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Triboelectric nanogenerators for self-powered neurostimulation

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ABSTRACT

The burgeoning field of soft bioelectronics heralds a new dawn in medical treatment for neurological and psychiatric conditions, presenting innovative methods for the stimulation, inhibition, and precise sensing of neuronal activities. Central to these advancements is the challenge of power supply; devices dependent on traditional batteries face limitations regarding miniaturization and require invasive surgeries for battery replacement. Triboelectric nanogenerators (TENGs), which generate power from biomechanical movements, offer a promising solution for developing self-powered neurostimulation devices without the need for an external power supply. This review delves into recent progress in TENGs, with a focus on their application in self-powered neurostimulation systems. The utility of TENGs across various nervous systems—including the center, autonomic, and somatic nervous systems—is explored and presented, highlighting the potential for these devices to facilitate neurological treatments. By summarizing TENGs' operational details and the potential for clinical translation, this review also identifies challenges associated with the implantation and integration of neural electrodes and presents recent advances in solutions, aiming to reshape electric treatments for neurological diseases.

KEYWORDS

triboelectric nanogenerators, neurostimulation, self-powered, soft bioelectronics, biomechanical energy harvesting

1 Introduction

The advent of soft bioelectronics marks a significant leap forward in the treatment of neurological disorders and the integration of humans with computational technologies [1–10]. These devices, notably electrical neuro-stimulators and sensors have ushered in a new era of nervous system machine bioelectronics, with commercialization efforts accelerating to develop the next generation of neuromodulation bioelectronics [11–17]. This burgeoning field aims to regulate neuronal activity within the central and peripheral nervous systems (PNS) through precise electrical signals [18–21], offering promising treatments for conditions such as epilepsy, Parkinson's disease, psychiatric disorders, and chronic pain [22–26].

The reliance on batteries as the primary power source for these neuromodulation bioelectronics, however, presents several limitations, including the risks and costs associated with surgical replacements for non-rechargeable batteries and the discomfort associated with routine recharging [27–31]. Therefore, the pursuit of battery-free, durable power solutions has become paramount for the wide adoption and enhanced patient experience of neuromodulators [32–34]. In the quest for autonomous power sources [35–37], biomechanical energy harvesting technologies, particularly triboelectric [5, 38], piezoelectric nanogenerators [39–46], and magnetoelastic generators [35–37, 47–56], stand out for their potential to convert the body's biomechanical energy into electrical energy. These technologies promise to offer long-term, possibly lifelong, power solutions for neuromodulators without the need for external power sources [57], marking a significant shift toward self-powered neurostimulation systems.

Among these, triboelectric nanogenerators (TENGs) have gained significant attention due to their flexibility, diverse operational modes [58–64], ease of fabrication, low cost, and broad material diversity [65, 66]. Since their inception in 2012, TENGs have seen a dramatic increase in research interest [67], driving innovations in design, materials, energy management, and *in vivo* implantation, thus enhancing their power output and bringing them closer to commercial viability [39, 59, 68]. Four working modes of TENG have been developed since then, including the vertical contact separation mode [69–75], the in-plane sliding mode [76–80], the single-electrode mode [81–85], and the free-standing triboelectric layer mode [86, 87].

Operating on the principles of triboelectrification and electrostatic induction between two dissimilar materials, for example, polymer membranes, TENGs excel in converting tiny biomechanical pressure of body organs into electricity [88, 89]. This capability has propelled TENGs into the forefront of self-powered brain and nerve stimulation, offering a new paradigm for treating a wide range of neurological conditions [90–97]. However, to fully harness the potential of TENGs in clinical settings, several challenges must be addressed, including the need for consistent and controlled neurostimulation [98, 99], overcoming the intermittent nature of energy harvesting, and ensuring the long-term stability and biocompatibility of soft bioelectronics [100–102].

Moreover, the application of TENGs extends beyond neurostimulation to include powering therapeutic neural prostheses and driving optogenetic and drug-delivery devices for deeper brain therapies [103, 104]. This integrative approach, combining TENG with advanced therapeutic devices, has the potential to revolutionize neurological treatments, offering patients a seamless, self-powered solution that eliminates the

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dependency on external power sources and charging devices [38]. While TENGs present a promising avenue for self-powered neurostimulation [38], achieving clinical adoption requires addressing biocompatibility and integration with neural electrodes, alongside enhancing design and energy harvesting efficiency for direct and controlled neurostimulation [105, 106].

This review highlights the potential and advancements of TENGs in self-powered neuromodulation, focusing on their diverse operational modes and their significant role in neurostimulation across central and peripheral nervous systems. It assesses current challenges and areas ripe for innovation, aiming to facilitate the transition of TENGs from experimental models to viable clinical solutions. By advocating for further research and development, this review seeks to inspire the creation of self-powered neurostimulation devices that could reshape neurological therapies, making them more accessible and seamlessly integrated with the human body's natural movements and energy. The realization of TENG-powered neuromodulation systems could significantly impact the treatment of neurological disorders, ushering in a new era of self-sustained and personalized therapy.

2 Working principles of TENGs

TENGs for neurostimulation are versatile, with multiple operational modes offering varied implantation and integration options for developing soft neurostimulation bioelectronics [107–136]. These modes each have distinct mechanisms and applications, highlighting the potential of TENGs to revolutionize soft bioelectronics through their adaptable and customizable energy harvesting capabilities.

2.1 Design modes and electrical generation

Since the 18th century's pioneering applications, electrical neurostimulation has evolved into a pivotal tool in treating various neurological disorders. This evolution has spanned from employing spinal cord stimulation to enhance movement and sensation to utilizing deep brain stimulation (DBS) for the management of Parkinson's disease and epilepsy [137, 138]. TENGs, with their ability to convert mechanical energy into electrical energy, are paving the way for innovative therapies in both the central nervous system (CNS) and PNS, showing promise in axonal regeneration, neural differentiation, and autonomic nerve modulation (Fig. 1(a)). Their application spectrum is expanding into the realms of sensory–motor systems, the development of visual and olfactory sensors, and advancements in cochlear implants. These endeavors represent significant progress toward the realization of fully implantable neurostimulation systems, marking a new era in medical technology's capability to interface with and modulate the nervous system.

Figure 1(b) showcases the principle of contact electrification as the foundation of TENG [139]. This process, involving the formation of a chemical bond or adhesion between two surfaces, facilitates charge transfer to balance electrochemical potentials. The atomic-scale-electron-cloud-potential-well model explains this phenomenon by describing how the overlapping electron clouds of materials in close proximity allow for the transfer of high-energy electrons, leading to triboelectric charging. This mechanism underscores the nuanced interaction between materials and the importance of selecting the appropriate pairings for optimal TENG performance. The operational modes of TENGs, including vertical contact separation, lateral sliding, single electrode, and freestanding (Fig. 1(c)), each offer distinct advantages and challenges for neurostimulation [140].

Vertical contact-separation mode stands out for its efficacy in converting biomechanical movements directly into electrical energy, an attribute that aligns perfectly with the spatial and functional requirements of neurostimulation devices [69–75]. This mode's ability to produce controlled electrical signals through triboelectrification makes it highly suitable for precise neurostimulation tasks. Its operation, which involves the contact and separation of two triboelectric layers, allows for efficient energy conversion without significant material deformation, making it a robust choice for both CNS and PNS applications. However, the necessity for physical contact could introduce wear over time, potentially limiting the device's lifespan and necessitating careful material and design considerations to ensure durability. Lateral sliding mode, by contrast, leverages the parallel movement between two triboelectric layers to generate energy [76–80]. The requirement for lateral motion introduces complexity within the constrained and dynamic environment of the human body, making it less favored for direct neurostimulation implementations. While it may offer high energy efficiency, the spatial limitations and potential for dimensional changes during device operation present significant engineering challenges that need addressing for this mode to be viable for neurostimulation, particularly in areas with limited space or where direct biomechanical interaction is difficult to achieve.

Freestanding triboelectric layer mode could harvest bioenergy from the subtle vibrations in body organs [86, 87]. Its design, which allows for an independent layer to move freely between two stationary electrodes, can potentially provide a durable and stable source of energy for neurostimulation without the need for direct

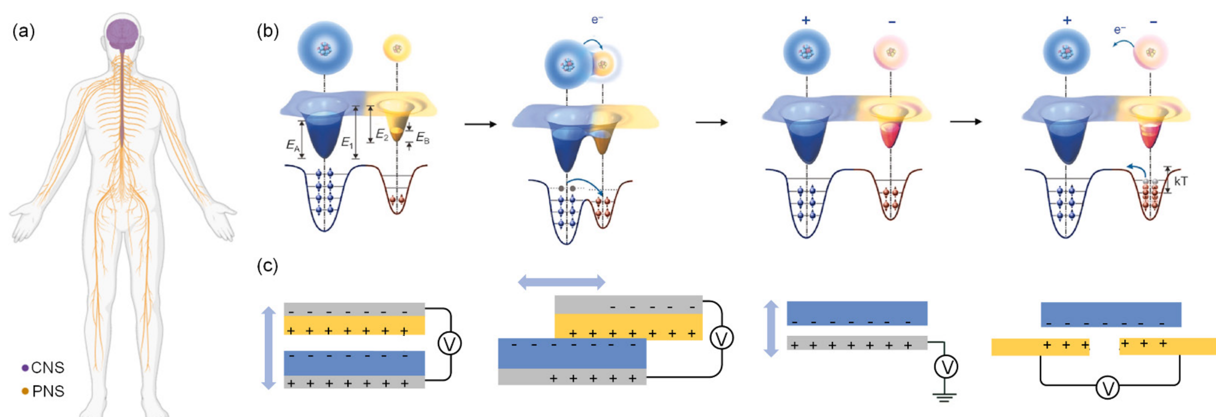

Figure 1 Working principle of TENG for electricity generation and self-powered neurostimulation. (a) TENGs for neurostimulation: enhancing CNS functions and PNS pathways. (b) TENG contact electrification: contact electrification, electron transfer, and electric field-driven electron flow. Reproduced with permission from Ref. [139], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2018. (c) TENGs' operational modes: Vertical separation, lateral sliding, single-electrode, and freestanding layer. Reproduced with permission from Ref. [140], © Babu, A. et al. 2022.

solid–solid friction [86, 87]. Single electrode mode presents a simpler yet effective design by involving only one electrode in interaction with an external, freely moving dielectric material [81–85]. This design simplicity comes with the challenges of lower power output and difficulties related to grounding and operation within the body's aqueous environment. Overcoming these hurdles requires encapsulation and material engineering strategies, making this mode potentially useful for specific neurostimulation scenarios where minimal energy harvesting is sufficient and direct contact with internal organs is not feasible. In integrating TENGs into neural electrodes, the selection of operational mode must consider not only the efficiency of energy conversion but also the anatomical and functional complexities of the targeted nervous system. The vertical contact-separation mode emerges as the most applicable and efficient, especially for soft bioelectronics requiring precise and controlled neurostimulation.

2.2 Mechanism of TENGs for neurostimulation

The foundation of TENGs in neurostimulation is a stride in biomedical engineering, signaling a transformative approach to neurological disorder treatments. These devices leverage the triboelectric effect, a phenomenon where contact electrification between differing materials generates surface charges, paving the way for the conversion of mechanical energy into electrical stimuli conducive to nerve and spinal cord stimulation [141]. The high-voltage and low-current output properties make TENGs particularly suitable for precise neurostimulation applications, presenting them as a viable alternative to conventional electric stimulations [5]. Maxwell's displacement current principle, crucial for understanding TENG operation, highlights the addition of a mechano-driven polarization term to account for the electrostatic charges induced by contact electrification [83, 84]. This conceptual advancement integrates the mechanical and electrical realms, offering a comprehensive view of TENGs' capacity to interact with and stimulate the nervous system.

TENGs stand at the confluence of safety, reliability, cost-effectiveness, and flexibility of application—from wearable devices to implantable neurostimulators [121, 142–146]. This adaptability is underpinned by their scalable and tunable nanofibrous membrane architectures, ensuring long-term and versatile neurostimulation solutions. Furthermore, the potential of TENGs extends beyond traditional applications, showing promise in nerve repair [147], obesity treatment [68], muscle system modulation [98, 148–150], and even atrial fibrillation therapy [151]. In essence, TENGs for neurostimulation, blending the principles of physics and material science heralds a new era in therapeutic interventions for neurological disorders, offering a path towards accessible, personalized, and effective treatments. At the intersection of mechanical energy conversion and neurobiology, the integration of TENGs in neurostimulation marks a pivotal advancement in the development of non-invasive and efficient therapeutic technologies. TENG leveraging human biomechanical movements to generate electrical impulses is vital for *in vitro* cellular stimulation, enabling insights into cellular mechanisms, drug testing, and the development of therapeutic strategies [103].

3 TENGs for peripheral nervous system stimulation

The PNS comprises two primary segments: the autonomic nervous system (ANS), which regulates involuntary body functions and gland activities, and the somatic nervous system (SNS), which is involved in muscle movements and relaying sensory information to the central nervous system [105]. TENGs, with their ability to convert mechanical energy into electrical power, offer a promising avenue for the self-powered neuromodulation of both the ANS and SNS, potentially revolutionizing the treatment of peripheral nerve disorders.

3.1 Sciatic nerve stimulation

Exploring the potential of TENGs in sciatic nerve stimulation is crucial for pain management and muscle rehabilitation [98, 148–150]. The use of TENG for sciatic nerve activation, a critical component of the peripheral nervous system that branches into the common peroneal, tibial, and sural nerves, represents a significant step forward in applying mechanical energy conversion for innervating various muscles [142, 150] (Figs. 2(a)–2(c)). This system leverages the direct conversion of mechanical energy to electrical pulses for nerve stimulation, utilizing a closed-loop configuration with electrodes connected to the sciatic nerve to demonstrate TENG's capability for targeted neural activation [142] (Fig. 2(a)). The observation of induced leg movements under anesthesia signifies successful muscle stimulation through the sciatic nerve by the TENG [142] (Fig. 2(b)). The mechanism of action showcases a stacked-layer TENG designed for efficient mechanical-to-electrical energy conversion [150] (Fig. 2(c)). The design incorporates a polyethylene terephthalate (PET) sheet in a zigzag structure for mechanical support, allowing the TENG to revert to its original position after each press, thus facilitating continuous energy generation for muscle stimulation. The incorporation of aluminum films as electrodes enhances charge output, while the dual role of one aluminum film as both electrode and active triboelectric surface, complemented by a polytetrafluoroethylene (PTFE) layer on the second film, maximizes energy conversion efficiency. This flexibility underscores the capacity of TENGs to harness everyday body movements for muscle stimulation, offering a promising avenue for rehabilitation and therapeutic treatments.

Building on the foundational use of TENGs for direct sciatic nerve stimulation, recent advances in TENG structures have broadened performance and application scope, highlighting their adaptability in meeting the specific demands of functional electrical stimulation and rehabilitation in neurostimulation device design. The development of a liquid TENG array represents a significant leap forward [152] (Fig. 2(d)), offering selective neural electrode stimulation. This approach solves key challenges such as liquid evaporation and secure liquid fixation within the device, ensuring consistent performance and expanded application potential in neurostimulation. By integrating sponge elements into the device, this design effectively maintains the presence of the liquid medium, optimizing electrical output and enhancing the stimulator's reliability and effectiveness. The concept of using a liquid-based array allows for multiple and selective stimulations, pointing towards versatile applications in functional electrical stimulation and rehabilitation, bridging the gap between TENG and practical clinical applications. Further introduction of an arch-shaped structure with rough surfaces marks a pivotal improvement in TENG output performance [153] (Fig. 2(e)). The fabrication process involving aluminum foils and surface textured polydimethylsiloxane (PDMS) films achieves a TENG that excels in converting mechanical energy into electrical energy. This high-performance TENG design, with its micro/nano hierarchical structures, promises to enhance neurostimulation device efficiency and effectiveness, signaling a new era of structurally engineered TENGs that optimize energy conversion and meet the operational demands of therapeutic interventions [154].

The evolution from the development of advanced TENG structures for neurostimulation to their integration with neural interfaces for direct muscle activation and continuous bio-signal monitoring encapsulates the transformative potential of TENG in

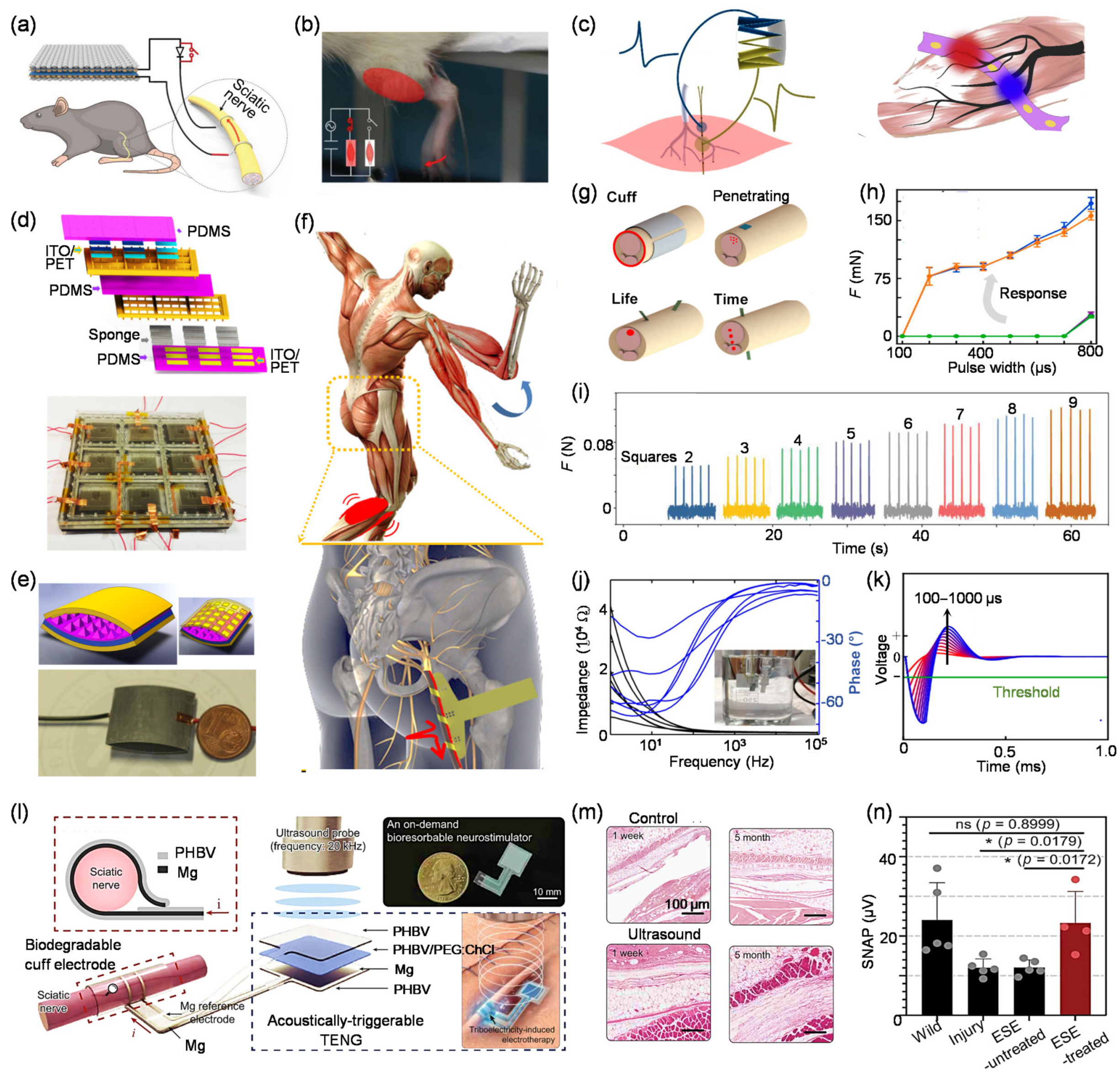

Figure 2 TENGs for self-powered sciatic nerve stimulation. (a) TENG sciatic nerve stimulation in rats. (b) Rat leg movement upon tibialis anterior muscle stimulation. (c) Asymmetric TENG-powered electrical muscle activation. (d) Battery-free neuromodulation with TENG and neural electrodes. (e) PDMS structuring TENG three-dimensional (3D) schematic and final device photo. (f) Human-integrated flexible sling and TENG interface. (g) Flexible neural interfaces with TENGs, detailing extra-neural, penetrating, and intra-fascicular designs. (h) Waveform polarity on stimulation efficiency in dual-animal measurements. (i) Force profile of rat leg movement induced by activating varying squares of the TENG. (j) Impedance characteristics of neural electrodes, highlighting suitability for muscle tissue stimulation at 1 kHz. (k) Motoneuron voltage waveform profiles. (l) Neurostimulator architecture featuring TENG, bioresorbable cuff, and device photo inset. Protocol for peripheral nerve electrotherapy. (m) Hematoxylin and eosin (H&E)-stained images showing inflammation from natural and high-intensity ultrasound-induced biodegradation. (n) Nerve function post-electrotherapy in compression nerve injury mice: Wild type, injury, ESE-untreated, ESE-treated (ESE: electrical stimulation events). (a), (b), and (i) Reproduced with permission from Ref. [142], © He, T. Y. Y. et al. 2019. (c), (h), (j), and (k) Reproduced with permission from Ref. [150], © American Chemistry Society 2019. (d) Reproduced with permission from Ref. [152], © Elsevier Ltd. 2018. (e) Reproduced with permission from Ref. [153], © Elsevier Ltd. 2013. (f) and (g) Reproduced with permission from Ref. [148], © Elsevier Ltd. 2017. (l)–(n) Reproduced with permission from Ref. [157], © Lee, D. M. et al. 2023.

the biomedical field [155]. A pioneering closed-loop system was developed to use TENGs to convert muscle movements into electrical energy for direct neuromodulation [148] (Fig. 2(f)), enabling the dynamic interaction between TENGs and neural interfaces to activate targeted muscles for therapeutic applications. The versatility of neural electrodes, including extra-neural and intra-fascicular interfaces, is brought to the forefront [148] (Fig. 2(g)), illustrating the broad applicability of TENG across various clinical needs. E-skin represents a significant stride in measuring bio-signals, showcasing the integration of flexible and stretchable electronics for real-time monitoring of physiological functions [156]. This multifaceted approach not only enhances the capabilities of TENGs in neurostimulation but also opens new avenues for diagnosing and treating a wide range of medical conditions.

The waveform polarity's impact on motoneuron activation reveals the critical role of electrode configuration in achieving precise and effective stimulation [150] (Fig. 2(h)). This underscores the importance of nuanced control and understanding electrophysiological dynamics for developing neuroprosthetic devices using TENG-generated signals. The nearly linear correlation between stimulation current and force output in muscle activation identified through the stimulation of the tibialis anterior muscle simplifies the process of determining the necessary activation area for desired force output [142] (Fig. 2(i)). This finding is instrumental for the development of prosthesis control mechanisms, offering a methodical approach to tailoring neurostimulation for rehabilitation and therapeutic applications. The neurostimulation system's examination of electrode site impedance and mechanical durability validates its efficiency in current delivery and suitability for long-term neuromodulation, highlighting its resilience and reliability under physiological conditions [150] (Fig. 2(j)). The consistency in voltage waveform output across different pulse directions [150] (Fig. 2(k)), a critical aspect for the predictable operation of TENG-based neurostimulation systems guarantees a stable and reliable therapeutic intervention, crucial for the successful implementation of TENG in neurostimulation. Delving into waveform polarity, force output measurement, and electrode impedance reveals the intricate design considerations essential for harnessing TENG in effective sciatic nerve stimulations.

To reduce inflammatory responses in sepsis and ease atrial fibrillation symptoms, an acoustically triggerable on-demand bioresorbable neurostimulator, featuring an acoustically triggerable transient TENG and a bioresorbable cuff electrode was developed [157] (Fig. 2(l)). This battery-free system utilizes ultrasound sources for targeted peripheral nerve electrotherapy, ensuring biological safety and enabling non-invasive clinical plan adjustments. Its potential in treating peripheral neuropathies, including compression injuries and Charcot–Marie–Tooth disease, marks a significant leap in nonpharmacological therapy. The mechanical disintegration and complete elimination of the device under high-intensity ultrasound waves highlight the transient nature and compatibility with therapeutic timelines [157] (Fig. 2(m)). The efficacy of electrical stimulation on nerve recovery is revealed by improved nerve conduction velocities and action potentials in compression injury models [157] (Fig. 2(n)). Ultrasound-assisted TENG implants demonstrate significant therapeutic efficacy in treating peripheral neuropathies by enabling the adjustment of stimulation parameters, such as frequency and current amplitude, through non-contact ultrasound methods, marking a paradigm shift in neurostimulation therapies.

3.2 Vagus nerve stimulation (VNS)

The introduction of ultrasound-assisted TENG implants signifies a transformative development in treating peripheral neuropathy with a minimally invasive and battery-free solution [72, 74, 158, 159]. The use of ultrasound as an external trigger for TENG implants revolutionizes the way electrical stimulation is delivered internally, enabling the precise tailoring of therapies to individual needs through the non-invasive penetration of biological tissues and compatibility with existing medical imaging techniques [159–162]. A pioneering application of this technology is the ultrasound-driven hydrodynamic TENG designed for vagus nerve stimulation [158] (Fig. 3(a)), showcased in subcutaneous rat models. This device incorporates a polyacrylamide (PAM)-graphene conductive hydrogel that, when activated by ultrasound vibrations, generates electrical outputs by exploiting the interface between the hydrogel and phosphate buffer saline (PBS). Ensuring biosafety, the TENG connects to the vagus nerves with flexible gold wires encased in PDMS, effectively maintaining cardiac rhythm stability and minimizing thermal effects during stimulation. Evidence of the TENG implant's integration and biosafety three months post-implantation includes healed suture wounds and tissue compatibility [158] (Fig. 3(b)), demonstrating its viability as a wireless power source for bioelectronic devices and a sustainable option for neurostimulation. The electrical output under varying load resistances reveals its potential for wireless power supply to implanted bioelectronic devices and as a battery-free neurostimulator [158] (Fig. 3(c)). Furthermore, the precise synchronization of electrophysiological responses with ultrasound pulses, observed in electrocardiogram (ECG) recordings, underscores the device's capability to provide targeted neurostimulation without interfering with normal cardiac functions [158] (Fig. 3(d)).

Integrating TENG into VNS also presents a promising approach to addressing obesity and body weight management through neurostimulation. This advanced technique utilizes the natural movements of the stomach, converting them into electrical signals that modulate vagus nerve activity to influence appetite and food intake [68] (Fig. 3(e)). By affixing a TENG device directly onto the stomach's surface, this system harnesses peristaltic movements to produce biphasic electric pulses. These pulses are strategically directed towards the anterior and posterior vagus nerves, ensuring precise stimulation while avoiding interference with the heart and lungs [108, 121, 163]. The device's encapsulation in durable and biocompatible materials, verified through *in vitro* testing, underscores its potential for safe long-term implantation. The operational dynamics of the TENG within the VNS system revealed the cyclical generation of electrical pulses in sync with stomach contractions [68] (Fig. 3(f)). This self-sustaining mechanism highlights the direct correlation between physiological activities and therapeutic outcomes, making it a promising solution for non-invasively regulating body weight. A significant reduction in body weight and food intake among subjects equipped with the VNS device, compared to controls, demonstrates the potential of TENG-based VNS in combating obesity [68] (Figs. 3(g) and 3(h)). The VNS device's adaptability to various stomach movements [68] (Fig. 3(i)) ensures the device's effectiveness across a wide range of stomach dynamics, making it a versatile tool in the realm of neurostimulation for weight control. TENG designs employing biocompatible materials such as PDMS for encapsulation demonstrate harmonious integration with bodily tissues [151] (Fig. 3(j)), showing no adverse biological responses post-subcutaneous implantation.

Beyond traditional weight control interventions, the application of TENG in VNS systems opens avenues for neurostimulation across a variety of biomedical applications. Recent advance in a closed-loop, self-powered low-level VNS system marks an advancement in managing atrial fibrillation [151] (Fig. 3(k)), showcasing the application of TENGs in therapeutic devices that respond to physiological cues for prompt medical intervention and underlining their promise in cardiac care. The mechano-neuromodulation captures mechanical movements to stimulate nerve activity, exemplified by a bladder modulation prototype that underscores the broad potential of TENGs in diverse neuromodulation applications and their role in developing interactive, responsive medical devices [106] (Fig. 3(l)). In the advancement of VNS for therapeutic treatments, a hybrid nanogenerator has been engineered to efficiently bridge the gap between the demand for continuous energy supply and the intermittent energy generation inherent to TENGs. This hybrid TENG employs a dual-layered structure that combines the dynamic energy harvesting capabilities of triboelectric layers with the stable energy output of piezoelectric materials. This hybrid design is specifically tailored to enhance the VNS devices' effectiveness in managing conditions like atrial fibrillation, showcasing a novel approach to self-powered medical interventions. Its operational principle initiates with the device in a neutral state, devoid of any electrical potential across its layers [151] (Fig. 3(m)). Upon mechanical stimulation—mimicking the physiological movements associated with the vagus nerve's vicinity—the device undergoes deformation. This leads to the triboelectric layers coming into contact, generating an electrical charge, while simultaneously compressing the piezoelectric material to augment the energy output. This ensures a continuous flow of electrical pulses necessary for effective VNS, even in the absence of constant mechanical energy. The "switch" mechanism inherent to the hybrid structure not only optimizes energy capture from bodily movements but also significantly reduces the risk of unintentional nerve stimulation, enhancing the safety profile of

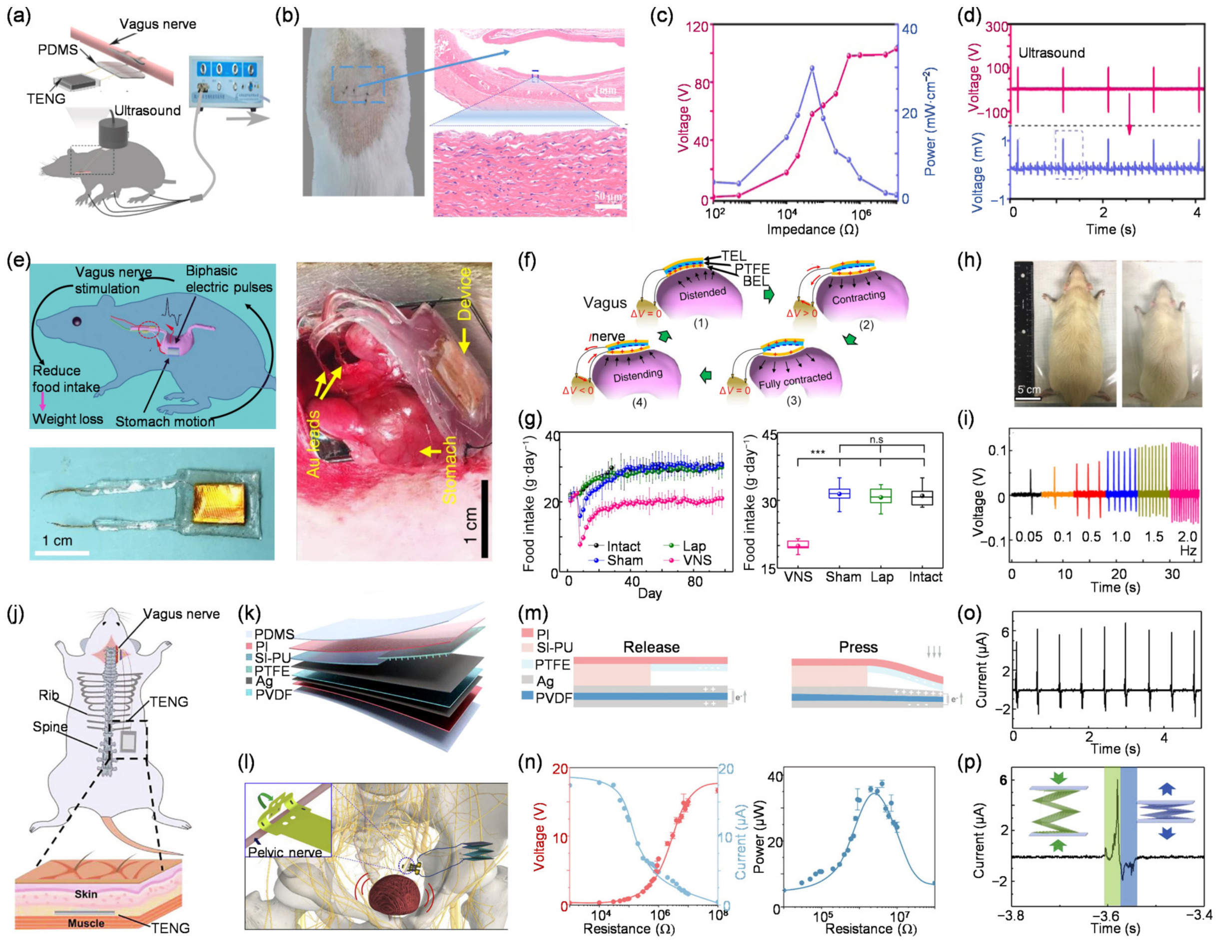

Figure 3 TENGs for self-powered vagus nerve stimulation. (a) Subcutaneous ultrasound-responsive TENG implant for vagus nerve stimulation. (b) TENG three months post-implantation site photo. (c) Ultrasound-responsive TENG output voltage and power as a function of load resistors. (d) Voltage synchronization with ultrasound input pulses. (e) Overview of a biocompatible VNS system: Operation schematic for biphasic signal pathway, implantation with gold leads to vagal trunks, and the final packaged device. (f) Working schematics of a VNS device across various stomach motion stages. (g) Rat food consumption patterns and steady-state daily intake across groups. (h) Weight management in rat growth phase: VNS vs. control group sizes. (i) Voltage response in phosphate-buffered saline with varying agitation frequencies via VNS device connected to a load-matching implant impedance. ((j) and (k)) Subcutaneous TENG implant. (l) Bladder anatomy schematic. (m) Hybrid TENG neurostimulation principle. (n) Voltage, current variation, and TENG power across varying load resistances. ((o) and (p)) TENG output currents at a heart rate of 100 BPM. (a)–(d) Reproduced with permission from Ref. [158], © Elsevier Ltd. 2021. (e)–(i) Reproduced with permission from Ref. [68], © Yao, G. et al. 2018. (j), (k), (m), and (n) Reproduced with permission from Ref. [151], © Science China Press 2022. (l), (o), and (p) Reproduced with permission from Ref. [106], © Elsevier Ltd. 2019.

the VNS system. The efficiency of this hybrid structure is evident, where improvements in electron transfer are quantitatively demonstrated through increased current and voltage outputs [151] (Fig. 3(n)). This showcases the technical advancements in TENG design that contribute to more effective neurostimulation devices. Transitioning from this sophisticated design, the multilayer TENG activated by manual hand-tapping shows the versatility and user accessibility to generate significant electrical energy with minimal mechanical input [106] (Fig. 3(o)), tailored specifically to meet the impedance characteristics of neural interfaces. Further extending TENG's practical utility, a compact, handheld mechano-neuromodulator prototype for bladder modulation [106] (Fig. 3(p)) underscores the technology's adaptability to everyday use, offering advanced neurostimulation capabilities in a user-friendly format. These advances mark significant strides towards integrating TENG into a variety of neurostimulation applications, from precise energy delivery mechanisms to accessible and practical devices for daily therapeutic use.

4 TENG in central nervous system stimulation

The evolution of brain bioelectronics has introduced a variety of neuromodulation techniques that have significantly expanded our capacity to stimulate, inhibit, and monitor brain activities [97, 104, 164–168]. These techniques encompass electrical, electromechanical, optogenetic, magnetic, and ultrasonic approaches, each tailored to address specific neurological conditions and restore sensory functions. Brain neuromodulation, through its diverse methodologies, plays a crucial role in treating neurological disorders such as Parkinson's disease [24], epilepsy [22, 23], and chronic pain [25, 26], while also offering potential management strategies for psychiatric conditions including schizophrenia, depression, obsessive-compulsive disorders, and autism [21]. The application and effectiveness of these neuromodulation strategies depend on multiple factors including the target location within the brain, size of the stimulated area, and the desired therapeutic outcomes. TENGs, serving both as electromechanical energy harvesters and power sources, are particularly instrumental in CNS stimulation, where they can be integrated into systems for sensory substitution and enhanced perceptions [165], providing a pathway to restore or augment sensory functions like smell and touch. Moreover, TENGs offer a reliable power solution for DBS devices [164], which are crucial for the management of severe neurological disorders. Their ability to generate power through biomechanical activities makes them suited for powering optogenetic modulation devices as well, enabling precise neuronal activation with unparalleled spatial and temporal resolution [166, 169].

4.1 Deep brain stimulation for neurological disorders

The evolution of DBS technologies for neurological disorders is witnessing a shift towards self-sustainability, addressing the challenges of energy supply in implantable neurostimulators. This transformation is spearheaded by the integration of TENGs into neurostimulation systems, exemplified by the development of a self-sustainable, intermittent DBS approach [164] (Fig. 4). This pioneering method capitalizes on the unique properties of TENGs to bridge the gap between the low energy yield from biomechanical movements and the high energy demands typical of neurostimulation devices. The bio-TENG is optimized to capture the mechanical energy from the natural breathing motion of the lungs (Fig. 4(a)). When coupled with a supercapacitor for energy storage and a pulse generator for the delivery of precise stimulation pulses, this system marks a significant leap in neurostimulation. The TENG's multilayer design effectively harnesses the kinetic energy of respiratory movements to charge the supercapacitor, which in turn, powers the pulse generator. This generator is then able to produce highly regulated electrical pulses tailored in frequency and width to meet specific therapeutic needs (Fig. 4(b)). This DBS system showcases its functionality through *ex vivo* experiments in genetically modified mouse brain tissue, where stimulated regions are indicated by fluorescence signaling (Fig. 4(c)).

A key feature of this system is its intermittent operation mode, alternating between stimulation and charging phases to achieve a balance that ensures self-sustainability. This intermittent stimulation pattern not only conserves energy but is also posited to be effective in eliciting therapeutic responses with brief or periodic neural activation. This system reshapes DBS to treat neurological conditions by offering a self-powered and intermittently operating neurostimulator, which addresses the longstanding challenge of aligning the relatively low power production of TENGs with the substantial energy requirements of implantable neurostimulators. Through TENG structural design and strategic integration of energy management, the promise of efficient, self-powered DBS devices for neurological disorders is becoming an achievable reality [58, 170, 171].

4.2 Sensory substitution and enhanced perceptions

TENGs have emerged as a groundbreaking tool in advancing CNS neurostimulation, offering novel approaches for sensory substitution and enhancing sensory perceptions. The application of TENG in neural prosthetics represents a significant shift towards more interactive and responsive therapeutic interventions, paving the way for sensory augmentation and the treatment of sensory deficits [167, 172, 173]. Recent advance in sensory substitution in the brain is highlighted [165] (Fig. 5(a)), where a self-powered multi-perception electronic skin, when connected to the mouse brain, simulates the tactile sensation of whiskers. This device's ability to convert external tactile stimuli into electrical signals that are then processed by the brain's primary somatosensory barrel cortex (S1BF area) demonstrates TENGs' potential in bridging sensory gaps. This advance reveals the feasibility of TENGs in replicating and enhancing natural sensory feedback mechanisms, offering potential applications in prosthetics and sensory aids that could restore or augment tactile sensations for individuals with sensory impairments. The design's flexibility and transparency, coupled with a novel architecture that supports various sensory units for detecting mechanical deformation, sonic waves, gases, pH levels, and light [165] (Fig. 5(b)), underscore the versatility of TENGs in monitoring and interacting with the environment. This approach not only shows the potential to enhance human sensory capabilities but also has implications for safety and environmental awareness, demonstrating the potential for TENGs in creating more adaptive and responsive human–machine interfaces [174, 175]. The detailed response analysis against varying concentrations of acetone vapor showcases the precision and reliability of TENG-based sensors [165] (Fig. 5(c)). This specificity in detection illustrates the potential of TENGs in environmental sensing and monitoring [176], providing valuable insights into their application in developing devices that can accurately and selectively respond to a wide range of stimuli. Such capabilities highlight the potential for TENGs to create advanced sensory substitution systems or restore lost senses, thus enhancing the quality of life for individuals with sensory deficits.

4.3 Powering micro light-emitting diode (μLED) for optogenetic brain modulation

Optogenetics, a technique that allows for the control of neuronal activity using light, has traditionally relied on external power sources such as batteries or wireless transmission. The advent of TENGs has introduced a self-sustaining power solution [168, 177,

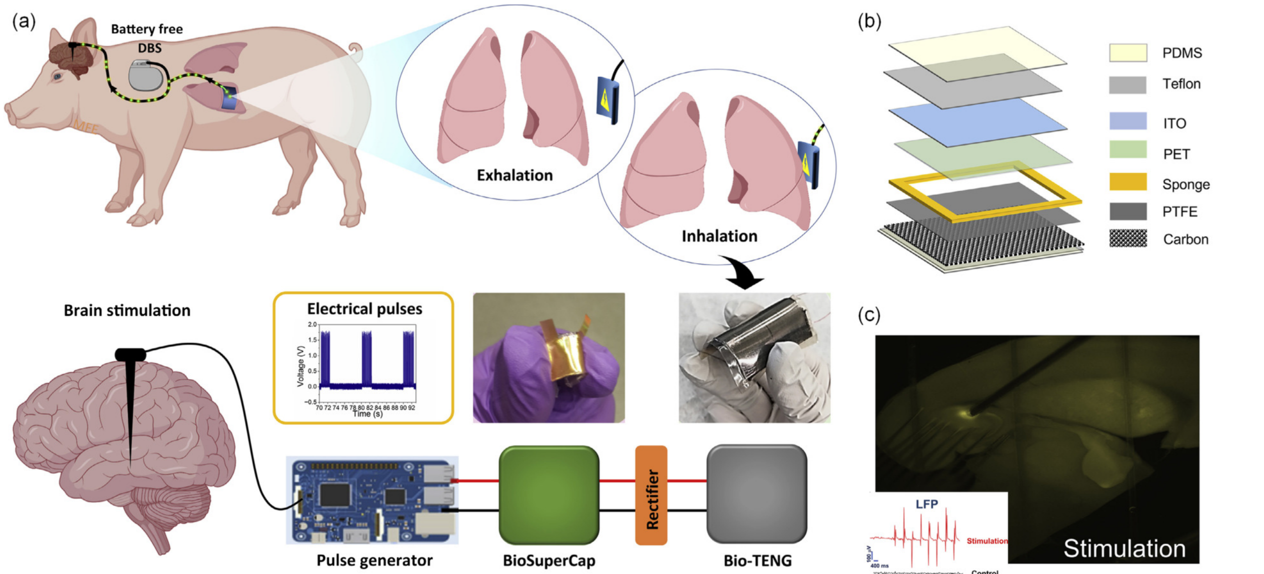

Figure 4 TENGs for self-powered deep brain stimulation. (a) Schematic of a self-sustaining DBS harvesting energy from a breathing swine lung, comprising energy harvesting bio-TENG, storage supercapacitor, and a microchip for regulated stimulation via an implantable microelectrode. (b) The structure of a bio-TENG. (c) Fluorescent emission at the hippocampus from a microelectrode, powered by a TENG-generated signal. (a)–(c) Reproduced with permission from Ref. [164], © Elsanadidy, E. et al. 2022.

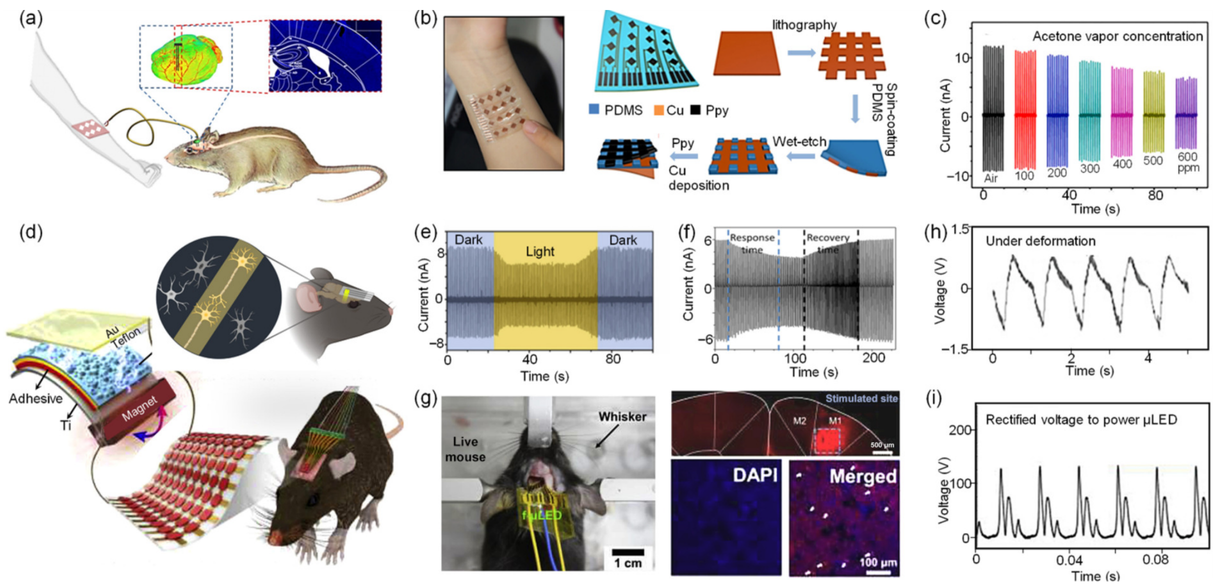

Figure 5 TENGs for self-powered brain neurostimulation and optogenetics. (a) Self-powered TENG e-skin connected to mouse somatosensory barrel cortex stimulation for obstacle navigation. (b) TENG e-skin photo and fabrication process. (c) The sensor exhibits high sensitivity, stability, and selectivity for acetone vapor detection. (d) Flash-induced TENG energy harvesting for optoelectrical stimulation. (e) Sensor unit sensitivity to light: detection of intensity, wavelength, and response/recovery rate. (f) TENG e-skin's response and recovery dynamics. (g) Mouse M1 region μLED stimulation, and confocal images showing Chrimson (red) and 4',6-diamidino-2-phenylindole (DAPI, blue) at the motor cortex. (h) Open circuit voltage under deformation. (i) Rectified voltage from TENG to power μLED in a 60 Hz magnetic field from a hairdryer cable. (a)–(c), (f), and (h) Reproduced with permission from Ref. [165], © Elsevier Ltd. 2017. (d), (g), and (i) Reproduced with permission from Ref. [166], © Elsevier Ltd. 2020. (e) Reproduced with permission from Ref. [169], © Elsevier Ltd. 2019.

178]. The integration of TENGs with optogenetic stimulation represents a groundbreaking convergence of mechanical energy harvesting and precise neuronal control. This synergy offers a novel approach to neuromodulation, enabling the stimulation or inhibition of specific neuron populations in the brain through light.

Figure 5(d) elucidates the fabrication of a flash-enhanced micro magnetic TENG, which integrates a red flexible μLED for *in vivo* optogenetic brain modulation [166]. This design comprises a nylon substrate as the positive triboelectric layer and Teflon as the negative layer, with gold layers serving as current collectors. The assembly is then affixed to a titanium plate adorned with small magnets, enabling the conversion of ambient alternating current (AC) magnetic fields—common in household appliances—into the mechanical vibrations necessary to activate the TENG. The enhancement of the Nylon substrate's surface through photothermal interaction significantly boosts the TENG's efficiency, thereby facilitating targeted activation of neurons with pulsed light, a technique that could offer novel insights into neural pathway functions and behavioral outcomes. The development of a methylammonium lead iodide ($MAPbI_3$)-based TENG for stimulating hippocampal tissue in mouse brains represents a notable advance in neurostimulation [169] (Fig. 5(e)). This device utilizes a perovskite $MAPbI_3$ layer, serving dual roles as both a positive triboelectric component and a photosensitive element, combined with PDMS acting as the negative triboelectric layer and structural support, with copper employed for current collection. The integration of these materials allows for the harvesting of human motion through triboelectrification between the $MAPbI_3$ and PDMS layers, which can then be utilized for direct brain stimulation. Further enhancing its functionality, the $MAPbI_3$ layer' s photosensitivity enables the electronic skin to act as an "on/off" wireless switch in response to photo illumination [169] (Fig. 5(e)). This capability not only underscores the material's versatility but also opens up possibilities for nuanced control over neurostimulation processes. Additionally, this technology has been applied in a pioneering manner to investigate neuroplasticity—the changes and modifications in synaptic strength between neurons. By implanting stimulation electrodes in the hippocampus's CA3 region and recording electrodes in the CA1 region, the device facilitates the observation of evoked brain activity and synaptic responses, manifesting as field excitatory postsynaptic potentials. This pioneering application demonstrates TENG-based e-skin's potential for self-powered characterization of synaptic plasticity, marking a significant step forward in exploring the complexities of neural mechanisms and synaptic dynamics. The TENG e-skin's rapid oscillation in current during illumination, followed by a swift return to baseline indicates its sensitivity and quick adaptability to changes in light stimuli [165] (Fig. 5(f)).

Positioned under the mouse skull, the μLED array is powered by the TENG to illuminate specific regions of the mouse brain, such as the primary motor cortex (M1), responsible for whisker movements [166] (Fig. 5(g)). TENG's open-circuit voltage response under mechanical stress [165] (Fig. 5(h)), and the rectified sharp voltage spikes up to nearly 200 V to power μLED [166] (Fig. 5(i)) reveal TENG's capacity for light-induced responses and its versatility in sensing diverse environmental stimuli such as vibration, sound, and light, crucial for the development of integrated sensing devices in self-powered optogenetics and multifunctional environmental sensing. However, the reliance on external magnetic fields for operation introduces a degree of variability in the generated signals, potentially affecting the precision and control of optogenetic stimulation. This limitation underscores the necessity for developing TENG optogenetic systems to be fully encapsulated and isolated from bodily fluids, equipped with long-term implantation capabilities, and integrated with energy storage and electrical circuits for enhanced control and efficiency.

5 Challenges and perspectives

The burgeoning field of TENGs is reshaping neurostimulation technologies, propelling them towards groundbreaking applications in e-skins [156, 179], wearable devices [180–189], and self-powered medical implants [149, 190] (Fig. 6). However, the journey from laboratory prototypes to clinically approved devices is fraught with hurdles that necessitate ingenious solutions including device engineering, power management, implantation techniques, and biosafety [173, 191, 192]. Addressing these challenges will not only advance the field of neurostimulation but also unlock new dimensions in personalized therapy and rehabilitative medicine.

5.1 Device metrics and controlled neurostimulation

Despite their significant potential, the integration of TENGs into neurostimulation therapies confronts challenges such as uncontrolled electrical outputs due to the variable nature of biomechanical movements and the technical demand for consistent therapeutic signal parameters [193]. Traditional TENG applications have predominantly relied on mechanical energy conversion from movements such as hand tapping or bodily functions, resulting in electrical signals that may lack the consistency required for therapeutic applications. Clinically, neurostimulation demands precise control over signal parameters like amplitude, frequency, and pulse duration to ensure therapeutic efficacy. Innovations in device design, incorporating fast-charging energy storage units and pulse-generating microcircuits, are essential [194]. These enhancements would allow the storage of TENG's electrical output for generating consistent neurostimulation patterns. Moreover, the long-term durability of TENG components, including the energy storage unit and implanted electrodes, necessitates rigorous testing and validation to ensure sustained performance [100, 101].

Another significant challenge lies in TENG's power output specifications [195]. The intermittent nature of TENG-generated alternating current, combined with the low mechanical impact from human movements and the high-power demands of conventional neurostimulators, poses a considerable barrier. Strategies for enhancing the efficiency of mechanical-to-electrical conversion and developing power management units capable of optimizing TENG outputs to meet clinical requirements are under exploration [105, 154, 155]. Furthermore, the integration of efficient energy storage systems could bridge the gap between TENG's energy production, and the continuous power supply needed for effective neurostimulation.

5.2 Implantation and neural interface challenges

The prospect of chronic *in vivo* TENG implantation introduces complexities related to biocompatibility, device fixation, and minimally invasive surgical techniques [196]. Materials like PDMS offer a promising solution for biocompatible encapsulation, but the challenge of securely affixing TENG devices near soft tissues remains [99]. Advances in surgical techniques and TENG/neural interfaces are critical to mitigate potential tissue damage from TENG's electrical outputs. Innovating micro-electrode designs with neuro-biocompatible materials could significantly reduce adverse effects at the neural interface during electrical stimulation. TENG's interaction with various body organs for biomechanical energy harvesting raises biosafety concerns, particularly regarding potential tissue damage during operation. Ensuring smooth, edge-free TENG surfaces and proper device positioning can minimize injury risks [4]. Additionally, anti-biofouling coatings on TENG surfaces may reduce post-surgical inflammation and infection risks, enhancing the biosafety profile of these devices in clinical settings [154].

5.3 Perspectives in TENG neurostimulation

The integration of TENGs into the realm of neurostimulation

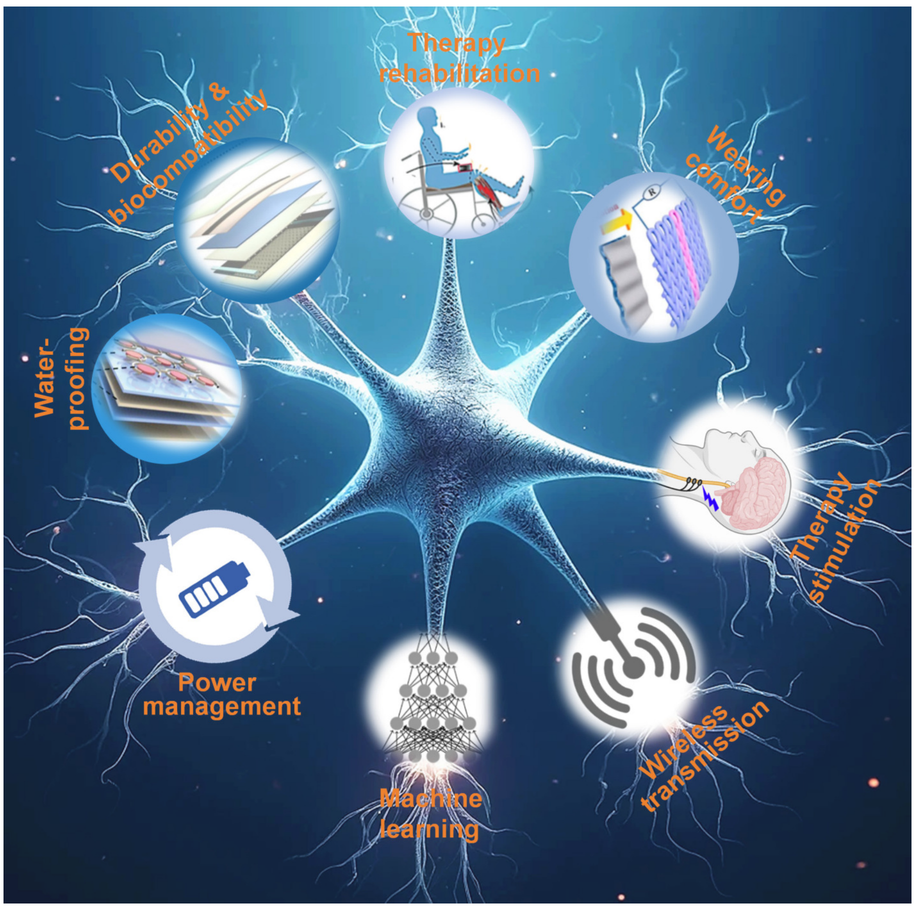

Figure 6 Perspectives of TENGs in neurostimulation: waterproofing; biocompatibility and durability enhancements, therapy and rehabilitation integration, and the development of wearable TENGs. Waterproof TENG e-skin. Reproduced with permission from Ref. [179], © Wiley-VCH GmbH 2020. Rehabilitation image. Reproduced with permission from Ref. [149], © Wang, J. H. et al. 2019. Durability image. Reproduced with permission from Ref. [196], © Ouyang, H. et al. 2019. Wearable TENG. Reproduced with permission from Ref. [189], © Elsevier Ltd. 2019.

heralds a new era in bioelectronic medicine, blending the lines between energy harvesting and therapeutic interventions. Advances in stretchable, waterproof, ultra-thin e-skin TENGs are revolutionizing the way to capture human motion energy, opening doors to self-powered haptic sensing and novel interactions between humans and machines [179, 197–202]. This shift towards wearable electronics emphasizes a seamless fusion with daily life, enhancing user experience and interaction modalities. Moreover, the potential of TENGs to facilitate direct muscle or nerve stimulation offers a groundbreaking approach to rehabilitation and therapy [90, 149]. Ultrasound-assisted TENG implants stand out for their capacity to deliver localized and controlled stimulation, along with drug delivery, through non-invasive methods [158, 159, 190]. By providing targeted neurostimulation, TENGs open pathways for addressing muscle atrophy and peripheral neuropathy without reliance on pharmacological solutions, which significantly enhances patient comfort and compliance, marking a substantial advancement in peripheral neuropathy treatment. The seamless fusion of ultrasound technology with TENGs underscores the immense potential of this integrated approach to transform the landscape of bioelectronic medicine and rehabilitation.

Meanwhile, the drive towards materials with biocompatibility and long-term implantation durability is reshaping TENG design [100, 101, 203]. To address biocompatibility challenges associated with chronic implantation, there is a need to explore materials that minimize inflammatory reactions and fibrotic encapsulation. Strategies such as employing advanced bioinert materials, surface coating technologies that can mimic the biological interfaces, and designing TENGs that can adapt to bodily movements without degradation, could significantly improve their integration and functionality over extended periods [196]. The exploration and development of such wearable TENGs not only highlight the adaptability of this technology but also its potential to be seamlessly integrated into daily life, thus broadening the scope of their applicability. By harnessing the power of human motion for continuous, self-powered neurostimulation, these devices promise to transform health monitoring and neurostimulation therapies, making them more accessible and effective. In addition, the integration of adaptive algorithms holds promise for enhancing stimulation precision, allowing for more targeted and personalized therapy [175, 204] (Fig. 6). Wireless transmission capabilities further enhance the usability and convenience of TENG-based neurostimulation devices, freeing patients from cumbersome wired connections [158, 169, 205–208]. Moreover, advancements in power management and structural miniaturization contribute to making TENGs more practical and user-friendly [154, 173, 191]. By optimizing energy consumption and reducing device size, these developments pave the way for the widespread adoption of TENG technology in clinical settings. The convergence of these technologies not only promises to enhance e-skin functionalities and develop wearable neurostimulation devices but also opens new avenues for treatments in bioelectronic medicine.

6 Conclusion

The integration of TENGs in neurostimulation represents a significant leap toward realizing self-powered and wireless neural modulation systems. These developments herald a new era in the treatment of a wide array of neurological disorders and the creation of advanced brain-machine interfaces. Distinguished from traditional medical electronics, TENGs harness the low-frequency movements of human body organs to generate electrical power, opening avenues for a variety of self-powered neurostimulation systems. These range from enhancing neurostimulation therapies to energizing therapeutic neural prostheses such as bionic limbs and cochlear implants.

Leveraging the mechanical energy of the human body to operate prosthetic devices promotes a more seamless integration between the user and the prosthetic, enhancing user experience and functionality. Moreover, TENGs are being investigated for their potential in powering devices for optogenetics and targeted drug delivery, providing precise control over neuronal activity and offering innovative treatments for mental health issues. The concept of an integrated care loop, which encompasses real-time sensing, diagnostic analysis, and therapeutic intervention, represents the cutting edge of personalized medicine. This approach is further bolstered by advancements in wireless communication, enabling the continuous and real-time monitoring of biological signals from various brain regions. Recent research has shown TENGs' significant promise in nerve stimulation and spinal cord injury treatments, offering new avenues for repairing damaged nerves and modulating physiological functions in preclinical models. However, the emergence of fibrotic tissue around implants, the potential for localized thermal effects, persistent inflammation, and discomfort due to electrical stimulation highlight areas requiring further investigation and refinement [5].

The materials choices for TENG construction are also advancing, with a focus on biodegradable materials for transient neuromodulation applications [99]. These materials aim to reduce secondary surgical interventions by allowing the devices to naturally degrade and exit the body metabolically. TENGs offer numerous advantages, including straightforward manufacturing processes, cost efficiency, a wide range of material options, and flexibility, making them ideal for soft bioelectronics. Their therapeutic applications have been demonstrated in fields such as weight control, bladder regulation, muscle rehabilitation, and cognitive enhancement. The adoption of TENGs in neurostimulation opens promising new treatment avenues for conditions from epilepsy and Parkinson's disease to essential tremors and various psychiatric disorders. Overcoming existing challenges and leveraging TENGs' unique capabilities, the future of neurostimulation promises enhanced efficiency, personalization, and patient benefit, signifying a transformative milestone in medical technology and the treatment of neurological conditions to improve quality of life.

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