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Recent Advances in Implantable Neural Interfaces for Multimodal Electrical Neuromodulation

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Electrical neuromodulation plays a pivotal role in enhancing patient outcomes among individuals suffering from neurological disorders. Implantable neural interfaces are vital components of the electrical neuromodulation system to ensure desirable performance; However, conventional devices are limited to a single function and are constructed with bulky and rigid materials, which often leads to mechanical incompatibility with soft tissue and an inability to adapt to the dynamic and complex 3D structures of biological systems. In addition, current implantable neural interfaces utilized in clinical settings primarily rely on wire-based techniques, which are associated with complications such as increased risk of infection, limited positioning options, and movement restrictions. Here, the state-of-art applications of electrical neuromodulation are presented. Material schemes and device structures that can be employed to develop robust and multifunctional neural interfaces, including flexibility, stretchability, biodegradability, self-healing, self-rolling, or morphing are discussed. Furthermore, multimodal wireless neuromodulation techniques, including optoelectronics, mechano-electrics, magnetoelectrics, inductive coupling, and electrochemically based self-powered devices are reviewed. In the end, future perspectives are given.

1. Introduction

The nervous system, which includes the peripheral and central nervous systems, plays a crucial role in regulating various physiological functions such as sensory perception, motor control,[1] and cognitive activity[2] through the generation and transmission of electrical signals known as action potentials. Electrical neuromodulation involves the use of man-made human-machine interface to deliver electrical cues at the brain, spinal cord, or peripheral nerves to enhance or inhibit neural excitability, which can ultimately modulate the functioning of neurons and neural circuits.[3] Such technique has been employed to alleviate symptoms associated with neurological disorders,[4] chronic pain,[5] and movement[6] or perception disorders,[7] specific examples include deep brain stimulation,[8] sacral nerve stimulation,[9] and spinal cord stimulation.[10] While implantable neural interfaces have made remarkable progress, there still remain several challenges that need to be addressed to optimize therapeutic outcomes.

First, from the materials perspectives, most conventional devices are built on bulky and rigid materials,[11] which often results in mechanical mismatch when interacting with soft and delicate biological tissues and can potentially lead to irritating effects and cause unwanted inflammatory response.[12] To address these issues, devices in a miniaturized,[13] flexible, and stretchable format[14] would be desirable to mimic the mechanical properties of soft tissues,[15] ensuring excellent biocompatibility[16] and minimizing foreign body reactions.[17] While conventional devices are typically designed to maintain physical and chemical stability for long-term use,[18] the capability of biodegradation would offer unique advantages for temporary implants to eliminate unnecessary materials retention and avoid secondary surgeries for device removal.[19]

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Additionally, biological systems are time-dynamic and possess complex 3D structure, and implantable neural interfaces that can adapt to these features can ensure robust data acquisition and minimize tissue damage.[20] For example, devices with self-healing properties allow prolonged utility,[20a] neural electrodes with shape memory capabilities can facilitate the in situ formation of 3D structure matching the curvilinear surface of various organs and enhance the convenience of implantation,[20b,c] and self-morphing characteristics enable device adaptation to growing tissue and reduce associated inflammatory response.[20d]

Second, current implantable neural interfaces utilized in clinical settings primarily rely on wire-based techniques.[21] In these approaches, stimulation electrodes are either connected to bulky batteries implanted in another location,[22] or are percutaneously connected to an external power source.[23] These conventional methods are associated with complications such as increased risk of infection, limitations on positioning, restrictions on movement, etc. The development of miniaturized wireless devices that are minimally invasive and do not constrain routine activity has attracted great interest.[24] Strategies in this regard involve the advancement of novel materials and device structure that enable wireless optoelectronic stimulation utilizing deep-red or near-infrared illumination,[25] mechano-electrical stimulation based on various sources of mechanical stimuli,[26] magnetoelectric implants coupling magnetostrictive and piezoelectric components,[27] electrical stimulation based on inductive coupling,[28] and electrochemical reaction induced self-powered electrical stimulators based on bio-batteries[29] or fuel cells.[30]

In this review, we will focus on the discussion of the latest research progress in implantable devices for electrical neuromodulation, with a particular emphasis on advanced materials strategies and innovative multimodal wireless techniques. We will first introduce examples of the state-of-art applications of electrical neuromodulation. Material schemes and device structures that can be utilized to develop robust neural electrodes for wire-based techniques will be explored. These discussions will include key aspects like miniaturization, flexibility, stretchability, and biodegradability, etc. Furthermore, we will delve into the realm of multimodal wireless neuromodulation, which encompasses various techniques such as optoelectronics, mechanoelectrics, magnetoelectric, inductive coupling, and electrochemically based self-powered stimulation. Future perspectives will be given in the end.

2. State-of-the-Art Applications of Electrical Neuromodulation

Electrical neuromodulation has the capability to selectively active or inhibit neural activity by delivering specific patterns and parameters of electrical pulses. This technique has a broad range of clinical applications, including deep brain stimulation, spinal cord stimulation, transcutaneous electrical nerve stimulation, etc.[31] Recent advancements of electrical neuromodulation have been achieved through the development of closed-loop system and algorithm-assisted spatiotemporal stimulation, enabling the management of epileptic disorders and atrial fibrillation, and remarkably, the restoration of different types of motor functions in human subjects.

For instance, the responsive neurostimulation (RNS) system represents a closed-loop medical treatment approach for epilepsy. This system uses a neurostimulator device designed to detect and immediately address abnormal brain activity.[32] It continuously monitors the brain's electrical activity and identifies abnormal patterns that signal impending seizures. When these irregularities are detected, the neurostimulator delivers targeted, low-intensity electrical pulses to the specified area of the brain, effectively interrupting the seizure activity and preventing its spread. Based on similar concept, Yu Sun et al. proposed a flexible low-level vagus nerve stimulation (LL-VNS) system utilizing a hybrid nanogenerator (H-NG).[33] The device combines self-powering capabilities with a closed-loop system, providing new strategies for the treatment of atrial fibrillation. Specifically, this system comprised a piezoelectric nanogenerator (PENG) sensor incorporated into a wristband that monitor pulse waves. It leveraged Bluetooth technology to wirelessly transmit the data to mobile phones for real-time signal processing, which facilitated prompt diagnosis. Once atrial fibrillation occurred, a warning massage will be triggered, urging users to activate responsive stimulation of the vagus nerve, thereby preventing the onset of atrial fibrillation, as shown in **Figure 1a**. In vivo results showed that with LL-VNS therapy, the duration of atrial fibrillation was significantly reduced by 90%.

The integration of computational protocols to identify optimal stimulation sites and temporal structure mimicking motoneuron activation have been shown to effectively improve stimulation efficacy and enhance motor control in closed-loop neuromodulation following spinal cord injury (SCI). For example, Nikolaus Wenger et al. developed innovative spatiotemporal strategies to precisely modulate extensor and flexor muscle synergies.[34] This improvement was accomplished through the experimental mapping of activation regions linked to muscle synergies by injecting Fluorogold into the tibialis anterior muscle, and computationally determining the best sites for electrode placement targeting dorsal roots (Figure 1b). Together with precise real-time control, improved gait features of locomotion were accomplished after SCI. Further advances of multielectrode customized for the ensemble of dorsal roots and the development of activity-specific stimulation programs enabled the restoration of movements within a single day of three individuals suffered from complete sensorimotor paralysis.[35] Figure 1c shows the procedure allowed for walking. This procedure involved first identifying the sequence of leg muscle activity in healthy individuals. Next, electrode configurations were injected into each motor hotspot. Finally, the hotspots are stimulated through optimized sequences determined by a combination of pre-established sequences and simulation software.

In addition, electrical stimulation of cervical spinal cord can also facilitate the recovery of dexterous control of arm and hand movements. Marco Powell et al. conducted a pioneering study on human subjects, applying electrical stimulation to cervical spinal circuits to enhance arm and hand motor control with cerebral strokes.[36] Wireless EMG was used to monitor muscle activity in the arm and hand during upper-limb motor tasks. For cervical spinal cord stimulation, two 8-contact leads (rostral, R; caudal, C) were utilized, linked to an external stimulator to deliver effective stimulation (Figure 1d). The findings revealed that stimulation facilitated movements previously impossible without spinal

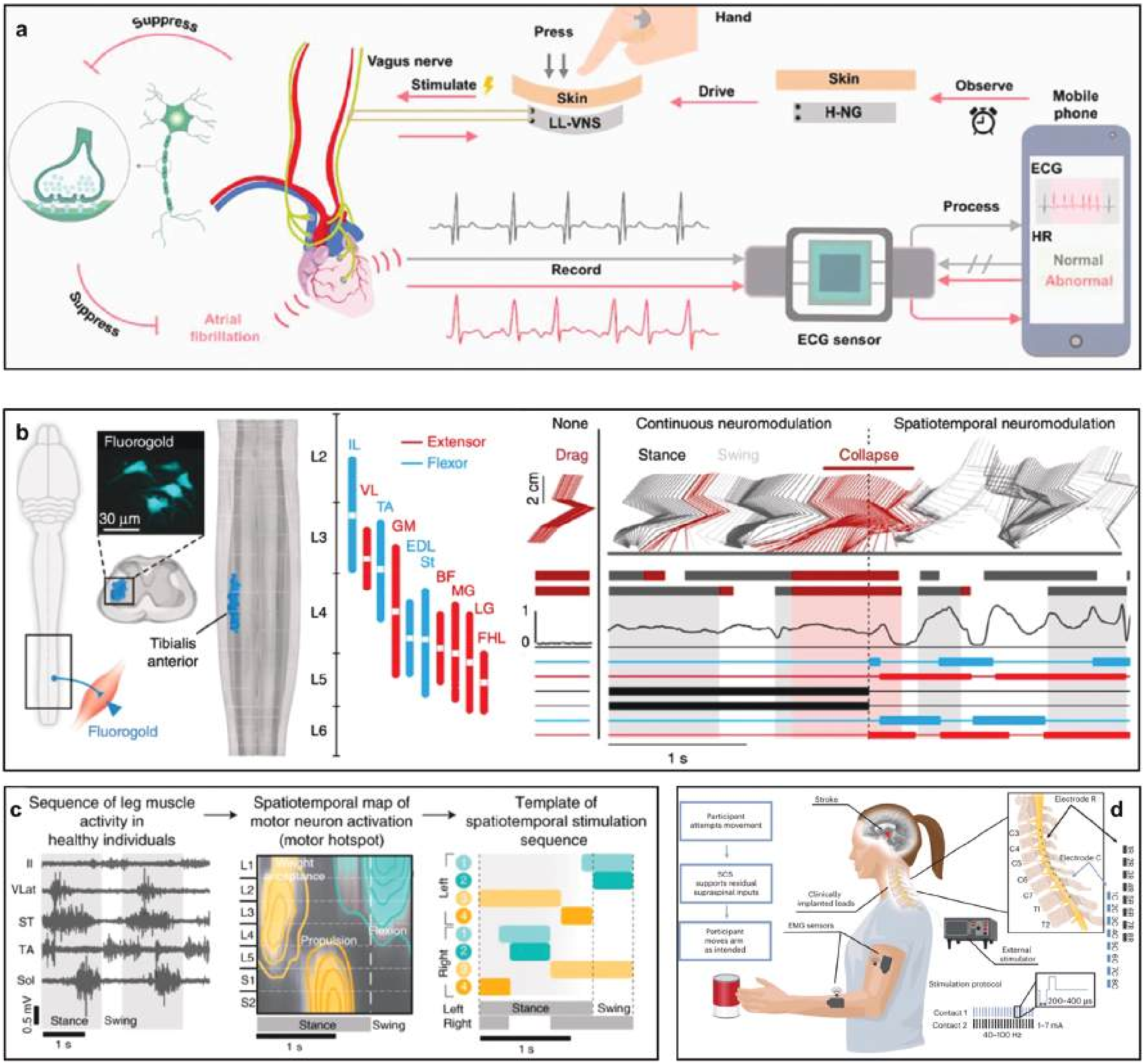

Figure 1. State-of-art application of electrical neuromodulation. a) A self-powered closed-loop vagus nerve stimulation system for atrial fibrillation treatment in rodents. Reproduced with permission.[33] Copyright 2022, Elsevier. b) A spatiotemporal neuromodulation to engage muscle synergies after spinal cord injury in rats. Reproduced with permission.[34] Copyright 2016, Springer Nature. c) Activity-specific stimulation programs to enable trunk movement control for human. Reproduced with permission.[35] Copyright 2022, Springer Nature. d) An electrical stimulation of cervical spinal circuits to improve arm and hand motor control in chronic post-stroke hemiparesis for participants. Reproduced with permission.[36] Copyright 2023, Springer Nature.

cord stimulation, and these enhancements were maintained for 29 days post-stimulation.

3. Advanced Materials Strategy and Device Structure for Wire-Based Neural Interfaces

Robust neural interfaces that can support the aforementioned electrical neuromodulation are of growing interests to restore neural functions, alleviate symptoms, and treat neurological disorders. Although with great advances, traditional neural interfaces rely on bulky, rigid, and durable materials that is challenging to seamlessly integrate with biological systems. By contrast, recently proposed devices with soft, stretchable, biodegradable, self-healing, or self-morphing characteristics that mimic the nature of tissues could potentially minimize mechanical mismatch, reduce inflammatory response, prolong operational timeframes, and maximize therapeutic outcomes.

Generally, strategies to construct soft and stretchable neural interfaces include both materials and architecture design. The first approach involves utilizing advanced materials that are intrinsically flexible and stretchable, such as soft elastomers, hydrogels, and liquid metals (LMs) whose mechanical modulus matches soft tissues and can minimize the discomfort and irritation at the electrode interface. For example, Yuxin Liu et al. reported soft elastic electronics based on micropatterned electrically conductive hydrogel electrodes (MECH) and stretchable fluorinated photoresist as encapsulation materials.[37] This neural interface is shown in **Figure** 2a, consisting of a conductive poly(3,4-ethylenedioxythiophene): poly(styrenesulfonate) (PEDOT:PSS)-base hydrogel as the electrode, and dimethacrylate-functionalized perfluoropolyether (PFPE-DMA) as both the substrate and encapsulation layer. These materials enable soft neural interface with Young's modulus in the kilopascal range, minimizing tissue damage and inflammatory responses even with repetitive movement. Remarkably, MECH enabled significantly enhanced current-injection density, facilitating neural stimulation at lower voltages.[37] In order to further minimize stiffness mismatch with viscoelastic tissues, Christina Tringides et al. proposed a viscoelastic electrode array consisting of electrically conductive viscoelastic hydrogels (alginate loaded with carbon nanomaterials) and bi-layer viscoelastic encapsulation (alginate based tough gels and polydimethylsiloxane (PDMS) based insulating materials), as shown in Figure 2b.[38] The unique viscoelastic characteristics allow enhanced conformal interface with different geometry with biological tissues, and epicardial and electrocorticography signals were successfully recorded.[38] In contrast to conductive hydrogels, LMs remain liquid state at room temperature and exhibit superior electrical conductivity, ensuring reliable and low-impedance interfaces. Additionally, LMs provide mechanical flexibility and durability, essential for long-term neuromodulation. Rongyu Tang et al. developed a fluidic neural electrodes utilizing gallium-based LM conductors that encapsulated by silicone rubber for prolonged neural recording and stimulation on freely moving rats (Figure 2c).[39] These flexible LM-based neural interfaces enabled high-quality and long-term recording of signals on sciatic nerves and effective stimulation.

Alternatively, inorganic materials with proper geometrical structure design can also achieve neural interface with flexible and stretchable features. For example, inorganic materials in ultrathin and/or mesh format can ensure minimal stresses imposed on tissues and highly conformal coverage on complex curvilinear surfaces.[40] Dae-Hyeong Kim et al. reported the use of a bioresorbable silk fibroin substrate as a support for ultrathin electronics consists of gold (Au) nanomembrane electrodes and ultrathin polyimide (PI) layers.[41] The dissolution of temporary silk substrates facilitated a spontaneous and conformal wrapping on surfaces with complex geometries, which is driven by capillary forces at the interface. As illustrated in Figure 2d, the degree of conformal coverage increases as the PI thickness decreases, and the introduction of mesh design can further enhance the coverage. Jia Liu et al. reported an ultra-flexible microporous mesh electronics (porosity greater than 99%) that can be injected by syringe into biomimetic cavities and brain tissues (Figure 2e).[42] The components of the mesh network included silicon nanowires and metal interconnects that were encapsulated by a photodefinable epoxy (SU-8). This work provides a new strategy for the minimally invasive delivery of soft electronics through small injection sites.

To achieve high channel counts with high electrode density in clinical systems, many efforts have been devoted to develop flexible and scalable neural interfaces. Neuralink took an initial step toward developing a scalable, high-bandwidth brain-machine interface system, comprising arrays of tiny, pliable electrode "threads", featuring 3072 electrodes per array over 96 threads.[43] Recognizing the difficulties presented by the threads' low bending stiffness, they built a neurosurgical robot. This robot is adept at inserting the threads (at an insertion rate of six threads per minute) with micron-level accuracy, allowing for the targeting of precise brain regions, as depicted in Figure 2f. S. Guan et al. achieved a self-assembled Neurotassel (Figure 2g) consisting of 1024 microelectrodes (100 nm Au encapsulated by PI layers) through elastocapillary interactions.[44] Specifically, the Neurotassel was created by immersing and withdrawing high-density electrode arrays into molten polyethylene glycol (PEG). After implantation, the Neurotassel transitioned into flexible microelectrodes once the PEG dissolved in body fluids. The Neurotassel presents a scalable method for efficiently packaging high-density flexible microelectrodes in a 3D structure. Moreover, to achieve integration of 3D high-density neural interfaces with flat complementary metal-oxide semiconductor (CMOS)-based chips, Abdulmalik Obaid et al. formulated bundles of microwires with an extremely high channel count, consisting of metallic materials such as Au, tungsten (W), etc.[45] The connection with CMOS chips were accomplished by encasing the connecting ends of the microwires in medical epoxy, followed by compressing and bonding these ends to the pads on a bare CMOS die (Figure 2h). Furthermore, this configuration can be adapted to accommodate a variety of microwire types and sizes for integration with different CMOS array designs.

In addition to flexibility and stretchability, the increasing demand for personalized medicine in neuromodulation has motivated efforts to explore other functions of electrodes. These include biodegradability for short or mid-term applications, self-climbing characteristics facilitating easy device deployment and stable conformability, self-morphing feature enabling accommodation of rapid tissue growth, and self-healing properties for prolonged usability. Biodegradable electrodes, which can eliminate the risks of infection and reduce the costs associated with secondary surgeries for device removal, have attracted great attentions. For example, Geumbee Lee et al. have designed a bioresorbable neural interface with potential applications in pain management, as illustrated in Figure 2i.[19a] Molybdenum (Mo) was used for the electrodes, poly(lactic-co-glycolic acid) (PLGA) as the substrate, and two layers of polyanhydride (PA) were used for encapsulation. Furthermore, magnesium (Mg) foils, encased in a bioresorbable polymer, were employed to create a stable interconnection to an external power source through a woven configuration. The bioresorbable neural interface can block action potential propagation associated with pain sensations, delivering kilohertz-frequency alternating current without causing axonal damage. The device was capable of complete biodegradation, eliminating the need for a retraction procedure. To facilitate the deployment of neural interface, Yingchao Zhang et al. put forward a concept for an adaptable self-climbing neural interface.[20b] This design involves intertwining stretchable mesh serpentine Au/titanium (Ti) wires with a flexible shape memory polymer, enabling the electrode to self-climb toward

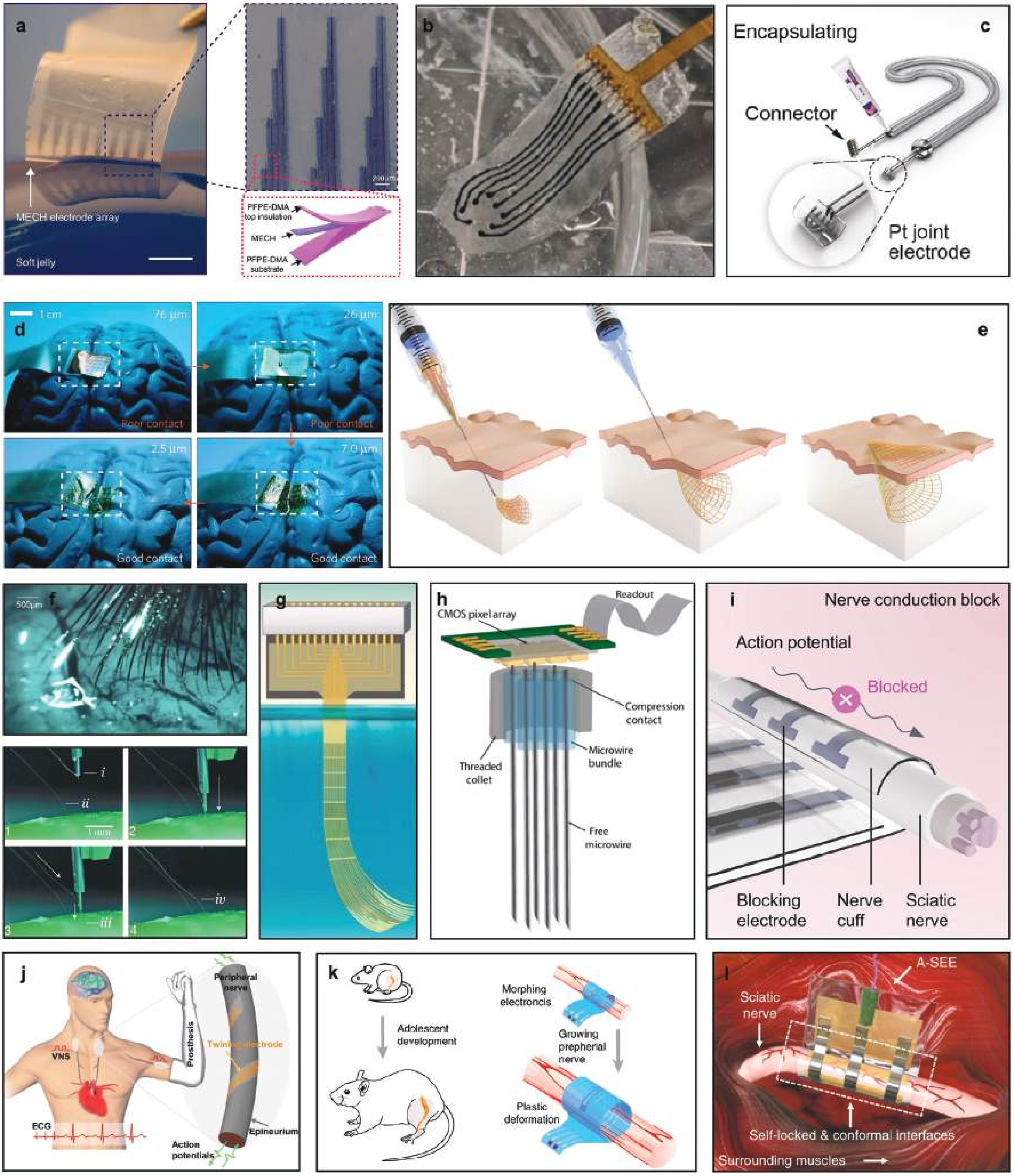

Figure 2. Advanced materials strategy and device structure for wire-based neural interfaces. a) Hydrogel-based elastic electrodes. Reproduced with permission.[37] Copyright 2019, Springer Nature. b) Hydrogel-based viscoelastic electrodes. Reproduced with permission.[38] Copyright 2021, Springer Nature. c) Liquid metal-based fluidic cuff electrodes. Reproduced with permission.[39] Copyright 2022, Elsevier. d) Flexible electrodes based on biodegradable substrates. Reproduced with permission.[41] Copyright 2010, Springer Nature. e) Injectable microporous mesh electrodes. Reproduced with permission.[42] Copyright 2015, Springer Nature. f) An integrated interface with thousands of channels by Neuralink. Reproduced with permission.[43] Copyright 2019, JMIR Publications. g) Self-assembled Neurotassels with 1024-channel Reproduced with permission.[44] Copyright 2019, American Association for the Advancement of Science. h) Massively parallel microwire arrays integrated with CMOS chips. Reproduced with permission.[45] Copyright

nerve structures, triggered by body temperature, as illustrated in Figure 2j. This neural interface can be conveniently attached to vagus nerves for electrical stimulation, presenting possible treatments for heart rate variability disorders. The self-climbing property of the electrode not only simplifies the implantation process, but also minimizes tissue damage during device deployment.

In addition, to adapt to growing nerve tissue without imposing mechanical restrictions, Yuxin Liu et al. proposed a morphing neural interface that possesses the ability to dynamically conform to the growth of nerve tissue (Figure 2k).[20d] This advanced interface exhibited a notable ability to expand its diameter by 2.4 times, facilitating continuous chronic electrical neuromodulation for up to two months, while maintaining functional behavior without interruption. The primary materials for the morphing electronics include a viscoelastic conductive PEDOT:PSS/glycerol polymer and a self-healing composite consisting PDMS-isophorone bisurea (IU) and PDMS-IU-4,4′-methylenebis(phenyl urea) (MPU). Kang-Il Song et al. reported an adaptive self-healing electronic epineurium (A-SEE), which facilitated the development of electronic neural interfaces that are free from compressive stress and insensitive to strain. Moreover, the inherent stretchability and self-repairing capabilities of the materials enable the integration of self-locking features in long-term bidirectional neural interfaces. The A-SEE was composed of PDMS-MPU0.4-IU0.6 substrate/insulation layers and self-healing conductive polymer composite electrodes based on silver (Ag) flakes, as shown in Figure 2l. Through A-SEE, successfully bidirectional neural recording and stimulation on sciatic nerves of 14 weeks were accomplished.[20a]

4. Wireless Electrical Neuromodulation Strategies

While traditional wire-based electrical stimulation electrodes have significantly improved patients' quality of life though neuromodulation, several fundamental engineering obstacles required to be overcome to ensure optimal clinical outcomes. One of the main challenges is to miniaturize the implanted devices and provide wireless long-term stable powering for the activation and control of neural interfaces. The aforementioned material strategies and device schemes for wire-based techniques are also applicable for multimodal wireless neural interfaces. Wireless methods based on optoelectronics, piezoelectrics, triboelectrics, magnetoelectrics, inductive coupling and electrochemical reaction can potentially realize fully implantable, miniaturized, and wireless neural stimulation minimizing complications associated with conventional wire connection such as infection risk and inflammatory response.

In **Figure 3**, we illustrate the working principles of representative wireless electrical neuromodulation methods, including optoelectronics, magnetoelectronics, triboelectronics, piezoelectronics, inductive coupling and electrochemical devices. In the optoelectrical method, a heterojunction such as a pn diode is often involved. For example, when tissue penetrating light (red to near-infrared) irradiates at a pn junction interface, the separation of charge carriers occurs in the sense that electrons move toward the n-type side while holes move toward the p-type side. The excessive electrons at the n side can result in cell depolarization and activate action potentials through photocapacitive and/or photoelectrochemical effects.[46] Due to the scattering and absorption by tissues, light penetration depth is often limited. Moreover, mechano-electric stimulation is achieved based on ultrasound or body motion utilizing piezoelectric transducers or triboelectric nanogenerators to convert mechanical vibrations into electrical signals. Ultrasound can enable deeper interaction and the powering of miniaturized bioelectronics in mm size, but it is sensitive to impedance mismatch and misalignment. To couple with ultrasound, a piezoelectric transducer often has a three-layer structure consist of matching layer, piezoelectric layer, and backing layer. The matching layer can improve the energy transmission efficiency by alleviating the acoustic impedance mismatch between piezoelectric materials (≈30 MRayl) and biological tissues (≈1.5 MRayl). The piezoelectric layer can transform acoustic wave into electricity, while the backing layer can be used to dampen the echo to decrease the absorption part of the energy from the backward sound wave.[47] A triboelectric nanogenerator typically consists of two materials with different triboelectric properties, which are referred as the triboelectric layers. When external mechanical force or acoustic wave is applied to the triboelectric nanogenerators (TENG), the triboelectric layers come into contact and then separate, causing the transfer of electrons between the materials due to the triboelectric effect.[48] Magnetoelectric stimulation is an alternative wireless neuromodulation strategy. In this approach, the magnetic field first generates strain in the magnetostrictive layer as the magnetic dipoles rotate to align with the applied field, and then the strain exerts a force on the piezoelectric layer that convert the mechanical signal into electrical field.[49] Magnetoelectrics offer the advantages of device miniaturization and the ability to achieve deep penetration depth by utilizing magnetic fields. On the other hand, inductive coupling is another strategy that utilizes electromagnetic induction to wirelessly induce currents in the target receiver by varying magnetic field between the source and the implant. For self-powered electrochemical devices such as galvanic cells and fuel cells that consist of anode, cathode and electrolyte, the basic working principle involves the conversion of chemical energy into electrical energy through electrochemical reactions.[50] All of the aforementioned methods realize neuromodulation through polarization and depolarization of cell membranes caused by electrical stimulation. By adjusting the parameters of electrical field, different activity can be induced. For example, depolarization can occur through the activation of voltage-gated ion channel and the recruitment of neuronal populations, while inhibition can be achieved by activating inhibitory neurons or by modulating the release of inhibitory neurotransmitters.[51] Specific example

2020, American Association for the Advancement of Science. i) Biodegradable electrodes for pain management. Reproduced with permission.[19a] Copyright 2022, American Association for the Advancement of Science. j) Self-climbing electrodes using shape memory polymeric substrates. Reproduced with permission.[20b] Copyright 2019, American Association for the Advancement of Science. k) Morphing electrodes for neuromodulation in growing tissue. Reproduced with permission.[20d] Copyright 2020, Springer Nature. l) Adaptive self-healing electronic epineurium (A-SEE) for chronic bidirectional neural interfaces. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License.[20a] Copyright 2020, the Authors. Published by Springer Nature.

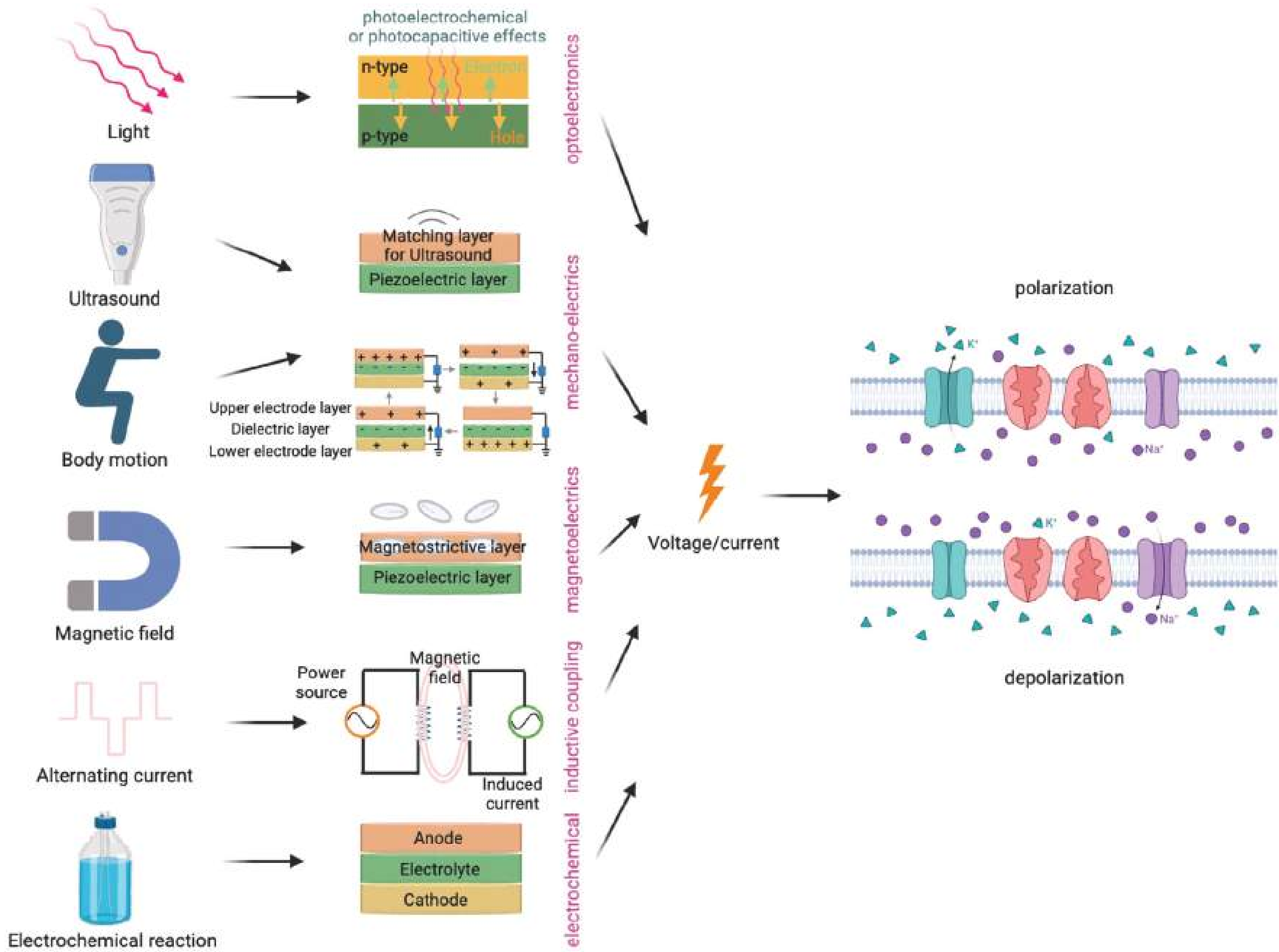

Figure 3. Strategies of wireless electrical neuromodulation.

of each type of wireless neural interface will be discussed in the following sessions.

4.1. Optoelectronics for Neuromodulation

Optically controlled electrical neuromodulation represents a promising wireless and minimally invasive method for the clinical treatment of neurological diseases. For example, to improve both visual acuity and visual field size for patients in one wireless optical device, Laura Ferlauto et al. developed a foldable photovoltaic wide-field epiretinal prosthesis that can be implanted through a small scleral incision, offering wireless stimulation of retinal ganglion cells for individuals with blindness (**Figure** 4a).[52] The prosthesis was composed of PDMS as both the substrate and encapsulation materials, and 2 215 stimulating pixels (80 and 130 µm in diameter) that consist of PEDOT:PSS bottom anodes, P3HT:PCBM semiconductor layers, and Ti top cathodes. Moreover, the inherent versatility of PDMS molds used for creating PDMS substrates and encapsulation layers facilitates the development of an optimized retinal prosthesis that can be tailored to meet individual needs. Moreover, the design of implantable devices intends for chronic wireless modulation necessitates consideration of long-term safety and reliability. To address these requirements, Malin Silverå Ejneby et al. leveraged organic molecular thin films to construct an implantable photocapacitor capable of transducing deep-red light (wavelength of 638 nm or 660 nm) into electrical currents as illustrated in Figure 4b.[25] This innovative approach enabled successful stimulation of the sciatic nerve in rats for a duration exceeding 100 days. In the photocapacitor, phthalocyanine (H_2Pc) serves as the p-type semiconductor, *N,N'*-dimethyl perylenetetracarboxylic bisimide (PTCDI) as the n-type semiconductor, parylene C as the substrate material, and evaporated thin Au films with thickness of 10 nm as the semi-transparent conducting back electrode layer on the substate. The device size is up to 3 mm in diameter. Transdermal light irradiation (638 nm diode laser with 2×2 mm^2 spot, maximum of 700 mW) on the implanted photocapacitor can activate repeatable compound muscle action potentials (CMAPs) and associated large-amplitude muscular twitches.[25]

In addition, silicon (Si) is a highly advantageous material among the available candidates for converting light into electrical cues, due to its tunable electrical and optical properties, versatile formats, capacity to absorb a wide range of light, and

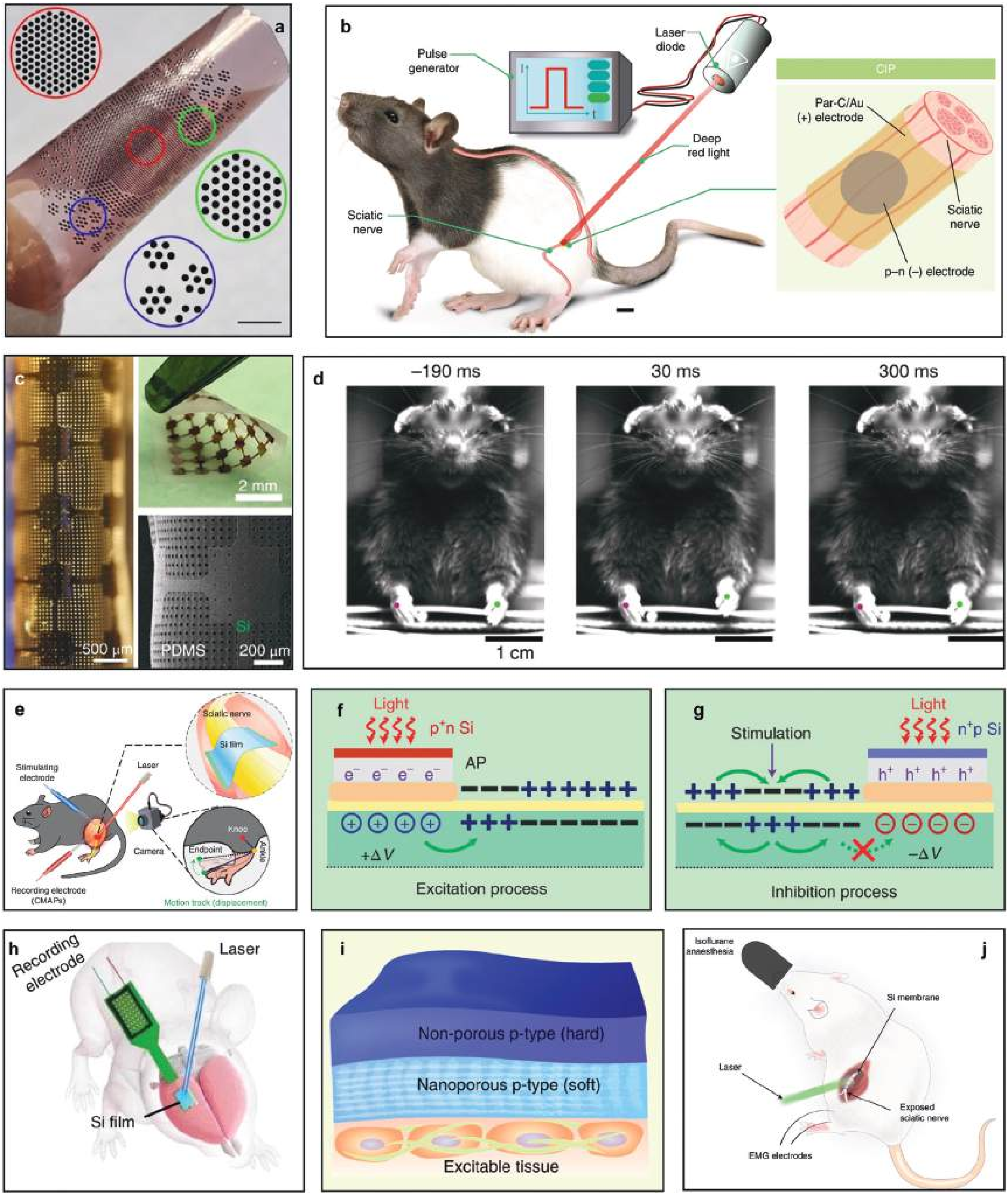

Figure 4. Optoelectronics for neuromodulation. a) A foldable photovoltaic wide-field epiretinal prosthesis. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License.[52] Copyright 2018, the Authors. Published by Springer Nature. b) An organic photocapacitor to chronically stimulate the sciatic nerve in rats. Reproduced with permission.[25] Copyright 2022, Springer Nature. c) A Si-based flexible neural interface. d) Snapshots of flexion-extension movement of forelimb after optoelectronic stimulation. Reproduced with permission.[53] Copyright 2018, Springer Nature. e) A bioresorbable Si diode implanted on the sciatic nerve to modulate the hindlimb movement. f) Mechanism of the excitation process. g) Mechanism of the inhibition process. h) A Si diode implanted on the mouse brain to excite or inhibit neural activity. Reproduced with permission.[54] Copyright 2023, Springer Nature. i) A porosity-based heterojunction in p-type Si on the tissue surface. j) A flexible Si membrane wrapping around the sciatic never to selectively activated different muscles determined by EMG. Reproduced with permission.[55] Copyright 2022, Springer Nature.

excellent biocompatibility and biodegradability. Yuanwen Jiang et al. conducted a thorough analysis of material structures and mechanics, which established a rational set of design principles for silicon-based neural interfaces, which include configurations for intracellular (nanowire structures), intercellular (planar structures), and extracellular (mesh structures) applications.[53] Figure 4c illustrates the flexible device consisting of a stack of a distributed Si mesh and a holey PDMS membrane used to create a conformal interface with biological organs such as brain cortex. When illuminating the Si mesh attached on the right side of the forelimb primary motor cortex in rat, a rapid flexion-extension movement of contralateral left forelimb was evoked, and vice versa (Figure 4d). Furthermore, Yunxiang Huang et al. reported a bioresorbable thin-film monocrystalline Si pn diode to optoelectronically excite or inhibit neural activities through constructing polarity-dependent positive or negative photovoltages on interfaces (Figure 4e).[54] The thin-film Si diodes are decorated by a thin layer of Au nanoparticles to improve stimulation efficacy and were transformed onto a flexible polyethylene terephthalate (PET) substrate to achieve a flexible device. In vitro results showed that the p^+n structure realized photoexcitation by inducing more positive charges in cells that can cause cell depolarization and evoke CMAPs (Figure 4f). By contrast, the n^+p structure can alternatively achieve photoinduced inhibition through generating more negative charges in cells that block the positive-charged signal transmission and suppress CMAPs (Figure 4g). The optoelectrical modulation of thin-film Si diodes on sciatic nerve with a laser beam (635 nm) evoke a significant hindlimb motion. Besides, this p^+n Si diodes can also cause photoactive results when mounted on the cerebral cortex (Figure 4h), while obtain photoinhibition effects by reversing the diode polarity (n^+p).[54] However, the formation of semiconductor junctions often necessitates the utilization of materials with distinct doping, resulting in increased costs, intricate fabrication processes, and the potential for adverse effects. In order to mitigate these concerns, Aleksander Prominski et al. introduced a porosity-based heterojunction in pure-silicon that exhibits an efficient photoelectrochemical response, as shown in figure 4i.[55] Additionally, they demonstrated the utility of these materials by creating a flexible silicon membrane and performing optoelectrical stimulation on the sciatic nerve in rats. The results indicated that the device was capable of eliciting action potentials and selectively triggering different muscles to varying degrees, as determined by EMG, through alterations in laser beam power and positioning (Figure 4j). Overall, optoelectronics has the advantages of miniaturization to sub-mm size. However, the output power drops linearly with decreased size and the penetration depth is limited due to light scattering and absorption by biological tissues. Optoelectronic devices are therefore expected to be suitable for low-power neural modulation, with sub-mm size, and positioned a few mm beneath the skin.

4.2. Mechano-Electric Devices for Neuromodulation

Ultrasound[56] or body motions[57] can provide mechanical forces that can be converted into electrical energy for neural stimulation through the use of piezoelectric[58] or triboelectric transducers.[59] As ultrasound utilizes high frequency sound waves that transmit well through soft tissues,[60] it allows stimulation in deep tissues[61] and the reduction of implant size.[62] Ultrasonically powered electrical neuromodulation based on piezoelectric or triboelectric devices have therefore attracted great interests and have been extensively investigated.[63] For example, Ping Chen et al. proposed an implantable nerve stimulator that responds to ultrasound, utilizing soft PENGs comprised of inorganic piezoelectric particles and organic piezoelectric films.[63a] They successfully achieved direct and controllable electrical stimulation of sciatic nerves in rodents by wirelessly programming external ultrasonic pulses. Piezoelectric films (≈30 µm) containing $0.5Ba(Zr_{0.2}Ti_{0.8})O_3$-$0.5(Ba_{0.7}Ca_{0.3})TiO_3$ (BZT-BCT) nanowires and PVDF polymers served as the transducer and were subcutaneous implanted. This work eliminates the requirement for wired-based power sources or batteries. (**Figure 5a**). The development of a highly miniaturized wireless stimulator offers significant benefits, including enhanced safety, improved access to anatomical locations, and the facilitation of minimally invasive delivery. These advantages also help reduce tissue trauma during implantation and minimize immune responses.[64] Utilizing ultrasound as an effective means for powering and communicating with tiny implants deep within tissues, David K. Piech et al. introduced one of the smallest neural stimulators ("StimDust", 1.7 mm^3), moving past the trade-off between safe, predictable stimulation and compact stimulator size as shown in Figure 5b.[26] This implantable neural stimulator permits ultrasonically powered two-way communication and has demonstrated various stimulation-induced physiological responses.

TENG can work as an alternative transducer that transforms ultrasonic vibrations into electricity.[65] Hydrogel-based materials with acoustic impedance similar to tissue offer significant advantages in the in vivo harvesting of ultrasound energy. In particular, a liquid-based TENG[66] has been proposed to deliver alternating current by utilizing ultrasound-induced vibrations in a compressible double electric layer at the conductive hydrogel/electrolyte interface. Moreover, Ping Chen et al. investigated implantable, programmable and battery-free neurostimulators utilizing high-performance hydrogel nanogenerators (HENG) based on polyacrylamide/graphene conductive hydrogels, achieving real-time responsiveness to programmable ultrasound pulses and stimulating the vagus nerves for anti-inflammatory therapy in sepsis.[63b] As shown in Figure 5c, HENG driven by ultrasound can deliver a power density of 0.3 W cm^2, and the inhibition of pro-inflammatory cytokines has been shown through ultrasound therapy.

To avoid potential risks of infection posed by a second surgery operation to remove the implanted neural interface,[67] several research groups have explored biodegradable mechano-electric devices.[68] Ping Wu et al. utilized ultrasound-driven wireless and biodegradable PENGs to achieve in vivo electrical stimulation and real-time monitoring of peripheral nerve tissue repair, which can play an important role in promoting neural regeneration, as well as other tissue regeneration processes.[69] As shown in Figure 5d, composites consisting potassium sodium niobate (KNN) and poly (L-lactic acid) (PLLA)/poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) are used as the piezoelectric transducer. Upon the application of external ultrasound stimulation, the degradable PENG can deliver electrical cues to the conductive nerve conduit without any percutaneous leads to promote

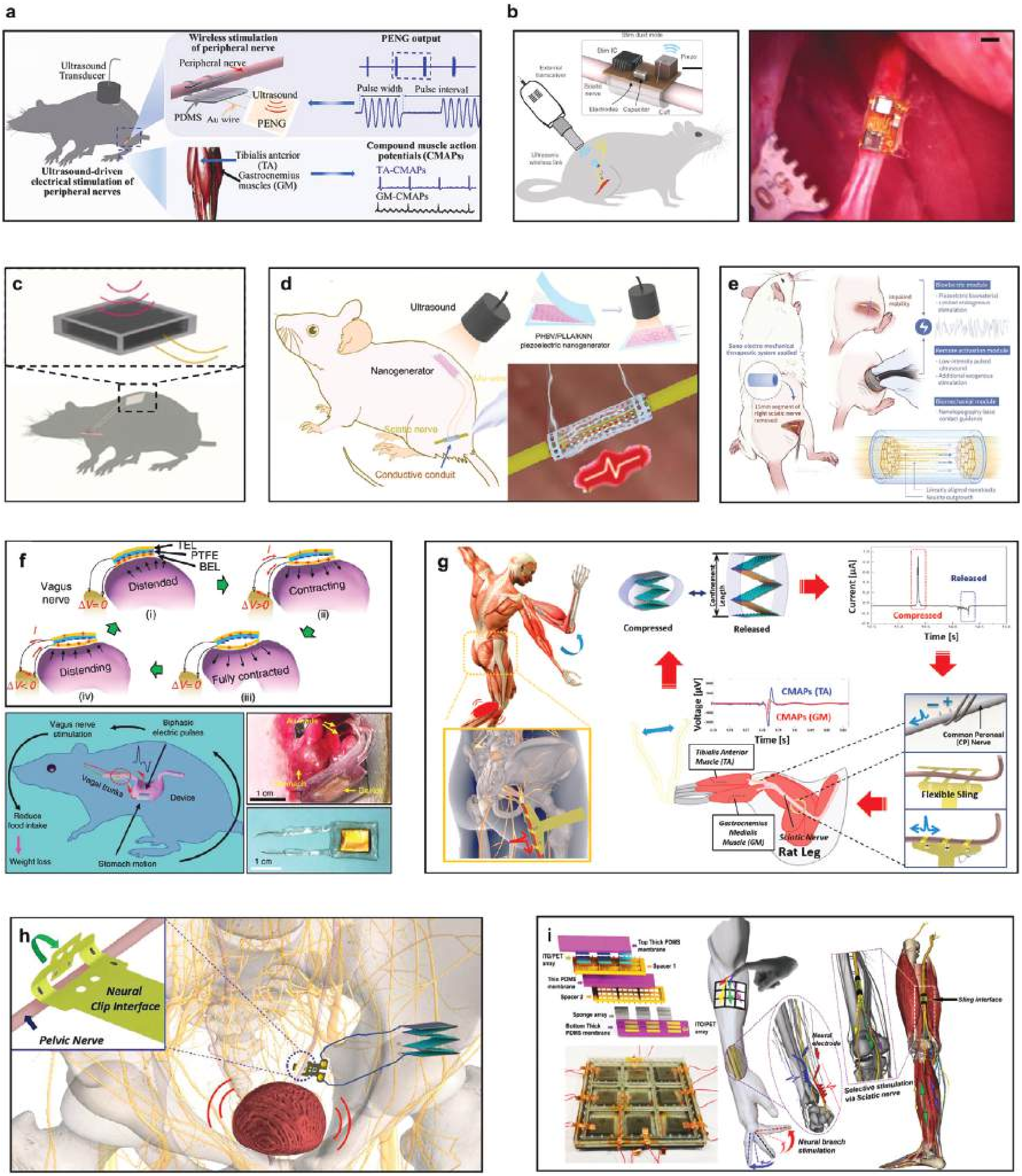

Figure 5. Mechano-electric devices for neuromodulation. a) US induced programmable stimulation of peripheral nerves in rats with soft PVDF/BZT-BCT@PDA piezoelectric thin films as the transducer. Reproduced with permission.[63a] Copyright 2021, Elsevier. b) A ultrasonically powered millimeter-scale neural stimulator (StimDust). Scale bar: 1 mm. Reproduced with permission.[26] Copyright 2020, Springer Nature. c) A ultrasonically powered vagus nerves stimulators based on implantable high-performance hydrogel nanogenerators for the anti-inflammatory therapy of sepsis. Reproduced with permission.[63b] Copyright 2021, Elsevier. d) The delivery of in vivo electrical stimulation via ultrasound transduced by degradable PHBV/PLLA/KNN nanogenerator to promote peripheral nerve regeneration. Reproduced with permission.[69] Copyright 2022, Elsevier. e) Biodegradable sono-electro-mechanical PCL/PVDF nanotracts converting exogenous and endogenous mechanical forces to electrical stimulation for peripheral nerve regeneration. Reproduced with permission.[68] Copyright 2023, Elsevier. f) Flexible vagus nerve stimulation (VNS) device based on a triboelectric nanogenerator.

tissue regeneration. In addition, Wei Pi et al. developed a multimodal sono-electro-mechanical approach that synergistically integrated electrical stimulation induced by low-intensity pulsed ultrasound (LIPUS) and topological structural guidance for the purpose of long-gap peripheral nerve repair.[68a] As shown in Figure 5e, the nano-topography is derived from biodegradable directional piezoelectric nanofibers composed of polycaprolactone (PCL) and polyvinylidene fluoride (PVDF) fabricated by electrospinning. This sono-electro-mechanical therapeutic system successfully restored motor functions and axonal maturity in rodents.

Besides external ultrasound, human body motion can also deliver mechanical force[47b,48a,70] to generate electricity for neural stimulation through piezoelectric[71] or triboelectric transducers.[72] For example, Guang Yao et al. developed a flexible and biocompatible TENG that adhered to the stomach's surface, responding to its peristalsis, and producing biphasic electrical pulses.[59] The self-responsive device was connected to vagal afferent nerve fibers and enabled neural modulation that reduced food intake and ultimately achieved weight control (Figure 5f). Moreover, TENG can achieve greater power output by stacking multiple layers.[73] Sanghoon Lee et al. demonstrated wearable stacked TENGs acted as a neural interface to stimulate the sciatic nerve to activate the anterior tibial anterior muscle without damage (Figure 5g).[74] As shown in Figure 5h, electrical cues generated by the stacked TENG by the motion of fingers can also be applied onto the pelvic nerve of rats to regulate bladder function. The same group also developed a flexible neural clip (FNC) that has been adopted as a promising method for achieving a reliable and long-term nerve interface for self-powered mechano-neuromodulation to modulate bladder functions.[75] Moreover, the water/air-hybrid triboelectric nanogenerator (WATENG) has also been proposed in order to achieve efficient nerve stimulation by the same group.[76] As shown in Figure 5i, efficient stimulation of sciatic nerves using better linear control can lead to the selective activation of leg muscles, with the level of muscle activation modifiable by adjusting the applied pressure. The integration of battery-free and WATENG can effectively provoke plantar flexion (PF) and ankle dorsiflexion (DF) via the tibial and common peroneal nerve branches.

In all, body motion can enable self-powered electrical stimulation through implantable piezoelectric or triboelectric devices, eliminating the need of external equipment. However, the selection of implantation sites may be limited to locations where adequate body movement is accessible. On the other hand, ultrasonically powered stimulation allows miniaturized implants in mm size and penetration depth to 1–2 cm, which could potentially allow minimally invasive delivery of implants through laparoscopy or injection to reduce tissue trauma and inflammation response. Nevertheless, ultrasound is highly sensitive to impedance mismatch at the interface, requiring direct contact between the ultrasound transmitters and the skin with the use of acoustically matching gels.

4.3. Magnetoelectric Devices for Neuromodulation

Magnetoelectric devices can be driven at weak magnetic fields on the order of a few mT,[77] and possess advantages of miniaturization[78] and deep penetration depth[79] utilizing magnetic fields, which makes magnetoelectrics a promising strategy for wireless neuromodulation.[80] With tunable stimulation parameters and patterns, magnetoelectric nanoparticles (MENPs) have been investigated for therapeutic functions.[81] It has been successfully demonstrated that MENPs can be delivered to the brain via blood brain barrier in a non-invasive and brain-cell compatible way.[82] To achieve desirable conversion efficiency, MENPs is constructed with a ferromagnetic core and a piezoelectric shell to generate electric fields when an alternating magnetic field is applied. For example, Yusheng Zhang et al. reported a magnetoelectric core/shell structure composed of Fe_3O_4/$BaTiO_3$ (FO/BTO) nanoparticles for remote delivery of electrical cues.[80a] FO/BTO nanoparticles were loaded in a hydrogel designed to mimic the native neural extracellular matrix (ECM). This was to facilitate in vivo electrical stimulation via magnetic fields, thereby regulating neurogenesis at both the cellular level and in cases of in vivo SCI (**Figure 6**a). Moreover, Amanda Singer et al. successfully achieved miniaturization of magnetoelectric device to mm scale, comparable to the size of a grain of rice. When fully implanted into the skin, the device effectively stimulated the brains of freely moving rodents for the treatment of Parkinson's disease (Figure 6b).[80b]

Furthermore, the miniaturized magnetoelectric devices can enable minimally invasive endovascular neuromodulation through percutaneous catheters.[27,80b] Joshua C. Chen et al. proposed a millimeter-scale MagnetoElectric-powered Bio ImplanT (ME-BIT) to deliver electricity and receive data through percutaneous catheters in vasculature.[77] Endovascular nerve stimulator devices were implanted near the femoral artery in pigs and the leads were introduced into the blood vessel which successfully stimulate adjacent nerve targets (Figure 6c). This work offers new avenues for minimally invasive bioelectronic therapies based on endovascular nerve stimulator (EVNS), opening up exciting opportunities for future medical treatments. Additionally, magnetoelectric devices can also serve as power sources for electrical therapies of wearable systems.[83] For example, Fatima T Alrashdan et al. reported a proof-of-principle wearable wireless Power Transfer (WPT) system for ME-BIT.[27] Weighing less than half a pound, the wearable transmitter was able to provide a sufficient magnetic field to power ME-BIT for different types of nerve stimulation at a distance of 4 cm, which demonstrated the practicality of a wearable system to power miniaturized ME implants (Figure 6d). Overall, magnetoelectric

The stimulation of vagal afferent nerve fibers can reduce food intake and achieve weight control. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License.[59] Copyright 2018, the Authors. Published by Springer Nature. g) TENGs driven by muscle movement from human body generate electrical stimulation to sciatic nerves and peroneal nerves to activate tibialis anterior muscles. Reproduced with permission.[74] Copyright 2017, Elsevier. h) Mechano-electric device based a stacked TENG and flexible neural clip interface to modulate bladder function by pressing and releasing of fingers. Reproduced with permission.[75] Copyright 2019, Elsevier. i) Water/air-hybrid triboelectric nanogenerator (WATENG) for multiple and selective activation of muscles. Reproduced with permission.[76] Copyright 2018, Elsevier.

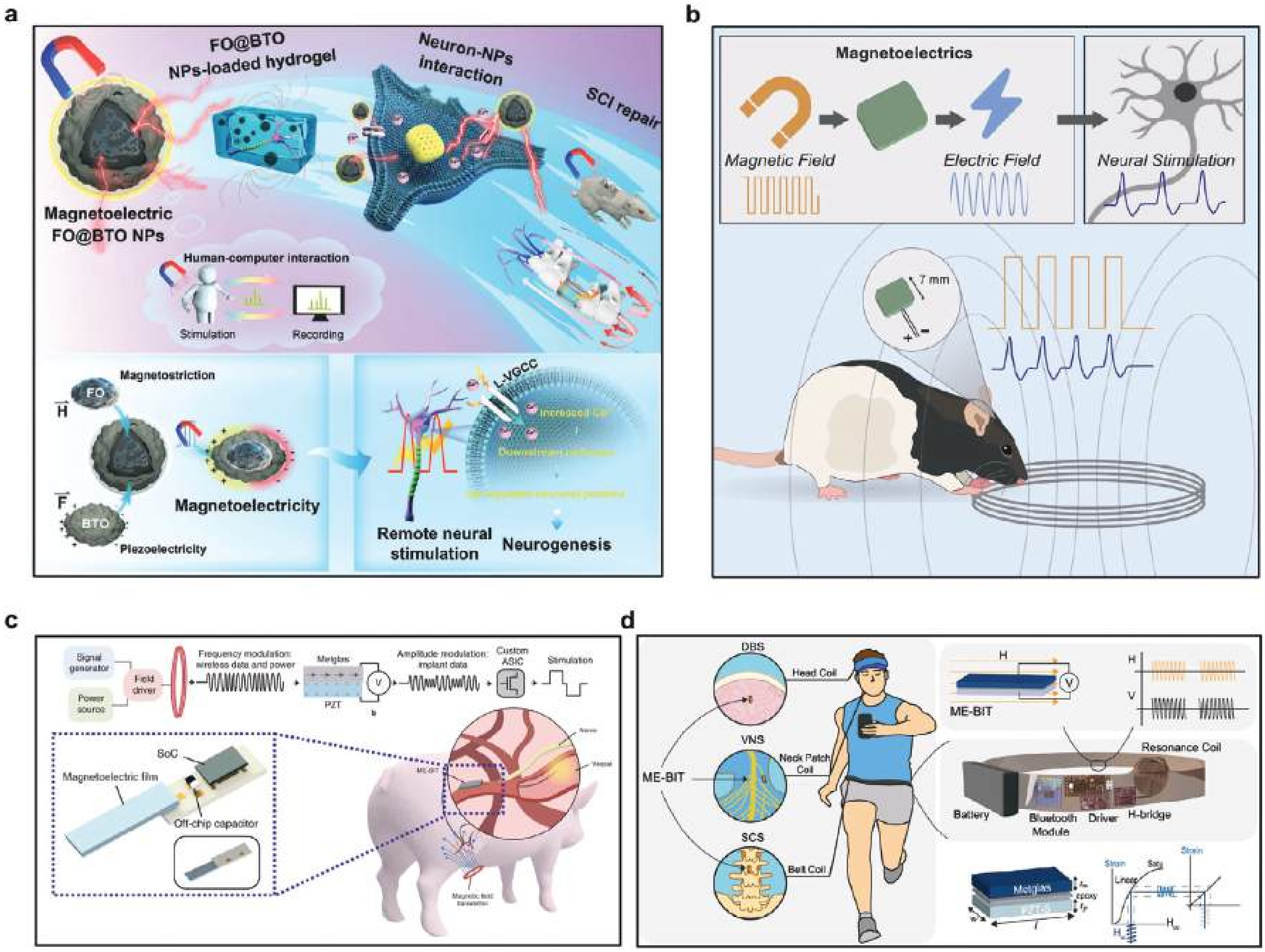

Figure 6. Magnetoelectric devices for nerve regulation. a) Remote electrical stimulation based on magnetoelectric FO@BTO nanoparticles for the regulation of neurogenesis and repair of spinal cord injury. Reproduced with permission.[80a] Copyright 2021, Wiley-VCH. b) Magnetoelectric devices enable miniaturized magnetically powered neural stimulators for therapeutic deep brain stimulation in a freely moving rodents with Parkinson's disease. Reproduced with permission.[80b] Copyright 2020, Cell Press. c) MagnetoElectric-powered Bio ImplanT (ME-BIT) implanted proximally to blood vessels and wirelessly powered by a magnetic coil and. The leads are percutaneously delivered into the vasculature and successfully stimulate adjacent nerve targets. Reproduced with permission.[77] Copyright 2017, Springer Nature. d) Wearable ME-BIT for different types of nerve stimulation. Reproduced with permission.[27] Copyright 2021, Springer Nature.

devices have the advantages of miniaturization, great penetration depth, desirable power levels (≈mW), and improved tolerance of misalignment. They are suitable for nerve stimulation with mm-sized implants and penetration depth of a few cm.

4.4. Inductive Coupling Devices for Nerve Stimulation

Inductive coupling devices represent one of the most widely employed wireless energy transfer method for electrical stimulation. For example, Iman Habibagahi et al. demonstrated a device system that wirelessly powered vagus nerve stimulation in pigs, with an operational depth of over 5 cm utilizing inductive coupling at a frequency of 13.56 MHz, as depicted in **Figure** 7a.[84] This system showed comparable efficiency in reducing heart rate to conventional wire-based systems. To eliminate the need for secondary surgeries in short-term therapies, Jahyun Koo et al. developed a bioresorbable wireless stimulator based on inductive coupling for peripheral nerve regeneration.[28] The receiver consisted of two Mg coils forming a bilayer loop antenna, a PLGA dielectric interlayer, a diode constructed from doped Si nanomembranes, and a Mg/silicon dioxide (SiO_2)/Mg capacitor (Figure 7b). Monophasic electrical impulses ranging from 100–300 mV was successfully generated at the nerve interface, with effective operation at distances of up to 8 cm. Furthermore, the device exhibited complete degradation within 25 days in a PBS solution, as shown in Figure 7c. In general, inductive coupling performs well with relatively large devices (5–10 mm) and small misalignment. It is able to deliver high power (up to ≈10 mW) with excellent penetration depth (several cm).[85]

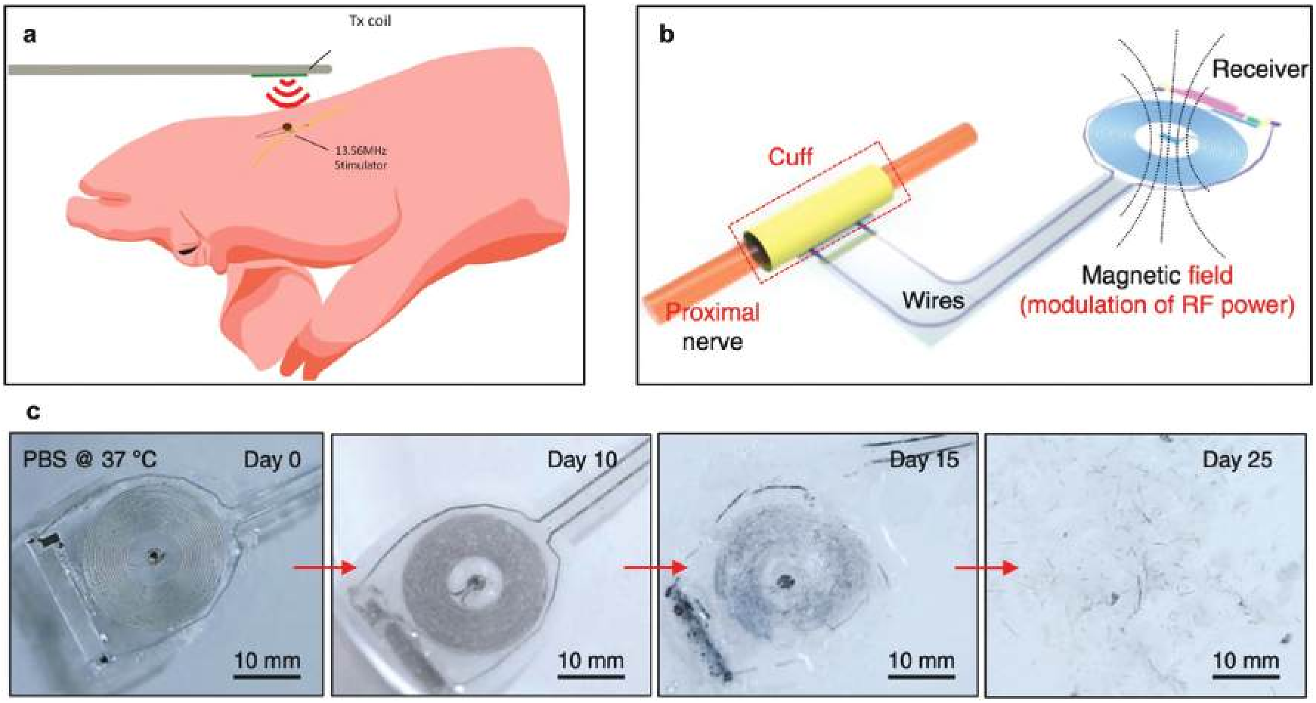

Figure 7. Inductive coupling devices for nerve stimulation. a) A wirelessly powered vagus nerve stimulator in pigs using inductive coupling at 13.56 MHz. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License.[84] Copyright 2022, the Authors. Published by Springer Nature. b) A bioresorbable wireless stimulator based on inductive coupling for peripheral nerve regeneration. c) Dissolution process of the bioresorbable wireless stimulator in a PBS solution. Reproduced with permission.[28] Copyright 2018, Springer Nature.

4.5. Electrochemical Devices for Nerve Stimulation

Neuromodulation interfaces powered by miniaturized electrochemical devices such as fuel cells that are exploiting glucose and oxygen, and primary batteries that are utilizing physiological fluids present in human body have drawn increasing attention as they can achieve self-powering and eliminate the need of external equipment such as coils or ultrasound sources. For instance, Yi Sun et al. reported a self-powered electrical stimulation device that consumes glucose and oxygen in human body, as shown in **Figure** 8a. This device generated a potential of ≈300 mV and has been shown to enhance neurite length of dorsal root ganglions in vitro and promote nerve regeneration in vivo. This device was composed of platinum nanoparticles as the anode, nitrogen-doped carbon nanotubes as the cathode, and an in situ polymerized polypyrrole on the nanofibers of bacterial cellulose as the conductive substrates.[30] To enhance power efficiency, Luhe Li et al. proposed a zinc-oxygen primary battery using body fluid as electrolyte, with a high volumetric energy density of 231.4 Wh cm^{-3} and a small volume of 0.86 mm^3. The battery served as the power source for electrical stimulation to promote the regeneration of injured sciatic nerve. The battery was composed of PLGA substrates with aligned structure, Zn wire anodes, carbon nanotube/platinum film cathodes, and a PLGA encapsulation layer (Figure 8b).[86] Liu Wang et al. developed a bioresorbable and self-electrified device consisting of a galvanic cell.[29] The cell was made of Mg and iron-manganese alloy and was integrated with a multilayer conduit comprising porous PCL and PLLA-PTMC to promote peripheral nerve regeneration (Figure 8c). Successful peripheral nerve regeneration and motor functional recovery in SD rats were achieved. The device is completely biodegradable, thereby eliminating the need for retrieval procedures and minimizing the associated risk of infection. Overall, electrochemical devices offer the advantage of self-powered electrical stimulation, eliminating the reliance on external equipment and therefore minimizing interference with routine activities. The flexibility in implantation location allows for applications in deep tissues. As power decreases with device size, further research on electrochemical devices with higher power density holds potential for expanding opportunities in various types of neuromodulations.

5. Conclusions

This review highlights the state-of-the-art approaches in electrical neuromodulation, with a focus on recent advancements in materials options and device schemes of neural interfaces and multimodal wireless stimulation methods.

First, the properties of neural interface, such as flexibility, biodegradability, miniaturization, self-healing capabilities, have significant impacts on therapeutic outcomes of neuromodulation. These characteristics are closely related to chosen materials and device schemes, and therefore innovative materials and device structure are critical to maximize stimulation efficacy. For example, the development of soft and biocompatible materials is critical for establishing stable interfaces that minimize immune responses. When paired with robust encapsulation materials, long-term neural interfaces become attainable. Moreover, the

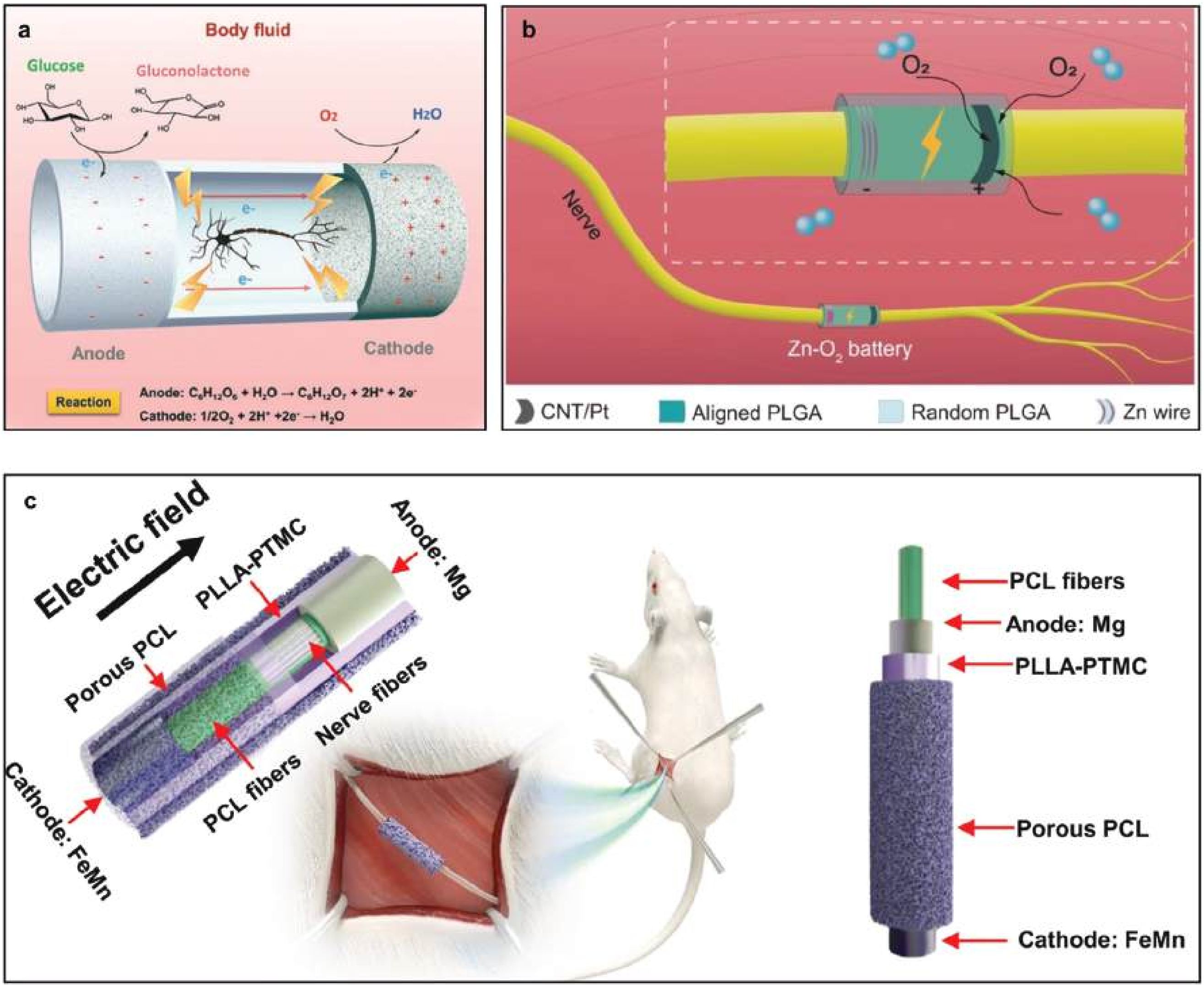

Figure 8. Electrochemical devices for nerve stimulation. a) A self-powered glucose fuel cell for sciatic nerve regeneration. Reproduced with permission.[30] Copyright 2019, Wiley-VCH. b) A zinc-oxygen battery for injured long-segment sciatic nerve repair. Reproduced with permission.[86] Copyright 2023, Wiley-VCH. c) A fully biodegradable and self-electrified device based on Mg-FeMn galvanic cells for sciatic nerve regeneration. Reproduced with permission.[29] Copyright 2020, American Association for the Advancement of Science.

incorporation of stretchable materials is essential to achieve extended operational periods in highly mobile body areas. Exploration of materials that enable durable adhesion at the device/tissue interface is also crucial to maintain prolonged effective neural stimulation. By contrast, studies on versatile biodegradable materials and devices for neuromodulation offers alternative solutions for temporary treatments, eliminating unnecessary materials retention and avoid retraction surgeries, which is essential for clinical applications of electrical therapy. Achieving controllable degradation rates to ensure suitable lifetimes for various targeting applications remain a challenge. Stimuli-responsive and shape memory materials with smart functionalities, such as self-healing, self-rolling, self-expansion, or morphing, enable biomimetic devices to more effectively adapt to dynamic and complex biological structures. Moreover, electrode materials with high spatiotemporal resolutions are essential to enable site specific stimulation at sub-cellular dimensions.

Second, wireless techniques provide a number of advantages over conventional wired-based methods. However, it is important to acknowledge that there are also inherent limitations to different approaches. Optical method, for instance, have limitations in terms of penetration depth, resulting in limited modulation distances. Force-driven piezoelectric and triboelectric methods necessitate implantation in frequently moving locations. Although ultrasound-driven piezoelectric and triboelectric methods do not require implantation in frequently moving locations, they are very sensitive to misalignment and acoustic matching layers needs to be carefully designed. Similarly, inductive coupling methods typically require precise alignment, proximity between the transmitter and receiver coils, and relatively large device geometry. Enzymes employed as catalysts in biofuel cells facilitating the conversion of biological fuels can be susceptible to the surrounding conditions, including temperature and pH. Miniaturizing and extending the operational lifetime present challenges when it comes to integrating primary batteries into minimally invasive applications for longer-term use. While it may be challenging to meet all requirements with a single technique, selecting the appropriate approach for a specific application can ensure optimal efficacy. Going forward, integrating different modes of wireless approach can minimize the limitation of a single method and could potentially create a network for multi-channel stimulation. The incorporation of feedback devices allows close-loop systems to enable precise modulation of neural activity.

Third, simulation and modeling techniques could provide powerful routes to optimize the arrangement of stimulation sites and associated parameters. To further enhance the effectiveness of neural modulation, it is also crucial to precisely identify neural circuits associated with different diseases and selectively stimulate the key sites within these circuits. Additionally, the integration of machine-learning techniques with medical databases can offer efficient and precise insights into health status and progression, which is crucial for optimizing intervention strategies. Collectively, these interdisciplinary strategies will boost the development of robust, efficient, and minimally invasive electrical neuromodulation systems to achieve optimal therapeutic outcomes in the treatment of neurological diseases.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

electrical neuromodulation, flexible, multifunction, neural interfaces, wireless

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