



Self-powered neural intervention via piezoelectric nanogenerators

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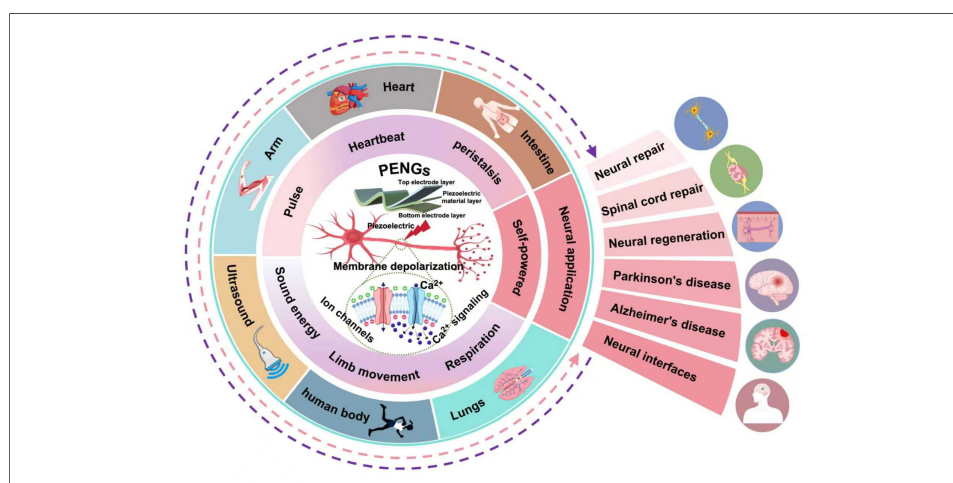
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Abstract

Piezoelectric nanogenerators (PENGs) are electromechanical energy-conversion devices constructed from piezoelectric materials. They convert physiological motion, local tissue deformation, or externally applied mechanical stimuli into localized electrical signals and have attracted considerable interest in self-powered neural interventions. Despite the rapid expansion of research in this field, the systematic understanding needed to guide translational optimization remains limited. This review delineates the current research landscape by organizing the discussion around mechanical inputs, piezoelectric transduction, neural responses, and functional restoration, thereby linking fundamental principles with representative application studies. This review discusses

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neural-interface-compatible materials, device architectures, and powering strategies for PENGs; the underlying neurobiological mechanisms; and recent advances in their applications across the peripheral, central, and autonomic nervous systems, neurodegenerative diseases, and neural interfaces. It further examines key barriers related to the precision of deep-tissue targeting, the long-term safety of implanted devices, and the lack of standardized frameworks for clinical translation. To this end, PENGs are systematically compared with other self-powered and wirelessly powered transduction technologies, and a standardized reporting framework linking device output to the biologically effective dose is proposed, while outlining future directions in multimodal energy coupling, closed-loop feedback, intelligent energy management, and the integration of piezoelectric stimulation with genetic, immune, and metabolic reprogramming. Collectively, this review aims to advance both fundamental research and clinical translation of PENGs in neural engineering.

INTRODUCTION

Piezoelectric nanogenerators (PENGs) exploit the direct piezoelectric effect to convert dynamic mechanical energy into electrical output. Their nanoscale character arises from the micro- or nanoscale dimensions of the piezoelectric functional phases or structural units^[1,2]. In 2006, Wang *et al.* used ZnO nanowire arrays to convert minute mechanical deformations into measurable electrical signals, advancing piezoelectric research from material-level characterization toward miniaturized devices and integrated systems^[3]. Subsequent advances in flexible piezoelectric materials, electrode integration, and encapsulation technologies enabled PENGs to enter the field of implantable bioelectronics^[4,5]. Between 2010 and 2019, their self-powered capability was increasingly explored for neural stimulation and regenerative modulation, with flexible piezoelectric systems conformally integrated with the heart, lungs, and diaphragm demonstrating the feasibility of harvesting biomechanical energy *in vivo*^[6,7]. From 2020 to 2025, the development of PENG-based neural applications accelerated markedly. ZnO-nanogenerator-based biomimetic scaffolds first demonstrated self-powered motor recovery^[8]. Barium zirconate titanate–barium calcium titanate/poly(vinylidene fluoride) (BZT-BCT/PVDF) films enabled ultrasound-driven sciatic nerve stimulation^[9], whereas biodegradable poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/poly(L-lactic acid)/potassium sodium niobate ($K_{0.5}Na_{0.5}NbO_3$) (PHBV/PLLA/KNN) devices provided transcutaneous lead-free electrical stimulation of the sciatic nerve while supporting concurrent repair monitoring^[10]. In parallel, molecular piezoelectric materials and piezoelectrets were successively incorporated into PENG platforms for wireless deep brain stimulation and vagus nerve stimulation (VNS)^[11,12]. By 2025, programmable ultrasonic wireless implants had extended self-powered neuromodulation to personalized chronic pain management^[13]. By 2026, the emergence of bioresorbable Rochelle salt/PLLA devices and piezoelectric neuromodulation of the subthalamic nucleus further indicated that PENGs were evolving beyond single-function proof-of-concept studies toward a versatile technological platform integrating flexible implantation, remote powering, biodegradable construction, and combined diagnostic and therapeutic capabilities^[14,15].

Two decades of technological evolution have converged on two longstanding challenges in clinical neural engineering. First, although autologous nerve grafting remains the gold standard for peripheral nerve repair^[16], its clinical use is constrained by limited donor availability, size mismatch between donor and recipient nerves, donor-site functional deficits, and the additional trauma associated with a second surgical procedure^[17]. Second, commercially available nerve conduits rely predominantly on passive structural guidance and are therefore unable to reconstitute, particularly across long-segment defects, the cellular, trophic, vascular, and bioelectrical microenvironments required for sustained axonal extension and remyelination^[18]. At the core of both challenges is the inability of existing approaches to provide sustained, physiologically relevant electromechanical cues at the site of injury. Owing to their distinctive electromechanical transduction capability, PENGs can address these limitations at three levels^[19]. At the level of power delivery, endogenous mechanical inputs—including respiration, cardiac motion, vascular pulsation,

muscle contraction, and rehabilitative movement—can directly actuate implanted devices to generate self-powered electrical pulses^[20]. Exogenous mechanical fields, such as transcutaneous ultrasound, further enable battery-free, wireless, and on-demand stimulation of deep neural targets^[12]. At the interface level, transduction units can be placed directly on nerve bundles, within lesion cavities, or in targeted brain regions to generate localized electric fields and charge transfer, thereby reducing the need for long interconnecting leads and bulky implanted power sources^[21,22]. At the material level, aligned fibrous scaffolds, nerve conduits, and piezoelectric hydrogels can modulate the electrophysiological microenvironment at the injury site while simultaneously providing mechanical support and directional guidance for cell growth^[23–25]. Bioresorbable piezoelectric materials, including PLLA, PHB, and their copolymers, can be integrated with biodegradable electrodes and encapsulation layers, allowing the device to gradually degrade after the therapeutic period and potentially reducing the risks of secondary surgery and chronic inflammation^[26,27]. Together, these three complementary dimensions establish an integrated technological framework that combines localized electrical intervention, mechanical conformity to tissue, and a programmable therapeutic lifetime.

However, existing studies remain fragmented across the fields of piezoelectric materials, energy-harvesting devices, tissue engineering, and neurobiology, underscoring the urgent need for systematic integration at the system level. Accordingly, this review conceptualizes PENGs as electromechanical-biological interfaces comprising four interconnected elements: mechanical input, piezoelectric transduction, tissue loading, and neural response. It systematically reviews their operating principles, neural-interface-compatible materials, device architectures, and powering strategies; elucidates mechanisms involving membrane potential, ion channels, and Ca^{2+} signaling; summarizes advances in peripheral nerve regeneration, central and autonomic neuromodulation, interventions for neurodegenerative diseases, and neural interfaces; and critically evaluates key challenges related to dose calibration, deep-tissue targeting, long-term safety, device reliability, and clinical assessment. Finally, this review outlines emerging directions in multimodal energy coupling, intelligent energy management, closed-loop feedback, and integration with genetic regulation, immune modulation, and metabolic reprogramming, thereby establishing a systematic conceptual framework for the design, mechanistic validation, and clinical translation of self-powered neural intervention systems.

ENGINEERING FOUNDATIONS OF PENG-MEDIATED NEURAL INTERVENTIONS

Operating principles and system architecture of PENGs

PENGs exploit the linear electromechanical coupling of piezoelectric materials to convert dynamic mechanical inputs into electrical potential and current^[28]. Under the direct piezoelectric effect, an applied force induces ionic displacement within a non-centrosymmetric crystal lattice or reorientation of molecular dipoles in an organic piezoelectric phase^[29,30]. The resulting separation of positive and negative charge centers produces macroscopic polarization, generating bound charges on the material surfaces and a potential difference between the electrodes. As the deformation varies, charges redistribute through the external circuit to generate an electric current, thereby converting mechanical energy into electrical energy^[31], as shown in [Figure 1A and B]. Conversely, the converse piezoelectric effect refers to the reversible mechanical deformation of a piezoelectric material induced by an applied electric field and is primarily exploited in piezoelectric actuators, acoustic transduction, and the design of electrical stimulation interfaces. Piezoelectric operating modes are defined by the corresponding piezoelectric coefficients. In the d_{33} mode, the applied stress is parallel to the polarization direction, making this mode suitable for through-thickness compression; in the d_{31} mode, the stress is perpendicular to the polarization direction and is commonly exploited in thin-film bending or in-plane stretching^[32], as shown in [Figure 1C]. Under Voigt notation, d_{14} and d_{15} describe the coupling of electric displacement along the 1-direction with shear stresses in the 2-3 and 1-3 planes, respectively^[33], as shown in [Figure 1D]. A PENG device system primarily comprises a piezoelectric active layer, substrate, electrodes, interconnects, and insulating encapsulation [Figure 1E]^[34]; For implantable PENGs, biocompatible encapsulation and tissue-conformal interfaces are additionally required

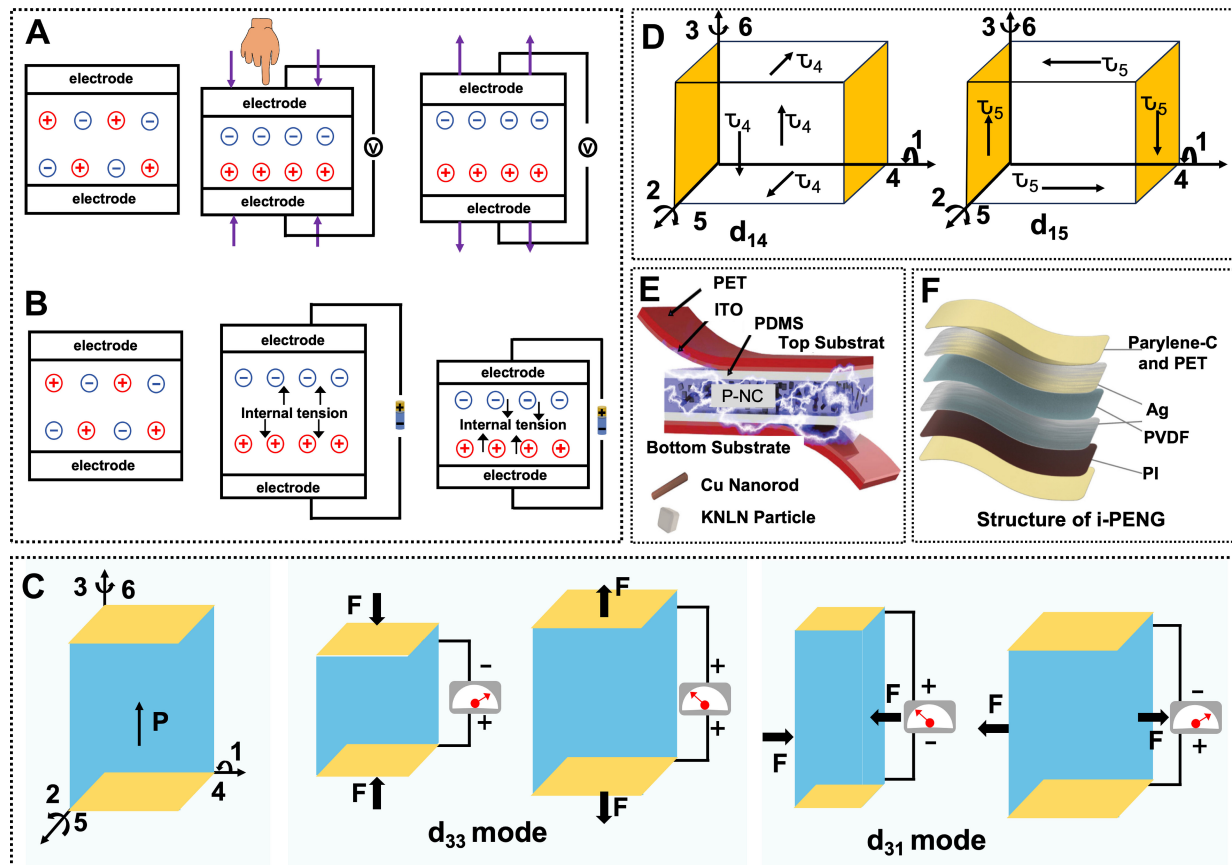


Figure 1. Working principles, operating modes, and system architecture of PENGs. (A) Direct piezoelectric effect; (B) Converse piezoelectric effect. (C) Schematic illustrations of the d_{31} and d_{33} strain modes in piezoelectric materials. (D) Schematic illustrations of the shear piezoelectric strain modes associated with d_{14} and d_{15} . (E) Structural components of a PENG based on KNLN particles and Cu, adapted with permission from Ref. [34]. Copyright © 2014 Wiley-VCH. (F) Multilayer structure of an implantable piezoelectric nanogenerator (i-PENG), adapted from Ref. [35] under CC BY 4.0 license.

[Figure 1F]^[35]. The substrate supports the device and transmits mechanical inputs; the piezoelectric layer converts deformation into polarization charge; the electrodes collect and conduct surface charges; and the encapsulation layer isolates the device from bodily fluids, suppresses current leakage, and maintains structural integrity^[27,36]. Rectification, energy-storage, and output-conditioning modules may be integrated when required^[37]. The electrical output is jointly determined by the piezoelectric coefficient, dielectric properties, elastic modulus, dimensions and orientation of the piezoelectric layer, electrode configuration, interfacial capacitance, and load impedance^[38].

Piezoelectric materials for neural interfaces

Piezoelectric materials used in neural applications encompass inorganic ceramics and single crystals, conventional and biodegradable polymers, naturally piezoelectric biomaterials^[39], polymer-ceramic composites, and conductive or multifunctional composites. Collectively^[40], these materials can be classified into three principal categories: organic, inorganic, and composite piezoelectric systems^[41]. Organic piezoelectric materials are represented primarily by PVDF, poly(vinylidene fluoride-co-trifluoroethylene) (P(VDF-TrFE)), and PLLA. Their flexibility and amenability to electrospinning into aligned fibrous architectures have enabled their use in studies of Schwann-cell adhesion, axonal extension, myelination, and the neuronal differentiation of stem cells^[42-45]. Inorganic materials, including BaTiO₃ (BT), ZnO, boron nitride (BN), boron nitride nanotubes (BNNTs), lead zirconate titanate (Pb(Zr,Ti)O₃) (PZT), and lead-free (K, Na)NbO₃-based ceramics, exhibit high piezoelectric responses and can generate localized electrical

stimulation under ultrasound or mechanical perturbation^[46,47]. However, mechanical mismatch with soft neural tissues, particle retention, and, in the case of lead-containing materials, heavy-metal safety concerns constrain their direct implantation. Composite systems combine PVDF-based polymers, poly(ϵ -caprolactone) (PCL), silk fibroin, or hydrogels with functional fillers such as BaTiO₃, ZnO, and MXene. In addition to enhancing electrical output, these combinations improve flexibility^[48], cell-material interactions, and processability into nerve conduits, making them particularly important for central nervous system repair^[49]. Recent advances have further incorporated emerging nanomaterials, including MoS₂, SbSeI, and hBN, into flexible piezoelectric systems^[50].

Representative neural-interface studies include aligned PVDF-TrFE scaffolds supporting Schwann cells, neurite extension, and myelination^[51]; biodegradable PLLA piezoelectric transducers^[52]; PHBV-based neural scaffolds and conduits^[53–54]; collagen nerve guides and collagen-mimetic piezoelectric systems^[55,56]; piezoelectric silk-fibroin fibers and scaffolds^[57,58]; ZnO nanogenerators for functional nerve stimulation^[59]; BNNT- and hBN-based piezoelectric systems^[60,61]; PZT-based neural and cochlear interfaces^[62,63]; Aluminum nitride (AlN) acoustic transducers for auditory applications^[64,65]; self-powered PVDF/PCL scaffolds for peripheral nerve regeneration^[66]; high-performance ferroelectric perovskites^[67]; and directional PHBV-based neurosupport scaffolds^[68]. Table 1 summarizes representative fabrication methods, piezoelectric properties, and neural applications of these material systems.

Device architectures

As PENGs have progressed from nanoscale material validation toward implantable and tissue-interfacing applications, neural-interface devices have diversified into aligned fibrous membranes, porous or continuous films, nerve conduits, cuff-type interfaces, piezoelectric hydrogels, multilayer composites, and systems with biodegradable encapsulation^[69–70]. Early devices were predominantly based on continuous films and multilayer thin-film architectures. Zhang *et al.* fabricated a multiunit P(VDF-TrFE)/BaTiO₃ membrane through layer-by-layer electrospinning to redistribute pulsatile mechanical loads, increasing the open-circuit voltage and short-circuit current to 3.3- and 2.1-fold those of a single-layer device, respectively^[71]. For interfacing with nerve bundles, planar films were further developed into conduits, cuffs, and tubular architectures. Ma *et al.* established a radially compartmentalized structure comprising an outer piezoelectric membrane and an inner multichannel conductive scaffold^[72]. Tai *et al.* rolled an aligned P(VDF-TrFE) fibrous mat into a hollow cylindrical conduit and incorporated electrodes on opposite sides, thereby supporting regeneration across sciatic nerve defects^[73]. Xu *et al.* further integrated BaTiO₃/P(VDF-TrFE) piezoelectric fibers with an outer hydrogel layer, transforming the integration of piezoelectric, conductive, and tissue-contacting functions from simple material blending into a spatially organized three-dimensional interfacial architecture^[23]. More recently, design priorities have expanded to include stable fixation under wet physiological conditions and control over the functional lifetime of the device. Wu *et al.* integrated a biodegradable PHBV/PLLA/KNN piezoelectric film with Mg electrodes, Mo interconnects, and polylactic acid/PCL encapsulation^[10]. Under wireless ultrasonic actuation, the system delivered tunable electrical stimulation to a biodegradable conductive nerve conduit, enabling the device's functional lifetime, the time course of nerve repair, and the degradation of the implanted materials to be coordinately designed. To further optimize piezoelectric performance, Dai *et al.* increased the dipole density of an electrospun Rochelle salt/PLLA membrane through mechanical compression, achieving an effective piezoelectric coefficient of 43.1 ± 3.0 pC N⁻¹. The membrane was subsequently integrated with Mo electrodes, PLCL encapsulation, and laser patterning to construct a multichannel device^[14]. Qi *et al.* subsequently constructed a Janus membrane comprising adhesive hydrogel fibers and piezoelectric silk fibroin fibers, enabling wet adhesion and suture-free fixation across complex nerve defects^[74]. Overall, device development has shifted from maximizing a single piezoelectric parameter toward the coordinated optimization of stress transfer, dipole orientation, electrode coverage, conformability to curved tissue surfaces, and encapsulation lifetime.

Table 1. Representative materials for piezoelectric nanogenerators in neural applications: properties and applications

Material type	Materials	Preparation technology	Piezoelectric coefficient	Application	References
Organic piezoelectric	P(VDF-TrFE)	Electrospinning; Thermal annealing	$d_{33} \approx -40$ to -20 pC N ⁻¹	Dorsal root ganglion; Sciatic nerve; Spinal cord	[42,51]
	PLLA	Electrospinning; Thermal treatment	$d_{14} \approx 6$ -19 pC N ⁻¹	Rat pheochromocytoma PC12 cells	[52]
	PHBV	Solution casting; Electrospinning	$d_{14} \approx 1.2$ -2.0 pC N ⁻¹	Peripheral nerve	[53,54]
	COL/CMP	Magnetic alignment; Self-assembly	COL: $d_{14} \approx 0.2$ -2.0 pC N ⁻¹ ; CMP: $d_{35} \leq 27$ pm V ⁻¹	Peripheral nerve	[55,56]
	SF	Electrospinning; Dry spinning	$d_{33} \approx 3.24$ -18.0 pm V ⁻¹	Human neural stem cell-derived neuronal networks; Rat pheochromocytoma PC12 cells	[57,58]
Inorganic piezoelectric	BTO	Hydrothermal synthesis; Solid-state synthesis	$d_{33} \approx 75$ -350 pC N ⁻¹	Human SH-SY5Y neuroblastoma cells	[53]
	ZnO	Hydrothermal growth; Chemical bath deposition	$d_{33} \approx 9$ -14 pC N ⁻¹	Frog sciatic nerve and gastrocnemius neuromuscular pathway	[62]
	BNNT/h-BN	Chemical vapor deposition; Non-covalent glycol-chitosan coating	$d_{31} \approx 1$ -30 pC N ⁻¹	Rat pheochromocytoma PC12 cells	[63,64]
	PZT	Poling and sintering; Radio-frequency magnetron sputtering	$d_{33} \approx 350$ -650 pC N ⁻¹	Guinea pig cochlea and auditory nerve pathway; rat cerebral cortex	[65,66]
	KNN	Solid-state synthesis; Ceramic film preparation	$d_{33} \approx 100$ -560 pC N ⁻¹	Mouse hippocampus; substantia nigra pars compacta; nigrostriatal dopaminergic pathway	[67]
Polymer-based and composite piezoelectric	Sm-PMN-PT	Modified Bridgman growth; Array microfabrication	$d_{33} \leq 4,000$ pC N ⁻¹	Rat periaqueductal gray and deep-brain analgesia pathway	[68]
	AlN	Reactive radio-frequency magnetron sputtering; Microelectromechanical-system micromachining	Effective $d_{33} \approx 3.52$ pm V ⁻¹	Cochlea and auditory nerve pathway	[69,70]
	PHBV/CA	Electrospinning; Post-drying	Effective $d_{33} \approx 6.68$ pm V ⁻¹	Unspecified neural cells	[54]
	PVDF/PCL	Solvent casting; Annealing	$d_{33} \approx 13$ pC N ⁻¹	Rat sciatic nerve	[66]
	Organic-inorganic perovskite ferroelectric	Solution crystallization	Large piezoelectric response	Deep-brain neuronal circuits	[67]
	PHBV/MgOl/NAC	Electrospinning; Drug incorporation	NR	Rat pheochromocytoma PC12 cells	[68]

P(VDF-TrFE): Poly(vinylidene fluoride-co-trifluoroethylene); PLLA: poly(L-lactic acid); PHBV: poly(3-hydroxybutyrate-co-3-hydroxyvalerate); COL/CMP: collagen/collagen-mimetic peptide; SF: silk fibroin; BTO: barium titanate (BaTiO₃); ZnO: zinc oxide; BNNT/h-BN: boron nitride nanotube/hexagonal boron nitride; PZT: lead zirconate titanate; KNN: potassium sodium niobate; Sm-PMN-PT: samarium-doped lead magnesium niobate-lead titanate (Pb(Mg_{1/3}Nb_{2/3})O₃-PbTiO₃); AlN: aluminum nitride; PHBV/CA: poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/cellulose acetate; PVDF/PCL: poly(vinylidene fluoride)/poly(ϵ -caprolactone); PHBV/MgOl/NAC: poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/magnesium oleate/N-acetylcysteine.

Powering strategies

PENG powering strategies can be classified according to their energy source into endogenous physiological motion and exogenous mechanical fields^[75]. The former harnesses cardiac motion, respiration, gastrointestinal peristalsis, and limb movement, offering the advantages of continuous energy availability and autonomous power generation^[76,77]. Harnessing cyclic organ motion, Wang *et al.* transversely sutured an instantaneous-discharge PVDF i-PENG onto the surfaces of the left and right ventricles in pigs^[78]. Cardiac motion increased the output voltage from 1.6 ± 0.4 V for a conventional device to 10.5 ± 0.5 V and charged a

100- μ F capacitor to 4.53 V within 1,000 s. A flexible piezoelectric energy harvester integrated on the epicardium similarly converts cardiac contraction into voltage outputs [Figure 2A]^[79]. Cheng *et al.* deployed a PVDF film on the porcine ascending aorta, achieving a sensitivity of 14.32 mV mmHg⁻¹ and an instantaneous power output of 40 nW. These results indicated that conformal electrode contact and integrated energy storage could compensate for the limited mechanical input associated with low-frequency cardiovascular deformation^[80]. However, fixation through open-chest surgery increases implantation complexity. Li *et al.* used a bioadhesive to attach a PLLA/glycine core-shell nanofibrous PENG to the outer wall of the rat transverse colon. Under enema-induced peristalsis at approximately 0.2 Hz, the device generated a stable output exceeding 2 V and distinguished different states of colonic motility from the signal envelope^[27], extending endogenous energy harvesting to conformal *in situ* coupling with soft, folded organs. Yu *et al.* developed a mesoporous PVDF/polydimethylsiloxane (PDMS) device that generated an open-circuit voltage of approximately 200 mV^[81]. Zhang *et al.* reported a mesoporous piezoelectric polymer composite film with a tunable mechanical modulus, which can further harvest energy from liquid-pressure fluctuations [Figure 2B]^[82]. To further harness the larger deformations associated with limb movement, Yang *et al.* attached PVDF/ZnO core-shell nanofibers to the lower leg, where muscle contraction produced an output of approximately 0.85 V and enabled gait recognition as well as the recording of movement angle and frequency^[83]. An electrospun P(VDF-TrFE) nerve conduit has similarly been characterized *in vivo* for bridging a rat sciatic nerve [Figure 2C]^[73]. Nevertheless, this energy source remained dependent on active physical movement. For neural repair, the PCL/ZnO conduit developed by Mao *et al.* generated an output of 40–120 mV, demonstrating that deformation of adjacent tissues could be converted into localized electrical stimulation^[84]. Razbin *et al.* developed a poly(3-hydroxybutyrate) (P3HB)/ZnO piezoelectric nanofiber smart insole, which has also been used for AI-driven gait monitoring [Figure 2D]^[85]. When physiological motion is insufficient or on-demand stimulation is required, exogenous mechanical fields provide more reliable temporal and dose control. Chen *et al.* implanted an approximately 30- μ m-thick BZT-BCT/PVDF film subcutaneously adjacent to the rat sciatic nerve^[9]. Following transcutaneous energy transmission at 1 MHz, ultrasonic actuation generated programmable electrical pulses with amplitudes of up to approximately 13.5 V, establishing a wireless pathway for peripheral nerve stimulation^[9]. To reduce angular mismatch inherent to planar receivers, Li *et al.* constructed a nerve-encircling NeuroRing from PVDF/ZnO fibers. The device generated 6 V under 1-MHz ultrasound at 0.5 W cm⁻² and maintained an output of 6 $\pm$ 1 V for 6 months, advancing ultrasonic energy conversion toward conformal fixation directly around the target nerve [Figure 2E]^[12]. Beyond continuous-wave ultrasound, Wang *et al.* employed dual-frequency ultrasound at 1 and 3 MHz to drive a lead-free composite transducer. After rectification, the system produced 17.5 V with an average charging power of 2.47 mW and retained 70%–80% of its voltage after transmission through 20 mm of porcine tissue^[24]. The output amplitude, pulse width, and frequency could also be independently adjusted. Overall, endogenous powering is well suited to continuous, low-power sensing and state-triggered operation, whereas exogenous powering enables deep, on-demand stimulation through programmable control of frequency, intensity, and pulse parameters. Integrating these complementary strategies will require tissue-conformal fixation, stable charge management, and closed-loop control of stimulation dosage.

Ultrasound-driven PENGs must operate within established acoustic-exposure limits. Diagnostic-ultrasound guidance restricts the mechanical index (MI) to $\leq$ 1.9 and the thermal index to $\leq$ 6.0, with lower thresholds for ophthalmic and fetal applications, and caps the spatial-peak temporal-average intensity at 720 mW cm⁻² for most exposures^[86,87]; MI values of 0.4–0.7 have been linked to cavitation-related bioeffects. Attenuation also rises steeply with frequency and tissue path: soft tissue attenuates by approximately 0.5–1 dB cm⁻¹ MHz⁻¹, and the human skull attenuates transcranial transmission by 8–20 dB while introducing pronounced phase aberration^[88]. These frequency-dependent losses directly constrain wireless power-transfer efficiency: a dual-frequency (1 and 3 MHz) lead-free implant retained only 70%–80% of its output voltage after transmission through 20 mm of porcine tissue^[24], which is why most deep-brain PENG studies operate at 0.5–1 MHz to

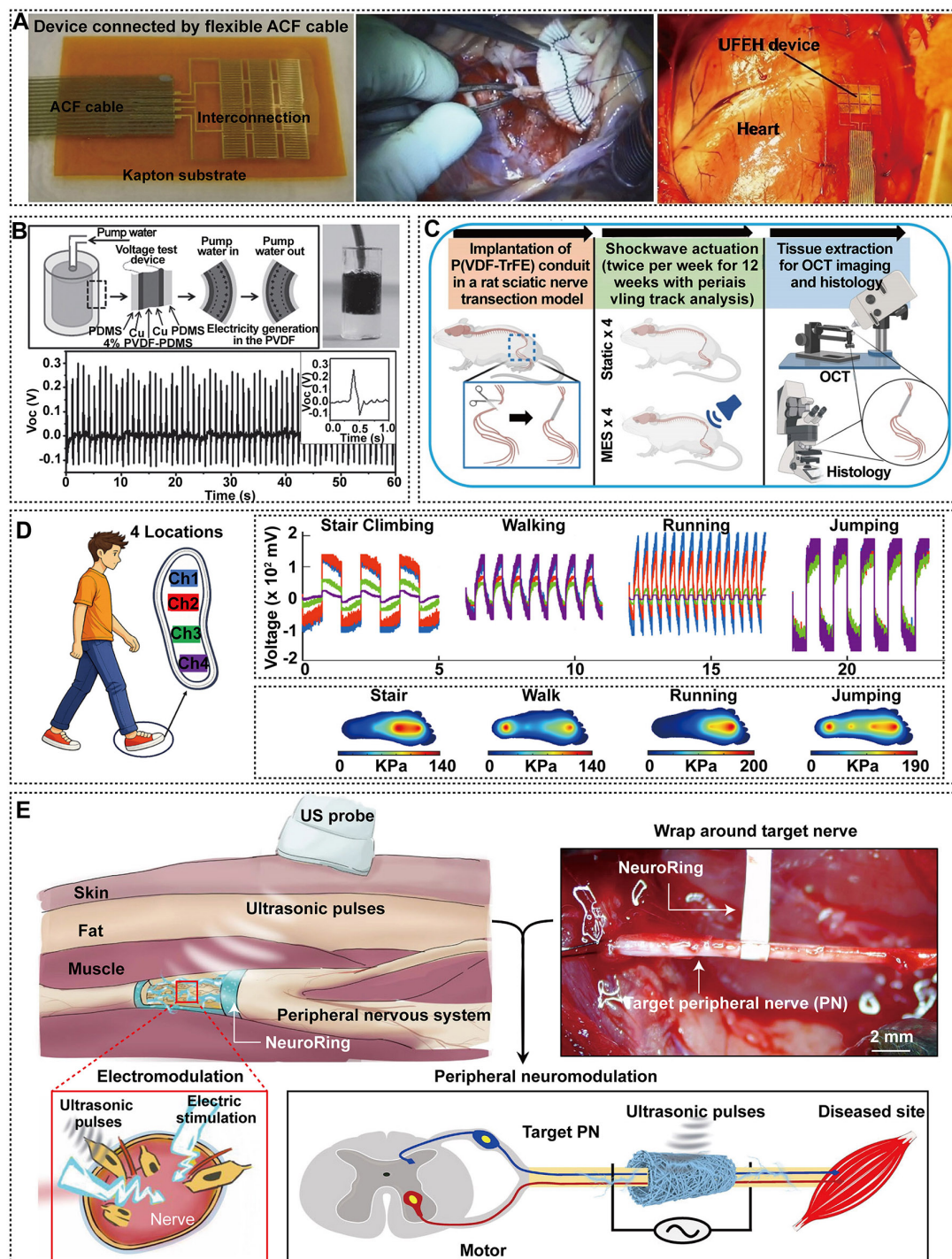


Figure 2. Representative endogenous and exogenous powering strategies for piezoelectric nanogenerator-based systems. (A) *In vivo* cardiac biomechanical energy harvesting: a flexible piezoelectric energy harvester integrated on the epicardium (between the left-ventricular apex and the right ventricle, and between the atrioventricular groove and the right-ventricular outflow tract) converts cardiac contraction into voltage outputs, adapted from Ref.^[79] under CC BY 4.0 license. (B) Mesoporous PVDF/PDMS piezoelectric nanogenerator with a tissue-matched mechanical modulus for harvesting energy from pulsatile liquid pressure (simulated blood pressure), adapted with permission from Ref.^[82]. Copyright © 2016 Wiley-VCH. (C) *In vivo* piezoelectric characterization of an electrospun P(VDF-TrFE) nerve conduit bridging the rat sciatic nerve and the outline of the animal experiments, Adapted from Ref.^[73] under CC BY 4.0 license. (D) AI-driven gait monitoring using a P3HB/ZnO piezoelectric nanofiber smart insole: multichannel voltage outputs, plantar-pressure mapping, and gait recognition, adapted from Ref.^[85]. under the CC BY 4.0 license. (E) Ultrasound-driven peripheral neuromodulation using a ferroelectric NeuroRing wrapped around the sciatic nerve, adapted from Ref.^[12] under CC BY 4.0 license.

Table 2. Comparison of PENGs with alternative self-powered and wireless powering technologies for neural applications

Technology	Output characteristics	Key advantages	Key limitations	References
PENGs	Capacitive high-impedance pulses; V_{oc} ~0.2–84 V; I_{sc} nA–mA	Battery-free; conformable; biodegradable; intrinsically charge-limited	Output input-dependent; dose calibration required	[9,71]
Electromagnetic induction	Near-field power (mW–W)	Mature technology; high power	Coil alignment; tissue heating; bulky receiver	[91]
TENGs	High V (~kV); low I (μ A); contact electrification	Low cost; high sensitivity	Charge leakage and instability in wet environments	[93]
Magnetoelectric generators	Charge via magnetostrictive-piezoelectric coupling	Deep-tissue access; injectable forms	External field required; loss at small dimensions	[94]
Biofuel cells	Low-voltage DC (μ W–mW)	Continuous operation; endogenous fuel	Low power; enzyme deactivation	[95]

PENGs: Piezoelectric nanogenerators; V_{oc} : open-circuit voltage; I_{sc} : short-circuit current; TENGs: triboelectric nanogenerators; DC: direct current.

balance penetration depth against transducer size and focusing^[89]. Acoustic modeling that accounts for layer-by-layer attenuation and phase aberration is therefore a prerequisite for the rational design of ultrasound-powered PENGs.

Technological positioning and advantages of PENGs

Conventional electrical stimulation relies on implantable pulse generators, transcutaneous leads, or subcutaneous batteries. Although these approaches have an established clinical track record, they remain constrained by several limitations, including lead fracture, infection, battery replacement, and the lack of synchronization with physiological states^[90]. Inductive and radiofrequency power transfer eliminates the need for an implanted battery, but it relies on external coils and precise spatial alignment and may cause localized tissue heating^[91]. Optogenetics and chemogenetics offer cell-type-specific neuromodulation but are constrained by the need for transgene expression and exogenous light or drug delivery. By harnessing piezoelectric electromechanical transduction, PENGs can directly convert physiological motion or externally applied ultrasound into localized electrical pulses, enabling neural stimulation without implanted batteries or transcutaneous leads. This platform can further be engineered into flexible, conformable, and biodegradable devices^[92]. Compared with triboelectric nanogenerators (TENGs), magnetoelectric generators, and biofuel cells, PENGs offer distinct advantages in terms of output characteristics, tissue compatibility, and device integration. Although TENGs can generate relatively high voltages, charge leakage in the humid implantable environment can compromise their long-term stability^[93]. Magnetoelectric generators and biofuel cells, in contrast, are constrained by their dependence on external magnetic fields and by limitations in power output and enzymatic stability, respectively^[94,95]. Existing PENG devices can already generate electrical outputs sufficient for neural stimulation. For example, a five-layer P(VDF-TrFE)/BaTiO₃ film can produce an output voltage of 84 V and a current of 1.32 μ A^[71], whereas a BZT-BCT/PVDF thin film can generate an output voltage of 13.5 V under ultrasound actuation^[9]. Accordingly, Table 2 provides a detailed comparison of the advantages and limitations of different self-powered technologies for neural applications. Overall, PENGs integrate energy conversion and neural stimulation within a single platform, while offering the potential for wireless actuation, flexible tissue conformability, and biodegradability. Furthermore, hybrid systems that combine piezoelectric transduction with triboelectric, magnetoelectric, or biofuel-cell mechanisms may further enhance the continuity of power delivery and the stability of neural stimulation.

NEUROBIOLOGICAL MECHANISMS OF PENG-MEDIATED ELECTRICAL STIMULATION

Membrane-potential perturbation and ion-channel gating

Neuronal membranes combine capacitive charge storage with selective ionic conductance. Mechanical deformation of a PENG generates a localized polarization potential that perturbs the resting membrane potential. Once depolarization exceeds the excitation threshold^[92], voltage-gated Nav channels initiate the

action potential, K_v channels drive repolarization, and Ca_v channels mediate Ca^{2+} influx, thereby translating transient electrical activity into sustained cellular responses such as neuronal differentiation and neurite outgrowth^[96]. Ion-channel blockade provides the most direct causal evidence for this mechanism. Marino *et al.* compared piezoelectric tetragonal-phase $BaTiO_3$ particles with non-piezoelectric cubic-phase particles and found that TTX and Cd^{2+} attenuated the cellular responses, supporting the involvement of Na_v channels in excitation initiation and Ca_v channels in downstream signaling^[7]. Han *et al.* further combined patch-clamp recordings with multiple pharmacological blockers, showing pronounced inhibition by TTX and Cd^{2+} but only limited effects of Gd^{3+} and ruthenium red^[97]. These findings refined the mechanism from a correlative observation into a sequential process involving piezoelectric depolarization, Na_v -dependent initiation, and Ca_v -mediated amplification. With respect to downstream effects, Genchi *et al.* observed that $P(VDF-TrFE)/BaTiO_3$ membranes elicited Ca^{2+} transients and increased β III-tubulin expression, indicating that Ca^{2+} signaling links electrical activity to neuronal differentiation^[98]. Using β -phase and α -phase PVDF controls together with $LaCl_3$ -mediated channel blockade, Hoop *et al.* attributed enhanced neurite outgrowth in PC12 cells to Ca^{2+} influx driven by piezoelectric polarization^[99]. This mechanism is not restricted to a single material system^[100]. Fan *et al.* demonstrated the involvement of voltage-gated channels in Ca^{2+} flux using MoS_2 nanosheets^[101], whereas Zhang *et al.* employed cell-anchored KNN particles to simultaneously record membrane depolarization and Ca^{2+} responses, thereby extending the applicability of this mechanism across distinct piezoelectric materials^[102]. Collectively, these studies have established membrane depolarization and Na_v/Ca_v coupling as the principal mechanistic axis of PENG-mediated neuromodulation. The response originates from perturbation of the membrane potential by a localized piezoelectric field, which drives the membrane beyond the excitation threshold and subsequently activates voltage-gated ion channels.

Ca²⁺-mediated translation of neural function

Ca^{2+} signaling serves as the central hub through which PENGs convert transient piezoelectric stimulation into sustained neural functional responses^[103]. Following membrane depolarization and the opening of voltage-gated Ca^{2+} channels, elevated cytosolic Ca^{2+} engages calmodulin (CaM)-dependent intracellular signaling^[104]. The resulting signals proceed through Ca^{2+} /calmodulin-dependent protein kinase, adenylyl cyclase/cAMP (cyclic adenosine monophosphate)/PKA (protein kinase A), and rat sarcoma GTPase/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (Ras/MEK/ERK) pathways, which converge on cAMP response element-binding protein (CREB) to encode electrical activity into cytoskeletal remodeling and gene transcription^[105]. Jiang *et al.* fabricated PLLA nanofibers with a piezoelectric output of approximately 260 mV, which increased intracellular Ca^{2+} levels in stimulated PC12 cells to nearly twice those of the control group and significantly enhanced neurite elongation^[106]. However, this study remained largely correlative, linking electrical output to cellular phenotype. Wayman *et al.* subsequently demonstrated in hippocampal neurons that Ca^{2+} /CaM signaling activates ERK and CREB through the CaMKK (Ca^{2+} /calmodulin-dependent protein kinase kinase)-CaMKI (Ca^{2+} /calmodulin-dependent protein kinase I) pathway, thereby defining the transcriptional link between transient Ca^{2+} influx and dendritic remodeling^[107]. These findings shift the design emphasis from simply maximizing peak output toward controlling pulse duration and repeated stimulation patterns. Building on this mechanistic framework, Yan *et al.* combined electrical stimulation with Ca^{2+} blockade, Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) inhibition, and gene knockdown to demonstrate that the Ca^{2+} /CaM-dependent CaMKII-CREB axis drives brain-derived neurotrophic factor (BDNF) transcription and neurite outgrowth in dorsal root ganglion neurons^[108]. Wang *et al.* further applied brief electrical stimulation to spinal cord neurons and found that blockade of L-type Ca^{2+} channels only partially attenuated BDNF expression, whereas ERK inhibition completely abolished its upregulation^[109]. These findings indicate that Ca^{2+} entry occurs through partially redundant routes, while ERK serves as a critical convergence node for amplifying neurotrophic signaling. Building on this understanding, Spencer *et al.* shifted the therapeutic objective from

promoting neurite growth to overcoming myelin-associated inhibition^[110]. They demonstrated that CaMKIV (Ca²⁺/calmodulin-dependent protein kinase IV) and PKA must be activated in parallel, indicating that engagement of a single signaling pathway is insufficient in complex injury environments. Cohen *et al.* further extended this framework to CaM nuclear translocation, CREB-dependent gene expression, and late-phase long-term potentiation (LTP), thereby linking acute stimulation to sustained synaptic plasticity and demonstrating that Ca²⁺ signaling can translate localized neural activity into long-lasting functional adaptations^[111]. More recently, Huang *et al.* applied electrical stimulation to cultured Schwann cells and observed an approximately 4.1-fold increase in NGF secretion that was dependent on Ca²⁺ signaling. This finding indicates that Ca²⁺ can extend neuronal excitation beyond neurons themselves to promote glial-derived trophic support^[112]. Collectively, these mechanistic relationships establish a progressive paradigm in which PENG-mediated piezoelectric stimulation advances from threshold-triggered excitation and signaling convergence to cooperative overcoming of inhibitory cues, long-term plasticity, and multicellular amplification. Along this cascade, Ca²⁺ influx activates CaM, PKA, and ERK-dependent signaling, which converges on CREB and progressively amplifies neural responses through neurotransmitter release, neurite extension, neurotrophic factor expression, and sustained synaptic plasticity.

Piezoelectric output-neural response relationship

The neural effects of PENGs are not determined directly by the open-circuit voltage, but primarily by the local electric field delivered to neural tissue, charge per phase, and pulse waveform. The local electric field must induce sufficient membrane depolarization to reach the excitation threshold of the target neural population. The charge per phase determines both neural activation efficacy and the electrochemical safety limit, with typical charge levels of approximately 1–50 nC per pulse for retinal prostheses and 135–400 nC per phase for deep brain stimulation (DBS)^[113,114]. Pulse duration and stimulation intensity follow the strength-duration relationship, with shorter pulses generally requiring higher stimulation currents. Stimulation frequency further modulates neuronal firing patterns and plasticity; frequencies of 1–100 Hz are generally associated with promoting neural regeneration and plasticity, whereas frequencies > 100 Hz are typically used to suppress abnormal neural activity^[92,115]. Stimulation safety can be evaluated using the Shannon model, $k = \log^{10}(D) + \log^{10}(Q)$, where $k < 1.5$ is generally considered within the safe range, whereas $k > 2.0$ indicates an increased risk of tissue damage^[116]. McCreery *et al.* further demonstrated that neural injury is jointly governed by charge density and charge per phase, providing experimental support for the Shannon criterion^[117]. Meanwhile, the charge-injection capacity and effective area of the electrode, together with tissue impedance, collectively determine the efficiency of PENG output transfer to neural tissue. The charge-injection capacities of platinum and activated iridium oxide are approximately 50–150 $\mu\text{C cm}^{-2}$ and 1–4 mC cm^{-2} , respectively^[114]. Previous studies have shown that an output of approximately 260 mV from PLLA nanofibers can increase intracellular Ca²⁺ levels to nearly twice those of the control group and promote neurite extension, whereas a biomimetic hollow conduit generating 0.95 V can enhance axonal elongation and myelination *in vivo*^[106,118]. Table 3 summarizes these quantitative reporting guidelines. Therefore, the neural stimulation performance of PENGs should be quantitatively evaluated in terms of the electric field, delivered charge, pulse parameters, and interface safety, rather than using open-circuit voltage as a standalone performance metric.

APPLICATIONS OF PENGs IN NEURAL INTERVENTION

Peripheral nerves

Repair of peripheral nerve defects

Peripheral nerve defects represent a major application of PENGs in neural regeneration. Repair of traumatic nerve transection, crush injury, and segmental defects requires the simultaneous restoration of gap bridging, directional axonal regeneration, and electrophysiological conduction^[22,36]. The field has therefore evolved by progressively addressing three principal limitations: insufficient electrical stimulation after bridging,

Table 3. Proposed standardized reporting guidelines for PENG neural stimulation studies

Parameter	Metric (unit)	Reference range	References
Device output	V_{oc} , I_{sc} at defined load (V; nA- μ A)	0.2–84 V; nA- μ A	[71,81]
Pulse parameters	Pulse width; frequency (μ s; Hz)	60–200 μ s (DBS); 1–100 Hz; > 100 Hz	[90,114,115]
Electric field	Depolarization at target membrane (mV)	20–100 mV	[90,114]
Delivered charge	Charge per phase (nC)	1–50 (retinal); 135–400 (DBS)	[113,114]
Electrode interface	Material; area; charge-injection capacity	Pt 50–150 μ C cm ² ; IrOx 1–4 mC cm ²	[114]
Charge density	Per phase (μ C cm ²)	≤ 30 (safe; Shannon $k < 1.5$); DBS: 2.3–6.7	[116,117]
Functional outcome	CAP; NCV; behavior	Not yet standardized	[118]

V_{oc} : Open-circuit voltage; I_{sc} : short-circuit current; DBS: deep brain stimulation; Pt: platinum; IrOx: iridium oxide; CAP: compound action potential; NCV: nerve conduction velocity.

inadequate spatial guidance, and a lack of microenvironmental support. Pi *et al.* developed aligned PCL/PVDF nanofiber bundles (piezoelectric nanotracts) that, under ultrasound-driven piezoelectric stimulation, restored motor function and axonal maturity across a 15 mm rat sciatic nerve defect to levels comparable with autologous nerve grafting^[119]. In parallel, Jeon *et al.* constructed polyethylene glycol (PEG)-modified PLLA four-channel conduits that achieved substantial reinnervation at 12 weeks after repair of an 8-mm defect, with regenerative outcomes approaching those of autologous nerve grafting [Figure 3A]^[38]; Huang *et al.* similarly combined longitudinally oriented guidance cues with a porous sheath in a compound scaffold that promoted peripheral nerve regeneration *in vivo*^[120]. However, these therapeutic effects remained dependent on an external acoustic field. One strategy to address this limitation is to alter the mode of mechanical input. More recently, Chen *et al.* constructed a biodegradable PENG conduit from aligned PCL/ β -glycine nanofibers [Figure 3B]. Following 15-Hz vibrational stimulation delivered using a massage gun in a 10-mm nerve-defect model, motor function and nerve conduction recovered to 99% and 96%, respectively^[121]. Zhang *et al.* instead enhanced piezoelectric performance through structural innovation, developing a bamboo-inspired, aligned hollow bilayer conduit whose collaborative oriented architecture increased the electrical output from approximately 20 mV to 0.95 ± 0.02 V, accelerated axonal elongation and myelination by 3.1- and 1.6-fold, respectively, and promoted peripheral nerve and muscle regeneration *in vivo* [Figure 3C]^[118]. Compared with the preceding approaches, these findings suggest that structure-mediated stress concentration may provide greater performance gains than material substitution alone. However, although stress concentration can increase peak voltage, the effective charge output remains limited. More recently, Li *et al.* integrated piezoelectric and triboelectric energy-harvesting units into a liquid-metal/ZnO-reinforced PVDF conduit, increasing the d_{33} coefficient from 0.9 to 4.6 pC N⁻¹^[122]. This hybrid design enhanced effective charge generation while concurrently improving functional recovery of the sciatic nerve. As electrical stimulation performance improved, the evaluation focus shifted toward whether the generated electrical signals could act stably on cells along the direction of regeneration. To address this requirement, Zhou *et al.* combined PLGA/PVDF microgrooves with a reduced graphene oxide (rGO)/gelatin methacryloyl (GelMA) filling matrix to simultaneously enhance longitudinal guidance, interfacial conductivity, and cell adhesion, thereby coupling electrical stimulation with structural guidance within a single nerve conduit [Figure 3D]^[123]. To overcome the inability of planar microstructures to reconstruct the complex spatial organization of nerve fascicles, Qi *et al.* further combined digital light processing printing with directional freezing to create hierarchically aligned channels across multiple length scales, advancing interfacial design from surface patterning toward three-dimensional spatial compartmentalization^[124]. After the physical and electrical design parameters had been progressively optimized, Yin *et al.* further integrated self-powered electrical stimulation with sustained NGF release^[125]. In a 10 mm nerve-defect model, this system attenuated muscle atrophy and promoted axonal regeneration and remyelination, thereby addressing the insufficient long-term trophic support provided by material interfaces

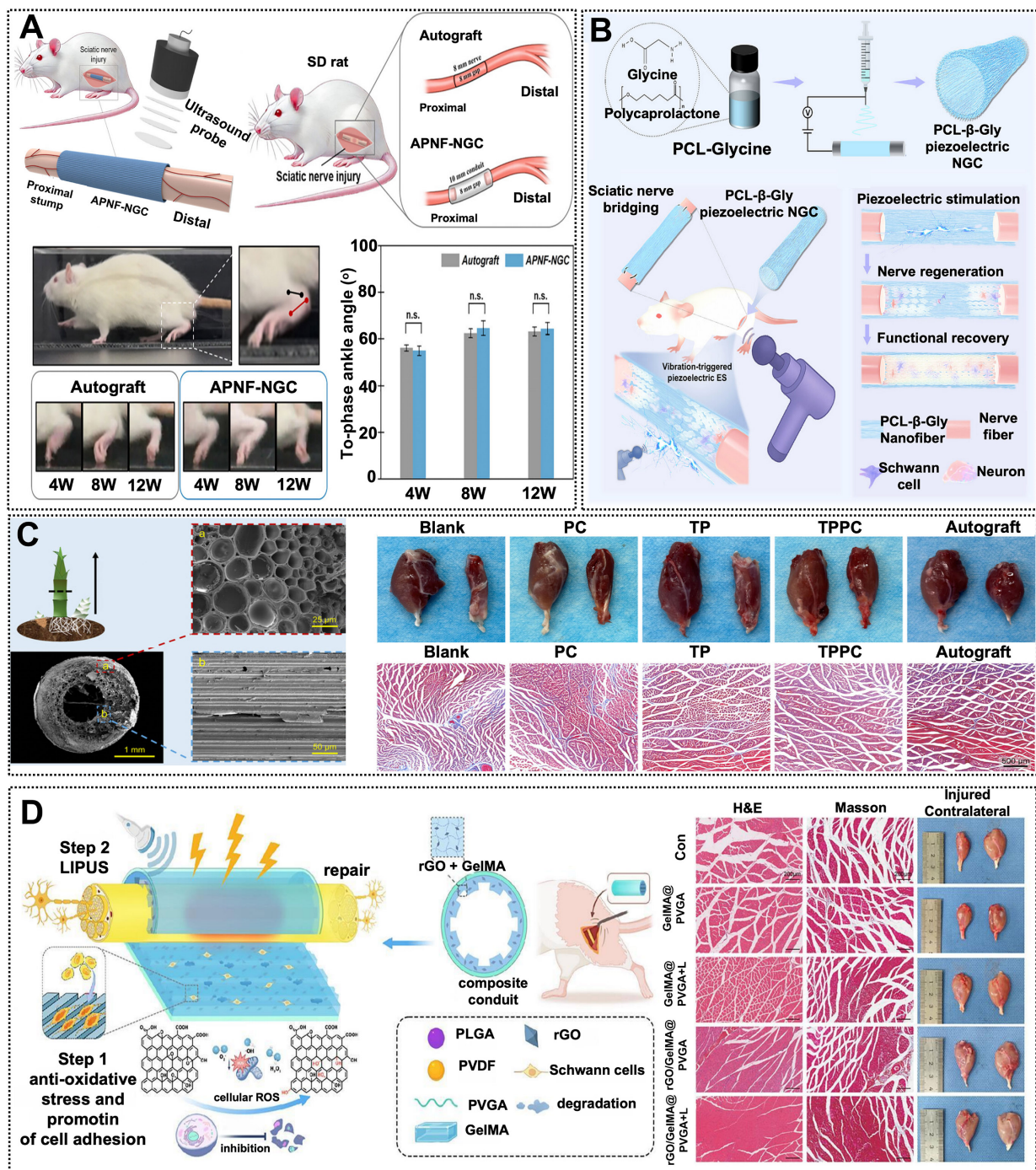


Figure 3. Representative applications of PENGs in nerve injury repair. (A) Ultrasound-driven aligned piezoelectric nanofibers nerve guidance conduit (APNF-NGC) for peripheral nerve regeneration, comparative analysis of the autograft group and the NGC group in an 8-mm sciatic nerve defect model, showing comparable outcomes, adapted from Ref.^[38] under CC BY 4.0 license. (B) Biodegradable PCL-β-glycine piezoelectric nerve guidance conduit activated by low-frequency mechanical vibration for peripheral nerve regeneration, adapted with permission from Ref.^[121]. Copyright © 2026 Wiley-VCH. (C) Structural characterization of the bamboo-inspired hollow bilayer conduit and its synergistic oriented architecture for piezoelectric acceleration of peripheral nerve and muscle regeneration, adapted with permission from Ref.^[118]. Copyright © 2026 Wiley-VCH. (D) Schematic of the conductive-piezoelectric integrated microstructured nerve conduit (rGO/GelMA@PVGA), where piezoelectric stimulation combined with structural guidance promotes nerve and target muscle regeneration, adapted from Ref.^[123] under CC BY 4.0 license.

alone. This integration transformed the PENG conduit from a passive bridging scaffold with intermittent electrical stimulation into a regenerative platform that combines energy supply, spatial guidance, and biochemical modulation.

Sensorimotor functional restoration

Sensorimotor reconstruction determines whether regenerated nerves can re-establish sensory input and motor output. Accordingly, the evaluation focus has shifted from axonal regeneration alone toward the coordinated recovery of sensory afference, motor efference, and target-muscle control. Qian *et al.* embedded a ZnO nanogenerator within a biomimetic scaffold and demonstrated, through electrophysiological and motor-function improvements, that piezoelectric stimulation could yield functional benefits; however, the duration of stimulation remained limited^[8]. To extend the effective stimulation window, Jin *et al.* developed a respiration-driven triboelectric-piezoelectric biofeedback implantable electrical stimulation system for long-lasting neural modulation^[126]. This hybrid nanogenerator produced 1.5 V and 0.071 μ A and maintained stable operation for 14 weeks, enabling gait and neuromuscular function after repair of a 15 mm nerve defect to approach those achieved with autologous nerve grafting [Figure 4A]. The design paradigm therefore shifted from intermittent exogenous activation toward sustained endogenous powering, thereby overcoming interruptions in electrical stimulation. Nevertheless, efficient energy transfer to regenerating axons and target muscles remained dependent on the contact configuration and charge-transport properties of the conduit interface. To address this limitation, Hu *et al.* incorporated rGO and a microneedle architecture into a PCL/ZnO system. The rGO conductive network enhanced charge transport, whereas the microneedles improved local fixation and stimulation delivery, enabling an output voltage of 4.6 V^[127]. This design extended the therapeutic effects beyond axonal regeneration to target-muscle reinnervation and protection against denervation-induced muscle atrophy. A millimeter-scale implantable magneto-mechano-electric transducer based on BTO piezoelectric ceramics enables remote wireless electrical stimulation of injured sciatic nerves [Figure 4B]^[128]. However, a high peak output alone does not ensure stable action-potential propagation. Lv *et al.* therefore developed a P(VDF-TrFE)/rGO/PCL scaffold that integrated piezoelectric stimulation, conductive signal transmission, and myelin sheath reconstruction within a single regenerative system^[129]. As therapeutic efficacy improved, matching the stimulation dose to motor recovery emerged as a new challenge. Shan *et al.* therefore repurposed PLLA/BaTiO₃ from a therapeutic material into a biodegradable sensor^[28]. Its linear pressure-output relationship $R^2 = 0.9445$ and close agreement with electromyographic signals enabled wireless monitoring of functional recovery [Figure 4C]. Because passive monitoring cannot actively adjust therapeutic intervention in response to rehabilitative activity, Tan *et al.* further converted movement-derived mechanical energy into a drug-release trigger, enabling on-demand delivery of aspirin/lysine and increasing the mass of denervated muscle^[130]. Gu *et al.* developed an aligned PLLA/poly(ethylene oxide) (PEO)/Mg₂Si piezoelectric fibrous scaffold whose optimized composition generated a piezoelectric current of 144.11 ± 1.55 pA and, under ultrasound activation, improved electrophysiological conduction and gait recovery while mitigating gastrocnemius muscle atrophy in a 15 mm rat sciatic nerve defect model [Figure 4D]^[131]. Moving beyond the local combination of individual powering, conduit, and training modules, Nan *et al.* integrated massage-driven actuation, a hybrid nanogenerator, and a conductive nerve conduit into a mechanoneuromodulatory electrical biointerface system^[132]. The system was further translated from rats to miniature pigs, with compound muscle action potentials, nerve conduction velocity, muscle strength, gait performance, and dorsal root ganglion tracing collectively demonstrating coordinated sensory-motor reconnection. This work shifted the research paradigm from optimizing individual output parameters toward the coordinated integration of energy harvesting, stimulation delivery, functional monitoring, and rehabilitative training.

Central nervous system

Spinal cord injury repair

In traumatic spinal cord injury repair, PENG-based therapeutic constructs have evolved from passive bridging scaffolds into multifunctional platforms that can be remotely activated, deliver therapeutic cells, and modulate the lesion microenvironment^[40]. In an early study, Lee *et al.* constructed a Schwann cell-loaded conduit from aligned P(VDF-TrFE) fibers. In a rat model of complete spinal cord transection, the conduit

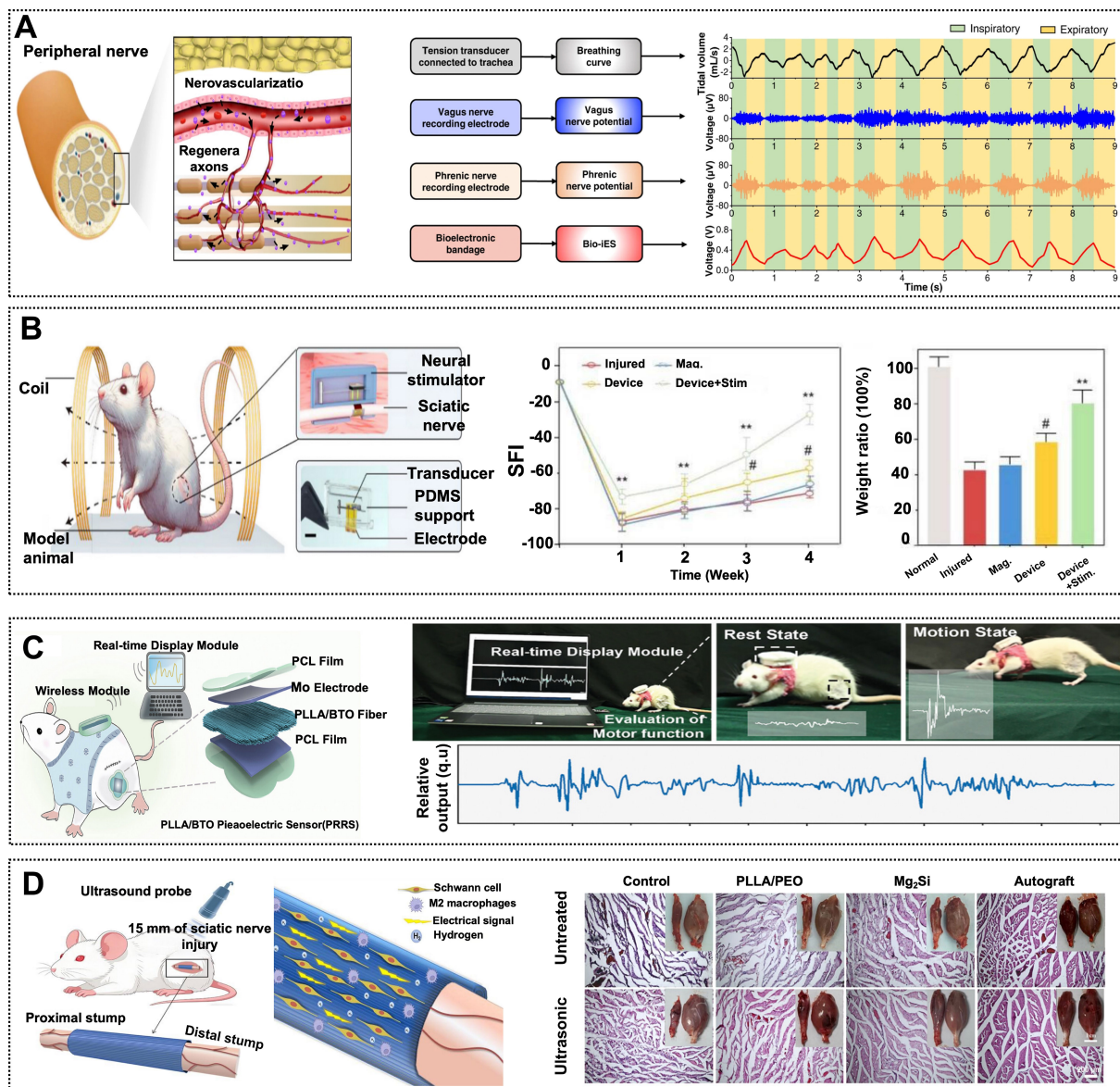


Figure 4. Representative piezoelectric and piezoelectric-hybrid strategies for sensorimotor functional restoration after peripheral nerve injury. (A) Implantable electrical stimulation (iES) system, including signal generation and its effects on neural cell and tissue regeneration, adapted from Ref.^[126] under CC BY 4.0 license. (B) Wireless electrical stimulation of the injured sciatic nerve by a millimeter-scale implantable magneto-mechano-electric transducer based on BTO piezoelectric ceramics, adapted from Ref.^[128] under CC BY 4.0 license. (C) Monitoring of rat motor function and output signals using a PLLA/BTO piezoelectric sensor (PBRs), adapted with permission from Ref.^[28]. Copyright © 2024 Wiley-VCH. (D) Ultrasound-activated aligned PLLA/PEO/Mg₂Si piezoelectric fibrous scaffold for repair of a 15 mm sciatic nerve defect, with evaluation of gastrocnemius muscle morphology and muscle-fiber area, adapted from Ref.^[131] under CC BY 4.0 license. ** $P < 0.01$; # $P < 0.05$ vs. the indicated control group.

provided longitudinal bridging and promoted the ingrowth of brainstem-derived noradrenergic axons, astrocytic processes, and blood vessels into the graft, thereby establishing the feasibility of piezoelectric scaffolds for structural reconstruction of the injured spinal cord^[133]. Li et al. developed a wirelessly activatable silk fibroin/BaTiO₃-5 piezoelectric hydrogel that generated an output current of 124 nA, reduced lesion-cavity formation, and improved Basso-Beattie-Bresnahan (locomotor rating scale) (BBB) locomotor scores and gait performance^[134]. This study marked the transition from static scaffolds to remotely activated electroactive implants. Because piezoelectric stimulation alone cannot simultaneously control post-injury excitotoxicity and myelin loss, an SFBP (silk fibroin/BaTiO₃/polypyrrole)/PER (perampanel) conductive

piezoelectric hydrogel incorporating PER was subsequently developed. Ultrasound activation concurrently provided electrical stimulation and pharmacological intervention, thereby further enhancing remyelination and locomotor recovery^[135]. As the functional scope of these systems expanded, the research focus shifted toward recapitulating the spinal cord extracellular matrix while ensuring long-term biosafety^[136]. Shi *et al.* incorporated KNN nanoparticles into a porous GelMA-reinforced decellularized spinal cord matrix hydrogel to construct a biomimetic piezoelectric porous decellularized spinal cord matrix gel/KNN (pDGK) system. Under ultrasound irradiation at 0.4 W cm^{-2} , the integration of KNN with the decellularized spinal cord matrix simultaneously promoted vascularization and tissue repair while maintaining systemic organ safety over an 8-week period [Figure 5A]^[137]. However, acellular materials remain unable to replenish the neural and supportive cell populations lost after injury. Zhong *et al.* therefore co-transplanted a wireless piezoelectric hydrogel with neural stem cells and human umbilical cord-derived mesenchymal stem cells (NSCs (neural stem cells)-hUCMSCs), thereby reducing lesion-cavity formation and supporting axonal regeneration [Figure 5B]^[138]. Building on this strategy, Wang *et al.* further employed a three-dimensional system for the co-delivery of NSCs and Schwann cells, which enhanced transplanted-cell survival, synaptic density, and remyelination. These advances shifted the design paradigm from material-mediated repair toward the reconstruction of an electroactive regenerative niche^[139]. Zhang *et al.* combined ultrasound with MgFe-layered double hydroxide (LDH)/NT3 nanoparticles to promote neural stem cell differentiation and improve locomotor and electrophysiological recovery after complete spinal cord transection [Figure 5C]^[140]. To overcome the requirement for direct implantation into the lesion site, Xiao *et al.* combined magnetically responsive piezoelectric nanocapacitors with transspinal magnetic stimulation^[141]. Without open surgery, this approach promoted distal regeneration of the corticospinal tract, restored functional connectivity, and improved hindlimb locomotion [Figure 5D], marking a transition of PENG-based therapies from implantable local stimulation toward minimally invasive neuromodulation of deep neural tissue. Overall, the field has established a progressive trajectory encompassing structural bridging, wireless stimulation, pharmacological synergy, cellular niche reconstruction, and non-invasive activation. However, the available evidence remains dominated by short-term BBB/Basso mouse scale locomotor assessments and histological outcomes in rodent models.

Functional modulation of brain regions

Piezoelectric modulation of brain regions has evolved from unidirectional power delivery toward state sensing and precise neural encoding. Accordingly, therapeutic evaluation has expanded beyond transient stimulation to encompass target-region specificity, behavioral reversibility, and long-term safety across applications involving synaptic plasticity, epilepsy, pain, and homeostatic regulation^[142]. In an early study, Zhao *et al.* developed a body-motion-powered PZT/PVDF system that induced LTP and long-term depression in the hippocampal CA3-CA1 pathway through frequency-conditioned stimulation, demonstrating that piezoelectric energy could support bidirectional neural encoding^[143]. However, stimulation timing remained externally prescribed by the operator, and the system therefore addressed energy delivery without achieving state-dependent control. To incorporate sensing and decision-making capabilities, Yang *et al.* integrated an enzyme/ZnO sensor into a stimulation circuit targeting the dorsomedial ventromedial hypothalamus. Hypoglycemic signals automatically triggered intervention, increasing blood glucose levels by 39% within 10 min^[144]. This system provided an integrated closed-loop demonstration encompassing physiological-state detection, threshold-based decision-making, target-specific stimulation, and corrective restoration of glucose homeostasis. Within this architecture, Liang *et al.* combined a PZT arch-shaped transducer with a PVDF/ZnO membrane to convert respiratory motion into stimulation of the medial forebrain bundle^[145], whereas Xu *et al.* integrated a PVDF pulse sensor with a piezoelectric generator to drive electrodes in the median preoptic nucleus^[146]. Xiang *et al.* similarly used a PZT arch-shaped transducer and PVDF/ZnO membrane to encode carotid pulsation into periaqueductal gray stimulation^[147]. Collectively, these studies extended a common piezoelectric platform to the regulation of

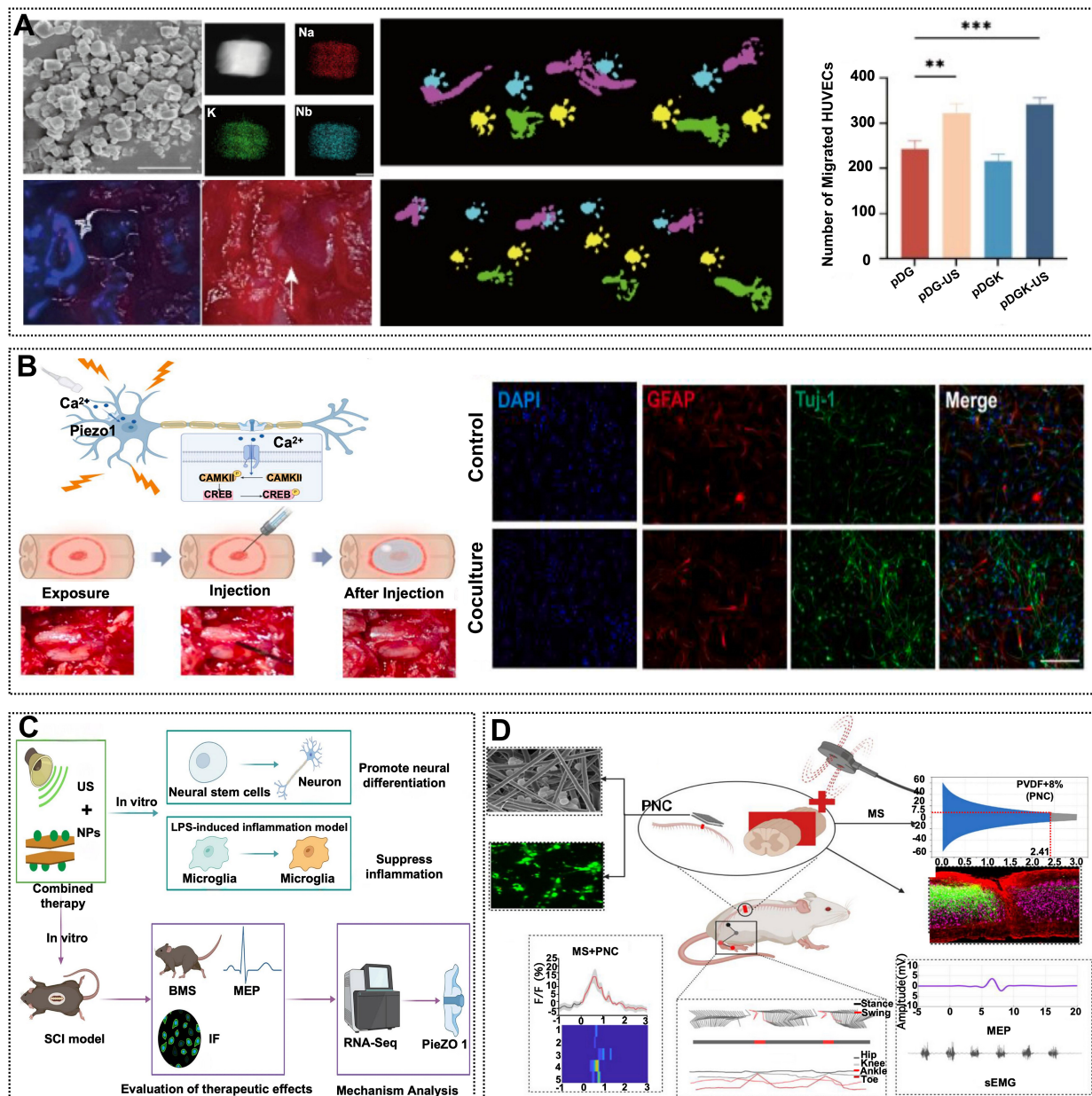


Figure 5. Representative applications of PENGs in spinal cord injury repair. (A) *In vivo* repair of spinal cord injury using a biomimetic piezoelectric hydrogel (decellularized spinal-cord matrix reinforced with KNN nanoparticles, pDGK), adapted from Ref.^[137] under CC BY 4.0 license. (B) Ultrasound-activated wireless conductive piezoelectric hydrogel (PEDOT/polydopamine@BaTiO₃, WPC) for spinal cord injury repair, and its immunofluorescence images promoting nerve regeneration, adapted from Ref.^[138] under CC BY 4.0 license. (C) Ultrasound-assisted MgFe-LDH/NT3 nanoparticle therapy for neural stem cell differentiation and spinal cord injury recovery, adapted from Ref.^[140] under CC BY 4.0 license. (D) BaTiO₃-modified PVDF-based piezoelectric nanocapacitors (PNCs) for improving spinal cord injury outcomes and restoring neural innervation, adapted from Ref.^[141] under CC BY 4.0 license. ***P* < 0.01, ****P* < 0.001.

exercise endurance, body temperature, and behavior. These studies indicate that system optimization has progressed from establishing whether sufficient power can be generated toward matching specific physiological sensing variables with the functions of targeted brain regions. However, the input signals remain derived from normal physiological activity and therefore cannot directly capture pathological neural discharges. Epilepsy provided a more stringent test of whether state-triggered control could be extended from normal physiological variables to disease-related signals. Lin *et al.* developed a PVDF/ZnO system that used seizure-associated body movements to trigger stimulation of the dentate gyrus-hilus circuit, reducing cumulative seizure duration by 40%-50%^[148]. However, motor activity represents a delayed surrogate that

occurs only after the onset of pathological electrical discharges. Guan *et al.* integrated a piezoelectric element, resonator, and signal-conditioning circuit into a system comprising smartphone-generated acoustic commands and an implantable resonant probe^[149]. This design replaced uncontrollable body-motion inputs with programmable energy delivery and waveform control, and its therapeutic efficacy was verified by electroencephalography; however, implanted electrodes remained necessary. To further reduce the hardware load, BaTiO₃ nanoparticles modified with PEG can be used to shrink the energy conversion interface to the nanoscale and directly regulate the calcium ion activity in epileptic-like neurons. Tang *et al.* further employed BTO@PDA (polydopamine) nanoparticles, using membrane adhesion to enhance retention within the target region. Under low-intensity 1-MHz ultrasound, the system suppressed epileptic activity in the CA1 region while maintaining a low inflammatory response for at least 14 weeks^[150]. Collectively, these advances have driven the field from energy-autonomous operation, state-dependent closed-loop control, and remote neural encoding toward a paradigm in which the material itself serves as the stimulation interface, offering clear advantages for clinical translation.

Autonomic nervous system

Cardiac neuromodulation

Cardiac neuromodulation aims to convert cardiac motion, arterial pulsation, or ultrasound into electrical stimulation delivered through the cervical vagus nerve, auricular vagal branches, or intrinsic cardiac neural plexuses to regulate cardiac rhythm and preserve cardiac function. The central objective is to transform cardiac mechanical energy from a passive power source for implanted devices into neural stimulation that is matched to the underlying pathological state^[6,78,151,152]. A flexible single-crystalline lead magnesium niobate–lead titanate (Pb(Mg_{1/3}Nb_{2/3})O₃-PbTiO₃) (PMN-PT) piezoelectric energy harvester attached to the beating heart enables self-powered cardiac pacing [Figure 6A]^[151]. Azimi *et al.* used PVDF/ZnO/rGO composite fibers to harvest 0.487 µJ of energy from each canine heartbeat and power a cardiac pacemaker, demonstrating the feasibility of using cardiac mechanical energy to support implantable electrotherapy^[70]. This study established a power-output benchmark for the subsequent development of self-powered cardiac neuromodulation systems. Building on this concept, Zhang *et al.* constructed a multilayer PENG by layer-by-layer assembly of P(VDF-TrFE)/BaTiO₃ nanofibers^[71]. The five-layer device generated 84 V and 1.32 µA *in vitro*. When attached to the canine carotid artery, it harvested mechanical energy from arterial pulsation and drove cervical VNS, thereby reducing heart rate and integrating energy harvesting, stimulation delivery, and rhythm modulation within a single system. However, the system lacked pathological state-dependent temporal control. Sun *et al.* subsequently integrated a PVDF sensing layer with a PTFE-based power-generating unit. The system first detected atrial fibrillation-associated pulse signals and then used manual pressing to trigger low-intensity VNS, reducing episode duration by 90%^[153]. This design advanced continuous activity-coupled stimulation toward event-responsive therapy and established temporal control of neuromodulation. A fully automated, closed-loop wireless-VNS system that tunes stimulation according to heart-rate feedback further achieves steady-state control [Figure 6B]^[154]. The magneto-responsive piezoelectric CoFe₂O₄-PVDF system developed by Jing *et al.* has also been used for on-demand electrical modulation of infarcted myocardium [Figure 6C]^[155], extending piezoelectric regulation from the myocardium to the central autonomic network. Further studies, reported by Zhang *et al.*, demonstrated that a KNN-based ferroelectric heterojunction enabled ultrasound-driven modulation of the paraventricular nucleus to suppress sympathetic hyperactivity after myocardial infarction [Figure 6D]^[156]. However, achieving spatially selective modulation within the cardiac autonomic network remains a major challenge. Han *et al.* therefore directly injected BaTiO₃ particles into the right inferior cardiac ganglionated plexus of dogs and used ultrasound to locally reduce the ventricular rate during atrial fibrillation, without inducing evident thermal injury or inflammation^[157]. This strategy shifted the stimulation target from the mixed vagal trunk to the intrinsic cardiac autonomic network. The achievement of targeted acute rate control further shifted therapeutic endpoints toward the prevention of chronic myocardial remodeling. Wang *et al.* applied

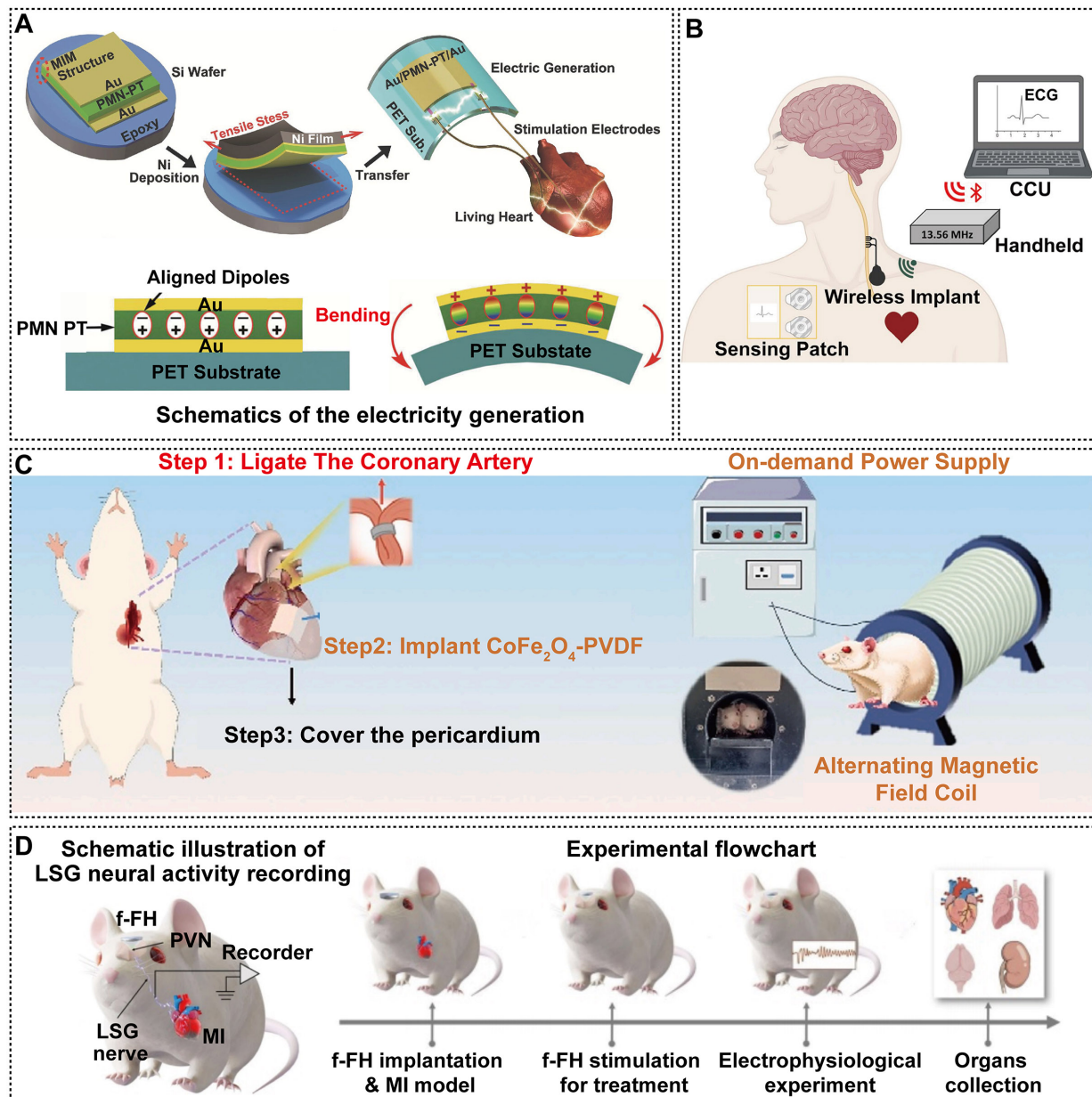


Figure 6. Representative applications of PENGs in cardiac neuromodulation. (A) Self-powered cardiac pacemaker enabled by a flexible single-crystalline PMN-PT piezoelectric energy harvester attached to the beating heart, adapted with permission from Ref.^[151]. Copyright © 2014 Wiley-VCH. (B) Fully automated wireless vagus nerve stimulation (FAW-VNS) system incorporating electrocardiogram (ECG) sensing, closed-loop control, and a 13.56-MHz wirelessly powered implant, Adapted from Ref.^[154] under CC BY 4.0 license. (C) Magneto-responsive piezoelectric CoFe_2O_4 -PVDF system for on-demand electrical modulation of the infarcted myocardium, adapted from Ref.^[155] under CC BY 4.0 license. (D) Schematic illustration of ultrasound-driven paraventricular nucleus (PVN) neuromodulation using a KNN-based ferroelectric heterojunction for myocardial infarction treatment, with left stellate ganglion (LSG) neural activity recording, adapted from Ref.^[156] under CC BY 4.0 license.

ultrasound-driven piezoelectret-mediated VNS for 28 days in rats with myocardial infarction, increasing left ventricular ejection fraction and fractional shortening by 20.42% and 11.76%, respectively, while attenuating inflammation, fibrosis, and sympathetic remodeling^[25]. Xu *et al.* used cardiac deformation at the chest surface to drive a PENG for transcutaneous auricular VNS^[158]. Continuous treatment for 4 weeks improved cardiac function, attenuated ventricular remodeling, and reduced central neuroinflammation after myocardial infarction, while avoiding electrode implantation on the cervical vagus nerve. Collectively, these studies delineate a continuous progression from energy-harvesting validation and demonstration of neuromodulatory efficacy to pathological event-triggered intervention, intrinsic cardiac targeting, and long-term minimally invasive regulation.

Gastrointestinal neuromodulation

Gastrointestinal neuromodulation exploits continuous gastrointestinal deformation and accessible mucosal interfaces to convert mechanical energy into localized electrical stimulation or physiological-state signals for metabolic, motility, and neuroimmune interventions. Early studies first established the piezoelectric readout of gastrointestinal motility^[159–163]. Li *et al.* constructed an adherent PENG from PLLA/glycine core-shell nanofibers, stabilizing the piezoelectric β -phase of PLLA and enabling the device to maintain a consistent electromechanical response under wet physiological conditions and deformation along the curved colonic surface^[127]. Following implantation onto the transverse colon of rats, the device recorded distinct peristaltic signals during healthy, colitic, and remission states, thereby advancing gastrointestinal motility monitoring toward the identification of disease progression. Dai *et al.* embedded Rochelle salt within PLLA nanofibers to fabricate a biodegradable three-channel sensor with a d_{33} coefficient of 43.1 pC N⁻¹^[14]. When implanted on the rabbit colon, the device wirelessly resolved the amplitude, frequency, and propagation velocity of peristaltic contractions, thereby transforming motility signals into spatially resolved inputs for gastrointestinal regulation. Once physiological-state encoding had been established, piezoelectric outputs began to be translated into therapeutic stimulation. Poling *et al.* activated a P(VDF-TrFE) nanofibrous scaffold using low-intensity pulsed ultrasound, promoting cell proliferation in human intestinal organoids and demonstrating that gastrointestinal tissue models can respond to remotely delivered piezoelectric stimulation^[164]. Building on this concept, Mac *et al.* conjugated capsaicin to BaTiO₃ particles to target transient receptor potential vanilloid 1-positive sensory terminals in the gastric mucosa^[165]. Peristaltic motion activated the particles to generate piezoelectric signals, which enhanced vagal afferent signaling of satiety and improved body-weight control and glucose-lipid metabolism in obese mice. A subsequent study further employed ultrasound-activated, gastric mucosa-adherent piezoelectric particles, extending localized piezoelectric stimulation to vagus nerve-mediated immunomodulation. In septic mice, this strategy reduced systemic inflammation and organ injury while improving survival^[166]. Within non-piezoelectric gastrointestinal neuroelectronics, Srinivasan *et al.* further developed an integrated neuroprosthetic platform combining sensing, stimulation, and endoscopic implantation^[167]. The system used multichannel inputs to drive the myenteric plexus and restore coordinated peristalsis, providing a transferable system architecture for the future integration of PENGs into closed-loop gastrointestinal neuromodulation.

Neurodegenerative diseases

Parkinson's disease (PD)

PD is the second most common neurodegenerative disorder and is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra^[168]. The resulting dopamine deficiency profoundly impairs motor function and also affects mood, cognition, gastrointestinal function, and olfaction. PENG-based research for PD has progressed sequentially through advances in acoustoelectric conversion, intracerebral delivery, circuit-specific targeting, and stimulation selectivity. The central objective is to achieve stable, precise, and sustained deep-brain neuromodulation while minimizing the burden associated with implanted hardware. Zhao *et al.* first fabricated carbon-coated BaTiO₃ (barium titanate) (C@BT) piezoelectric nanoparticles from a BaTiO₃/carbon composite to improve acoustic impedance matching with brain tissue^[169]. Under 1-MHz ultrasound at 0.64 W cm⁻², the nanoparticles modulated the midbrain of 6-hydroxydopamine (6-OHDA)-treated zebrafish, restoring tyrosine hydroxylase (TH) expression and swimming performance [Figure 7A]. This study demonstrated that ultrasound-induced localized electric fields could protect degenerating dopaminergic neurons, although the mechanisms underlying neural recovery remained unclear. Building on this strategy, Chen *et al.* coated BaTiO₃ with PEP and assembled the particles into pomegranate-like nanoclusters, increasing heterointerfacial density to concentrate mechanical energy^[26]. The resulting piezoelectric stimulation sequentially induced membrane depolarization and Ca²⁺ influx, increased TH levels, and reduced α -synuclein aggregation. This study advanced the field beyond behavioral recovery toward the restoration of dopamine synthesis and clearance of pathological protein

aggregates. However, local injection limits access to deep brain regions. To overcome this constraint, Kim *et al.* investigated blood-brain barrier penetration using polydopamine-coated BaTiO₃ nanoparticles loaded with the nitric oxide donor BNN6 (BTNP-pDA-BNN6). Focused ultrasound triggered NO release, transiently opened the blood-brain barrier, and facilitated nanoparticle entry into the brain^[21]. Once distributed within the brain parenchyma, the particles generated a piezoelectric direct-current output, thereby advancing the therapeutic route from intracerebral administration to systemic delivery and ameliorating Parkinsonian symptoms in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice. Chen *et al.* instead focused on correcting pathological activity within the basal ganglia circuitry. They constructed a subcutaneously implantable piezoelectric-triboelectric hybrid nanogenerator using a PVDF/TMCM-MnCl₃ film. Under 100-kHz ultrasound, the device generated an output current of 0.9 mA, which powered deep brain stimulation of the subthalamic nucleus and improved motor function in 6-OHDA-treated rats^[11]. In parallel, an implantable piezoelectric ultrasound stimulator enables wireless activation of subcortical neurons [Figure 7B]; stimulation of substantia nigra pars compacta dopaminergic neurons further elicited time-locked nigrostriatal dopamine release^[170]. The design of freely dispersed particle interfaces subsequently evolved toward directional and cell-selective stimulation. Han *et al.* employed magnetic Janus particles to constrain particle orientation and electric-field direction, while antibody functionalization enabled selective binding to dopaminergic neurons [Figure 7C]^[97]. Cui *et al.* further clustered BaTiO₃ nanoparticles around a UiO-66 core and applied a PDA coating to enhance localized electric-field coupling, enabling effective neural activation under low-intensity focused ultrasound^[171]. Together, these strategies established a materials-design foundation for subsequent modulation of deep brain circuits in PD. Building on these advances, Zhao *et al.* localized PDA@BaTiO₃ particles to the subthalamic nucleus and showed that repeated stimulation concurrently improved gait, pain, and anxiety-related behaviors^[15], while also incorporating particle retention and sustained therapeutic benefit into the evaluation framework^[15]. Song *et al.* further validated the efficacy of *in situ* PENG stimulation across multiple levels, including neuronal excitability, circuit activity, striatal dopamine release, and both motor and cognitive behaviors^[172]. Collectively, these studies demonstrate that PENG-based interventions for PD have progressed from dopaminergic neuroprotection toward subthalamic circuit modulation integrating targeted delivery, acoustic focusing, and stimulation selectivity. This evolution has established a materials and methodological foundation for reducing the invasiveness of conventional deep brain stimulation and enabling long-term, precision neuromodulation.

Alzheimer's disease (AD)

AD is the most common cause of dementia and is characterized by progressive decline in cognitive and memory functions, predominantly affecting older adults^[173]. Extensive evidence indicates that the abnormal accumulation of self-assembled amyloid- β (A β) species, including oligomers, fibrils, and plaques, constitutes a major pathological hallmark of AD^[174]. By converting mechanical energy into electrochemical reactions or patterned electrical stimulation, PENGs offer a new therapeutic strategy that may simultaneously promote pathological protein clearance and cognitive recovery. Jang *et al.* first used piezoelectric BiOCl nanosheets, which dissociated A β aggregates through ultrasound-induced redox reactions and destabilized the β -sheet structure of A β fibrils^[175]. However, freely dispersed particles offered limited control over lesion-site exposure and reactive oxygen species dosage. To improve spatial targeting, Ning *et al.* assembled Fe₃O₄ and BaTiO₃ on a helical biological template to construct a magnetically guided, ultrasound-activated PiezoBOT. The system reduced the size of A β aggregates by more than 80% within 10 min, although the evidence remained limited to *in vitro* disaggregation^[176]. For wireless deep-brain intervention, Wang *et al.* developed a flexible, lead-free dual-frequency piezoelectric implant that was ultrasonically powered to generate programmable biphasic pulses for wireless deep-brain stimulation in rats [Figure 8A]^[24]. Sharma *et al.* subsequently employed polydopamine-coated PVDF nanospheres, which, upon acoustic activation, promoted fibril disassembly, attenuated neurotoxicity, and improved cognitive performance in cellular and animal models, thereby

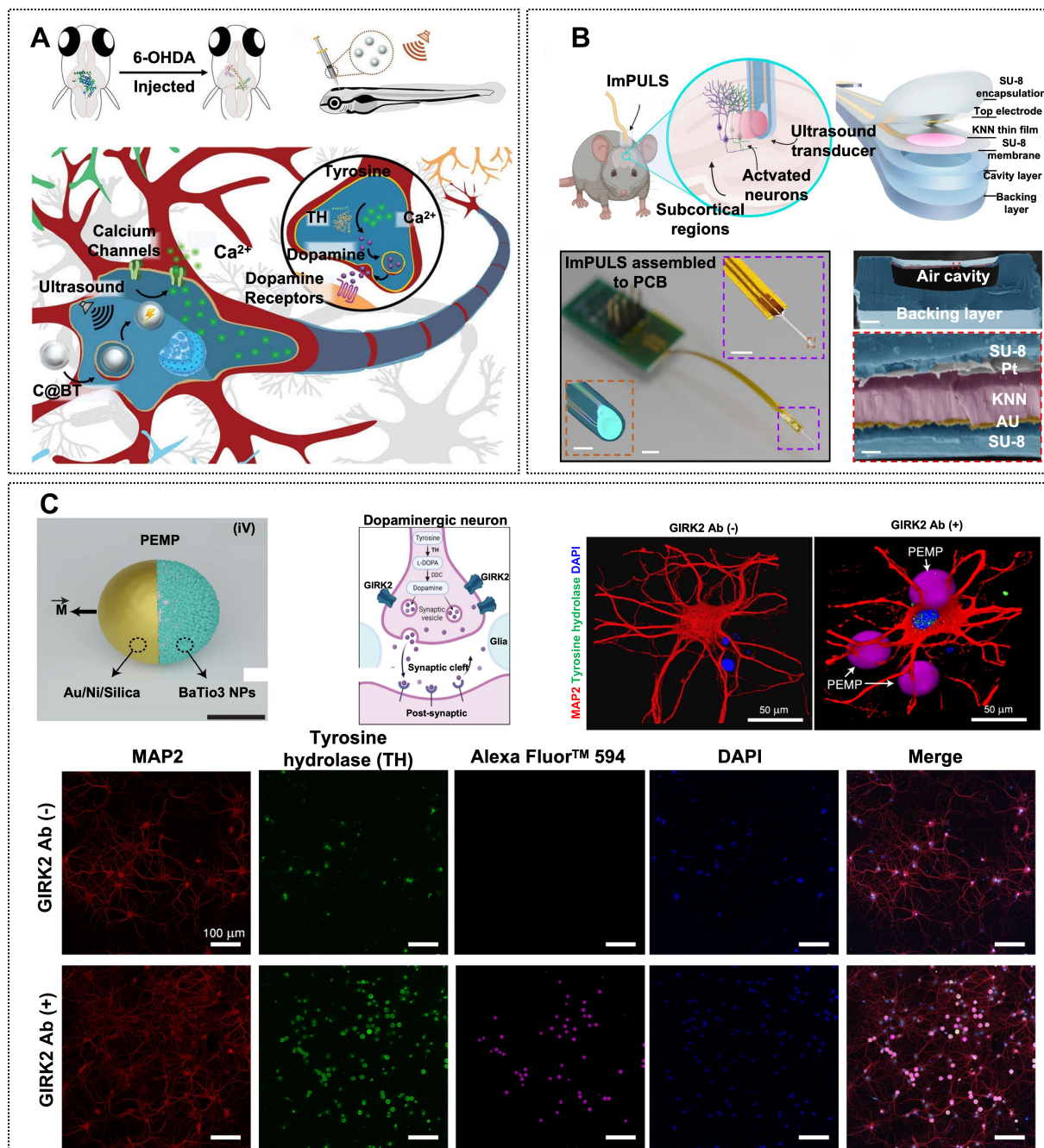


Figure 7. Representative applications of PENG-based neuromodulation for Parkinson's disease. (A) Recovery of degenerating midbrain dopaminergic neurons mediated by ultrasound-driven C@BT piezoelectric nanoparticles, adapted with permission from Ref.^[169]. Copyright © 2020 Wiley-VCH. (B) Representative design and subcortical implantation of an implantable piezoelectric ultrasound stimulator (ImPULS) for wireless deep-brain activation, adapted from Ref.^[170] under CC BY 4.0 license. (C) Specific targeting of dopaminergic neurons using piezoelectric magnetic Janus microparticles (PEMPs) and Immunofluorescence image of neurons, adapted from Ref.^[197], under CC BY 4.0 license.

extending therapeutic validation to disease-level phenotypes^[177]. In parallel, transcranial ultrasound stimulation pulsed at 40 Hz improves cognition and alleviates neuroinflammation in a mouse model of Alzheimer's disease [Figure 8B]^[178]. To clarify and calibrate these material-mediated effects, Jang *et al.* revealed that A β fibrils contain spiraling lateral piezoelectric domains and exhibit a lateral piezoelectric constant of 44.1 pC N⁻¹ [Figure 8C]^[179]. Das *et al.* further used BaTiO₃ nanorods to generate superoxide radicals, converting β -sheet-rich structures into less toxic random coils and providing a mechanistic basis for

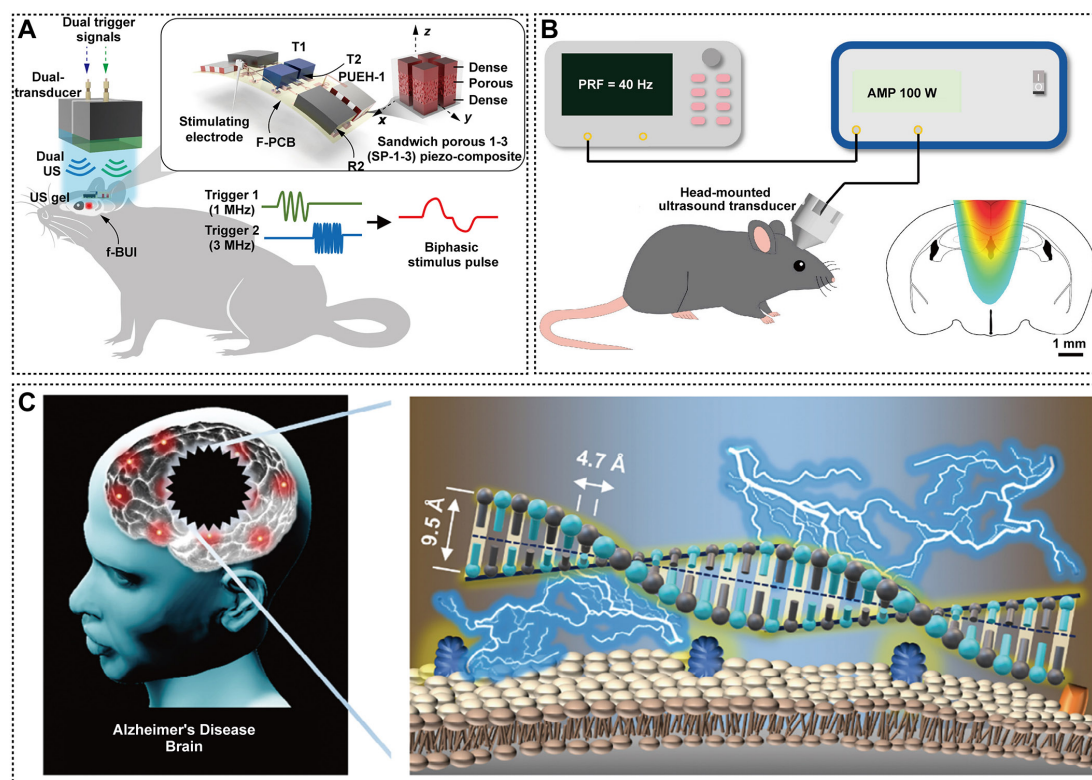


Figure 8. Representative piezoelectric mechanisms and ultrasound-enabled neuromodulation strategies relevant to Alzheimer's disease. (A) Flexible lead-free dual-frequency piezoelectric ultrasound implant for wireless, biphasic deep-brain stimulation, adapted from Ref.^[24] under CC BY 4.0 license. (B) Transcranial ultrasound stimulation pulsed at 40 Hz improves cognition and reduces neuroinflammation in female mice with Alzheimer's disease, adapted from Ref.^[178], under CC BY 4.0 license. (C) Giant piezoelectricity of amyloid- β ($A\beta$) fibrils in Alzheimer's disease: monomeric $A\beta$ peptides assemble into crystalline $A\beta$ fibrils by forming dimers spaced 9.5 Å and stacking dimers spaced 4.7 Å, and the accumulation of these fibrils is associated with ion-channel hyperexcitability and neurodegeneration, adapted from Ref.^[179], under CC BY 4.0 license.

regulating catalytic dosage through particle morphology^[180,181]. Luo *et al.* subsequently constructed a piezoelectrically enhanced, self-calibrating surface-enhanced Raman scattering platform based on PVDF/Ag nanocubes for the simultaneous detection of $A\beta_{40}$ and $A\beta_{42}$ ^[182,183]. This strategy was further extended to piezoelectric charge-regulated plasmonic films capable of identifying multiple AD biomarkers in tears, cerebrospinal fluid, and serum, thereby enabling continuous readout for therapeutic monitoring. Finally, Li *et al.* localized lead-free barium calcium zirconate titanate ($Ba_{0.85}Ca_{0.15}Zr_{0.1}Ti_{0.9}O_3$) nano-PENGs to the hippocampal CA3 region of amyloid precursor protein/presenilin 1 mice and applied 40-Hz rhythmic ultrasound to generate local electrical potentials at the γ frequency^[115]. After 7 days of stimulation, the treatment restored γ oscillations and hippocampal-prefrontal coupling and improved spatial memory, thereby advancing PENG-based intervention from $A\beta$ disaggregation toward the reconstruction of memory circuits. Overall, the field is progressing from nonspecific oxidative disaggregation toward targeted delivery, controllable dosing, repeated activation, and circuit-specific modulation, providing a potential translational pathway for simultaneously addressing $A\beta$ burden and neural network dysfunction.

Neural interfaces

Visual and auditory neural interfaces

Visual and auditory neural interfaces use piezoelectric transduction to convert images or acoustic vibrations into electrical signals that can be decoded by residual sensory pathways. Research in this area has progressed from single-site signal conversion toward spatial addressing, frequency discrimination, and validation of

neural output. In the visual domain, Qian *et al.* fabricated a 3.1-MHz focused transducer from DL-47 piezoelectric ceramic to stimulate the retina of Royal College of Surgeons blind rats, achieving a spatial resolution of 250 μm and a frame rate of 5 Hz, as verified by neural responses recorded in the superior colliculus and primary visual cortex (V1)^[184]. Jiang *et al.* subsequently constructed a 32-pixel flexible piezoelectric retinal array using a 1-3 PMN-PT/epoxy composite^[113]. The independently addressable pixels provided tunable outputs ranging from 0 to 4.3 V and from 0 to 22.6 mW cm^{-2} , encompassing the previously reported retinal stimulation charge threshold of 1–50 nC, and elicited spatially patterned neural responses in *ex vivo* retinas. Lu *et al.* developed a 16×16 , 4.5-MHz integrated imaging-stimulation array that enabled ocular localization, stimulation with arbitrary two-dimensional patterns, and mapping of superior colliculus responses in blind rats^[185]. The neural response maps exhibited a similarity of 0.91 ± 0.03 to the input patterns. When an independent 20-MHz focused transducer was used, the lateral full width at half maximum was further reduced to 81 μm . In the auditory domain, Yüksel *et al.* fabricated an eight-channel microelectromechanical systems transducer from thin-film PZT, covering a frequency range of 250–5,000 Hz and generating an output of 50.7 mVpp at 100 dB sound pressure level (SPL)^[186]. Uluşan *et al.* subsequently integrated a pulsed laser deposition-PZT front end with signal-conditioning circuitry and cochlear electrodes^[187]. At sound-pressure levels of 45–100 dB SPL, the system generated biphasic pulses of 250 μA^{-1} mA and elicited electrically evoked auditory brainstem responses in guinea pigs. Chang *et al.* fabricated a helical acoustic front end from aligned PVDF-TrFE/BaTiO₃ nanofibers, achieving 96% accuracy in sound-source direction recognition^[188]. Collectively, the visual systems established a foundation for spatial encoding, whereas the auditory systems advanced frequency-channel separation and integrated front-end sensing^[189]. Current evidence therefore indicates that visual interfaces have achieved pixelated retinal stimulation, while auditory interfaces have completed the functional pathway from acoustoelectric sensing to neural output.

Somatosensory interfaces

Somatosensory interfaces convert pressure, strain, and slip into neurally interpretable signals through PENG-based transduction and pulse encoding, with applications progressing from unit-level sensing toward tactile restoration and prosthetic control^[190–192]. Kumar *et al.* constructed a piezoelectric synapse based on a NiO/ZnO heterostructure, in which mechanical strain modulated excitatory and inhibitory responses as well as short-term plasticity, thereby integrating tactile sensing with synaptic computation within a single functional unit^[193]. Zhang *et al.* coupled a passive piezoelectric element to an NbOx Mott memristor to construct an artificial afferent nerve. The system exhibited a threshold voltage of approximately 2.05 V, consumed 38 pJ per pulse, and generated pulse trains spanning 0–1,100 Hz, thereby encoding pressure intensity as firing frequency^[194]. Birkoben *et al.* fabricated a PiezoFET using a 500-nm Al_{0.73}Sc_{0.27}N film. Under a load of approximately 50 mN, the device produced adaptive pulses with a progressively decreasing firing frequency, mimicking the physiological adaptation to sustained tactile pressure^[195]. Waseem *et al.* constructed rapidly and slowly adapting piezoelectric mechanoreceptors using intrinsic and Mg-doped GaN nanowires. At 1 Hz, the devices exhibited response and recovery times of 11 and 18 ms, respectively, and distinguished static grasping from dynamic texture exploration^[196]. Wang *et al.* subsequently integrated PLLA, thin-film transistor (TFT), and PVDF-TrFE arrays to detect pressure, temperature, and slip, enabling the reconstruction of contact location, object shape, and surface texture^[197]. Li *et al.* developed a tactile scanner by integrating a 10×10 PVDF array with TFT-based neuromorphic circuitry. At a scanning speed of 15 mm s^{-1} , the system classified five texture categories with an accuracy of 85% and achieved a correlation coefficient of 0.68 between acquired and reproduced tactile signals. Moreover, more than 75% of participants successfully distinguished the reconstructed levels of surface roughness^[198]. For prosthetic control, Jiang *et al.* fabricated a flexible PENG from porous P(VDF-TrFE), achieving a sensitivity of 38.4 mV kPa^{-1} and stable performance after 10,000 loading cycles. The device converted muscle deformation into control commands for robotic-hand grasping^[199]. Wang *et al.* further developed a dual-modal electronic skin by integrating PVDF-TrFE/2DBP with a TFT array^[200]. Across a pressure range of 0–310 kPa, the system achieved a

sensitivity of 3.2 mV kPa^{-1} , a spatial resolution of $50 \text{ }\mu\text{m}$, and a response time of 40 ms , while maintaining stable performance after 1,500 pressure-loading cycles and 4,000 bending cycles^[201]. These interfaces have already enabled mechanical sensing, event encoding, and motor control. However, current studies remain largely confined to neuromorphic circuits, robotic systems, and body-surface interactions^[202]. Future research should prioritize long-term, bidirectional closed-loop validation that integrates sensory detection, implanted stimulation of sensory nerves, and *in vivo* perceptual and behavioral outcomes.

CONCLUSIONS AND PERSPECTIVES

PENGs have advanced from energy-harvesting demonstrations to functional neural interfaces across the peripheral, central, and autonomic nervous systems, and cellular and animal studies have established their capacity to promote axonal regeneration, remyelination, and functional recovery. A growing number of systems now integrate sensing, closed-loop control, and biodegradable construction, yet the field has not produced a single clinical trial, and the reasons are instructive. Most studies still characterize devices by open-circuit voltage, short-circuit current, or power density, parameters that describe the generator rather than the stimulus. The biological response is governed by the charge delivered per phase, the charge density at the electrode-tissue interface, the field strength at the target, and the temporal structure of the pulse train, none of which can be recovered from a single voltage reading. Because PENGs, TENGs, magnetoelectric generators, and biofuel cells differ fundamentally in output impedance, waveform, and load dependence, their power figures are not interchangeable, and device-level output cannot be equated with the biologically effective dose^[93-95]. The field therefore needs a reporting framework in which delivered charge, charge density, field strength, pulse parameters, cumulative dose, and electrode characteristics are stated together with functional outcomes and anchored to the safety limits established for conventional neurostimulation, in particular the Shannon criterion and the charge-injection capacities of electrode materials^[114,116,117]. The checklist summarized in Table 3 is intended to provide such a framework, so that dose-response relationships become quantitatively comparable across studies and therapeutic windows can be defined before clinical protocols are designed.

Biodegradability illustrates a second, subtler tension. Resorbable PENGs eliminate the need for device removal, but the device must retain its piezoelectric output for the duration of the therapeutic window and then clear from the tissue without adverse effects. PLLA-based systems typically degrade over 12-24 months, whereas nerve regeneration in most experimental models requires electrical stimulation for only 3-6 months^[203]. A device that loses its output before repair is complete fails therapeutically; one that persists beyond recovery leaves unnecessary foreign material in the body. Degradation kinetics can in principle be programmed to match the therapeutic window by tuning molecular weight, crystallinity, copolymer composition, crosslinking density, and encapsulation design, yet such programming remains largely empirical, and chronic studies must confront failure modes that are rarely reported, including encapsulation breakdown, electrode corrosion and delamination, and interfacial failure under cyclic mechanical loading, each of which can terminate function before nominal degradation is complete. Reporting degradation profiles, failure modes, and functional lifetime together would make the reliability of biodegradable PENGs directly comparable across studies and would allow device design to be matched to the repair process rather than to the material alone.

Extending PENGs from peripheral nerve repair to central neuromodulation raises the question of targeting. Deep brain regions, the spinal cord, and autonomic ganglia are heterogeneous in structure and function, and a diffusing electric field can readily activate off-target circuits. Focused ultrasound offers a spatially confined energy source, but acoustic access to deep structures is constrained by attenuation and phase aberration through the skull and intervening tissue, and stimulation parameters, including frequency, current density, and pulse width, remain difficult to regulate precisely without auxiliary circuitry. Progress will require the

integration of acoustic-field modeling, image-guided targeting, and localized electric-field simulation with real-time electrophysiological feedback, so that the activated tissue volume can be predicted and verified. The chronic environment imposes further constraints: fluctuations in pH, ionic strength, enzymatic activity, and mechanical loading alter material structure and interfacial properties, so that *in vitro* performance frequently diverges from *in vivo* behavior. Standardized manufacturing procedures, quality-control specifications, and unified validation protocols are therefore prerequisites for consistent electromechanical performance, mechanical compliance, and long-term reliability.

The path forward is likely to be multimodal and closed-loop rather than a refinement of individual devices. Because no single transduction mechanism simultaneously provides high power and deep-tissue access, hybrid systems combining piezoelectric, triboelectric, magnetomechanical, and electromagnetic-induction elements with biofuel cells and microscale energy storage offer a rational response to the intermittency of physiological motion and the limited reach of external triggers^[93–95]. Intelligent energy management can match harvested energy to stimulation demand, and closed-loop feedback can adjust stimulation parameters according to neural activity and tissue state, allowing device output to track biological response in real time. Mechanistically, the pathways through which piezoelectric stimulation acts, including voltage-gated channel recruitment, Ca²⁺ signaling, and downstream transcriptional programs, are understood in outline, but the interconnected neural, immune, and metabolic responses remain largely uncharted, and transcriptomic, proteomic, and metabolomic analyses will be needed to map them. Computational design that couples finite-element modeling of electromechanical and acoustic fields with machine-learning-based optimization could reduce the empirical iteration now required to match device output to a defined dose. The convergence of PENGs with iontronic logic and 2D-material biosensors points toward adaptive interfaces that combine energy harvesting, neural-state sensing, and closed-loop decision-making in a single biocompatible platform^[204,205]. Integration with genetic, immune, and metabolic reprogramming, including sonogenetics, immune-modulatory vagus stimulation, and bioenergetic activation, offers therapeutic possibilities beyond electrical excitation alone. With coordinated progress in materials science, neurobiology, and clinical engineering, PENGs are well positioned to move from proof-of-concept devices toward clinically valuable self-powered neural interfaces.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception and design of the study: Li, S.; Zhang, K.; Zhang, H.

Performed literature search, data organization and initial draft preparation: Li, S.; Li, W.; Yang, J.

Revised and polished the manuscript: Chen, S.; Li, W.

Provided funding acquisition and supervision: Zhang, K.; Zhang, H.

All authors read and approved the final manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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