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Advances in Triboelectric Nanogenerators for Self-powered Neuromodulation

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Advances in implantable bioelectronics for the nervous system are reinventing the stimulation, inhibition, and sensing of neuronal activity. These efforts promise not just breakthrough treatments of several neurological and psychiatric conditions but also signal the beginning of a new era of computer-controlled human therapeutics. Batteries remain the major power source for all implanted electrical neuromodulation devices, which impairs miniaturization and necessitates replacement surgery when the battery is drained. Triboelectric nanogenerators (TENGs) have recently emerged as an innovative power solution for self-powered, closed loop electrical neurostimulation devices. TENGs can leverage the biomechanical activities of different body organs to sustainably generate electricity for electrical neurostimulation. This review features advances in TENGs as they pave the way for self-sustainable closed loop neurostimulation. A comprehensive review of TENG research for the neurostimulation of brain, autonomic, and somatic nervous systems is provided. The direction of growth of this field, publication trends, and modes of TENG in implantable bioelectronics are also discussed. Finally, an insightful outlook into challenges facing self-sustainable neuromodulators to reach clinical practice is provided, and solutions for neurological maladies are proposed.

1. Introduction

Rapid innovation in implantable biomedical devices has allowed innovative treatments for many neurological diseases and the connection of humans to computers.[1] Implantable electrical neuro-stimulators and sensors are rapidly emerging as a new paradigm in nervous system-machine bioelectronics.[2] Fast-growing commercialization efforts by many companies such as Neuralink and others are underway to create next generation neuromodulation bioelectronics.[1a,3] In the process of electrical neuromodulation, the neuronal activity of the central or the peripheral nervous system is regulated by electrical signals from the implantable devices.[4] Examples of electrical neuromodulation devices are deep brain,[5] cortical,[6] vagus nerve,[7] spinal cord,[8] and muscle stimulators.[9] These neuromodulation bioelectronics significantly improve the patient's quality of life, allowing the management of multiple neurological conditions such as epilepsy,[10] Parkinson's disease,[11] essential tremors,[12] psychiatric disorders,[11b,13] and chronic pain.[14]

Batteries are the sole power source for all commercially available implanted electrical neuromodulators. Some neuromodulators are powered by non-rechargeable batteries, and the implanted device must be replaced when the battery is drained. This exposes the patients to risk of infection, pain, and extra costs of surgeries. Some neuromodulators are powered by rechargeable batteries that have longer lifespan before replacement surgery is necessary. However, the routine recharging process is significantly discomforting to patients.[15] Therefore, battery-free,

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and long-lasting power approaches would make a huge impact on the fast adoption of implantable neuromodulators and the patient treatment experience.

Several strategies for battery-free implantable neuromodulators have been explored that led to important advances in sensing, stimulation, and controlled drug delivery to the brain and nerves.[16] External power transmission strategies such as ultrasound transduction,[17] near-field magnetic resonant coupling,[18] far-field RF,[19] and photon dependent power transmission[20] can efficiently deliver a stable and sufficient power supply, but they depend on power sources external to the body for operation, making them suitable for temporary applications only. In contrast, implantable energy harvesting technologies such as triboelectric and piezoelectric nanogenerators do not need external power transmission but rather harvest the internal biomechanical energy of body organs.[21] These nanogenerators have the potential to work as long-term, potentially life-lasting power sources for implantable neuromodulators. However, they face some challenges that need to be overcome to reach clinical maturity that we will discuss in detail this review.

Triboelectric nanogenerators (TENGs) have attracted attention as energy harvesters for implantable biomedical devices due to high flexibility, variety of operational modes, ease of fabrication, low cost, and diversity of materials.[22] The mechanism of TENG's energy harvesting is based on two phenomena named triboelectrification and electrostatic induction.[23] TENG was invented by Z.L. Wang and his research team in 2012.[24] Since inception, the number of TENG publications per year grew significantly based on the analysis of the published literature from the citation database Scopus (**Figure 1**A). Several innovations in the design, materials, energy management, and in vivo implantation have been achieved leading to significant enhancement of power output pushing the boundaries of these devices closer to commercial adoption.[21a,25] TENGs are linked to the growing field of self-powered brain and nerve stimulation and sensing as reflected in the data extracted from Scopus (Figure 1B).

In this review, we discuss advances in leveraging the TENG technology in neuromodulation, growth of the field and trends of publications. In addition, we discuss the different modes of TENGs specifically in implantable neuromodulation, highlighting challenges, and insights into future integration. Neurostimulation of brain and peripheral nervous systems including somatic and autonomic nerves and their therapeutic effects have been comprehensively discussed (**Figure 2**). Finally, we discuss current challenges and future research opportunities for TENGs to reach commercial maturity and inspire the future paradigm of self-powered neuromodulators.

2. Modes of TENGs in Implantable Bioelectronics

TENGs have the advantage of working under different modes that allow multiple options during TENG implantation, integrations, and customization for implantable bioelectronics.[23a] While not all common modes of TENG have been explored in implantable bioelectronics, we summarize here the four main modes and discuss their mechanism, examples of implantable applications, and the outlook of using each mode for future implantable TENGs (**Figure 3**).

2.1. Contact Separation Mode

This is the most common mode in implantable TENGs used for neuromodulators and other implanted bioelectronics. In this mode, a contact and separation occur between the two triboelectric layers in response to an external stimulus such

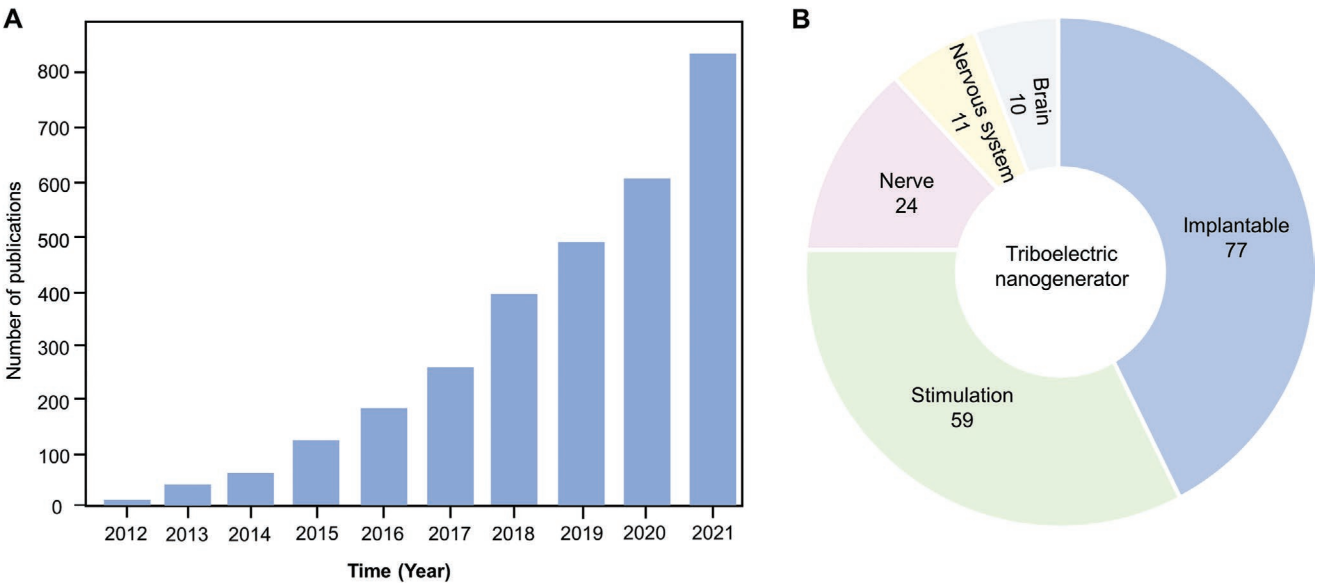

Figure 1. A). Growth in the number of publications in the field of TENGs over the past decade reflecting increasing interest in TENG research. B). Summary of the number of publications when the words "triboelectric nanogenerator" are combined with common words related to neuromodulation. Data were extracted from Scopus search in February 2022 for the appearance of these common words in title, abstract, and keywords of publications when combined with the words "triboelectric nanogenerator". This shows the growth of this new field.

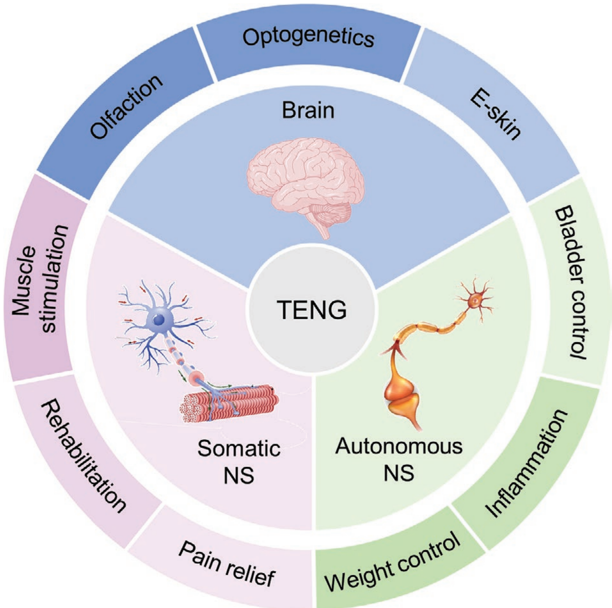

Figure 2. Overview of the role played by TENGs in the neuromodulation of brain, somatic, and autonomous nervous systems. In addition, the outer panel shows the research direction of the published work to date.

as the biomechanical movement of internal body organs in what is known as triboelectrification. In this process, opposite charges build up on the two triboelectric layers. When the two triboelectric surfaces of TENG are separated, a potential difference is generated that drives the electrons to flow between the external electrodes as the result of electrostatic induction until a balanced charge condition is reached (Figure 3A). This contact separation can occur between two tribo-dielectric layers or dielectric and metallic layers.[26] This mode is especially advantageous for neuromodulation implants due to the confined spaces inside the human body and the ability to harvest biomechanical energy without the necessity of extensive stretching or sliding.

2.2. Lateral Sliding Mode

In the lateral sliding mode, the structure of the TENG device is similar to that of the vertical contact separation mode above. However, the direction of the applied mechanical force is different. While the contact separation mode normally requires a mechanical force perpendicular to the triboelectric surfaces, the lateral sliding mode requires a mechanical force parallel to the triboelectric surfaces causing the sliding of one triboelectric layer over the other (Figure 3B). During the process of frictional sliding, the opposite triboelectric charges are generated between the two dielectric tribo-layers leading to a potential difference and a flow of electrons between the two electrodes through an external electrical circuit. The magnitude of potential difference changes momentarily during the sliding process based on the contact surface area between the engaged or separated dielectric tribo-layers.[23a,27] In neuromodulation implants, this mode is not favorable because of the drastic change of TENG dimensions during operation, while the in vivo implantation is limited by the confined spaces of the human body. In addition, sliding mode is technically more difficult for body organs to induce compared to the contact separation mode.

2.3. Freestanding Triboelectric Layer Mode

In this mode, an independent triboelectric layer moves freely against two stationary tribo-electrodes connected to the external

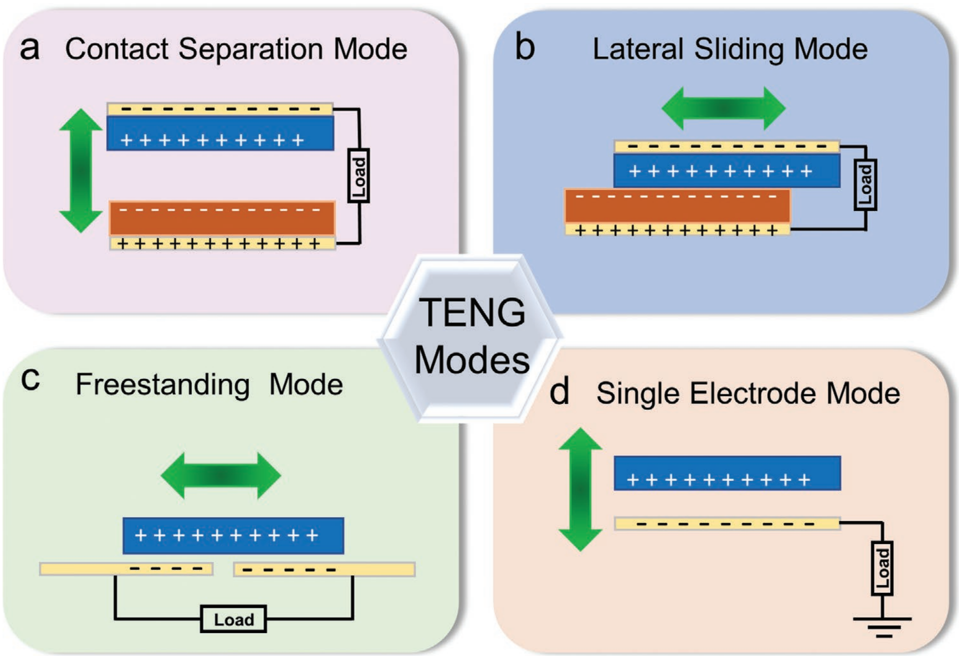

Figure 3. Basic modes of TENG under the influence of external mechanical force. The green arrows represent the direction of motions.

circuit as shown in Figure 3C. The freely moving independent layer moves in either a lateral sliding or a vertical contact-separation direction as previously illustrated. The power output generation in this mode is based on electrostatic induction between the two stationary electrodes.[23a,28] This mode is not common for TENG devices in neuromodulation but can potentially be used. We envision free-standing TENG devices fabricated from two symmetrical dielectric coated electrodes and a free-standing triboelectric liquid layer, all in a biocompatible encapsulated form. This structure of TENG in the freestanding mode would be very advantageous for harvesting the small vibrational energy of human body organs and is expected to be highly durable and stable compared to solid–solid friction based TENGs.

2.4. Single Electrode Mode

In the single electrode TENG mode, the device structure is simpler than the previous modes. A single electrode is attached to an external circuit that is connected to the ground. An external and freely moving dielectric tribo-layer such as a skin surface, polymer layer, or a body organ surface meets the single electrode TENG without being attached to the external circuit as depicted in Figure 3D. Electrostatic induction occurs when the freely moving, charged dielectric material comes in contact with the triboelectric electrode and then separates. This creates a potential difference that is then balanced by the flowing of the free electrons through an external circuit.[27,29] This working mode opens avenues for various TENG environmental energy applications; however, it faces challenges when it comes to applications in implantable devices. One is the low power output of single electrode mode vs. the contact separation mode. Second, grounding may be challenging inside the body. Last, the medium of the human body is aqueous that would affect the triboelectric mechanism by disrupting the surface charge. Encapsulation of the single triboelectric layer could make this mode useful in implantable bioelectronics.

2.5. Theory of TENGs

The driving force for the TENG is the Maxwell's displacement current, which is caused by a time variation of electric field plus a media polarization term. In the case of TENGs, triboelectric charges are produced on surfaces simply due to CE between two different materials. To account for the contribution made by the contact electrification induced electrostatic charges in the Maxwell's equations, an additional term P_s, called mechano-driven produced polarization, is added in displacement vector ***D*** by Wang in 2017,[23a] that is

$$D = \varepsilon_0 E + P + P_s \tag{1}$$

Here, the first term polarization vector P is due to the existence of an external electric field, and the added term P_s is mainly due to the existence of the surface charges that are independent of the presence of electric field and the relative movement of the media. Substituting Equation (1) into Maxwell's equations, and define

$$D' = \varepsilon_0 E + P \tag{2}$$

The conventional Maxwell's equations are for media whose boundaries and volumes are fixed and at stationary. But for cases that involve moving media and time-dependent configuration, such as the case in TENG, the equations have to be expanded. Starting from the integral forms of the four physics laws, Wang has derived the expanded Maxwell's equations in differential form by assuming that the medium is moving as a rigid translation object with acceleration. If the relativistic effect is ignored, the Maxwell's equation for a mechano-driven slow-moving media system is given by:[23b]

$$\nabla \cdot D' = \rho_f - \nabla \cdot P_s \tag{3a}$$

$$\nabla \cdot B = 0 \tag{3b}$$

$$\nabla \times (E - \mathbf{v} \times \mathbf{B}) = -\frac{\partial}{\partial t}\mathbf{B} \tag{3c}$$

$$\nabla \times \left[\mathrm{H} + \mathbf{v} \times (D' + \mathrm{P})\right] = Jf + \rho_f \mathbf{v} + \frac{\partial}{\partial \mathrm{t}}\mathrm{P_s} + \frac{\partial}{\partial \mathrm{t}} D' \tag{3d}$$

It is important to note that the moving velocity is time dependent and the media is assumed to be rigid object. The only requirement is that the moving velocity is much less than the speed of light in vacuum with the ignorance of relativistic effect. These equations are most useful for describing the electromagnetic behavior of moving media with acceleration, and they are fundamentals for dealing with the coupling among mechano-electric-magnetic multi-fields and the interaction. The expanded equations are the most comprehensive governing equations including electromagnetic interaction and power generation as well as their coupling for TENG.

In Equation (3d), $\frac{\partial D'}{\partial t}$ represents the displacement current due to time variation electric field and the electric field induced medium polarization. The second term $\frac{\partial P_s}{\partial t}$ is the displacement current due to non-electric field but owing to external strain field. The first term is dominant at high frequency for wireless communication, while the second term is the low frequency or quasi-static term that is responsible for the energy generation. The term that contributes to the output current of TENG is related to the driving force of $\frac{\partial P_s}{\partial t}$, which is simply named as the *Wang term* in the displacement current. In general case, the two terms are approximately decoupled and can be treated independently. However, if the external triggering frequency is rather high, so that the two terms $\frac{\partial D'}{\partial t}$ and $\frac{\partial P_s}{\partial t}$ can be effectively coupled, the interference between the two terms can be significant, but such case may occur in MHz – GHz range.

3. Self-Powered Brain Neuromodulation

Rapid advances in brain bioelectronics paved the way for several developed and experimental brain neuromodulation approaches. These neuromodulation devices use electrical,[30] electro-mechanical,[31] optogenetic,[32] magnetic,[33] and ultrasonic approaches.[17a] Current neuromodulators allow stimulation, inhibition, and sensing of various brain related activities.[16b] Brain neuromodulation is clinically applied as a treatment for several neurological conditions such as Parkinson's disease, essential tremors, epilepsy, and chronic pain.[34] In addition, brain neuromodulation is a key element in the investigation of bioelectronics designed to restore the sensory functions of the body such as smell, touch, etc.[35] Furthermore, brain neuromodulation is being investigated as a management tool for several psychiatric conditions such as schizophrenia,[36] medication resistant depression,[37] obsessive compulsive disorders,[38] and autism.[39] The brain neuromodulation level varies significantly based on the clinical context, the stimulated/sensing location, size of stimulated area, and the desired outcome.[40] In this section, advances in using TENGs as electromechanical energy harvesters and power sources of brain neuromodulation are discussed.

With the advantages of low cost and long implantation time, self-powered electronic skin has potential application value in clinical medicine, artificial intelligence and simulation of sensory organs. Fu et al. developed a TENG-based self-powered multisensory electronic skin for sensory substitution, such as touch, hearing, smell, taste, and vision (**Figure 4**A).[41] A contact-separated TENG made of a flexible substrate was used as an electrical stimulation and sensing unit, which could directly transmit triboelectric sensory signals to the brain for multiperception and actuated body motion feedback. The device was flexible and stable under long-term deformation. The friction factor pairs in the TENG-based sensing unit were doped with different polypyrrole derivatives to detect vibration, sound, gas, PH, and light. In addition, when electrodes were implanted in mouse brain, the sensory triboelectric signals output by TENG could stimulate specific brain regions and drive mouse activity.

Electronic skin (e-skin) based on TENG structure allowed the stimulation of hippocampal tissue of the mouse brain (Figure 4B).[42] The TENG is fabricated from a perovskite MAPbI3 that acts as both a positive triboelectric layer and a photosensitive layer. On the other hand, PDMS worked as the negative triboelectric layer and support while copper was used as a current collector. In this e-skin design, human motion can be harvested due to the triboelectrification between MAPbI3 and PDMS layers and used in brain stimulation. Moreover, the photo-illumination can be harvested by the MAPbI3 layer that was used for the neuromodulation in terms of "on/off" wireless switch.[42] Electrical neurostimulation is traditionally used for characterizing the changes and modifications in the synaptic strength between the neurons known as neuroplasticity. The TENG based e-skin was also used as a method for the self-powered characterization of synaptic plasticity. To do that, stimulation electrodes were implanted in the CA3 region of the hippocampus tissue while the recording electrodes were implanted in the CA1 region to record the evoked brain activity in voltage waveforms. The simultaneous electrical stimulation signals in the CA3 region and the synaptic response in the form of field excitatory postsynaptic potential (fEPSP) prove the ability of the e-skin to evoke brain stimulation. This work demonstrated that TENG can be used in characterizing synaptic plasticity.[42]

Zhong et. al. demonstrated that TENG can be coupled with a gas sensor and enable closed loop brain stimulation.[43] In this work, a flexible TENG/gas sensor was fabricated to harvest the mechanical energy of the body motion and produce a triboelectric-gas sensing electrical signal that was delivered to the somatosensory cortex of mouse brain and in turn induce behavioral change (Figure 4C). The TENG is composed of polyimide, polydimethylsiloxane (PDMS) as the negative triboelectric layer while the poly-pyrrole (Ppy) acts as the positive triboelectric layer. Patterned copper was used as a current collector for both positive and negative triboelectric layers. The dual role of Ppy and PDMS layers helped with the structure of the gas sensor where Ppy has a reactive surface to many chemical vapors such as acetone, methanol, and ethanol and hence is used as the active gas sensing surface. PDMS was also utilized here as a flexible substrate and support. In essence, the triboelectric signal output is sensitive to the surface modification of the Ppy layer based on reactivity to gasses, and therefore, the triboelectric-gas sensing output can be considered as a code that is sent to the brain. This way, the device acts as an olfactory receptor that can identify the smell and send the signal to the brain, and induce behavioral actions such as "run or approach".[43]

Figure 4C (ii) shows the triboelectric signal dependence on the concentration of acetone vapor. The sensor was also used to differentiate between different chemical vapors such as methanol, ethanol, acetone, toluene, and chloroform. The electrical triboelectric/sensing signal output of the device was delivered through nickel-chromium alloy electrodes to the somatosensory cortex of the mouse brain. Hand tapping has been used as the source of mechanical energy triggering the device functionality that influenced the mouse movements. This work shows the potential for closed loop behavior-triboelectricity-brain-behavior systems.[43] However, using hand tapping or inconsistent mechanical energy from the body motion will greatly influence the sensing signal output, and an operator-independent approach would be needed in the future. In addition, the low current generated from natural body motion (nA) using this approach need to be enhanced in future research to achieve sufficient levels for efficient brain stimulation.[43]

Optogenetic stimulation has recently emerged as an effective neuromodulation technique allowing stimulation or inhibition of neuron populations in different parts of the brain using light (Figure 4D).[44] Batteries or wireless power transmission have been used as power sources for the stimulating light of these optogenetic devices.[16b] A TENG was able to harvest the ambient magnetic energy to power a stimulating light emitting diode and hence stimulate a mouse brain.[45] Lee et. al. reported a flash enhanced magneto-mechano-TENG (MMTENG). The MMTENG was integrated with a red flexible micro light emitting diode (f-μLED) for an in vivo optogenetic brain neuromodulation. The MMTENG is composed of nylon as the positive triboelectric layer and Teflon as the negative triboelectric layer, while gold layers were sputtered on the back of the Nylon and Teflon as the current collector. Using adhesive, the Nylon/gold film was attached to a Titanium plate that had small magnets attached to it. The magnets allowed the conversion of the AC magnetic field of household appliances to mechanical vibration that triggers the MMTENG. The active friction area of the Nylon triboelectric layer of the MMTENG device was improved

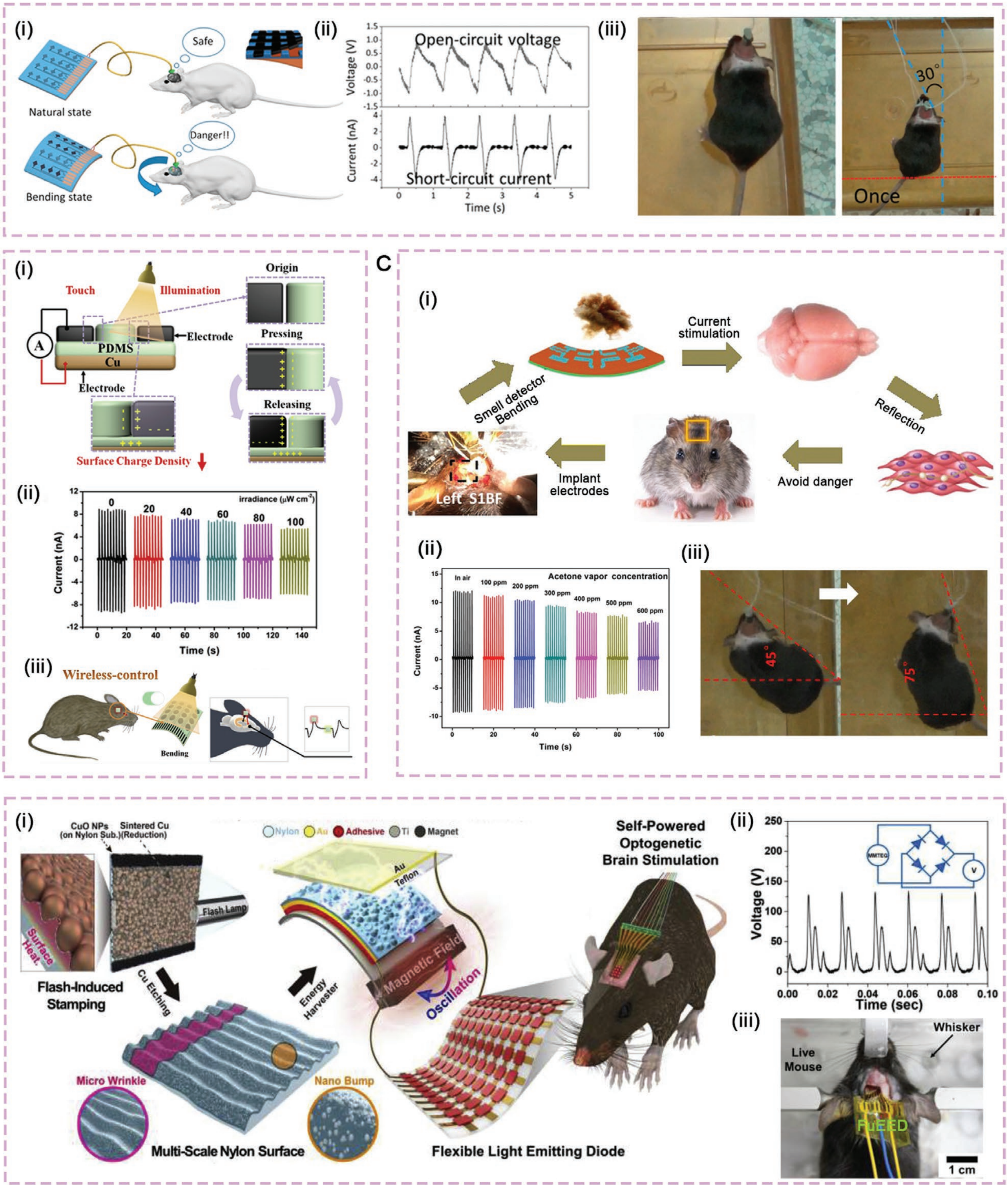

Figure 4. Self-powered brain stimulation. A) TENG-based multisensory e-skin for sensory substitution in the brain. i) Schematic diagram of the mouse activity with and without electrical stimulation signals. ii) Open circuit voltage and short circuit current of e-skin. iii) The mouse activities during operation of the device. Reproduced with permission.[41] Copyright 2018, Elsevier. B) E-skin based on TENG for brain stimulation. (G) The working principle of TENG-based e-skin. ii) The short circuit current of TENG-based e-skin. iii) The recorded field excitatory postsynaptic potential (fEPSP) stimulated by e-skin. Reproduced with permission.[42] Copyright 2020, Elsevier. C) Closed loop triboelectric/gas sensing couple for brain stimulation. i) The closed loop of behavior-triboelectricity-brain-behavior model. ii) The output current of the triboelectric sensor under the influence of different concentrations of acetone. iii) Behavioral change in the form of mouse movements due to brain stimulation by the TENG/sensing couple device. Reproduced with permission.[43] Copyright 2019, Elsevier. D) TENG driven optogenetic brain stimulation. i) Scheme for the fabrication of the flash enhanced magneto-mechano-TENG (MMTENG) and its connection to flexible light emitting diode for brain stimulation. ii) Open circuit voltage of the MMTENG after rectification. iii) Implantation of the self-powered optogenetic f-μLED array under the mouse skull. Reproduced with permission.[45] Copyright 2020, Elsevier.

by coating the Nylon layer with a CuO layer followed by a photothermal treatment then etching. This photothermal treatment increased the surface roughness of the Nylon layer by creating surface micro-wrinkles and nanopumps and hence increasing the power output as shown in Figure 4D.[45]

Under an AC magnetic field of 7 Oersted (Oe), the MMTENG generated an open circuit voltage signal of 870 V, and a short circuit current of 145 µA. Figure 4D (ii) shows the implantation of the self-powered optogenetic f-µLED array under the mouse skull. The brain stimulation here occurred by illuminating a micro red light emitting diode on the region of the mouse primary motor cortex (M1) that is responsible for the mouse whiskers movements. For the demonstration of the practicality of this approach, common household items such as hair dryers were used as the magnetic field source to trigger the MMTENG and f-µLED array for brain stimulation.[45] This work provides proof of concept for a self-powered optogenetic brain stimulation system. Although the reliance on external magnetic field of the household appliances demonstrates practicality, it may result in the fluctuation in the generated signal by MMTENG and hence lower precision and control over brain optogenetic stimulation. However, this work plants the seed for future TENG optogenetic systems that should be fully encapsulated and isolated from body fluids, implanted long-term, and have energy storage and electrical circuits for a well-controlled brain stimulation.

4. Peripheral Nerve Neuromodulation

The peripheral nervous system (PNS) represents all the body nerves excluding the brain and the spinal cords. The PNS can be categorized into two main parts: 1) The autonomic nervous system (ANS) that controls the involuntary functions of the body as well as the regulation of body glands, and 2) the somatic nervous system (SNS) that controls the voluntary muscle movements in addition to relaying sensations from the body to the central nervous system.[46] The development of TENG self-powered peripheral nerve neuromodulation can provide clinical treatment outcomes to multiple peripheral nerve disorders allowing the regulations of several body functions. In this section we will discuss the advances in the development of self-powered neuromodulation of ANS and SNS.

4.1. Self-Powered Neuromodulation of Autonomic Nerves

The development of battery-free, self-powered neuromodulation devices for the autonomic nervous system can result in a desirable non-destructive therapeutic for neurological and psychiatric health. Yao et. al. demonstrated a self-powered vagus nerve stimulation system using a biocompatible TENG attached to the outer surface of the stomach (**Figure 5**A).[47] Their device utilizes the wave-like contractions of the stomach muscles known as peristalsis to generate biphasic electrical signals. These generated electrical signals directly stimulated the vagal afferent fibers to reduce food consumption and allow control of the rat's weight. A contact separation mode TENG was used in a metal-dielectric design. The metal here is a copper electrode with gold leads interfacing with the vagal afferent nerves while the TENG dielectric layer is the PTFE. The TENG was encapsulated in 3 different layers of polyimide, polydimethylsiloxane (PDMS), and Ecoflex gel. The contraction movements of the stomach generate weak voltage signals <0.1 V in amplitude. Although the generated voltage signal is weak, the in vivo implantation of the TENG device in rats for 100 days led to 38% weight loss in the vagus nerve stimulation group versus the control group with no device implantation.[47] This work is the first work to demonstrate the in vivo implantation of TENG for months and paves the way for the future development of fully self-powered implantable bioelectronics for therapeutic purposes.[47]

Autonomic pelvic nerve stimulation using a TENG for bladder modulation has also been demonstrated (Figure 5B).[48] In this work, a zigzag-shaped TENG stack was constructed using PET as a support layer, while PTFE and Aluminum were used as the negative and positive triboelectric layers, respectively. TENG stacks produced biphasic minor and major pulses upon mechanical contact by hand tapping. These TENG devices were connected to each other in parallel to maximize the power output. Furthermore, the TENG stack was connected to flexible neural chip interfacing with the pelvic nerve. Different surface area TENG stacks (1, 4, and 16 cm^2), and different stimulations by hand tapping in the form of a beat per min (BPM: 25–150) were used to study the efficiency of this self-powered mechano-stimulation system to achieve control over micturition and bladder pressure. The frequency of stimulation by TENG, expressed here as beats per min, as well as the pulse width and amplitude significantly affected the bladder modulation. For example, low-frequency BPM of <0.4 Hz or 25 BPM was not sufficient to stimulate the bladder and ≈0.83 Hz (50 BPM) or more was needed for stimulation.[49] This work demonstrated the potential of using TENG for pelvic nerve stimulation, however, the self-powered in vivo aspect is yet to be achieved since this work depended on hand tapping for demonstrating the TENG stimulation rather than harvesting biomechanical energy or motion from the body organs. This is still an open challenge for future research in this area.

The choice of ultrasound as an external excitation source to the body and the utilization of implantable TENGs as internal energy harvesting units allow the conversion of the ultrasound vibration into internal electrical stimulation (Figure 5C). This ultrasound-TENG hybrid could provide an excellent solution for short-term therapeutic treatment sessions. In this context, a programmable ultrasound system external to the body was coupled with an implantable hydrogel-based TENG abbreviated as HENG.[49] This wireless and battery-free platform was used to stimulate the vagus nerve in rats and achieve an anti-inflammatory response in sepsis conditions. This nanogenerator was constructed using polyacrylamide (PAM)-graphene conductive hydrogel in a liquid-solid nanogenerator format. The PAM served the role of the solid triboelectric layer, while a phosphate buffer saline (PBS) acted as the liquid phase, while the graphene played the role of the current collector. The HENG utilized the ultrasound vibrations at a frequency of 70 kHz and a power density of 0.3 w cm^{-2} to produce alternating biphasic current waves of 1.6 mA. The direct electrical stimulation by the HENG to the vagus nerve alleviated the inflammatory response induced by endotoxin in rats.[49]

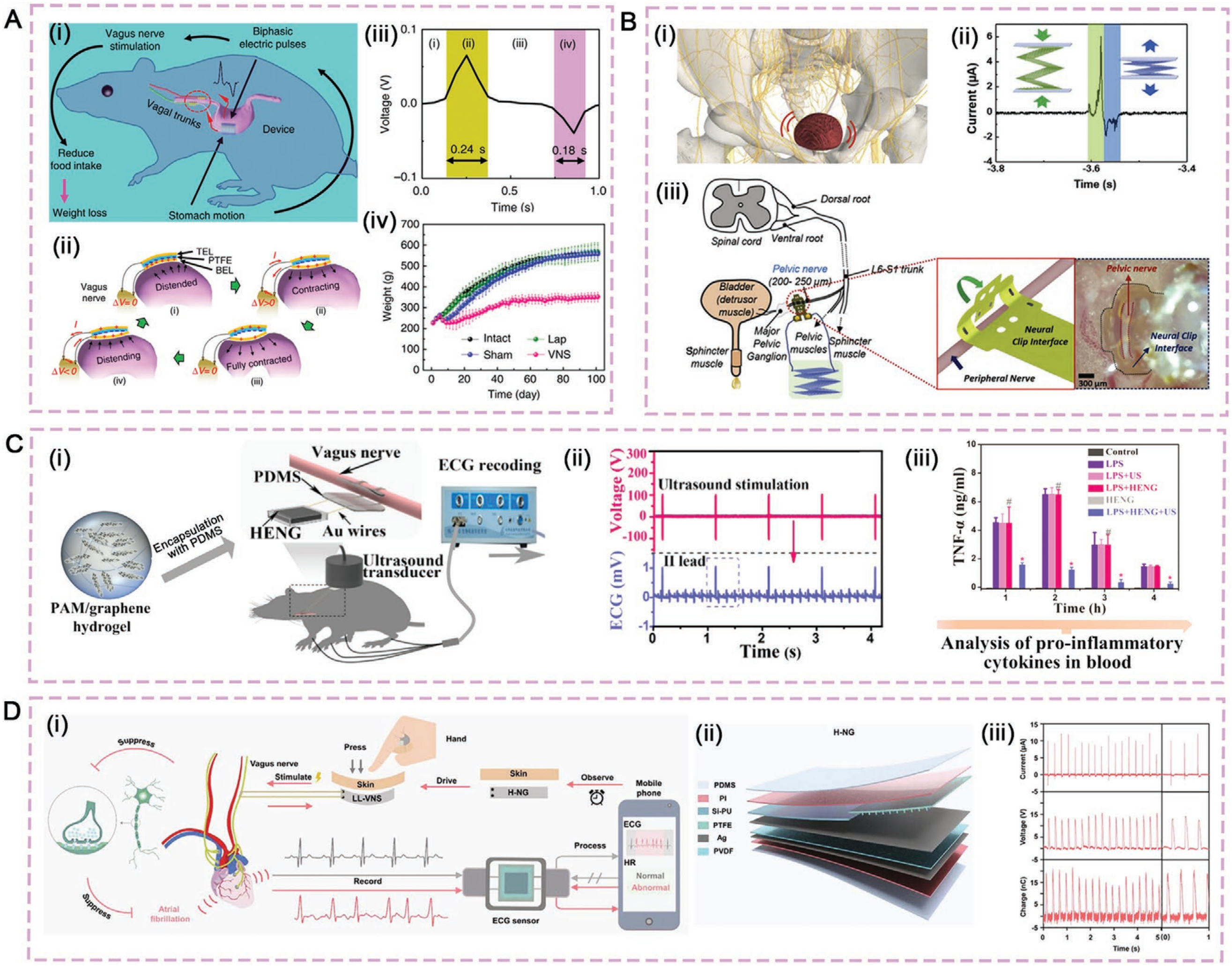

Figure 5. Self-powered neuromodulation of autonomic nerves. A) Self-powered vagus nerve stimulation (VNS) system in rats. i) Schematic representation of the pathway of self-powered VNS by TENG. ii) A scheme illustrating the working principle of the TENG-powered VNS. iii) Biphasic signal of TENG during stomach movements. iv) Weight changes in different groups. Reproduced with permission.[47] Copyright 2018, Springer Nature. B) Pelvic nerve stimulation induced by TENG for bladder control. i and ii) Schematic diagram of TENG connected to the neural clip interface to stimulate the pelvic nerve and control the bladder (in red). iii) Biphasic minor and major pulses generated by TENG after hand tapping. Reproduced with permission.[48] Copyright 2019, Elsevier. C) Ultrasound-driven solid-liquid TENG for VNS. i) Schematic representation of VNS by solid-liquid TENG. ii) The open circuit voltage of ultrasound-driven solid-liquid TENG and the ECG after VNS by TENG. iii) The ultrasound input and the HENG output, and analysis of the inflammatory biomarkers in blood. Reproduced with permission.[49] Copyright 2021, Elsevier. D) Integrated system based on H-NG for atrial fibrillation monitoring and treatment through low-level vagus nerve stimulation.[50] i) Schematic representation of the H-NG based closed-loop self-powered VNS system. ii) The structure of H-NG. iii) The performance of H-NG in vivo. Reproduced with permission.[50] Copyright 2022, Elsevier.

Cardiac vagus nerve is one of the main nerves controlling cardiac activity. Sun et al. designed a hybrid piezoelectric and triboelectric nanogenerator using piezoelectric PVDF and polyethylene terephthalate (PET) film (Figure 5D).[50] Based on the hybrid generator, they developed a closed-loop self-actuated low-level vagus nerve stimulation system (LL-VNS), which could provide real-time sensing, signal processing and treatment. The system was free of electronic circuits, components, and batteries, and was flexible, lightweight, and simple. In vivo experiments in rats showed that LL-VNS had good biocompatibility and could produce a peak current of 5–15 µA in vivo, which directly acted on the vagus nerve and greatly shorten the duration of atrial fibrillation, thereby alleviating the symptoms of atrial fibrillation. Cervical vagus nerve stimulation also ameliorated atrial fibrillation-induced myocardial fibrosis and atrial connexin levels, and triggered anti-inflammatory effects of NF-κB and AP-1 pathways.

4.2. Self-Powered Neuromodulation of Somatic Nerves

Voluntary muscle movement can be adversely affected as the result of several nervous system diseases that affect the patient's quality of life. Electrical stimulation to the nerves or directly to the motoneurons of the muscle is an effective approach to help patients with the rehabilitation as well as gaining key movements that were lost or affected.[12] In this section, advances in TENG-driven and self-powered muscle neuromodulation are discussed.

Therapeutic electrical stimulation combined with nerve cuff implantation has been shown to be effective and feasible for neuroprosthetic applications. Lee et al. designed a wearable stacked TENG with a universal electrode design, which can be used for selective electrical stimulation and recording of the sciatic nerve (**Figure 6**A).[51] TENG in combination with electrodes stimulated the sciatic and common peroneal nerves and was used to control the activity of the tibialis anterior muscle. The open-circuit voltage of the stacked TENG was 160 V and the short circuit current was 6.7 µA. The results of selective stimulation showed that the stimulation intensity of gastrocnemius and tibialis anterior muscles activated by sciatic and common peroneal nerve stimulation was different. In addition, another of their findings also showed that the TENG-based battery-free neural interface could directly and selectively stimulate the rat sciatic nerve to regulate different muscle activations.[52]

He et. al. developed another diode-enhanced TENG based on a textile format named D-T-TENG with 25 times larger closed-loop current compared to the diode-free textile TENG (Figure 6B).[53] The D-T-TENG was fabricated using two conductive textile electrodes, one is covered with a thin film of nitrile rubber as a positive triboelectric layer, while the other is coated with silicone as the negative triboelectric materials. The two sides of this D-T-TENG device were stitched to one another and covered with non-conductive textile as a protective sealing. The diode is introduced between the two electrodes in the outer circuit to amplify the current. The stacked and 4-parallel-connected D-T-TENGs generated a peak current of 124 µA under a force of 40 N. The advantage of the D-T-TENG is the high flexibility textile that allows it to be integrated into clothing to harvest mechanical energy of human motion at the elbows and knees. The electrical output of the D-T-TENG directly stimulated the tibialis anterior muscle and the gastrocnemius muscle, as well as the sciatic nerve.[53]

TENG-driven peripheral nerve stimulation for muscle modulation was first demonstrated by directly stimulating the sciatic nerve in a frog leading to the actuation of leg muscles. Sciatic nerve stimulation by TENG was further demonstrated successfully in tilapia[51] and rats.[54] In these studies, the sciatic nerve was connected to TENG devices through neural interface electrodes. TENGs were exposed to hand tapping at different forces that generate sufficient electrical power to stimulate the sciatic nerve that in turn led to muscle contractions. These early reports paved the way to directly stimulate the muscles by connecting a zigzag TENG device to the motoneurons that are distributed in the muscle tissue (Figure 6C).[55] The TENG was constructed using PTFE as the negative triboelectric layer and Aluminum as the positive triboelectric layer. The output current of this stacked TENG is only 35 µA, which is far below the mA level needed for most electrical muscle stimulation events. However, the optimized electrical pulse polarity and the use of a multi-channel intramuscular electrode array to map the distribution of motoneurons allowed the efficient stimulation of the tibialis anterior muscle in rats.[55] The optimization and mapping of the stimulating electrode position and the stability of stimulation by TENG are important factors when self-powered rehabilitation by TENG is considered.[56] In addition, to overcome the low stimulation current output, the TENG was further improved by adding current amplification using a diode (Figure 6D).[57] This diode-amplified TENG (D-TENG) gave up to 4-fold current enhancement and more feasible stimulation of the motoneurons in the tibialis anterior in rats leading to a stronger force generated by the muscles as the result of the stimulation.[57]

Although neural stimulation using TENGs has been actively investigated; however, only a limited neural response was demonstrated due to the inability of the previous TENG to alter the stimulation parameters due to the limited operating design and conditions. To overcome these challenges, Lee et al. report a rotation-based triboelectric nervestimulator (RoTENS), which consisted of a rotator and a stator that were in contact with each other to achieve a triboelectric effect. RoTENS required only a single device to modulate the required physiological responses of various peripheral nerves (Figure 6E).[58] It could adjust the stimulus parameters of frequency and current amplitude respectively by changing the speed and non-contact mode, while producing a constant charge output. RoTENS allowed physiological activation of the rat's hind limbs within a frequency (10–50 Hz), mimicking the natural movements of the hind limbs. When RoTENS was used in conjunction with a wearable device, it could convert the mechanical movement of the wearable device into instant electrical stimulation, enabling assisted walking or rehabilitation without any batteries. RoTENS can be used to stimulate and analyze a variety of nerves requiring different stimulation parameters, thereby facilitating the establishment of TENG-based neural stimulation criteria in the future and expanding applications in the fields of bioelectrical medicine and rehabilitation.[58]

TENG-based electrical stimulation can also rehabilitate muscles and delay muscle atrophy after nerve injury. Feng et al. developed an implantable self-regulated neural electrical stimulation (ISR-NES) system consisting of a contact separation TENG (Cs-TENG) and a nerve cuff electrode, which spontaneously generated bipolar electrical impulses in response to abdominal breathing movements in rats. The nerve stimulation signals provided by ISR-NES flowed to the sciatic nerve crush injury site through neurons, thereby effectively promoting sciatic nerve regeneration and having the ability to synchronously regulate muscle function. The ISR-NES system exhibited efficient energy harvesting and good biocompatibility, and this practical, self-reactive, battery-free nerve stimulation strategy offers promise for functional electrical nerve stimulation alternates.[59]

With the development of neuroprostheses, implanted medical electronics can replace damaged nerves, improving the lives of people with loss of sensation in limbs. Maoz et al. used TENGs to design an integrated tactile (IT) sensory restoration device (TENG-IT). TENG-IT consisted of a TENG and a nerve sleeve electrode. The device implanted in the injured limb could "bypass" a severed nerve in the area and connected directly to the healthy nerve, restoring the sense of touch through the healthy nerve's electrical current without the need for complicated implantation or charging. The TENG-IT was activated upon contact with an object and sent an electric current to a distal tibial nerve, thereby regenerating the sense of touch.

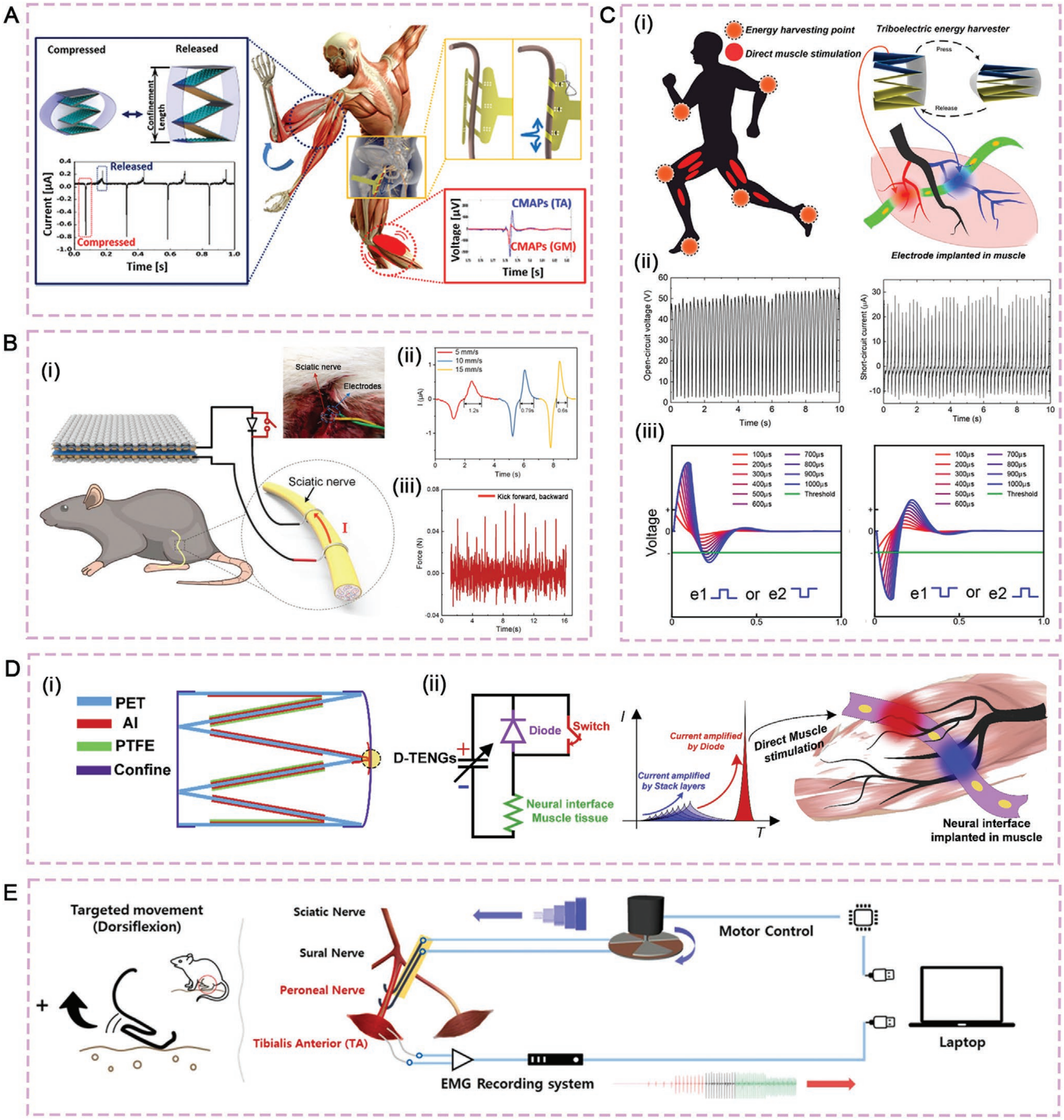

Figure 6. Self-powered stimulation of somatic nerves for muscle control. A) The stacked TENG-based neural interface directly stimulates the sciatic and common peroneal nerves for the control of the tibialis anterior muscle. Reproduced with permission.[51] Copyright 2017, Elsevier. B) Diode amplified textile-based TENG (D-T-TENG) for the stimulation of sciatic nerve and muscles in rats. i) Scheme and photograph of D-T-TENG. (L) Parallel stacking of D-T-TENG for muscle stimulation. ii) The short circuit current of D-T-TENG. iii)The force of the kick in vivo stimulation of sciatic nerve by D-T-TENG. Reproduced with permission.[53] Copyright 2019, Wiley-VCH. C) TENG stimulated motoneurons of the tibialis anterior muscle in rats. i) Schematic diagram of proposed spots to place the stacked TENG. ii) Open circuit current and short circuit current generated upon mechanical contact with stacked TENG. iii) Stimulation of the tibialis anterior muscle in rats by stacked TENG. Figures Reproduced with permission.[55] Copyright 2019, American Chemical Society. D) Enhanced current output by using diode amplified TENG (D-TENG) for muscle stimulation. i) Schematic diagram of TENG in action. ii) Role of the diode amplification in boosting the current output of D-TENG for muscle stimulation. Reproduced with permission.[57] Copyright 2019, Elsevier. E) Rotatable TENG-based RoTENS with adjustable parameters used to modulate peripheral nerve-controlled leg muscles. Reproduced with permission.[58] Copyright 2022, Elsevier.

TENG-IT also converted mechanical energy into electricity and recharged itself. The device was made of biocompatible materials and has the advantages of safe use, maintenance-free, and simple implantation. The groundbreaking new technology offers hope to people who have lost their sense of touch after amputation or injury.[60]

5. Self-Powered Intermittent Neuromodulation

A recently trending self-sustainable intermittent neurostimulation approach has been proposed to close the gap between the relatively low energy generation from biomechanical motion of body organs and the high energy demands of implantable neurostimulators (**Figure 7**).[61] Although TENG devices have many advantages as implantable energy harvesters, they are still limited because TENGs produce alternating power (not continuous). In addition, TENGs produce relatively low power output due to the weak mechanical impact of body organs with TENG. On the other hand, implantable neurostimulators generate high frequency electrical pulses that make them energy demanding devices (Table 1). This gap between energy generation by TENGs and energy demand by neurostimulators is a major challenge in the field. Elsanadidy et al. recently reported a self-sustainable neurostimulation system that uses TENG in a way that overcome the energy gap limitation.[61] In this work, a self-sustainable and intermittent deep brain stimulator was developed (Figure 7). This smart deep brain stimulator system has three main components, a bio-triboelectric nanogenerator (Bio-TENG) to harvest the mechanical energy of the breathing motion (Figure 7A), and biosupercapacitor as an energy storage, and a pulse generator that produces a highly regulated pulses to the brain with the desired frequency and pulse width (Figure 7B). This new intermittent deep brain stimulator utilizes the multilayer Bio-TENG (Figure 7C) to harvest mechanical motion of the swine breathing lungs to charge the biosupercapacitors and stimulate the brain. The electrical brain stimulation was demonstrated ex vivo in the hippocampus tissue of genetically modified mouse brain and appears as fluorescence (Figure 7D). The intermittent nature of this new design of deep brain stimulators comes from the fact that the devices alternated periods of stimulation and periods of charging that made the performance for this device self-sustainable. This work opens a new avenue for discovering self-powered and intermittent neurostimulation for central and peripheral nervous system where a short period or intermittent stimulation is sufficient to obtain a therapeutic response.[61]

6. Outlook and Future Research Opportunities

In the past few years, TENG are on a fast track to technological maturity. In particular, some TENG-based systems have been commercialized in the fields of personal protective equipment, air filtration systems, and smart buildings. However, TENG-based implantable medical devices are still in the research stage and have not yet reached clinical practice as the result of some challenges, which can be excellent future research opportunities in the field of smart neuromodulation bioelectronics (**Figure 8**).

6.1. Device Metrics

First, challenges in device components lead to a lack of controlled neurostimulation. Most published research discussed in this review utilized TENG to harvest mechanical energy from hand tapping or organ movement to directly stimulate the neurons. This approach may produce uncontrolled and irregular electrical signals based on the irregular mechanical impact of body organs. In clinical settings, neurostimulation requires a highly controlled signal in terms of voltage and current amplitude, frequency of the electrical signal, and pulse duration to achieve a consistent therapeutic outcome.[62] A proposed solution, in this case, is the addition of fast-charging energy storage units,[63] and a microcircuit with a pulse generator. This way, the electrical output from TENG can be readily stored and utilized to power the pulse generator producing consistent and desired neurostimulation patterns. In addition, the long-term stability of the different neuromodulator components including TENG, energy storage unit, circuit, implanted electrodes, and wiring need to be tested and verified.

6.2. Power Considerations

Second, challenges related to power specifications. Implantable TENGs produce an alternating current that is intermittent in nature based on the contact-separation motions with human body organs. With the high-power demand and pulse frequency of commercial neurostimulators, and the low mechanical impact from human body organs, a continuous and efficient power supply remains an open challenge. For example, TENGs normally produce current levels of nA–μA that is below the mA current level of commercial implantable neuromodulation systems.[16b] A proposed solution is designing a power management unit with high efficiency of mechanical to electrical conversion and has the capability to lower the voltage output and increase the current output. This is essential to efficiently evoke neurostimulation. In addition, using an efficient energy storage system would allow storing the AC electrical output and produce a stable DC power supply to operate a pulse generator.[64]

6.3. Implantation and Neural Interface

Third, the challenge of achieving chronic in vivo implantation. In humans in vivo long-term stability not only requires stable components but also stable biocompatible encapsulation. PDMS has emerged as a good candidate for encapsulation due to its passive and biocompatible surface as well as its flexibility and durability. Furthermore, the fixation of a TENG device in vivo remains another open challenge as the device is expected to be in constant vibration near to the soft tissues of body organs. A proposed solution is tissue fixation through surgical stapling or suture. The TENG implantation should be ideally achieved through a minimally invasive surgery that ensures a fast recovery time and

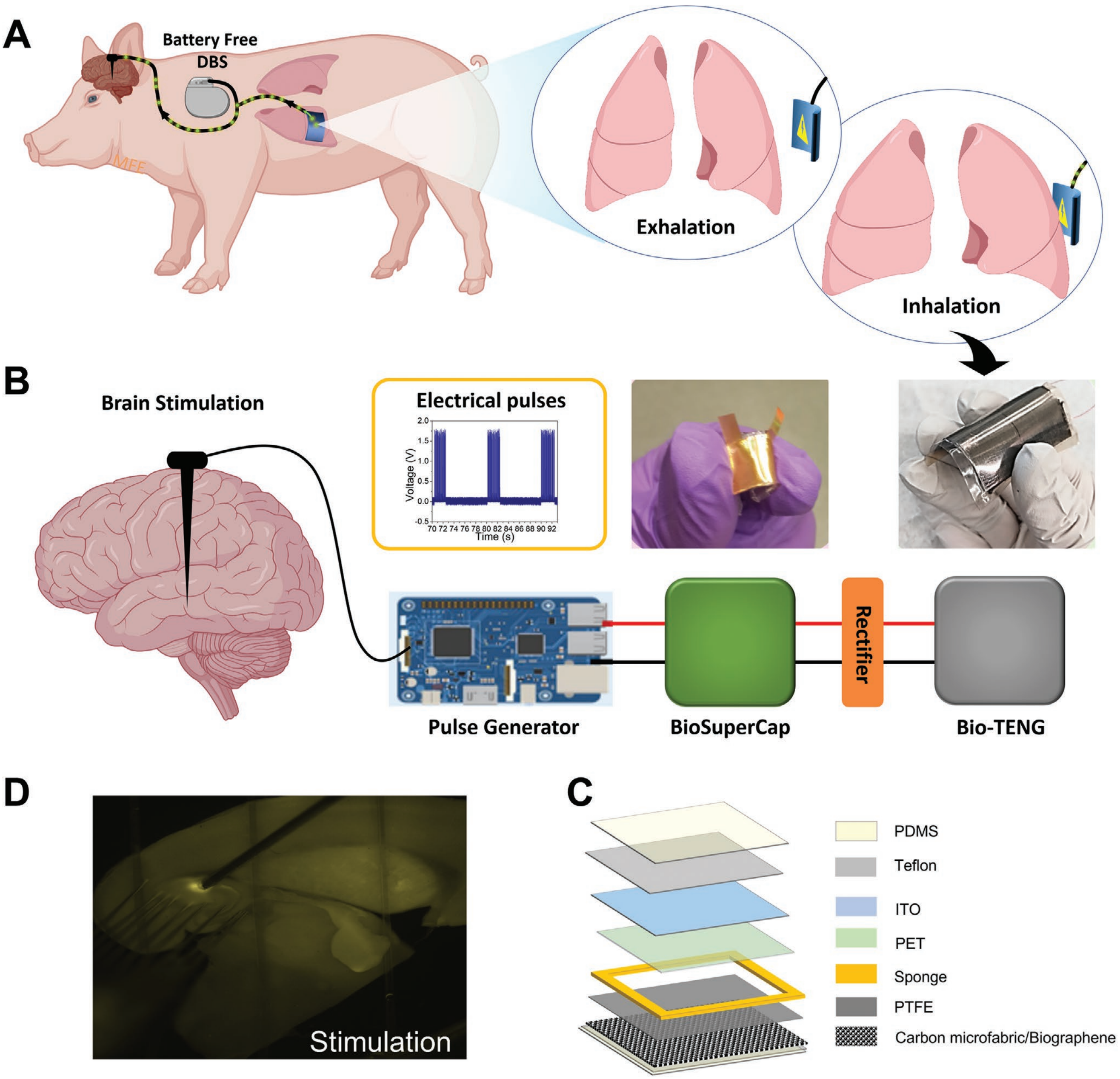

Figure 7. Self-powered, sustainable, and intermittent deep brain stimulation system. A) Schematic representation showing the biomechanical energy harvesting from a breathing swine lung using a bio-triboelectric nanogenerator (bio-TENG). B) Schematic representation supported by real photos for the components of the first fully self-sustainable system of the deep brain stimulation composed of Bio-TENG for energy harvesting, biosupercapacitor for energy storage, and a pulse generator microchip for regulated pulse generation delivered intermittently to the deep brain through an implantable microelectrode. C) Schematic diagram showing the different layers of Bio-TENG. D) Fluorescent light emission at the microelectrode insertion site in the hippocampus brain tissue. The electrical signal was generated through the Bio-TENG. Reproduced with permission.[61] Copyright Cell Press 2022.

lowers health complications post-surgery. Finally, innovation in the TENG/neuron interface would be necessary. Direct stimulation of TENG to the neurons could lead to tissue damage due to the high TENG voltage output. Designing new micro-electrodes with neuro-biocompatible materials could lower the adverse effects on the neurons at the interface during electrical stimulation. It is worth noting that on-skin or subcutaneous TENGs could be effective in stimulating certain peripheral nerves and muscles while avoiding invasive implantation surgeries.

6.4. Biosafety

TENG has been interfaced with multiple body organs such as the heart,[21a] diaphragm,[65] knee,[66] shoulder,[67] muscles,[43] stomach,[47] and others to harvest biomechanical energy required for stimulation. In a clinical scenario, there is a biosafety concern as TENG may induce injury to the contacting tissue during an operation. This biosafety concern could be minimized by considering a smooth and edge-free

Table 1. The application of TENG as self-powered neuromodulation.

Features of TENG	Role of TENG	Intensity/time/ frequency	Animal model	Position	Effect of electrical stimulation	Ref.
High output	Power supply	134 V; 20 h; 60 Hz	Mice	Brain	The voltage generated by the MMTENG could drive the f-μLED to glow and activate the whisker movements of a living mouse	[44]
Flexibility	Power supply	-	Mice	Brain	Under different gas environments, friction current stimulation of the cerebral cortex caused mice to produce a response to avoid toxic gas.	[43]
Flexibility; Wireless	Stimulator	Tens of micro amps	Mice	Brain	Triggering the hippocampus CA3 area of the mouse by light illumination on/off as a wireless switch control could successfully elicit postsynaptic responses.	[42]
Flexibility	Stimulator	-	Rats	Brain	Electrical stimulation of the cerebral cortex could replace sensation and treat sensory disorders.	[41]
Flexibility; Biocompatibility	Stimulator	200 mV; 0.3 (t/s); 100 days; 0.05 Hz	Rats	Vagus nerve	Electrical stimulation of vagal afferent fibers could reduce food intake and achieve weight control	[47]
High output; Wireless	Stimulator	40 v; 1 Hz	Rats	Vagus nerve	Vagus nerve stimulation reduced the release of proinflammatory factors and was used to treat sepsis.	[48]
Flexibility	Stimulator	1–5 μA; 1 Hz	Rats	Autonomic nerve	Pelvic nerve stimulation promoted bladder contraction and induced urination.	[49]
Flexibility; Miniaturization	Stimulator	5–15 μA; 7 day; 1–3 Hz	Rats	Vagus nerve	Vagus nerve stimulation in the neck could relieve the symptoms of AF and produce an anti-inflammatory effect.	[50]
Flexibility	Stimulator	6.7 μA; 4 Hz	Rats	Sciatic nerve/Common peroneal nerve	Different currents could selectively stimulate the sciatic nerve and common peroneal nerve, which could be used to regulate muscle activity.	[51]
Flexibility	Stimulator	≈0.6 μA; 2 Hz	Rats	Sciatic nerve	Electrical stimulation of the sciatic nerve regulated muscle movement.	[52]
Flexibility	Stimulator	47 V; 35 μA	Rats	Motor neuron	Stimulating motor neurons in muscles could lead to muscle movement	[55]
High output	Stimulator	40 μA	Rats	Motor neuron	The current amplified by the diode can provide neuromuscular electrical stimulation and activate the tibialis anterior muscle	[57]
Flexibility	Stimulator	20–125 μA; 0.67 Hz	Rats	Sciatic nerve	Sciatic nerve stimulation caused the gastrocnemius muscle to kick backwards.	[53]
Biocompat-ibility; Adjustable parameters	Stimulator	3–5 V; 100 μs; 20 Hz	Rats	Sciatic nerve	Electrical stimulation could relieve muscle atrophy after sciatic nerve injury	[59]
Adjustable parameters	Stimulator	10–50 Hz	Rats	Sciatic nerve branch	Directly stimulating the sciatic nerve branches may regulate dorsiflexion and plantar flexion	[58]
Flexibility; Biocompatibility	Stimulator	1–1.5 V	Rats	Distal tibial nerve	Electrical stimulation of healthy nerves replaced the damaged sense of touch.	[60]

TENG surface and a properly positioned TENG with an angle of fixation to the tissue that does not allow tissue penetration or damage. Finally, passivating the encapsulated surface of the TENG with an anti-biofouling coating may minimize the post-surgery inflammation and infection that could result from the accumulation of blood components or body fluids and proteins around the TENG implant.

7. Summary and Perspective

As the innovative concept of self-powered bioregulation is accepted and gradually realized, it is necessary and timely to review advances in self-powered neuromodulation systems that are battery-free and have the potential to work chronically. Currently, the rapid development of intelligent neuromodulation systems that stimulate and sense neuronal activity is revolutionizing the treatment of many neurological diseases and the development of brain-machine interface. Some neuromodulation systems have already been successfully commercialized by major biomedical device companies such as Medtronic and Boston Scientific (e.g. deep brain and spinal cord stimulators); Neuralink and its competitors are developing a new generation of brain-computer interface technology. The enormous commercial success of these conventional neuromodulation devices has encouraged the development of TENG-based neurostimulators. Compared with traditional medical electronics, TENG has the unique ability to harvest low-frequency motion of human body organs and convert it into electricity, making a variety of self-powered neurostimulation systems possible. Besides neurostimulation, TENG can be combined with therapeutic neural prostheses such as bionic limbs, cochlear implants, and bionic eyes to provide energy sources for them. Through this technology, users can get rid of the shackles of power supply and

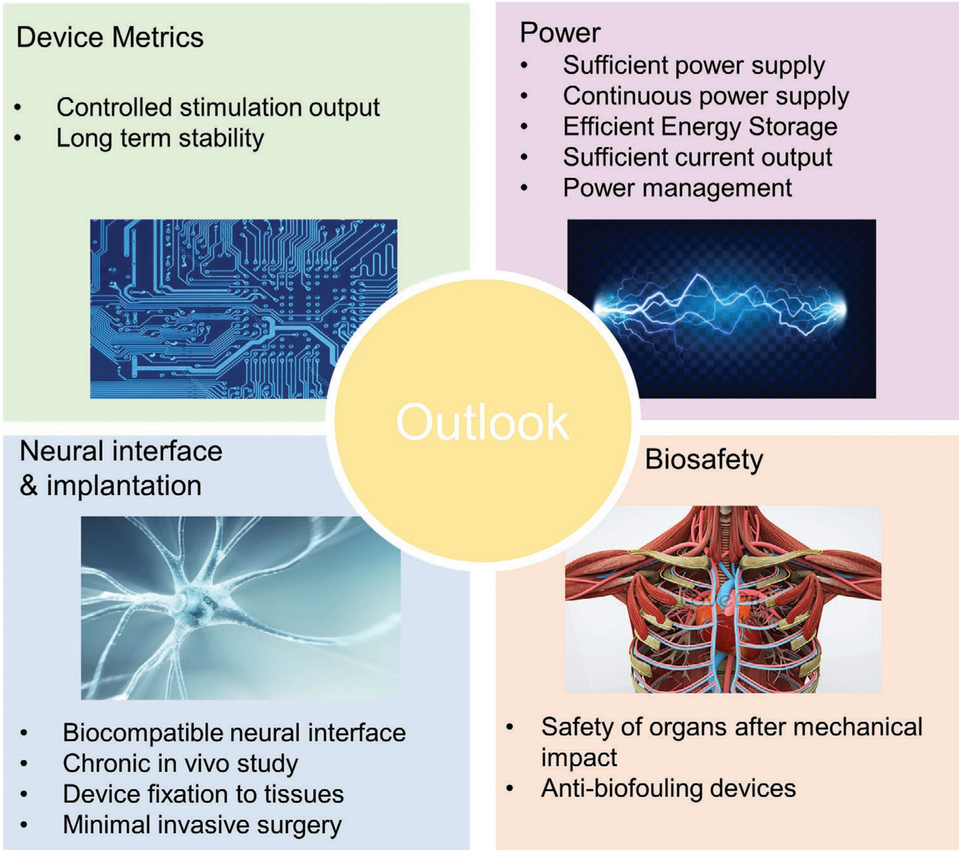

Figure 8. Outlook, challenges, and future research opportunities.

charging device, and use their own mechanical energy to drive the prosthesis, thereby building a bridge between the user and the prosthesis, making the prosthesis feel more like a natural organ. Moreover, TENG can further drive optogenetic and drug delivery devices to achieve precise regulation of neuronal activity and deep brain therapy for mental diseases.[16b] At the same time, TENG can also be used as an in vivo sensor to facilitate the optimization of subsequent treatment plans through real-time monitoring and feedback, forming a closed loop of "monitoring-diagnosis-treatment". It is worth mentioning that this technical route is inseparable from the development of wireless data transmission technology. The self-powered and wireless neural engineering detection platform facilitates real-time monitoring of biological signals in different parts of the brain, which helps us explore the process of disease development and realize closed-loop regulation physiological process. In terms of material selection, degradable materials can be widely used in the preparation of transient TENG-based neuromodulation devices in the future. In the in vivo environment, these devices can be gradually degraded and excreted through metabolism, thereby avoiding secondary surgical damage caused by removing the device. In addition, the ease of fabrication, low cost, broad spectrum of materials choices, high flexibility materials, and high durability are inherent advantages of many TENG systems, which facilitates their use as implantable devices.[68] To date, leveraging TENGs in the neuromodulation of the brain, and peripheral nervous system including the autonomic and somatic nervous system led to several therapeutic effects such as controlled weight loss, bladder control, muscular system rehabilitation, and improving memory.[47,51,56,57] Further advances in TENG structure, implantation, harvesting capability, and stimulation pattern can lead to new self-powered systems with therapeutic impact on neurological conditions such as epilepsy, Parkinson's disease, essential tremors, and psychiatric disorders.

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E.E. and I.M.M. contributed equally to this review.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

brain, neuromodulation, peripheral nerve, self-powered, triboelectric nanogenerators

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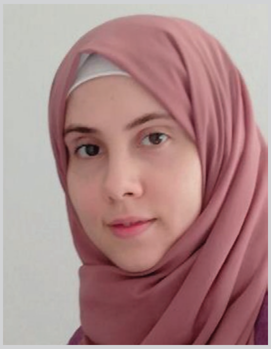

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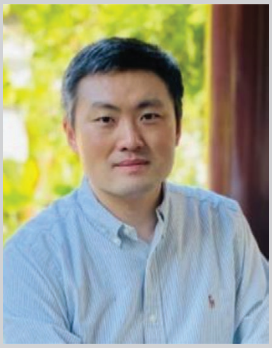

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