cause inflammation, cytotoxicity, and then blocked nerve regeneration. Therefore, maintaining the integrity of the CP coating can greatly avoid these risks.

Electrical stimulation can effectively promote nerve growth and functional recovery, and CP coating helps IFNEs to achieve more efficient electrical stimulation. Wang et al. [120] studied the effect of PANI on PC12 cells under electrical stimulation by applying a PANI coating on the surface of indium tin oxide (ITO) conductive glass. They confirmed that PANI coating is non-toxic to PC 12 cells, and electrical stimulation promoted the growth of PC12 cell axons effectively. Because nerve factors can further promote the growth of axons, Zhang et al. [121] doped NGF in the preparation of CP coating, which constituted the blend system of PANI and poly (L-lactic acid-*co*-3-caprolactone)/silk fibroin (PS) and NGF. They investigated the morphology of Schwann cells on aligned nanofibers after 5 days of incubation. The representative confocal laser micrographs of Schwann cells on the scaffolds and tissue culture plates (TCPs) show that the Schwann cells spread well on the nanofibers (Fig. 4e). The studies found that the electrical stimulation can increase NGF release, and effectively support the growth of PC12 neurites, increasing the percentage of neurite-bearing cells as well as the median neurite length. It is confirmed that NGF release and electrical stimulation have a synergistic effect on PC12 cell differentiation. It is demonstrated that the electronically controlled drug delivery system has the implementation basis and application value [121]. In addition to promoting cell growth, electrical stimulation provides new ideas for the treatment and research of cancer or tumor cells. Min et al. [122] found that the degree of sulfonation (DS) is helpful to increase the electrical conductivity of PANI, and proposed the use of self-doped sulfonated PANI (SPAN)-based interdigital electrodes (IDEs). Using an electric field exceeding a threshold limit to stimulate human osteosarcoma (HOS) cells accelerated the cell death.

2.3. Materials for encapsulation and modifications

At present, the limited functional life of IFNEs is due to the failure of dielectric (insulation) packaging to a certain extent, so for IFNEs to achieve high stability and good biocompatibility, it is usually necessary to encapsulate it before implantation. Packaging materials can prevent water vapor or ions from permeating the components or structures in the device, providing mechanical, chemical and biological protection for devices, and isolate the heat and optics [123]. Among them, organic polymer materials have been widely used in IFNEs due to their advantages of flexibility, low permeability, excellent insulation and biocompatibility. The common materials include parylene C, PI and silicone rubber. The adaptability of these materials to the micromachining process and the conformal deposition on the complex microstructures promote their applications in the neural interface [124]. In addition, the physiological environment is basically considered as an aqueous solution/hydrosol environment, in which the medium is water, so the hydrophilicity/hydrophobicity of the material has a greater impact on the adhesion of cells on the surface of the material. The results showed that the hydrophilicity of the material can promote the cell adhesion to some extent. For different kinds of cells, the suitable surface for cell adhesion and growth has the best hydrophilic/hydrophobic balance (HLB). Therefore, researchers usually used the acid-base treatment, oxygen plasma treatment, ion implantation and other methods to modify the surface of parylene C, PI, PDMS and other organic polymer films [125,126]. In addition to the above, Bao et al. [127] used perfluoropolyether dimethacrylate (PFPE-DMA) as the packaging material of IFNEs, and the Young's modulus of PFPE-DMA is 2–6 orders of magnitude lower than those of PDMS and PI.

In addition to the organic polymer films mentioned above, in recent years, some biomolecular materials with better biocompatibility have been used for surface modification of IFNEs. PDA is a kind of bionic mussel material, which can be self-polymerized by dopamine (DA) in weak alkaline environment. PDA has many advantages, such as facile preparation process, good biocompatibility and excellent photothermal performance. There are a lot of catechol and amino groups in the structure of PDA, which make PDA adsorb on the surface of almost all solid substances and form a layer of PDA film, can be used as a buffer layer of flexible electronic devices, instead of the physical adhesion of traditional technology [75]. PDA has great application prospect in IFNEs [128]. However, the traditional PDA's bionic film formation speed is slow, the modification process of electrode material is complex and the adhesion performance with the substrate is generally low. In order to solve the above contradictions, Huang et al. [129] innovatively proposed that the addition of nano-titanium dioxide (nano-TiO_2) greatly accelerated the formation of a bionic PDA adhesive film, which is used as a conductive adhesive layer, and then the excellent electrical performance of the electrode is obtained through modified Pt NWs. What's more, ECM can also be used as a coating material in IFNEs, which has the effect of alleviating inflammation and supporting neurons survival [115].

This section mainly introduces some functional materials other than the commonly used materials of traditional IFNEs, such as degradable materials, stretchable materials, SMP, liquid metal materials, CPs, etc. In addition to satisfying the basic functions of each component of the electrode, they also have special functions and outstanding advantages in some specific applications. Therefore, in preparing IFNEs, the choice of materials is purposeful and flexible, and the materials should be conducted according to the specific application of the device.

3. New structures of flexible nerve electrode

3.1. 2D/3d integrated neural electrodes

The structures of conventional IFNEs are mainly divided into 2D electrodes and 3D penetrating electrodes. Among them, the 2D electrodes are mainly ECoG arrays, which are less invasive and will cause weak foreign body reactions, allowing long-term recording (weeks to months), but at the cost of lower signal resolution [130]. The 3D electrodes tend to record with high fidelity, but the invasiveness of the 3D structure greatly damages the integrity of the neuronal cell membrane and neural network, and then triggers a strong immune rejection. The movement will further trigger inflammation, which in turn will form an insulating sheath around the electrodes, resulting in equipment insulation and failure. For neuroelectric signal recording, neuron adhesion and firm contact with the recording site are the prerequisites for long-term sustainable recording, so the 3D penetrating electrode can only perform signal detection within a short time (hours to days) [9].

To solve the above problems, combining 2D and 3D will be an effective way. Xiang et al. [131] used a new drawing lithography technology to prepare a 3D flexible microneedle electrode. Due to the sufficient stiffness of the electrode and the excellent flexibility of the mesh base, the electrode could penetrate the tissue and make the bottom layer completely coincide with the curved brain surface. The unique feature of this electrode is that the length of the 3D microneedle electrode could be changed from 400 μm to 3 mm through the design of the 2D mask pattern to achieve the purpose of accessing different functional layers in the brain. The results of in vivo tests conducted on rats shown that the flexible microneedle electrodes can be successfully implanted in the brain with curved surfaces and record nerve signals. Similarly, Wang et al. [132] prepared a novel spiked ultraflexible neural (SUN) interface by the same way, which was implanted in the PNS to capture sensory information from these mechanoreceptors in acute rat experiments.

In addition to this a long-term and high-resolution signal record can be obtained if the 2D electrode and the 3D penetrating electrode be organically combined. Therefore, the organic combination of 2D and 3D structures in the design and preparation of neural electrodes will also be an attractive innovation in the development of neural electrode structures. To effectively combine 2D and 3D electrodes, Goshi et al. [133] proposed a MEA for neural electrical signal recording. The array integrated glassy carbon-based MEA into a single flexible thin-film device. The origami effect is achieved *via* changing the thickness and mechanical strength of the PI film of 2D electrode and 3D penetrating electrode (Fig. 5a). When the device is spread, the pre-shaped PI handle fell off from the substrate automatically and formed the penetrating part of the device in 3D penetrating electrode, to realize the purpose of simultaneous recording of electricity physiological signals from the brain surface (ECoG) and single neuron. It is initially confirmed that the 2D and 3D electrodes showed the similar trends in the signal waveforms for spontaneous and stimulated activities, *via* recording the typical somatosensory evoked potential (beard deflection) in rats [133].

The structural integration of 2D electrode and 3D electrode mentioned above will achieve simultaneous long-term and high-fidelity recording while achieving simultaneous testing in the surface (cortical) and depth (intracortical), but the foreign body reactions caused by the 3D penetration electrode are still a major challenge for further long-term records [134]. To make long-term high-fidelity signal recording without destroying brain tissue and neuron cells as much as possible, Wijdenes et al. [135] are inspired by the morphology of synaptic gaps to propose a new research strategy, namely nano-edge technology. The nano-edge forms a nano-scale "fortress" at the edge of the electrode site. This structure is expected to prevent current from leaking into the surrounding extracellular environment, thereby retaining and enhancing the functional integrity of chemical and electrical neuron signal processing. By simulating a 2D microelectrode with nano-edges using COMSOL, the simulation results showed that the change in sealing resistance is the determinant behind the higher electrical amplitude signal compared with the traditional planar Au MEA. The neuron diameter is the determinant of the sealing resistance value, that is, when the diameter of neuron is greater than or equal to the diameter of electrode site, since the neuron completely covered the electrode, the current leakage between the neuron and the electrode gap decreased, and the sealing resistance value increased significantly. Therefore, Wijdenes et al. [135] added a 5–15 nm nano-edge to the original electrode and controlled the neuron diameter above the diameter of electrode, the sealing resistance remained approximately the same and is 6–7 times of the sealing resistance value without the nano-edge structure. In addition, the coupling coefficients between a 2D electrode with a nano-edge and a neuron are 0.15, 15 times of a conventional planar electrode and a resistance electrode, respectively, better than those of most 3D electrodes (0.1–0.3). The resolution of recording neural activity is significantly higher than those of any conventional 2D electrodes. This will be the reason for achieving high-fidelity recording. The introduction of nano-edge technology fills a huge technical gap and provides a breakthrough in the field of neural recording *via* combining the advantages of 2D electrode and 3D electrode. It is possible to maintain long-term (>1 month) high-fidelity records by maintaining stable records for an extended period of time (several weeks to months), providing a new research direction for future studies of long-term high-fidelity records [135].

3.2. Injectable flexible mesh nerve electrode

Implantable electrode array has made significant advances in neuroscience, brain-computer interface (BCI) and treatment of neurological diseases [136]. Ideally, implantable electrodes array is able to record a large number of neurons from multiple local circuits, however throughout the research, it is also important to track the evolution of these neurons in a stable manner [137]. Micromachined silicon-based probes such as the Utah electrode and the Michigan electrode can perform large-scale high-density recording, but due to its mismatch with the brain's machinery and structure, it will cause a chronic immune

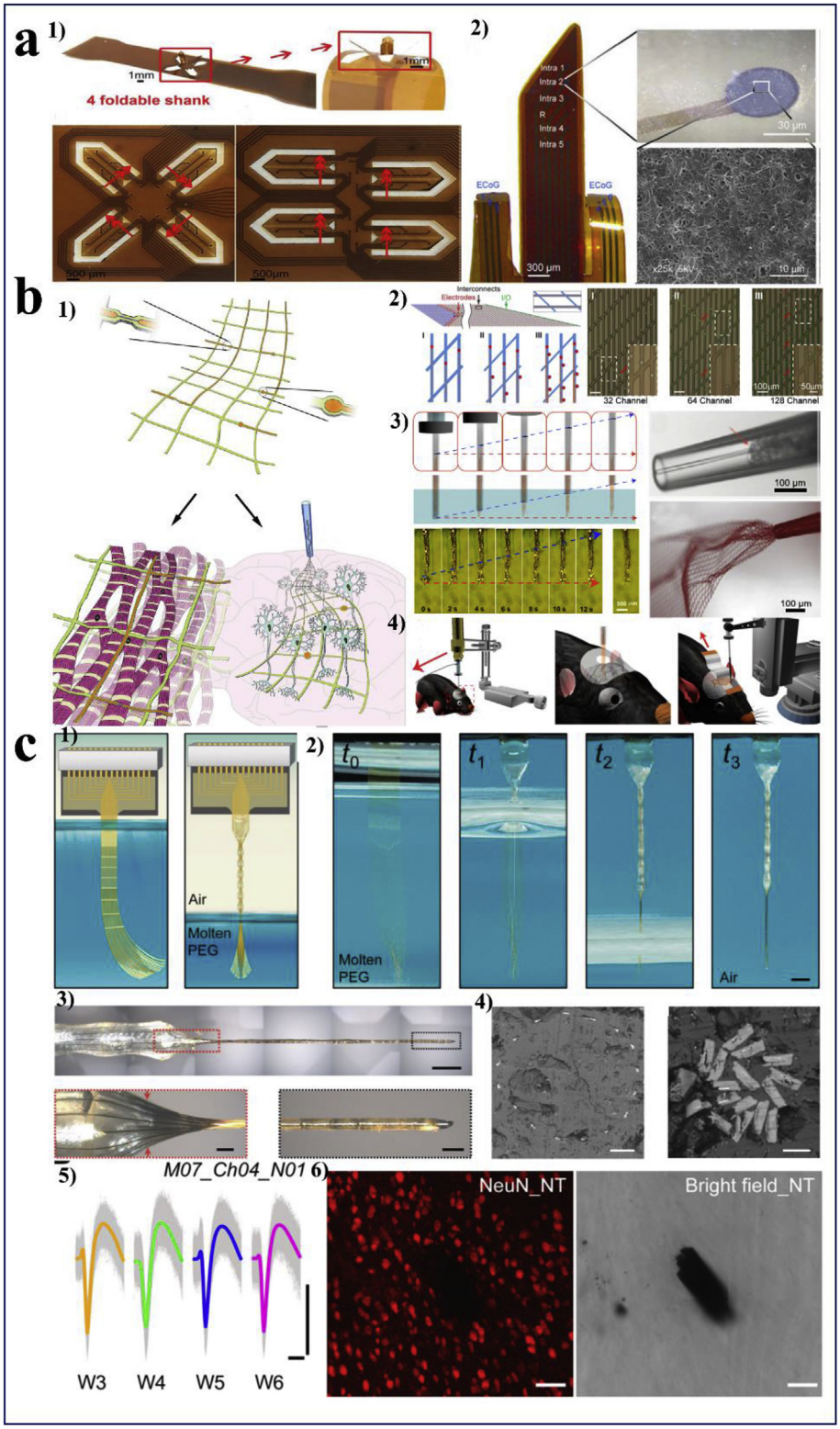

Fig. 5. New structures of INEs. (a) Origami MEMS portfolio. 1) four-shanks origami probes and the magnifications of two possible probe designs, 2) magnification of Epi-Intra Device and PEDOT-PSS-CNT coated microelectrodes, and the SEM image of the PEDOT-PSS-CNT, reproduced with permission [133]. Copyright 2018, J. Micromech. Microeng. (b) Injectable flexible mesh nerve electrode. 1) seamless integration of mesh nanoelectronics with synthetic tissues and live animals, reproduced with permission [141]. Copyright 2018, Acc. Chem. Res. 2) high-density multiplexed mesh electronics *via* standard photolithography, reproduced with permission [144]. Copyright 2017, Proc. Natl. Acad. Sci. 3) schematics illustrating controlled injection by the FoV method; The bottom series of images recorded at same time points shows the same injection process of an independent mesh structure obtained at the end of the mesh electronics in the gel, reproduced with permission [143]. Copyright 2015, Nano. Lett. The right is the bright-field image showing partially ejected mesh nanoelectronics through a glass needle, exhibiting significant expansion and unfolding of the mesh, reproduced with permission [141]. Copyright 2018, Acc. Chem. Res. 4) schematic of injection and automatic conductive ink printing methods, reproduced with permission [143]. Copyright 2015, Nano. Lett. (c) Flexible neurotassels electrode. 1–2) the self-assembly process of flexible neurotassels electrode, 3) flexible neurotassels electrode after assembly, 4) electrode section diagram, 5) a long-term, stable recording of *in-vivo* nerve signals, 6) the compatible interface between flexible neurotassels electrode and brain tissue, reproduced with permission [148]. Copyright 2019, Sci. Adv.

response to glial scarring, which depletes peripheral neuron cells, eventually causing signal attenuation in a short time [138,139]. Therefore, when the implanted neural electrode array is matched with the brain's machinery and structure, the electrode will be stably recorded in the brain environment for a long time. Neurons in the brain are interconnected with each other to form a neuron network with pores to ensure that protein molecules and fluids can pass through smoothly. Therefore, Charles et al. believed that the IFNE should also be a flexible cross grid, leaving holes for the attachment of neuron cells, rather than squeezing the neuron cells around with a boxy solid electrode. Therefore, they invented an IFNE with a super-flexible mesh structure, and the schematic diagram of seamless integration of mesh nanoelectronics with synthetic tissues and live animals is shown in Fig. 5b (1) [140,141]. A micro-sensor is used to inject it into the brain through a needle, achieving target

delivery with a spatial accuracy of 20 μm. With the expansion of this mesh, the mesh nerve electrode was softly attached to the surface of the dura mater. After injection into the brain, the impedance change of the flexible mesh nerve electrode is less than 7%, indicating that the flexible mesh nerve electrode had a higher performance. The stability of the needle injection method had a higher reliability [142]. Subsequently, the automatic conductive ink printing method was used to connect the mesh nerve electrode and the flexible flat cable to achieve a multi-channel I/O connection of up to 100%, as shown in Fig. 5b (4) [143]. The mesh structure designed by the research team consists of horizontal and vertical filaments at a certain angle. This structure facilitated the flexible mesh electrode to bend laterally to form a cylindrical structure that was filled into a syringe [141]. Because it's difficult to see what happens to the mesh nerve electrodes in the brain during an injection, they devised a general method based on visualization and real-time tracking of the upper I/O end of the mesh electronics in the field of view (FoV) of an eyepiece camera. The schematic of FoV and the bright-field images of a mesh nanoelectronics jet through a glass needle is shown in Fig. 5b (3). What's more, with the advancement of micromachining technology, the number and density of channels of a single grid probe are significantly increased through the implementation of a scalable solution, realizing 32 or 128 channels, as shown in Fig. 5b (2) [144]. The immune response between the injectable flexible grid nerve electrode and the brain tissue is studied and compared with the traditional flexible thin film probe, and the results showed that after the mesh electron probe in a short period of time, the inflammation and damage of the surrounding neurons are much smaller. Three months after implantation, the tissue interface is uniform, and neurons and nerve wires penetrated through the mesh structure, which did not adversely affect the natural distribution of neurons for a long time [145].

The minimal immune response achieved by the ultra-flexible open mesh electrodes and seamless interface with brain tissue after implantation has great advantages, and will provide extensive opportunities for long-term recording and regulation of brain activity in the body in future. However, due to the super softness of the flexible mesh structure, there will be wrinkles or entanglements in the injection device, which will cause the electrode recording to have a certain gap from the expected effect. Therefore, the mesh structure needs to be further optimized.

3.3. Flexible neurotassels electrode

The brain transmits, transforms, and integrates information through the electrical activity of neuronal cells, and then completes various functions. Neurons in the brain have the characteristics of small size, high density, and large numbers. The number of neurons in the human brain exceeds 1.0×10^{11} [1]. Therefore, the more information about the electrical activity of the neurons can be recorded through the implanted neural electrodes, and it is helpful for us to further understand the working mechanism of the brain and the pathogenesis of brain diseases. At present, Neuropixels technology, which is a "probe" for recording neuronal discharges in living animal brains, has been entered into commercialization [146,147]. Each probe has hundreds of electrodes and can simultaneously record hundreds of neuron discharges in the brain. However, because the silicon is a rigid material, it is very easy to cause immune rejection after implantation, and it is difficult to record the EEG signal with long-term stability. However, a flexible nerve probe adapted to the mechanical strength of the brain tissue can reduce the friction between the tissue and the electrodes, and can further improve the stability of the neural interface. However, one of the advantages of flexible probes is the "flexibility" which makes it difficult to implant the probe.

The emergence of flexible neurotassels electrode has brought new ideas to solve the above problems. Flexible neurotassels electrode was composed of thousands of ultra-fine flexible fibers with a cross-sectional area reaching the size of neuron axons ($3 \times 1.5\ \mu m^2$), which was an order of magnitude smaller than the current minimum reported internationally. The flexible neurotassels electrode was prepared into a planar mesh structure using micro-nano processing technology. The design of the planar mesh guaranteed the structural integrity of the neurotassels, and the filaments was arranged in a radial shape in the course of elastic deformation. Then, through rational design, the neurotassels were immersed in the molten PEG liquid, as shown in Fig. 5c 1–2). Under the action of the surface tension of the liquid, thousands of flexible neurotassels were self-assembled to form high-density INE/PEG composite filaments, as shown in Fig. 5c 3–4). This greatly decreased the damage to the brain tissue caused by electrodes during surgical implantation. PEG was degraded and metabolized in the brain, and the ultra-fine flexible nerve fiber electrodes released could accurately *in-situ* measure the electrical activities of multiple neurons in the medial prefrontal cortex. It was particularly important that the flexible neurotassels matched the mechanical properties of the brain tissue, thus forming a well-compatible interface, thereby achieving a long-term stable recording of the electrical activity of neurons in the living brain, as shown in Fig. 5c 5–6). And in the task of learning olfactory working memory in mice, neurotassels recorded the same neurons more steady than traditional microfilament electrodes. This allowed us to get more details about the changes in neuron firing characteristics of mice as their academic performance increased, and help us more easily discover the neural mechanisms involved in animals' cognitive processes [148].

3.4. Flexible NeuroGrid with wide-range recording

NeuroGrid is a neural electrode array based on a flexible organic material substrate. It has the advantages of super integration, biocompatibility, scalability, and ultra-high spatial resolution. It can record action potentials from the surface of the brain [149]. NeuroGrid contains 256 electrodes with an area of 10 μm × 10 μm (matching the size of the neurons) and a pitch of 30 μm [150]. At the electrode position, high-frequency signals (>500 Hz) were recorded using a low-resistance material PEDOT: PSS with high spatial resolution as the interface material. Structurally, NeuroGrid uses a grid-like structure design. Although the elastic substrate undergoes bending deformation, the inorganic conductive material embedded in the device doesn't fail, so it has good adhesion and ductility. The highly malleable NeuroGrid allows it to cover the somatosensory cortex of the rat brain. Based on the above characteristics, NeuroGrid can record the release of typical intermediate neurons and pyramidal neurons, and the time for stable recording of action potentials exceeds 1 week. Ultimately, NeuroGrid can also be used for epilepsy patients and language function positioning tasks during surgery. NeuroGrid has the following innovative features: it can obtain stable field potential and action potential signals without penetration, conformal contact with the brain, and the efficient abiotic/biological interface facilitates the high signal-to-noise ratio of the signal. Then the acquisition, the high ductility and the diversity of structural design, as well as the electrode density that matches the neuron, facilitate the separation of neuron action potentials [151].

As a result, NeuroGrid has the innovative characteristics such as stable field and action potential signals without penetration, conformal contact with the brain, high ductility, and a neuron-matched electrode density that is separate from the action potential of a single neuron. It is beneficial to enhance the understanding of neural processes across spatiotemporal scales and promote the diagnosis and treatment of brain diseases.

This section mainly introduces four new structures of IFNEs. Among them, in the measurement process of neuroelectric signal, the 2D/3D integrated neuroelectrode can realize the measurement of different dimensions, making the measurement more accurate. In addition, a huge challenge for current neuroelectric signal research is to record the activity of a large number of neurons at the same time, and to achieve high-resolution measurement of the neural activity of a single cell. Therefore, the design and preparation of small-sized, minimally invasive, high-density nerve electrodes is a current research trend. Therefore, in recent years, injectable flexible mesh nerve electrodes, flexible nerve

tassel electrodes and nerve grid electrodes emerged. These electrodes have their unique structure and demonstrate their advantages in achieving simultaneous recording of a large number of neuronal activities. In addition, new research directions are proposed in terms of implantation methods and multi-density integration, which provide a solid research foundation for subsequent research.

4. Applications

At present, IFNEs have extensive applications in the medical field. An important function of IFNEs is to make up for some of the human body's loss of function, so that the patients with neurological deficits can recover a certain ability of movement and perception. In addition, the emergence of IFNEs has also overcome the mechanical mismatch between rigid electrodes such as Utah electrodes and Michigan electrodes and soft biological tissues, and can achieve long-term, stable applications. In this chapter, the applications of IFNEs in neural prosthesis and neural signal recording are summarized and prospected. Fig. 6 shows the current and potential applications of a series of IFNEs [67,152–158].

4.1. Neural prosthesis

The brain contains hundreds of billions of neuron cells that control human behavior, thinking, and feeling. Taking human sense organs, such as eyes and ears, as examples, these sensory systems determine whether people can perceive the world. However, these systems sometimes fail, which is why the presence of neural prosthesis is important. Neural prosthesis is a class of electronic devices that can help restore nerve function. Common neural prosthesis often use artificial electrical stimulation to replace nerve impulses emitted by the brain, to control muscle activity [159–162], or to input external information to the brain to make the brain feel to the outside world [163]. The concept of neural prosthesis existed long time. Since the appearance of the first cochlear implant in 1957, patients can perceive ambient sounds and gain a sense of sound, which has greatly improved their quality of life [152]. Cochlear implants are a type of neural prosthesis. A microphone can record sound from the surrounding environment and transmit the signal to a speech processor. The transporter can then convert the signal into an electrical pulse. Finally, the INE is used to stimulate the patient, so that the patient can hear the sound [164,165]. This is just a small part of the application of neural prosthesis.

Vision is one of the most important sensations in the human body. The premise of obtaining vision is to have a complete and effective visual pathway. In fact, most of the blind people's visual pathways are not completely damaged. When the patient's retina, optic nerve and even the cerebral visual cortex are properly electrically stimulated, light perception will appear in the patient's visual image. The visual prosthesis achieves the connection between the prosthesis and the patient *via* relying on a microelectrodes array as a neural interface. Electrical stimulation of the functional part of the visual pathway helps blind patients to obtain a certain degree of artificial vision [166,167]. Both the retinal implant Argus II and the subretinal implant Alpha IMS have been approved in Europe. In addition, Argus II has been approved by the US Food and Drug Administration (FDA) [168,169]. However, existing visual prosthesis faces several challenges in electrodes, such as the contradiction between minimally invasive implantation and implantation of large-area electrodes for wide field of vision and high-resolution vision, and a mechanical and geometric mismatch between implanted electrodes and retinal tissue, and these challenges limit the effectiveness of stimulation [67]. Therefore, considering the actual implantation of the visual prosthesis, flexible, high-density and highly conductive electrodes are of great significance in the research of visual prosthesis.

What's more, neural prosthesis also has the following applications. For example, the paralyzed limbs can be revived by implanting electrodes in the cerebral motor cortex and electrically stimulating relevant parts [170]. And implanted electrodes could be employed to stimulate the brain, mimicking the EEG modes that create and store memories, thereby improving the patient's memory [171]. The key to transforming short-term memory into long-term memory is that the signals from hippocampal CA3 can be transmitted to CA1. Berger's research team developed an algorithm that allowed implanted electrodes to mimic CA3 signals to stimulate CA1 cells with an accuracy rate of 80%. Monkey experiment results proved that this method was effective in improving memory [172,173]. In the future, stimulation will be provided through implanted electrodes to support this transformation process. Moreover, neural prosthesis has applications in regulating chronic pain, hunger, and anxiety [174,175].

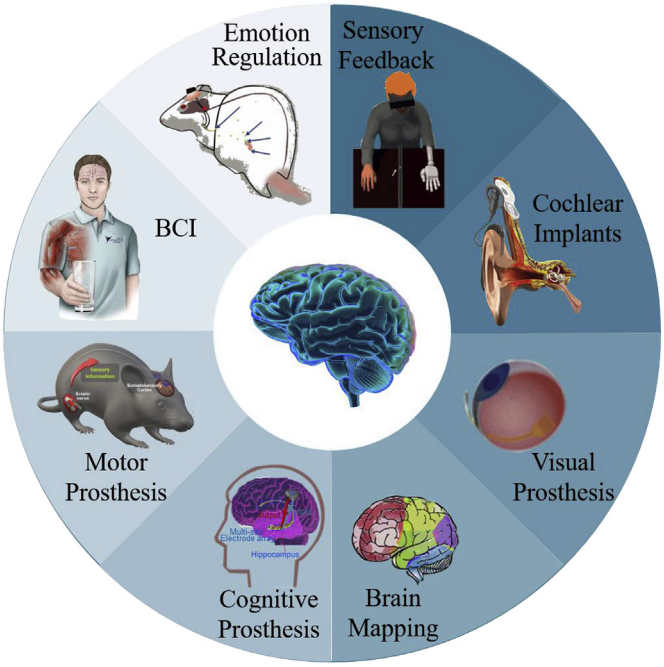

Fig. 6. Applications of implanted flexible nerve electrode (IFNEs), such as cochlear implants (working principle: The external speech processor converts the sound into a certain coded electrical signal, and directly excites the auditory nerve through the electrode system implanted in the body to restore, improve and reconstruct the hearing function of the deaf), reproduced with permission [152]. Copyright 2014, Curr. Biol. visual prosthesis (working principle: implantation of visual prosthesis in different links of the visual pathway, the prosthesis performs light-electrical stimulation of nerve tissue or neurons, so that blind patients can regain some vision), reproduced with permission [67]. Copyright 2019, Adv. Mater. Technol. brain mapping (working principle: by recording a large number of neurons at the same time, when one of the neurons is stimulated, the related neurons can be found in order to obtain a neural network diagram to help us understand the complex brain) [153], cognitive prosthesis (working principle: implanted electrodes can be used to stimulate the brain, imitating the EEG patterns that generate and store memories, thereby improving the patient's memory) [154], motor prosthesis (working principle: the implanted electrode electric stimulation is used to replace the nerve impulse sent by the brain, and a series of electric pulses are transmitted to the motor neurons, so as to induce the action potential pulse of the motor neurons, and finally achieve the purpose of muscle contraction and movement), reproduced with permission [155]. Copyright 2020, J. Neurosci. Methods. BCI, reproduced with permission [156]. Copyright 2018, Neuromodulation. emotion regulation (working principle: according to the therapeutic target and the feedback of the decoded emotional state, the emotional regulation can be realized by adjusting the electrical stimulation parameters and transmitting control instructions), reproduced with permission [157]. Copyright 2013, Biol. Psychiatry. And sensory feedback (working principle: peripheral intradural stimulation can provide tactile information for amputees, and through the use of complex bionic coding strategies to provide more natural and useful sensory feedback), reproduced with permission [158]. Copyright 2018, Neuron.

4.2. Neural signal recording

With the leap in technology, more and more technologies are directed to BCI. BCI technology can obtain the intention of movement *via* recording the brain's EEG activity, and then convert it into action instructions to control external equipment and directly command external machinery [176]. The most direct beneficiaries of this technology are paralyzed people. Miller et al. [177] utilized a multi-electrode array in the brain to detect brain activities and decode signals that trigger arm and hand movements. A functional electrical stimulation (FES) device then delivered electrical current to the paralyzed muscles to contract them. This neural prosthesis replaced the lost or damaged nervous system and allowed paralyzed monkeys to perform complex hand movements again [177]. Richard et al. [178] implanted neural prosthesis in areas of the brain that generate instructions. With the neural prosthesis, paralyzed patients used the artificial arm to shake hands, hold cups and drink drinks by simply imagining the entire movement they wanted to perform. The researchers decoded that the neural signals recorded by the implanted nerve could be a breath of fresh air for patients [178].

As mentioned above, EEG signals can be obtained through non-implantable EEG, but only limited information can be collected, and the spatial resolution is poor. However, implanted electrodes can achieve the control of external devices through signals recorded deep into the tissues below the skull, especially deep into the cerebral cortex which can record electrical signals at the neuron level, including the single neuron action potential recording and LFP. The signals recorded in this way have high spatial, temporal resolution and large amount of information, enabling real-time and precise control of complex tasks. In order to solve the mechanical mismatch between devices and tissues, IFNEs have been widely employed. In order to obtain more information, it is also required that the IFNEs have high-density collection sites, so the mesh structure, expandable structure and grid structure mentioned above adapt to its development trend. In addition, in order to avoid the risk of infection during the implantation operation, the electrodes are implanted through minimally invasive methods, such as forming electrode bundles and injections. The continuous development of IFNEs will further promote the progress of BCI.

The INEs can not only record nerve electrical signals, but also stimulate corresponding tissues, to achieve nerve recording and nerve regulation functions. In recent years, with the advancement of brain imaging technology, the further deepening of understanding of the brain, the rapid development of signal processing technology and computing technology, the application fields of neural electrodes have also been greatly expanded. In particular, the rise of wearable technology and devices has provided a new development for them, making them enter people's daily life. Its application fields are being further expanded.

5. Conclusion and prospection

As a bridge between external electronic devices and the biological interior, INEs have the function of understanding, restoring or perfecting the nervous system lost in injury or disease. With the development of materials science, INEs have also been continuously optimized. Compared with most conventional electrodes made of noble metals or semiconductor materials, IFNEs are more consistent with soft, dynamic neural tissue properties, with outstanding advantages in biocompatibility, conductivity and reliability. This review mainly introduces the latest development in materials and structural innovation of IFNEs, and discusses the applications of IFNEs in neural prosthesis and neural signal recording. Although the IFNE is in the period of rapid development, there are still some problems in its clinical application, which limit its practical applications. Therefore, the following points should be noted in the future development of IFNE: (1) implant stability is the basis for long-term implantation, which requires the material to remain stable in tissue fluid and the electrode to maintain the stability of electrical properties in the biological environment; (2) biocompatibility of IFNEs. If the biocompatibility is poor, foreign body reaction will be triggered, which will weaken signal acquisition and eventually loses its effect; (3) the implantation strategy of IFNEs. In the future, how to implant electrodes with less trauma technology will also be an important development direction of IFNEs; (4) conformal contact between electrodes and biological tissues will be an important factor influencing the acquisition of high SNR signals. In summary, the primary purpose of IFNEs is to provide a multimodal interface for specific neurons without causing chronic immune rejection. The continuous innovation and development of substrate materials, electrode materials and structures are all aimed at achieving this goal, paving the way for the realization of stable, biocompatible and high-precision neural electrodes with long-term compatibility of tissues.

In the future, IFNEs will be integrated with some progressing technologies and acquire better treatment and detection properties.

1. **Imaging.** The classic methods of brain nerve activity imaging are nerve electrical activity recording and electrical activity imaging technology. Imaging technology generally uses electrical activity to produce relevant biochemical changes [179]. The record of electrical activity was initially EEG, and then the electrical activity of neurons was collected directly through INEs. With the development of INEs, scientists can now conduct large-scale multi-neuron living recordings at the same time. In the future, these INEs will be further combined with other emerging technologies such as FMRI, MEG, molecular/cell optical imaging technology and biosensors. These technological advances have provided technical support for the study of brain function, and also provided technical reserves for the treatment of neurological diseases in the future. It is essential for us to fully understand structure and function of brain.
2. **Local drug delivery.** Microfluidics is a system that uses micropipes to process or manipulate tiny fluids. It has a wide range of applications in biomedicine. In recent years, the integrated system of IFNEs and microfluidic channels has been rapidly developed, providing the possibility of achieving local drug delivery. Local drug delivery causes fewer side effects and higher drug concentration, which provides an exciting prospect for nerve excitation regulation and enhanced neuroplasticity. For example, Song et al. [180] improved the selectivity and sensitivity of nerve bundles by delivering lysing agent and neurotrophic factors locally through polymer cuff electrodes integrated with microfluidic channels, which were conducive to the removal of redundant connective tissue and also can attract the growth of nerve fibers. In the future development, accurate and real-time drug release can be carried out based on the feedback of the acquired physiological electrical signals, which will be of great benefit to the treatment of serious diseases like epilepsy. By integrating IFNEs and microfluidic channels, multi-functional and smarter INEs can be realized.
3. **Long term and Self-powered.** At present, the application of INE as the interface to realize the external current to the target tissue is more and more extensive. What's more, to the nerve prosthesis mentioned above, neuromodulation is also an important application direction. However, how to realize wireless sustainable electrical stimulation is an important research direction in the future. At the moment, it mainly powered by battery, however, its power supply persistence is a major challenge. The mechanical energy of human movement and the chemical energy of the body, such as heartbeat, breathing, blood circulation, and redox of glucose, have the potential to be converted into electrical energy. Self-powered devices will achieve in-body energy harvesting, and development of self-powered devices will conform to biological tissues which can more effectively transfer energy to implanted devices, achieving a longer-term energy supply [181–187].
4. **Biodegradable.** With the continuous innovation of IFNEs materials, IFNEs based on biodegradable materials will slowly dissolve over time, effectively solving the key problem of implantable devices, which requires secondary surgery to remove the implantable devices. Avoiding secondary surgery not only eliminates the associated risks

and costs, but also greatly reduces the risk of infection and complications in patients, providing a wide range of new opportunities for biomedical equipment [188–190].

We believe that with the continuous development of IFNEs in terms of materials structure, biocompatibility and multi-technology integration, IFNEs will have great potential in medical applications.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 61971049, 61875015) (China), the Beijing Municipal Science and Technology Commission (Z181100004418004) (China), the Beijing Natural Science Foundation (7204333) (China), the Key Scientific Research Project of Beijing Municipal Commission of Education (KZ202010015024) (China), Key-Area Research and Development Program of Guangdong Province (2018B030331001) (China), the University of Chinese Academy of Sciences (Y954019) (China), and the National Youth Talent Support Program (China).

References

[1] C.S. von Bartheld, J. Bahney, S. Herculano-Houzel, The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting, J. Comp. Neurol. 524 (18) (2016) 3865–3895.
[2] D. Debanne, A. Bialowas, S. Rama, What are the mechanisms for analogue and digital signalling in the brain? Nat. Rev. Neurosci. 14 (1) (2013) 63–69.
[3] L.Y. Wang, M.J. Fedchyshyn, Y.M. Yang, Action potential evoked transmitter release in central synapses: insights from the developing calyx of Held, Mol. Brain 2 (2009) 36.
[4] Y. Yao, Exploring neural substrates underlying the execution of behavior across the whole brain, Neurosci. Bull. 32 (5) (2016) 505–507.
[5] G. Buzsáki, C.A. Anastassiou, C. Koch, The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes, Nat. Rev. Neurosci. 13 (6) (2012) 407–420.
[6] M. Lee, H.J. Shim, C. Choi, D.H. Kim, Soft high-resolution neural interfacing probes: materials and design approaches, Nano Lett. 19 (5) (2019) 2741–2749.
[7] G.T.A. Kovacs, C.W. Storment, M. Halks-Miller, C.R. Belczynski, C.C.D. Santina, E.R. Lewis, N.I. Maluf, Silicon-substrate microelectrode arrays for parallel recording of neural activity in peripheral and cranial nerves, IEEE Trans. Biomed. Eng. 41 (6) (1994) 567–577.
[8] C. Im, J.M. Seo, A review of electrodes for the electrical brain signal recording, Biomed. Eng. Lett. 6 (2016) 104–112.
[9] V.S. Polikov, P.A. Tresco, W.M. Reichert, Response of brain tissue to chronically implanted neural electrodes, J. Neurosci. Methods 148 (1) (2005) 1–18.
[10] R. Feiner, T. Dvir, Tissue–electronics interfaces: from implantable devices to engineered tissues, Nat. Rev. Mater. 3 (2017) 17076.
[11] J. Shi, Y. Fang, Flexible and implantable microelectrodes for chronically stable neural interfaces, Adv. Mater. 31 (45) (2019) 1804895.
[12] E. Spedden, J.D. White, E.N. Naumova, D.L. Kaplan, C. Staii, Elasticity maps of living neurons measured by combined fluorescence and atomic force microscopy, Biophys. J. 103 (5) (2012) 868–877.
[13] W.J. Tyler, The mechanobiology of brain function, Nat. Rev. Neurosci. 13 (12) (2012) 867–878.
[14] I.L. Jones, M. Warner, J.D. Stevens, Mathematical modelling of the elastic properties of retina: a determination of Young's modulus, Eye 6 (1992) 556–559.
[15] L.D. Huyer, M. Montgomery, Y. Zhao, Y. Xiao, G. Conant, A. Korolj, M. Radisic, Biomaterial based cardiac tissue engineering and its applications, Biomed. Mater. 10 (3) (2015), 034004.
[16] A. Kalra, A. Lowe, A.M. Al-Jumaily, Mechanical behaviour of skin: a review, J. Mater. Sci. Eng. 5 (4) (2016) 1000254.
[17] K. Choi, J.L. Kuhn, M.J. Ciarelli, S.A. Goldstein, The elastic moduli of human subchondral, trabecular, and cortical bone tissue and the size-dependency of cortical bone modulus, J. Biomech. 23 (11) (1990) 1103–1113.
[18] H. Sheng, X. Wang, N. Kong, W. Xi, H. Yang, X. Wu, K. Wu, C. Li, J. Hu, J. Tang, J. Zhou, S. Duan, H. Wang, Z. Suo, Neural interfaces by hydrogels, Extreme Mech. Lett. 30 (2019) 100510.
[19] S. Befahy, P. Lipnik, T. Pardoen, C. Nascimento, B. Patris, P. Bertrand, S. Yunus, Thickness and elastic modulus of plasma treated PDMS silica-like surface layer, Langmuir 26 (5) (2010) 3372–3375.
[20] B.D. Lawrence, S. Wharram, J.A. Kluge, G.G. Leisk, F.G. Omenetto, M.I. Rosenblatt, D.L. Kaplan, Effect of hydration on silk film material properties, Macromol. Biosci. 10 (4) (2010) 393–403.
[21] J. Gao, L. Guan, J. Chu, Determining the Young's modulus of SU-8 negative photoresist through tensile testing for MEMS applications, Sixth. Int. Symp. Precis. Eng. Meas. Instrum. 7544 (2010) 754464.
[22] F. Galeotti, A. Andicsova, Fabio Bertini, E. Laux, L. Hartmann, O. Khale, H. Damsir, W. Porzio, L. Stoppini, H. Keppner, C. Botta, Enhanced elasticity in parylene thin films by copolymerization approach, J. Mater. Sci. 49 (21) (2014) 7547–7555.
[23] M.A. Hopcroft, W.D. Nix, T.W. Kenny, What is the Young's modulus of silicon? J. Microelectromech. Syst. 19 (2) (2010) 229–238.
[24] S.M. Wellman, J.R. Eles, K.A. Ludwig, J.P. Seymour, N.J. Michelson, W.E. McFadden, A.L. Vazquez, T.D.Y. Kozai, A materials roadmap to functional neural interface design, Adv. Funct. Mater. 28 (12) (2018) 1701269.
[25] J.F. Wang, H.H. Tian, Y. Fang, Implantable and flexible electronics for in vivo brain activity recordings, Chin. J. Anal. Chem. 47 (10) (2019) 1549–1558.
[26] R. Atmaramani, B. Chakraborty, R.T. Rihani, J. Usoro, A. Hammack, J. Abbott, P. Nnoromele, B.J. Black, J.J. Pancrazio, S.F. Cogan, Ruthenium oxide-based microelectrode arrays for in vitro and in vivo neural recording and stimulation, Acta Biomater. 101 (2020) 565–574.
[27] K. Wang, C.L. Frewin, D. Esrafilzadeh, C. Yu, C. Wang, J.J. Pancrazio, M. Romero-Ortega, R. Jalili, G. Wallace, High-performance graphene-fiber-based neural recording microelectrodes, Adv. Mater. 31 (15) (2019) 1805867.
[28] Y. Liu, J. Li, S. Song, J. Kang, Y. Tsao, S. Chen, V. Mottni, K. McConnell, W. Xu, Y.Q. Zheng, J.B.H. Tok, P.M. George, Z. Bao, Morphing electronics enable neuromodulation in growing tissue, Nat. Biotechnol. (2020) 1–6, https://doi.org/10.1038/s41587-020-0533-0.
[29] N. de la Oliva, M. Mueller, T. Stieglitz, X. Navarro, J. del Valle, On the use of Parylene C polymer as substrate for peripheral nerve electrodes, Sci. Rep. 8 (1) (2018) 5965.
[30] B. Ji, Z. Guo, M. Wang, B. Yang, X. Wang, W. Li, J. Liu, Flexible polyimide-based hybrid opto-electric neural interface with 16 channels of micro-LEDs and electrodes, Microsyst. Nanoeng. 4 (1) (2018) 27.
[31] I. Sava, M. Asandulesa, K. Zocher, A. Kruth, J.F. Kolb, W. Bodnar, K. Witte, T. Ishizaki, C. Miron, Electrical and mechanical properties of polyimide films treated by plasma formed in water and isopropanol, React. Funct. Polym. 134 (2019) 22–30.
[32] A. Lecomte, A. Degache, E. Descamps, L. Dahan, C. Bergaud, In vitro and in vivo biostability assessment of chronically-implanted Parylene C neural sensors, Sens. Actuators, B 251 (2017) 1001–1008.
[33] R. Caldwell, M.G. Street, R. Sharma, P. Takmakov, B. Baker, L. Rieth, Characterization of Parylene-C degradation mechanisms: in vitro reactive accelerated aging model compared to multiyear in vivo implantation, Biomaterials 232 (2020) 119731.
[34] R. Das, F. Moradi, H. Heidari, Biointegrated and wirelessly powered implantable brain devices: a review, IEEE T. Biomed. Circ. S. 14 (2) (2020) 343–358.
[35] Z. Zhao, X. Li, F. He, X. Wei, S. Lin, C. Xie, Parallel, minimally-invasive implantation of ultra-flexible neural electrode arrays, J. Neural. Eng. 16 (3) (2019), 035001.
[36] T.D.Y. Kozai, D.R. Kipke, Insertion shuttle with carboxyl terminated self-assembled monolayer coatings for implanting flexible polymer neural probes in the brain, J. Neurosci. Methods 184 (2) (2009) 199–205.
[37] C.M. Boutry, H. Chandrahalim, P. Streit, M. Schinhammer, A.C. Hänzi, C. Hierold, Towards biodegradable wireless implants, Phil. Trans. R. Soc. A 370 (1967) (2012) 2418–2432.
[38] M. Leber, R. Bhandari, F. Solzbacher, S. Negi, Novel method of fabricating self-dissolvable and freely floating neural array, in: 19th International Conference on Solid-State Sensors, Actuators and Microsystems (TRANSDUCERS), 2017, pp. 1726–1729.
[39] B.A. Newcomb, Processing, structure, and properties of carbon fibers, Composites, Part A 91 (1) (2016) 262–282.
[40] P.R. Patel, H. Zhang, M.T. Robbins, J.B. Nofar, S.P. Marshall, M.J. Kobylarek, T.D.Y. Kozai, N.A. Kotov, C.A. Chestek, Chronic in vivo stability assessment of carbon fiber microelectrode arrays, J. Neural. Eng. 13 (6) (2016), 066002.
[41] L.W. Tien, F. Wu, M.D. Tang-Schomer, E. Yoon, F.G. Omenetto, D.L. Kaplan, Silk as a multifunctional biomaterial substrate for reduced glial scarring around brain-penetrating electrodes, Adv. Funct. Mater. 23 (25) (2013) 3185–3193.
[42] Y. Lee, C. Kong, J.W. Chang, S.B. Jun, Carbon-fiber based microelectrode array embedded with a biodegradable silk support for in vivo neural recording, J. Kor. Med. Sci. 34 (4) (2019) e24.
[43] Z. Xiang, S.C. Yen, S. Sheshadri, J. Wang, S. Lee, Y.H. Liu, L.D. Liao, N.V. Thakor, C. Lee, Progress of flexible electronics in neural interfacing-A self-adaptive non-invasive neural ribbon electrode for small nerves recording, Adv. Mater. 28 (22) (2016) 4472–4479.
[44] D.H. Kim, J. Viventi, J.J. Amsden, J. Xiao, L. Vigeland, Y.S. Kim, J.A. Blanco, B. Panilaitis, E.S. Frechette, D. Contreras, D.L. Kaplan, F.G. Omenetto, Y. Huang, K.C. Hwang, M.R. Zakin, B. Litt, J.A. Rogers, Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics, Nat. Mater. 9 (6) (2010) 511–517.
[45] M.E. Brogan, E.M. Manno, Treatment of malignant brain edema and increased intracranial pressure after stroke, Curr. Treat. Options Neurol. 17 (1) (2015) 327.
[46] S.K. Kang, R.K.J. Murphy, S.W. Hwang, S.M. Lee, D.V. Harburg, N.A. Krueger, J. Shin, P. Gamble, H. Cheng, S. Yu, Z. Liu, J.G. McCall, M. Stephen, H. Ying, J. Kim, G. Park, R.C. Webb, C.H. Lee, S. Chung, D.S. Wie, A.D. Gujar, B. Vemulapalli, A.H. Kim, K.M. Lee, J. Cheng, Y. Huang, S.H. Lee, P.V. Braun, W.Z. Ray, J.A. Rogers, Bioresorbable silicon electronic sensors for the brain, Nat 530 (7588) (2016) 71–76.
[47] E.J. Curry, T.T. Le, R. Das, K. Ke, E.M. Santorella, D. Paul, M.T. Chorsi, K.T.M. Tran, J. Baroody, E.R. Borges, B. Ko, A. Golabchi, X. Xin, D. Rowe, L. Yue, J. Feng, M.D. Morales-Acostai, Q. Wu, I.P. Chen, X.T. Cui, J. Pachter, T.D. Nguyen, Biodegradable nanofiber-based piezoelectric transducer, Proc. Natl. Acad. Sci. Unit. States Am. 117 (1) (2020) 214–220.
[48] Y. Wang, C. Zhu, R. Pfattner, H. Yan, L. Jin, S. Chen, F. Molina-Lopez, F. Lissel, J. Liu, N.I. Rabiah, Z. Chen, J.W. Chung, C. Linder, M.F. Toney, B. Murmann, Z. Bao, A highly stretchable, transparent, and conductive polymer, Sci. Adv. 3 (3) (2017), e1602076.

[49] L.V. Kayser, D.J. Lipomi, Stretchable conductive polymers and composites based on PEDOT and PEDOT: PSS, Adv. Mater. 31 (10) (2019) 1806133.
[50] C. Didier, A. Kundu, S. Rajaraman, Capabilities and limitations of 3D printed microserpentines and integrated 3D electrodes for stretchable and conformable biosensor applications, Microsyst. Nanoeng. 6 (2020) 15.
[51] Z. Qi, H.S. Park, D.K. Campbell, Atomistic simulations of tension-induced large deformation and stretchability in graphene kirigami, Phys. Rev. B 90 (24) (2014) 245437.
[52] T. Chen, H. Peng, M. Durstock, L. Dai, High-performance transparent and stretchable all-solid supercapacitors based on highly aligned carbon nanotube sheets, Sci. Rep. 4 (2014) 3612.
[53] J. Zhang, X. Liu, W. Xu, W. Luo, M. Li, F. Chu, L. Xu, A. Cao, J. Guan, S. Tang, X. Duan, Stretchable transparent electrode arrays for simultaneous electrical and optical interrogation of neural circuits in vivo, Nano Lett. 18 (5) (2018) 2903–2911.
[54] Y. Yu, L. Ye, Y. Song, Y. Guan, J. Zang, Wrinkled nitrile rubber films for stretchable and ultra-sensitive respiration sensors, Extreme Mech. Lett. 11 (2017) 128–136.
[55] K. Tybrandt, D. Khodagholy, B. Dielacher, F. Stauffer, A.F. Renz, C. Buzsáki, J. Vörös, High-density stretchable electrode grids for chronic neural recording, Adv. Mater. 30 (15) (2018) 1706520.
[56] Y. Morikawa, S. Yamagiwa, H. Sawahata, R. Numano, K. Koida, T. Kawano, Donut-shaped stretchable kirigami: enabling electronics to integrate with the deformable muscle, Adv. Healthcare Mater. 8 (23) (2019) 1900939.
[57] Y. Morikawa, S. Yamagiwa, H. Sawahata, R. Numano, K. Koida, M. Ishida, T. Kawano Ultrastretchable Kirigami Bioprobes, Adv. Healthcare Mater. 7 (3) (2018) 1701100.
[58] Y. Han, J. Hu, X. Chen, A skin inspired bio-smart composite with water responsive shape memory ability, Mater. Chem. Front. 3 (6) (2019) 1128–1138.
[59] A. Lendlein, O.E.C. Gould, Reprogrammable recovery and actuation behaviour of shape-memory polymers, Nat. Rev. Mater. 4 (2019) 116–133.
[60] Y. Zhang, N. Zheng, Y. Cao, F. Wang, P. Wang, Y. Ma, B. Lu, G. Hou, Z. Fang, Z. Liang, M. Yue, Y. Li, Y. Chen, J. Fu, J. Wu, T. Xie, X. Feng, Climbing-inspired twining electrodes using shape memory for peripheral nerve stimulation and recording, Sci. Adv. 5 (4) (2019), eaaw1066.
[61] Z. Xiang, S. Sheshadri, S.H. Lee, J. Wang, N. Xue, N.V. Thakor, S.C. Yen, C. Lee, Mapping of small nerve trunks and branches using adaptive flexible electrodes, Adv. Sci. 3 (9) (2016) 1500386.
[62] S. Lee, S.C. Yen, S. Sheshadri, I. Delgado-Martinez, N. Xue, Z. Xiang, N.V. Thakor, C. Lee, Flexible epineural strip electrode for recording in fine nerves, IEEE Trans. Biomed. Eng. 63 (3) (2016) 581–587.
[63] S. Lee, S. Sheshadri, Z. Xiang, I. Delgado-Martinez, N. Xue, T. Sun, N.V. Thakor, S.C. Yen, C. Lee, Selective stimulation and neural recording on peripheral nerves using flexible split ring electrodes, Sens. Actuators, B 242 (2017) 1165–1170.
[64] S. Lee, H. Wang, Q. Shi, L. Dhakar, J. Wang, N.V. Thakor, S.C. Yen, C. Lee, Development of battery-free neural interface and modulated control of tibialis anterior muscle via common peroneal nerve based on triboelectric nanogenerators (TENGs), Nanomater. Energy 33 (2017) 1–11.
[65] S. Lee, W.Y.X. Peh, J. Wang, F. Yang, J.S. Ho, N.V. Thakor, S.C. Yen, C. Lee, Toward bioelectronic medicine—neuromodulation of small peripheral nerves using flexible neural clip, Adv. Sci. 4 (11) (2017) 1700149.
[66] S. Lee, H. Wang, W.Y.X. Peh, T. He, S.C. Yen, N.V. Thakor, C. Lee, Mechano-neuromodulation of autonomic pelvic nerve for underactive bladder: a triboelectric neurostimulator integrated with flexible neural clip interface, Nanomater. Energy 60 (2019) 449–456.
[67] J. Wang, Q. Zhao, Y. Wang, Q. Zeng, T. Wu, X. Du, Self-unfolding flexible microelectrode arrays based on shape memory polymers, Adv. Mater. Technol. 4 (11) (2019) 1900566.
[68] L.J. Tang, M.H. Wang, H.C. Tian, X.Y. Kang, W. Hong, T.Q. Liu, Progress in research of flexible MEMS microelectrodes for neural interface, Micromachines 8 (9) (2017) 281.
[69] S.F. Cogan, Neural stimulation and recording electrodes, Annu. Rev. Biomed. Eng. 10 (1) (2008) 275–309.
[70] Q. Zeng, K. Xia, B. Sun, Y. Yin, T. Wu, M.S. Humayun, Electrodeposited iridium oxide on platinum nanocones for improving neural stimulation microelectrodes, Electrochim. Acta 237 (2017) 152–159.
[71] M. Vomero, E. Castagnola, F. Ciarpella, E. Maggiolini, N. Goshi, E. Zucchini, S. Carli, L. Fadiga, S. Kassegne, D. Ricci, Highly stable glassy carbon interfaces for long-term neural stimulation and low-noise recording of brain activity, Sci. Rep. 7 (2017) 40332.
[72] M. Li, Q. Zhou, Y.Y. Duan, Nanostructured porous platinum electrodes for the development of low-cost fully implantable cortical electrical stimulator, Sens. Actuators, B 221 (2015) 179–186.
[73] S.F. Cogan, J. Ehrlich, T.D. Plante, A. Smirnov, D.B. Shire, M. Gingerich, J.F. Rizzo, Sputtered iridium oxide films for neural stimulation electrodes, J. Biomed. Mater. Res., Part B 89B (2) (2009) 353–361.
[74] M.J. Mehl, D.A. Papaconstantopoulos, Applications of a tight-binding total energy method for transition and noble metals: elastic Constants, Vacancies, and Surfaces of Monatomic Metals, Phys. Rev. B Condens. Matter 54 (7) (1996) 4519–4530.
[75] G.G. Graziana, M. Attilio, T. Christos, C. Gianni, Smart materials meet multifunctional biomedical devices: current and prospective implications for nanomedicine, Front. Bioeng. Biotech. 5 (2017) 80.
[76] M. Mehrpouya, H.C. Bidsorkhi, MEMS applications of NiTi based shape memory alloys: a review, Micro Nanosyst. 8 (2) (2016) 79–91.
[77] G. Shull, J.J. Hu, J. Buschnyj, H. Koon, J. Abel, S.B. Kodandaramaiah, Shape Memory Alloy Actuatable Woven Neural Probes, ASME 2018 Conference on Smart Materials, Adaptive Structures and Intelligent Systems, 2018, https://doi.org/10.1115/SMASIS2018-8169.
[78] R. Zhao, X. Liu, Y. Lu, C. Ren, A. Mehrsa, T. Komiyama, D. Kuzum, 3D expandable microwire electrode arrays made of programmable shape memory materials, in: 2018 IEEE International Electron Devices Meeting (IEDM), 2018, pp. 2921–2924.
[79] R. David, N. Miki, Liquid metal electrodes micro-array for electrical stimulation via direct contact, in: 2018 IEEE Micro Electro Mechanical Systems (MEMS), 2018, pp. 373–375.
[80] R. Guo, J. Liu, Implantable liquid metal-based flexible neural microelectrode array and its application in recovering animal locomotion functions, J. Micromech. Microeng. 27 (10) (2017) 104002.
[81] M. Vatankhah-Varnosfaderani, W.F.M. Daniel, M.H. Everhart, A.A. Pandya, H. Liang, K. Matyjaszewski, A.V. Dobrynin, S.S. Sheiko, Mimicking biological stress-strain behaviour with synthetic elastomers, Nat 549 (7673) (2017) 497–501.
[82] P. Theato, B.S. Sumerlin, R.K. O'Reilly, T. Epps, Stimuli responsive materials, Chem. Soc. Rev. 42 (17) (2013) 7055–7056.
[83] L. Ren, S. Sun, G. Casillas-Garcia, M. Nancarrow, G. Peleckis, M. Turdy, K. Du, X. Xu, W. Li, L. Jiang, S.X. Dou, Y. Du, A liquid-metal-based magnetoactive slurry for stimuli-responsive mechanically adaptive electrodes, Adv. Mater. 30 (35) (2018) 1802595.
[84] A. Puiggalí-Jou, L.J. del Valle, C. Alemán, Encapsulation and storage of therapeutic fibrin-homing peptides using conducting polymer nanoparticles for programmed release by electrical stimulation, ACS Biomater. Sci. Eng. 6 (4) (2020) 2135–2145.
[85] R.A. Green, N.H. Lovell, L.A. Poole-Warren, Impact of co-incorporating laminin peptide dopants and neurotrophic growth factors on conducting polymer properties, Acta Biomater. 6 (1) (2010) 63–71.
[86] Y. Liu, J. Liu, S. Chen, T. Lei, Y. Kim, S. Niu, H. Wang, X. Wang, A.M. Foudeh, J.B.H. Tok, Z. Bao, Soft and elastic hydrogel-based microelectronics for localized low-voltage neuromodulation, Nat. Biomed. Eng. 3 (2019) 58–68.
[87] H. Yuk, B. Lu, X. Zhao, Hydrogel bioelectronics, Chem. Soc. Rev. 48 (6) (2019) 1642–1667.
[88] G. Justin, A. Guiseppi-Elie, Characterization of electroconductive blends of poly(HEMA-co-PEGMA-co-HMMA-co-SPMA) and poly(py-co-PyBA), Biomacromolecules 10 (9) (2009) 2539–2549.
[89] R.A. Green, S. Baek, L.A. Poole-Warren, P.J. Martens, Conducting polymer-hydrogels for medical electrode applications, Sci. Technol. Adv. Mater. 11 (1) (2010), 014107.
[90] C. Kleber, M. Bruns, K. Lienkamp, J. Rühe, M. Asplund, An interpenetrating, microstructurable and covalently attached conducting polymer hydrogel for neural interfaces, Acta Biomater. 58 (2017) 365–375.
[91] J. Goding, A. Gilmour, P. Martens, L. Poole-Warren, R. Green, Interpenetrating conducting hydrogel materials for neural interfacing electrodes, Adv. Healthcare Mater. 6 (9) (2017) 1601177.
[92] S. Manouchehri, B. Bagheri, S.H. Rad, M.N. Nezhad, Y.C. Kim, O.O. Park, M. Farokhi, M. Jouyandeh, M.R. Ganjali, M.K. Yazdi, P. Zarrintaj, M.R. Saeb, Electroactive bio-epoxy incorporated chitosan-oligoaniline as an advanced hydrogel coating for neural interfaces, Prog. Org. Coating 131 (2019) 389–396.
[93] Y. Bu, H.C. Xu, X. Li, W.J. Xu, Y.X. Yin, H.L. Dai, X.B. Wang, Z.J. Huang, P.H. Xu, A conductive sodium alginate and carboxymethyl chitosan hydrogel doped with polypyrrole for peripheral nerve regeneration, RSC Adv. 8 (20) (2018) 10806–10817.
[94] K.H. Sun, Z. Liu, C. Liu, T. Yu, C. Huang, M. Zhou, C. Liu, F. Ran, Y. Li, Y. Shi, L. Pan, Evaluation of in vitro and in vivo biocompatibility of a myo-inositol hexakisphosphate gelated polyaniline hydrogel in a rat model, Sci. Rep. 6 (2016) 23931.
[95] K. Wang, L. Tian, T. Wang, Z. Zhang, X. Gao, L. Wu, B. Fu, X. Liu, Electrodeposition of alginate with PEDOT/PSS coated MWCNTs to make an interpenetrating conducting hydrogel for neural interface, Compos. Interfac. 26 (1) (2019) 27–40.
[96] Y.Z. Long, M.M. Li, C. Gu, M. Wan, J.L. Duvail, Z. Liu, Z. Fan, Recent advances in synthesis, physical properties and applications of conducting polymer nanotubes and nanofibers, Prog. Polym. Sci. 36 (10) (2011) 1415–1442.
[97] D.A. Koutsouras, L.V. Lingstedt, K. Lieberth, J. Reinholz, V. Mailänder, P.W.M. Blom, P. Gkoupidenis, Probing the impedance of a biological tissue with PEDOT: PSS-coated metal electrodes: effect of electrode size on sensing efficiency, Adv. Healthcare Mater. 8 (23) (2019) 1901215.
[98] X. Chen, C. Liu, Z. Huang, X. Pu, L. Shang, G. Yin, C. Xue, Preparation of carboxylic graphene oxide-composited polypyrrole conduits and their effect on sciatic nerve repair under electrical stimulation, J. Biomed. Mater. Res. 107 (12) (2019) 2784–2795.
[99] Z. Zheng, L. Huang, L. Yan, F. Yuan, L. Wang, K. Wang, T. Lawson, M. Lin, Y. Liu, Polyaniline functionalized graphene nanoelectrodes for the regeneration of PC12 cells via electrical stimulation, Int. J. Mol. Sci. 20 (8) (2019) 2013.
[100] M.A. Chougule, S.G. Pawar, P.R. Godse, R.N. Mulik, S. Sen, V.B. Patil, Synthesis and characterization of polypyrrole (PPy) thin films, Soft Nanosci. Lett. 1 (1) (2011) 6–10.
[101] D. Qi, Z. Liu, Y. Liu, Y. Jiang, W.R. Leow, M. Pal, S. Pan, H. Yang, Y. Wang, X. Zhang, J. Yu, B. Li, Z. Yu, W. Wang, X. Chen, Highly stretchable, compliant, polymeric microelectrode arrays for in vivo electrophysiological interfacing, Adv. Mater. 29 (40) (2017) 1702800.
[102] S.A.A. Shah, M. Firlak, S.R. Berrow, N.R. Halcovitch, S.J. Baldock, B.M. Yousafzai, R.M. Hathout, J.G. Hardy, Electrochemically enhanced drug delivery using polypyrrole films, Mater 11 (7) (2018) 1123.

[103] Z.D. Kojabad, S.A. Shojaosadati, S.M. Firoozabadi, S. Hamedi, Polypyrrole nanotube modified by gold nanoparticles for improving the neural microelectrodes, J. Solid State Electrochem. 23 (2019) 1533–1539.
[104] N. Hosseini-Nassab, D. Samanta, Y. Abdolazimi, J.P. Annes, R.N. Zare, Electrically controlled release of insulin using polypyrrole nanoparticles, Nanoscale 9 (1) (2017) 143–149.
[105] L.V. Kayser, D.J. Lipomi, Stretchable conductive polymers and composites based on PEDOT and PEDOT: PSS, Adv. Mater. 31 (10) (2019) 1806133.
[106] M.R. Chuapoco, M. Choy, F. Schmid, B.A. Duffy, H.J. Lee, J.H. Lee, Carbon monofilament electrodes for unit recording and functional MRI in same subjects, Neuroimage 186 (2019) 806–816.
[107] A. Dominguez-Alfaro, N. Alegret, B. Arnaiz, J.M. González-Domínguez, A. Martin-Pacheco, U. Cossío, L. Porcarelli, S. Bosi, E. Vázquez, D. Mecerreyes, M. Prato, Tailored methodology based on vapor phase polymerization to manufacture PEDOT/CNT scaffolds for tissue engineering, ACS Biomater. Sci. Eng. 6 (2) (2020) 1269–1278.
[108] S. Lee, T. Eom, M.K. Kim, S.G. Yang, B.S. Shim, Durable soft neural micro-electrode coating by an electrochemical synthesis of PEDOT: PSS/graphene oxide composites, Electrochim. Acta 313 (2019) 79–90.
[109] H.S. Mandal, G.L. Knaack, H. Charkhkar, D.G. McHail, J.S. Kastee, T.C. Dumas, N. Peixoto, J.F. Rubinson, J.J. Pancrazio, Improving the performance of poly (3, 4-ethylenedioxythiophene) for brain-machine interface applications, Acta Biomater. 10 (6) (2014) 2446–2454.
[110] H. Charkhkar, G.L. Knaack, D.G. McHail, H.S. Mandal, N. Peixoto, J.F. Rubinson, T.C. Dumas, J.J. Pancrazio, Chronic intracortical neural recordings using microelectrode arrays coated with PEDOT-TFB, Acta Biomater. 32 (2016) 57–67.
[111] R. Kim, Y. Nam, Polydopamine-doped conductive polymer microelectrodes for neural recording and stimulation, J. Neurosci. Methods 326 (2019) 108369.
[112] M.H. Wang, B.W. Ji, X.W. Gu, H.C. Tian, X.Y. Kang, B. Yang, X.L. Wang, X. Chen, C.Y. Li, J.Q. Liu, Direct electrodeposition of Graphene enhanced conductive polymer on microelectrode for biosensing application, Biosens. Bioelectron. 99 (2018) 99–107.
[113] A.S. Pranti, A. Schander, A. Bödecker, W. Lang, PEDOT: PSS coating on gold microelectrodes with excellent stability and high charge injection capacity for chronic neural interfaces, Sens. Actuators, B 275 (2018) 382–393.
[114] M. Ganji, L. Hossain, A. Tanaka, M. Thunemann, E. Halgren, V. Gilja, A. Devor, S.A. Dayeh, Monolithic and scalable Au nanorod substrates improve PEDOT-metal adhesion and stability in neural electrodes, Adv. Healthcare Mater. 7 (22) (2018) 1800923.
[115] W. Shen, S. Das, F. Vitale, A. Richardson, A. Ananthakrishnan, L.A. Struzyna, D.P. Brown, N. Song, M. Ramkumar, T. Lucas, D.K. Cullen, B. Litt, M.G. Allen, Microfabricated intracortical extracellular matrix-microelectrodes for improving neural interfaces, Microsyst. Nanoeng. 4 (2018) 30.
[116] Y. Cho, R.B. Borgens, The preparation of polypyrrole surfaces in the presence of mesoporous silica nanoparticles and their biomedical applications, Nanotechnology 21 (20) (2010) 205102.
[117] C. Boehler, C. Kleber, N. Martini, Y. Xie, I. Dryg, T. Stieglitz, U.G. Hofmann, M. Asplund, Actively controlled release of Dexamethasone from neural microelectrodes in a chronic in vivo study, Biomater 129 (2017) 176–187.
[118] Y. Arteshi, A. Aghanejad, S. Davaran, Y. Omidi, Biocompatible and electroconductive polyaniline-based biomaterials for electrical stimulation, Eur. Polym. J. 108 (2018) 150–170.
[119] G. Wang, W. Wu, H. Yang, P. Zhang, J.Y. Wang, Intact polyaniline coating as a conductive guidance is beneficial to repairing sciatic nerve injury, J. Biomed. Mater. Res. Part B 108 (1) (2020) 128–142.
[120] L. Wang, Q. Huang, J.Y. Wang, Nanostructured polyaniline coating on ITO glass promotes the neurite outgrowth of PC 12 cells by electrical stimulation, Langmuir 31 (44) (2015) 12315–12322.
[121] J. Zhang, K. Qiu, B. Sun, J. Fang, K. Zhang, H. Ei-Hamshary, S.S. Al-Deyab, X. Mo, The aligned core–sheath nanofibers with electrical conductivity for neural tissue engineering, J. Mater. Chem. B 2 (45) (2014) 7945–7954.
[122] Y. Min, Y. Yang, Y. Poojari, Y. Liu, J.C. Wu, D.J. Hansford, A.J. Epstein, Sulfonated polyaniline-based organic electrodes for controlled electrical stimulation of human osteosarcoma cells, Biomacromolecules 14 (6) (2013) 1727–1731.
[123] W.H. Ko, Packaging of microfabricated devices and systems, Mater. Chem. Phys. 42 (3) (1995) 169–175.
[124] N. Khalil, Packaging of implantable microsystems, 2007 IEEE Sensors (2007) 58–63.
[125] B. Kasemo, Biological surface science, Curr. Opin. Solid State Mater. Sci. 3 (5) (1998) 451–459.
[126] B. Zhu, H. Iwata, I. Hirata, Y. Ikada, Hydrophilic modification of a polyimide film surface, J. Adhes. Sci. Technol. 14 (3) (2000) 351–361.
[127] Y. Liu, J. Liu, S. Chen, T. Lei, Y. Kim, S. Niu, H. Wang, X. Wang, A.M. Foudeh, J.B.H. Tok, Z. Bao, Soft and elastic hydrogel-based microelectronics for localized low-voltage neuromodulation, Nat. Biomed. Eng. 3 (2019) 58–68.
[128] W. Cheng, X. Zeng, H. Chen, Z. Li, W. Zeng, L. Mei, Y. Zhao, Versatile polydopamine platforms: synthesis and promising applications for surface modification and advanced nanomedicine, ACS Nano 13 (8) (2019) 8537–8565.
[129] Z. Huang, Q. Zeng, Y. Hui, M.E.E. Alahi, S. Qin, T. Wu, Fast polymerization of polydopamine based on titanium dioxide for high-performance flexible electrodes, ACS Appl. Mater. Interfaces 12 (12) (2020) 14495–14506.
[130] E.C. Leuthardt, G. Schalk, J.R. Wolpaw, J.G. Ojemann, D.W. Moran, A brain–computer interface using electrocorticographic signals in humans, J. Neural. Eng. 1 (2) (2004) 63–71.
[131] Z. Xiang, J. Liu, C. Lee, A flexible three-dimensional electrode mesh: an enabling technology for wireless brain-computer interface prostheses, Microsyst. Nanoeng. 2 (2016) 16012.
[132] J. Wang, X.Y. Thow, H. Wang, S. Lee, K. Voges, N.V. Thakor, S.C. Yen, C. Lee, A highly selective 3D spiked ultraflexible neural (SUN) interface for decoding peripheral nerve sensory information, Adv. Healthcare Mater. 7 (5) (2018) 1700987.
[133] N. Goshi, E. Castagnola, M. Vomero, C. Gueli, C. Cea, E. Zucchini, D. Bjanes, E. Maggiolini, C. Moritz, S. Kassegne, D. Ricci, L. Fadiga, Glassy carbon MEMS for novel origami-styled 3D integrated intracortical and epicortical neural probes, J. Micromech. Microeng. 28 (6) (2018), 065009.
[134] G. Schalk, E.C. Leuthardt, Brain-computer interfaces using electrocorticographic signals, IEEE Rev. Biomed. Eng. 4 (2011) 140–154.
[135] P. Wijdenes, H. Ali, R. Armstrong, W. Zaidi, C. Dalton, N.I. Syed, A novel bio-mimicking, planar nano-edge microelectrode enables enhanced long-term neural recording, Sci. Rep. 6 (2016) 34553.
[136] K. Xie, S. Zhang, S. Dong, S. Li, C. Yu, K. Xu, W. Chen, W. Guo, J. Luo, Z. Wu, Portable wireless electrocorticography system with a flexible microelectrodes array for epilepsy treatment, Sci. Rep. 7 (2017) 7808.
[137] J.E. Chung, H.R. Joo, J.L. Fan, D.F. Liu, A.H. Barnett, S. Chen, C. Geaghan-Breiner, M.P. Karlsson, M. Karlsson, K.Y. Lee, H. Liang, J.F. Magland, J.A. Pebbles, A.C. Tooker, L.F. Greengard, V.M. Tolosa, L.M. Frank, High-density, long-lasting, and multi-region electrophysiological recordings using polymer electrode arrays, Neuron 101 (2019) 21–31.
[138] R. Biran, D.C. Martin, P.A. Tresco, The brain tissue response to implanted silicon microelectrode arrays is increased when the device is tethered to the skull, J. Biomed. Mater. Res. 82A (1) (2007) 169–178.
[139] N.F. Nolta, M.B. Christensen, P.D. Crane, J.L. Skousen, P.A. Tresco, BBB leakage, astrogliosis, and tissue loss correlate with silicon microelectrode array recording performance, Biomaterials 53 (2015) 753–762.
[140] G. Hong, X. Yang, T. Zhou, C.M. Lieber, Mesh electronics: a new paradigm for tissue-like brain probes, Curr. Opin. Neurobiol. 50 (2018) 33–41, https://doi.org/10.1016/j.conb.2017.11.007.
[141] X. Dai, G. Hong, T. Gao, C.M. Lieber, Mesh nanoelectronics: seamless integration of electronics with tissues, Acc. Chem. Res. 51 (2) (2018) 309–318.
[142] J. Liu, T.M. Fu, Z. Cheng, G. Hong, T. Zhou, L. Jin, M. Duvvuri, Z. Jiang, P. Kruskal, C. Xie, Z. Suo, Y. Fang, C.M. Lieber, Syringe-injectable electronics, Nat. Nanotechnol. 10 (2015) 629–636.
[143] G. Hong, T.M. Fu, T. Zhou, T.G. Schuhmann, J. Huang, C.M. Lieber, Syringe injectable electronics: precise targeted delivery with quantitative input/output connectivity, Nano Lett. 15 (10) (2015) 6979–6984.
[144] T.M. Fu, G. Hong, R.D. Viveros, T. Zhou, C.M. Lieber, Highly scalable multichannel mesh electronics for stable chronic brain electrophysiology, Proc. Natl. Acad. Sci. Unit. States Am. 114 (47) (2017) E10046–E10055.
[145] T. Zhou, G. Hong, T.M. Fu, X. Yang, T.G. Schuhmann, R.D. Viveros, C.M. Lieber, Syringe-injectable mesh electronics integrate seamlessly with minimal chronic immune response in the brain, Proc. Natl. Acad. Sci. Unit. States Am. 114 (23) (2017) 5894–5899.
[146] N.A. Steinmetz, C. Koch, K.D. Harris, M. Carandini, Challenges and opportunities for large-scale electrophysiology with Neuropixels probes, Curr. Opin. Neurobiol. 50 (2018) 92–100.
[147] A.L. Juavinett, G. Bekheet, A.K. Churchland, Chronically implanted Neuropixels probes enable high-yield recordings in freely moving mice, Elife 8 (2019), e47188.
[148] S. Guan, J. Wang, X. Gu, Y. Zhao, R. Hou, H. Fan, L. Zou, L. Gao, M. Du, C. Li, Y. Fang, Elastocapillary self-assembled neurotassels for stable neural activity recordings, Sci. Adv. 5 (3) (2019), eaav2842.
[149] D. Khodagholy, J.N. Gelinas, Z. Zhao, M. Yeh, M. Long, J.D. Greenlee, W. Doyle, O. Devinsky, G. Buzsáki, Organic electronics for high-resolution electrocorticography of the human brain, Sci. Adv. 2 (11) (2016), e1601027.
[150] D. Khodagholy, J.N. Gelinas, T. Thesen, W. Doyle, O. Devinsky, G.G. Malliaras, G. Buzsáki, NeuroGrid: recording action potentials from the surface of the brain, Nat. Neurosci. 18 (2015) 310–315.
[151] B.V. Benjamin, P. Gao, E. McQuinn, S. Choudhary, A.R. Chandrasekaran, J.M. Bussat, R. Alvarez-Icaza, J.V. Arthur, P.A. Merolla, K. Boahen, Neurogrid: a mixed-analog-digital multichip system for large-scale neural simulations, Proc. IEEE 102 (5) (2014) 699–716.
[152] O. Macherey, R.P. Carlyon, Cochlear implants, Curr. Biol. 24 (18) (2014) R878–R884.
[153] K. Smith, How to map the circuits that define us? Nat 548 (7666) (2017) 150–152.
[154] T.W. Berger, D. Song, R.H.M. Chan, V.Z. Marmarelis, J. LaCoss, J. Wills, R.E. Hampson, S.A. Deadwyler, J.J. Granacki, A hippocampal cognitive prosthesis: multi-input, multi-output nonlinear modeling and VLSI implementation, IEEE Trans. Neural Syst. Rehabil. Eng. 20 (2) (2012) 198–211.
[155] H. Kim, A.M. Dingle, J.P. Ness, D.H. Baek, J. Bong, I.K. Lee, N.O. Shulzhenko, W. Zeng, J.S. Israel, J.A. Pisaniello, A.X.T. Millevolte, D.W. Park, A.J. Suminski, Y.H. Jung, J.C. Williams, S.O. Poore, Z. Ma, Cuff and sieve electrode (CASE): the combination of neural electrodes for bi-directional peripheral nerve interfacing, J. Neurosci. Methods 336 (2020) 108602.
[156] A.B. Ajiboye, R.F. Kirsch, Invasive Brain–Computer Interfaces for Functional Restoration, Neuromodulation, second ed., 2018, pp. 379–391.
[157] D.F. Peña, N.D. Engineer, C.K. McIntyre, Rapid remission of conditioned fear expression with extinction training paired with vagus nerve stimulation, Biol. Psychiatr. 73 (11) (2013) 1071–1077.
[158] G. Valle, A. Mazzoni, F. Iberite, E. D'Anna, I. Strauss, G. Granata, M. Controzzi, F. Clemente, G. Rognini, C. Cipriani, T. Stieglitz, F.M. Petrini, P.M. Rossini, S. Micera, Biomimetic intraneural sensory feedback enhances sensation

naturalness, tactile sensitivity, and manual dexterity in a bidirectional prosthesis, Neuron 100 (1) (2018) 37–45.
[159] J. Wang, H. Wang, N.V. Thakor, C. Lee, Self-powered direct muscle stimulation using a triboelectric nanogenerator (TENG) integrated with a flexible multiple-channel intramuscular electrode, ACS Nano 13 (3) (2019) 3589–3599.
[160] J. Wang, H. Wang, C. Lee, Mechanism and applications of electrical stimulation disturbance on motoneuron excitability studied using flexible intramuscular electrode, Adv. Biosystems 3 (7) (2019) 1800281.
[161] J. Wang, H. Wang, T. He, B. He, N.V. Thakor, C. Lee, Investigation of low-current direct stimulation for rehabilitation treatment related to muscle function loss using self-powered TENG system, Adv. Sci. 6 (14) (2019) 1900149.
[162] T. He, H. Wang, J. Wang, X. Tian, F. Wen, Q. Shi, J.S. Ho, C. Lee, Self-sustainable wearable textile nano-energy nano-system (NENS) for next-generation healthcare applications, Adv. Sci. 6 (24) (2019) 1901437.
[163] M. Gasson, B. Hutt, I. Goodhew, P. Kyberd, K. Warwick, Invasive neural prosthesis for neural signal detection and nerve stimulation, Int. J. Adapt. Control. 19 (5) (2005) 365–375.
[164] J. Boulet, M. White, I.C. Bruce, Temporal considerations for stimulating spiral ganglion neurons with cochlear implants, J. Assoc. Res. Oto. 17 (2016) 1–17.
[165] A. Dhanasingh, C. Jolly, An overview of cochlear implant electrode array designs, Hear. Res. 356 (2017) 93–103.
[166] F. Yang, M.Y. Chang, C.H. Yang, C.C. Teng, L.S. Fan, Flexible, high-density microphotodiode array with integrated sputtered iridium oxide electrodes for retinal stimulation, J. Nanolithogr. MEMS, MOEMS 15 (1) (2016), 015002.
[167] D.C. Rodger, W. Li, H. Ameri, A. Ray, J.D. Weiland, M.S. Humayun, Y.C. Tai, Flexible parylene-based microelectrode technology for intraocular retinal prosthese, in: 1st IEEE International Conference on Nano/Micro Engineered and Molecular Systems, 2006, pp. 743–746.
[168] R. Daschner, A. Rothermel, R. Rudorf, S. Rudorf, A. Stett, Functionality and performance of the subretinal implant chip Alpha AMS, Sensor. Mater. 30 (2) (2018) 179–192.
[169] Y.H.L. Luo, L. da Cruz, The Argus® II retinal prosthesis system, Prog. Retin. Eye Res. 50 (2016) 89–107.
[170] M.M. Shanechi, R.C. Hu, Z.M. Williams, A cortical-spinal prosthesis for targeted limb movement in paralysed primate avatars, Nat. Commun. 5 (2014) 3237.
[171] K.B. Clark, D.K. Naritoku, D.C. Smith, R.A. Browning, R.A. Jensen, Enhanced recognition memory following vagus nerve stimulation in human subjects, Nat. Neurosci. 2 (1999) 94–98.
[172] S.A. Deadwyler, R.E. Hampson, D. Song, I. Opris, G.A. Gerhardt, V.Z. Marmarelis, T.W. Berger, A cognitive prosthesis for memory facilitation by closed-loop functional ensemble stimulation of hippocampal neurons in primate brain, Exp. Neurol. 287 (4) (2017) 452–460.
[173] V.C. Sousa, J. Vital, A.R. Costenla, V.L. Batalha, A.M. Sebastião, J.A. Ribeiro, L.V. Lopes, Maternal separation impairs long term-potentiation in CA1-CA3 synapses and hippocampal-dependent memory in old rats, Neurobiol. Aging 35 (7) (2014) 1680–1685.
[174] B.A. Petersen, A.C. Nanivadekar, S. Chandrasekaran, L.E. Fisher, Phantom limb pain: peripheral neuromodulatory and neuroprosthetic approaches to treatment, Muscle Nerve 59 (2) (2019) 154–167.
[175] M.C. Lo, A.S. Widge, Closed-loop neuromodulation systems: next-generation treatments for psychiatric illness, Int. Rev. Psychiatr. 29 (2) (2017) 191–204.
[176] M.J. Vansteensel, E.G.M. Pels, M.G. Bleichner, M.P. Branco, T. Denison, Z.V. Freudenburg, P. Gosselaar, S. Leinders, T.H. Ottens, M.A. Van Den Boom, P.C. Van Rijen, E.J. Aarnoutse, N.F. Ramsey, Fully implanted brain–computer interface in a locked-in patient with ALS, N. Engl. J. Med. 375 (2016) 2060–2066.
[177] C. Ethier, E.R. Oby, M.J. Bauman, L.E. Miller, Restoration of grasp following paralysis through brain-controlled stimulation of muscles, Nat 485 (2012) 368–371.
[178] T. Aflalo, S. Kellis, C. Klaes, B. Lee, Y. Shi, K. Pejsa, K. Shanfield, S. Hayes-Jackson, M. Aisen, C. Heck, C. Liu, R.A. Andersen Neurophysiology, Decoding motor imagery from the posterior parietal cortex of a tetraplegic human, Sci 348 (6237) (2015) 906–910.
[179] A. Dance, The real-time technicolour living brain, Nat 539 (2016) 315–318.
[180] S. Elyahoodayan, C. Larson, A.M. Cobo, E. Meng, D. Song, Acute in vivo testing of a polymer cuff electrode with integrated microfluidic channels for stimulation, recording, and drug delivery on rat sciatic nerve, J. Neurosci. Methods 336 (2020) 108634.
[181] Z. Li, G. Zhu, R. Yang, A.C. Wang, Z.L. Wang, Muscle-driven in vivo nanogenerator, Adv. Mater. 22 (23) (2010) 2534–2537.
[182] B. Shi, Z. Liu, Q. Zheng, J. Meng, H. Ouyang, Y. Zou, D. Jiang, X. Qu, M. Yu, L. Zhao, Y. Fan, Z.L. Wang, Z. Li, Body-integrated self-powered system for wearable and implantable Application, ACS Nano 13 (5) (2019) 6017–6024.
[183] H. Ouyang, Z. Liu, N. Li, B. Shi, Y. Zou, F. Xie, Y. Ma, Z. Li, H. Li, Q. Zheng, X. Qu, Y. Fan, Z.L. Wang, H. Zhang, Z. Li, Symbiotic cardiac pacemaker, Nat. Commun. 10 (2019) 1821.
[184] H. Ouyang, Z. Li, The first technology can compete with piezoelectricity to harvest ultrasound energy for powering medical implants, Sci. Bull. 64 (21) (2019) 1565–1566.
[185] L. Zhao, H. Li, J. Meng, A.C. Wang, P. Tan, Y. Zou, Z. Yuan, J. Lu, C. Pan, Y. Fan, Y. Zhang, Y. Zhang, Z.L. Wang, Z. Li, Reversible conversion between Schottky and ohmic contacts for highly sensitive, multifunctional biosensors, Adv. Funct. Mater. 30 (5) (2019) 1907999.
[186] D. Jiang, B. Shi, H. Ouyang, Y. Fan, Z.L. Wang, Z. Li, Emerging implantable energy harvesters and self-powered implantable medical electronics, ACS Nano 14 (6) (2020) 6436–6448.
[187] H. Li, X. Zhang, L. Zhao, D. Jiang, L. Xu, Z. Liu, Y. Wu, K. Hu, M.R. Zhang, J. Wang, Y. Fan, Z. Li, A hybrid biofuel and triboelectric nanogenerator for bioenergy harvesting, Nano-Micro Lett. 12 (1) (2020) 1–12.
[188] K.J. Yu, D. Kuzum, S.W. Hwang, B.H. Kim, H. Juul, N.H. Kim, S.M. Won, K. Chiang, M. Trumpis, A.G. Richardson, H. Cheng, H. Fang, M. Thompson, H. Bink, D. Talos, K.J. Seo, H.N. Lee, S.K. Kang, J.H. Kim, J.Y. Lee, Y. Huang, F.E. Jensen, M.A. Dichter, T.H. Lucas, J. Viventi, B. Litt, J.A. Rogers, Bioresorbable silicon electronics for transient spatiotemporal mapping of electrical activity from the cerebral cortex, Nat. Mater. 15 (2016) 782–791.
[189] H. Li, C. Zhao, X. Wang, J. Meng, Y. Zou, S. Noreen, L. Zhao, Z. Liu, H. Ouyang, P. Tan, M. Yu, Y. Fan, Z.L. Wang, Z. Li, Fully bioabsorbable capacitor as an energy storage unit for implantable medical electronics, Adv. Sci. 6 (6) (2019) 1801625.
[190] Q. Zheng, Y. Zou, Y. Zhang, Z. Liu, B. Shi, X. Wang, Y. Jin, H. Ouyang, Z. Li, Z.L. Wang, Biodegradable triboelectric nanogenerator as a life-time designed implantable power source, Sci. Adv. 2 (3) (2016), e1501478.