

REVIEW

Electrospun Nanofibrous Scaffolds for Peripheral Nerve Regeneration: From Biomaterial Design to Multimodal Therapeutic Integration

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ABSTRACT

Electrospinning technology has shown great potential in the field of peripheral nerve injury repair due to its biomimetic fiber structure, controllable degradability, and multi-functional loading capacity. This article reviews the application of electrospinning technology in nerve repair, with a focus on discussing its research progress in material modification, scaffold design and construction, and multi-technology collaborative repair. Electrospinning scaffolds can optimize the biocompatibility, cell adhesion, and mechanical properties of nerve conduits through physical and chemical modifications, or through the design and construction of scaffolds. At the same time, by combining technologies such as electrical stimulation, drug-loaded sustained-release, hydrogel filling, and 3D printing, a multi-functional synergistic effect can be achieved. It demonstrates significant advantages in structural design, biological activity regulation, and functional regeneration, accelerating the repair and regeneration of nerves after injury. However, it also faces challenges such as preparation efficiency and clinical transformation verification. The future development direction focuses on achieving precise regulation of neural regeneration and functional recovery.

1 | Introduction

Peripheral nerve system (PNS) injury is a common disease with a high incidence in the world. The causes of peripheral nerve injury can be classified as: traction injuries, incisional trauma, compressive lesions, iatrogenic injection injuries, and other medically-induced neuropathies. Based on the depth of injury to the neural structure, the modified Seddon–Sunderland classification system is clinically utilized to categorize it into three distinct grades: neurapraxia, axonotmesis, and neurotmesis [1]. Peripheral nervous system injuries typically result in a range of neurological dysfunctions, including diminished or lost motor

and sensory functions in the corresponding innervated regions. This not only compromises patients' quality of life but may also lead to long-term disability, imposing a significant disease burden on both individuals and society.

The gold-standard technique for peripheral nerve injury management involves tension-free epineurial suturing through microsurgical approximation of severed nerve endings [2]. However, this method encounters substantial limitations when addressing long-segment nerve defects (>10 mm), where achieving tension-free coaptation becomes anatomically constrained. In such cases, end-to-end neuroorrhaphy remains the primary repair method,

though its application is contingent upon maintaining optimal anastomotic tension. When excessive tension precludes direct repair, autologous nerve grafting emerges as the conventional salvage procedure [3]. Nevertheless, this approach carries inherent donor-site complications including: functional impairment at the harvest site, restricted donor nerve availability, caliber mismatch between donor and recipient nerves, iatrogenic neuroma formation. Allogeneic transplantation, while circumventing donor scarcity issues, introduces immunological barriers such as graft rejection and mandatory immunosuppression regimens [4]. These pathophysiological constraints fundamentally limit the clinical efficacy of both autograft and allograft strategies.

An optimal neural scaffold must fundamentally satisfy four interlinked design criteria. Foremost is cytocompatibility, requiring non-cytotoxic substrates that actively support neural cell adhesion, proliferation, and neuritogenesis through biomimetic extracellular matrix interactions. Secondly, precisely engineered biodegradation kinetics must synchronize with tissue regeneration timelines (typically 8–12 weeks for peripheral nerves), progressively yielding spatial accommodation for axonal ingrowth while avoiding premature structural collapse. Mechanically, scaffolds require tensile strength modulation (0.1–2 MPa) to match native neural tissue compliance while maintaining structural integrity against surgical handling stresses. Architecturally, hierarchical topology combining submicron fiber dimensions (100–1000 nm), controlled porosity (60%–80% void fraction), and anisotropic alignment creates contact guidance cues directing axonal pathfinding.

At present, electrospinning technology is mainly divided into two categories: solution electrospinning and melt electrospinning. It uses high-voltage electric field force to stretch polymer solutions or melts into fibers with diameters ranging from nanometers to micrometers. Among them, conjugate spinning, coaxial spinning, and centrifugal spinning are several important spinning techniques. Zhang et al. used conjugate spinning to prepare materials [5]. Conjugate spinning, also known as parallel spinning, has two independent spinning liquid channels at the spinneret. The solutions come into contact side by side at the outlet, jointly forming a Taylor cone. During the jet flight, the two solutions are usually not completely mixed, ultimately resulting in a structure with two independent regions or interlocking segments within a single fiber. This method is applicable when two polymer solutions are immiscible or have different properties, and is typically used to construct biological scaffolds with self-curling or orientation functions, as well as dual-function sensing or catalytic materials. Coaxial electrospinning uses coaxial needles (with two layers of inner and outer tubes), and the resulting fibers have a clear “core-shell” structure. The core layer and the shell layer are separated in both the axial and radial directions of the fibers and theoretically do not mix with each other. Zhang et al. prepared materials by coaxial electrospinning [6]. This method is mainly applied to encapsulate drugs, growth factors, etc. that are prone to inactivation or require controlled release in the core layer, which can effectively protect the core material and achieve sustained release. Centrifugal electrospinning relies on the centrifugal force generated by high-speed rotation as the main driving force. It usually does not require a high-voltage electric field, has extremely high production efficiency, good safety, and is easy to be produced on a large scale [7].

The solvent must be capable of fully dissolving or uniformly dispersing the polymer to form a homogeneous solution with an appropriate degree of chain entanglement. Compared with polymers, solvents with overly strong volatility (such as dichloromethane and chloroform) are prone to cause the formation of flat or banded fibers or the appearance of porous structures on the fiber surface. However, solvents with too weak volatility (such as DMF and NMP) are prone to cause fiber fusion or uneven fiber diameters. When the voltage rises, the electric field force acting on the jet intensifies, and the tensile effect becomes more intense, which usually helps to reduce the fiber diameter. However, excessively high voltage may cause unstable jets, resulting in uneven diameter distribution or more defects. The concentration will directly affect the viscosity and surface tension of the solution. When the concentration is too low, the jet is prone to fracture and form bead-like defects. If the concentration is too high, it may lead to difficulties in jet stretching, an increase in fiber diameter, and even clogging of the needle tip. If the spinning distance is too short, it is easy for the fibers to stick together, flatten or fuse into a film, and the diameter will also be relatively thick. Conversely, if the distance is too long, the fibers will dry out and break, and the collection efficiency will decline. The spinning distance is closely coupled with parameters such as voltage and solution evaporation rate, jointly determining the entire process of the jet from formation to deposition. Emerging electrospinning technologies now enable fabrication of such multifunctional constructs through programmable deposition of piezoelectric nanofibers, 3D biomimetic architectures replicating endoneurial microenvironments, and neurotrophic gradient-incorporated surfaces. These advanced scaffolds demonstrate enhanced regenerative outcomes via three synergistic mechanisms: contact guidance-mediated directional neurite extension, haptotactic promotion of Schwann cell migration along aligned fibers, and spatiotemporal delivery of neuroregulatory molecules from biodegradable carriers [8, 9].

2 | Nerve Repair and Regeneration

2.1 | Nerve Repair Processes

Peripheral nerve regeneration and functional recovery following injury progress through distinct biological phases. The acute injury response initiates when transected nerve bundles trigger Schwann cells to undergo phenotypic reprogramming-dissociating their myelin sheaths, transitioning into a reparative phenotype, and detaching from distal ganglia to facilitate structural breakdown of damaged distal nerves. This transitions into the inflammatory clearance phase where injury-mediated signals recruit circulating monocytes that differentiate into tissue-resident macrophages. These immune effectors collaborate with repair-activated Schwann cells to phagocytose axonal debris and myelin fragments, establishing efficient microenvironmental clearance. Between post-injury days 3–7, the homeostasis restoration phase emerges as inflammatory mediators subside, clearance-completed macrophages undergo circulatory egress or programmed apoptosis, and tissue dynamics stabilize. Subsequently, the regeneration guidance phase commences with reparative Schwann cells establishing aligned Büngner bands through directional migration. These cellular

scaffolds serve dual functions: providing physical guidance channels for axonal regrowth while secreting neurotrophic factors (e.g., NGF, BDNF) to sustain neuronal viability and stimulate axonal elongation. The final myelination phase completes functional restoration as Schwann cells remyelinate regenerated axons traversing the injury bridge, reconstructing saltatory conduction nodes through segmental myelin ensheathment. This intricate cascade ultimately restores neuroelectrical signaling fidelity and enables gradual recovery of sensorimotor functions [10–12].

2.2 | Interaction of Axons With Biomaterials

Axons, as specialized cylindrical extensions originating from the neuronal soma, are exclusive to neural cells and function as the primary conduits for transmitting electrochemical impulses (i.e., action potentials) to postsynaptic targets, including neurons, muscle fibers, and secretory glands. These structures orchestrate critical roles in propagating neural signals, dynamically integrating synaptic inputs, sustaining neurophysiological homeostasis, and serving as the central pathway for interneuronal communication while forming the fundamental structural basis for synaptic plasticity and neural circuitry organization [13]. The extracellular matrix (ECM) protein serves as the central regulatory element orchestrating axonal regeneration processes. Both long-segment peripheral nerve injuries (PNI) and spinal cord injuries (SCI) exhibit shared pathophysiological characteristics involving insufficient biomechanical support and inadequate provision of molecular guidance cues for regenerating axons. In PNI, the structural collapse of collagen networks within the endoneurial ECM leads to disrupted axonal pathfinding and compromised regeneration efficiency due to loss of topographical guidance cues [14]. Conversely, in SCI pathologies, the cystic lesion microenvironment demonstrates inhibitory bioactivity characterized by aberrant CSPG deposition and inflammatory signaling cascades that actively suppress axonal extension through growth cone collapse mechanisms [15]. These distinct yet complementary failure modes in ECM organization-structural disintegration in PNI versus biochemical inhibition in SCI-collectively constitute major barriers to functional nervous system regeneration. This underscores the critical importance of ECM scaffolding properties and signaling composition in neural repair paradigms. Consequently, PNI and SCI interventions have driven significant efforts toward developing bioengineered neural conduits as synthetic ECM-mimetic alternatives. Electrospinning has emerged as a particularly promising technology for fabricating anisotropic nanofibrous scaffolds that recapitulate the hierarchical microarchitecture of native neural ECM. Compared to conventional textile techniques, electrospinning offers superior process control through adjustable electric field parameters and polymer solution properties, enabling precise modulation of fiber diameter, alignment, surface topography, and porosity [16]. The resulting 3D interconnected porous matrices exhibit exceptional biomimicry, featuring nanogrooved surface topographies that guide axonal extension via contact guidance. When functionalized with neurotrophic factors and neural progenitor cells, these scaffolds synergistically deliver topographical and biochemical cues to enhance Schwann cell migration, neurite orientation, and myelination. The technology's scalability and compatibility with biodegradable polymers facilitate customized designs for

bridging critical-length nerve gaps in PNI or creating permissive microenvironments across SCI lesion cavities-offering substantial advantages over autograft-dependent approaches. Matrix materials with neural affinity further ensure biocompatibility and tailored mechanical properties [17]. Surface modifications can confer specialized characteristics (e.g., electrical conductivity, hydrophilicity), enhance biocompatibility, and improve mechanical properties through functionalization or additives supporting neuroregeneration [18]. Such modifications also optimize in vivo degradation kinetics, enable sustained release of neurotrophic factors, and promote neural cell adhesion, proliferation, and differentiation [19]. Implanted at SCI sites, these scaffolds provide physical support to mitigate tissue collapse and create permissive growth channels as they degrade. Critically, they regulate the regenerative microenvironment by promoting angiogenesis, suppressing excessive inflammation, and inhibiting glial scarring. Electrospun fibers exhibit high purity, structural homogeneity, and tissue-like architecture for enhanced biocompatibility, positioning these scaffolds as highly promising therapeutic tools for neural repair (Figure 1).

Innovative strategies in biomaterials leverage biomimetic design to mimic the topology and biochemical properties of natural ECM, thereby providing functional attachment interfaces for axons. Scaffolds, such as collagen hydrogels, can be fabricated directly using ECM components like collagen and laminin, or ECM proteins can be modified onto synthetic material surfaces to enhance cell adhesion and axon guidance [20]. Numerous types of biomaterials are currently used in scaffold preparation for repairing PNIs and SCIs, primarily categorized as natural biomaterials, synthetic biomaterials, and composites. Natural biomaterials, a class of naturally occurring polymeric materials, are widely employed in biomedical applications due to their easy availability, resource abundance, biocompatibility, biodegradability, structural diversity, and weak antigenicity. Commonly used natural biomaterials for PNI and SCI scaffold repair include collagen, alginate, chitosan, agarose, and hyaluronic acid [21]. Among these, collagen hydrogels and laminin hydrogels find various tissue engineering applications. While characterized by biocompatibility, degradability, and non-toxicity, natural biomaterials also exhibit drawbacks such as poor mechanical properties, instability, and rapid degradation. Synthetic biomaterials, including poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and polyethylene glycol (PEG), offer tunable properties such as porosity, hardness, and degradation rates that can be tailored to specific tissue requirements-advantages often less achievable with natural biomaterials. The research by Cardoso et al. [22] indicates that the synergistic treatment of PLA conduit and inosine can promote the formation of myelin sheaths in nerve fibers. Among them, PLA conduit has low toxicity, high biocompatibility and absorbability, and also plays a good role in traction and support. However, due to their lack of inherent integrin-binding molecules, synthetic biomaterials frequently require ECM coatings or surface modifications. Electrospinning technology enables the fabrication of synthetic biomaterial-based scaffolds (e.g., PLA, PLGA, PCL), which hold significant promise for SCI repair [23]. Composites combine the benefits of both material classes; for instance, 3D polycaprolactone/gelatin/iron oxide nanofiber scaffolds exhibit mechanical stability, biodegradability, optimal porosity, and accelerated neural differentiation of olfactory ecto-mesenchymal stem cells (OE-MSCs) [24].

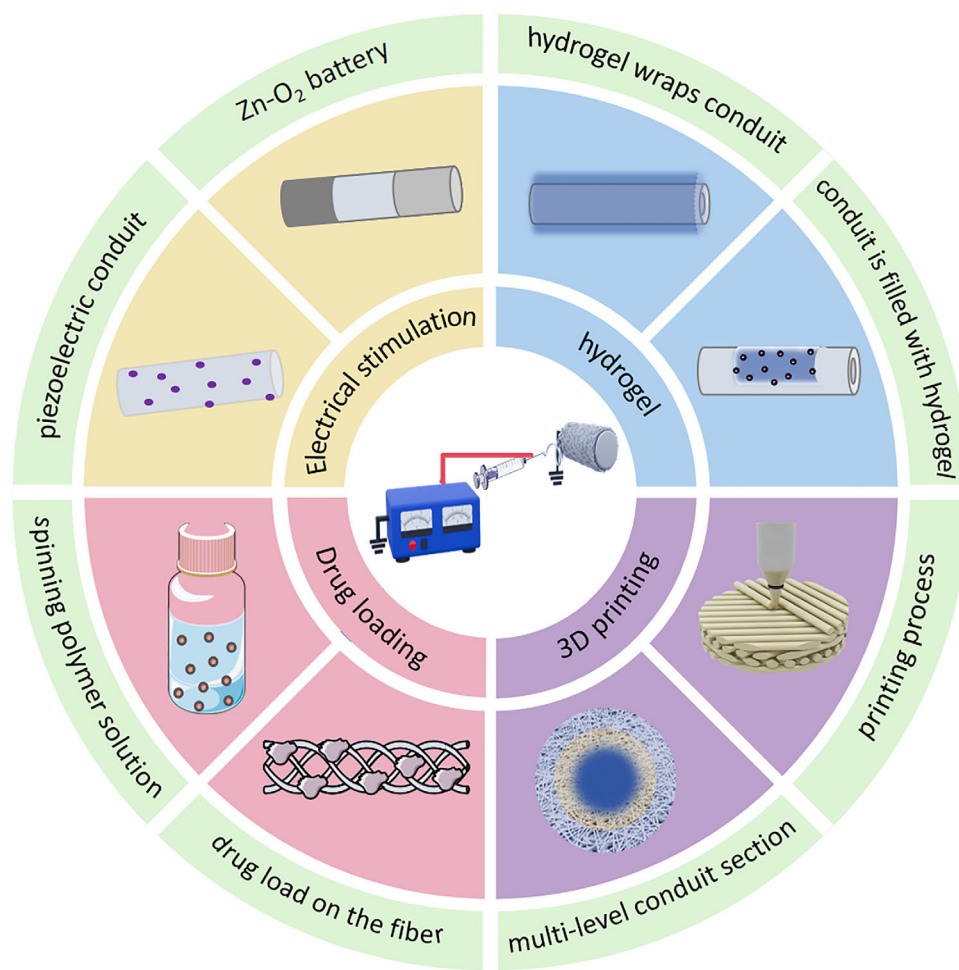


FIGURE 1 | The combination of electrospinning scaffold with electrical stimulation, drug-loaded sustained release, hydrogel filling, and 3D printing technology.

3 | Modification of Neuroelectrospun Scaffold Materials

3.1 | Selection of Neuroelectrospun Scaffold Materials

The selection of materials for neural electrospinning scaffolds requires prioritization of paramount biocompatibility, followed by comprehensive evaluation of degradation kinetics, immunogenicity of degradation byproducts, and fabrication feasibility [25–35]. These biomaterials reveal distinct comparative advantages: Natural biomaterials demonstrate superior biocompatibility, bioactivity, and neuroregenerative potential, yet suffer from inadequate mechanical strength and elevated production costs. Conversely, synthetic biomaterials offer enhanced mechanical properties and cost-effectiveness but necessitate surface modifications to achieve the requisite bioactivity and neural regeneration outcomes (Table 1).

Therefore, material selection for neural scaffolds should strategically combine natural and synthetic biomaterials to achieve synergistic complementarity, enabling holistic optimization of biocompatibility, bioactivity, degradation kinetics, and mechanical properties. Composite scaffolds effectively balance bioactivity with structural integrity while allowing degradation tuning

through surface modifications. For example, Zhao et al. fabricated polypyrrole/silk fibroin (PPy/SF) conductive scaffolds via integrated 3D-bioprinting and electrospinning. Under electrical stimulation, these constructs demonstrated enhanced neuronal viability, proliferation, and migration with concurrent upregulation of neurotrophic factors—validating composites' capacity to potentiate peripheral nerve repair [36].

3.2 | Modification of Neural Electrospinning Scaffold Materials

Electrospun nanofibrous neural scaffolds show significant potential, yet their surface properties (e.g., hydrophilicity, bioactivity, and mechanical characteristics) often require optimization to better support neuronal cell adhesion, proliferation, migration, and axonal extension. Surface modification techniques enhance material biocompatibility, cell adhesion, bioactivity, and mechanical properties through physical or chemical approaches [37]. Physical modification offers operational simplicity, avoids chemical reagents, and broad material applicability, though its effects are less stable with risks of modification layer detachment; whereas chemical modification provides stable functionalization with precise surface control, albeit involving more complex reaction conditions and potentially toxic reagents.

TABLE 1 | Comparison of neural electrospinning scaffold materials.

Categorization	Name	Source (of information etc)	Biocompatibility	Degradability	Mechanical property	whether it favors nerve cell growth (bioactivity)	Reference
Natural biological material	Collagen	Derived from animal connective tissue, e.g., bovine, porcine, fish, etc.	Highly biocompatible, low immunogenicity	Degradable, an enzyme-driven process	Weak mechanical properties, need to be modified to enhance	Favors nerve cell growth and promotes axon extension	[25]
	Hyaluronic acid	Derived from animal tissues, e.g., cockles, cow's eyes, etc.	Highly biocompatible, widely available in the human body	Degradable, with a relatively fast degradation rate	Weak mechanical properties, need to be modified to enhance	Favors nerve cell growth and promotes cell migration	[26]
	Fibrous protein	Derived from fibrinogen in the blood	High biocompatibility, promoting tissue regeneration	Degradation is rapid and usually complete within a few days	Strong ductility and toughness	Favors nerve cell growth and promotes cell adhesion	[27]
	Gelatine	Derived from collagen hydrolysis products	Highly biocompatible and easily absorbed by the body	Degradable, with a relatively fast degradation rate	Mechanical properties of weak, need to modification	Favors nerve cell growth and promotes cell adhesion	[28]
	Filaggrin	Silk from silkworms	Highly biocompatible, supports cellular activity	Degradable, with a relatively fast degradation rate	Good mechanical properties, with high strength and flexibility	Favors nerve cell growth and promotes cell adhesion	[29]
Synthetic Biomaterials	Chitosan	Derived from the shells of crustaceans	Highly biocompatible with antimicrobial properties	Degradable, slow degradation rate	Mechanical properties are good, but still need to be modified and strengthened	Favors nerve cell growth and has antimicrobial properties	[30]
	Polycaprolactone (PCL)	Chemical synthesis	Biocompatible, but not as good as natural materials	Degradable, slow degradation rate	Good toughness, high ductility, but the modulus is usually low	Requires surface modification to promote nerve cell growth	[31]

(Continues)

TABLE 1 | (Continued)

Categorization	Name	Source (of information etc)	Biocompatibility	Degradability	Mechanical property	whether it favors nerve cell growth (bioactivity)	Reference
	Poly(lactic acid (PLA)	Chemical synthesis	Biocompatible, but degradation products may cause inflammation	Degradable, medium rate of degradation	Better mechanical properties, high rigidity	Requires surface modification to promote nerve cell growth	[32]
	poly(lactic acid-hydroxyacetic acid copolymer (PLGA)	Chemical synthesis	Better biocompatibility and adjustable degradation rate	Degradable with adjustable degradation rate	Better mechanical properties and adjustability	Requires surface modification to promote nerve cell growth	[33]
	Polyurethane (PU)	Chemical synthesis	Better biocompatibility, but may cause an immune response	Degradable, slow degradation rate	Better mechanical properties, high elasticity	Requires surface modification to promote nerve cell growth	[34]
	Polypyrrole (PPy)	Chemical synthesis	Better biocompatibility	Degradable, slow degradation rate	Good mechanical properties, with a certain degree of flexibility	Favors the growth of nerve cells and can promote synaptic extension	[35]

3.2.1 | Physical Modifications

Plasma treatment introduces reactive groups (e.g., hydroxyl, carboxyl) to enhance material surface hydrophilicity and bioactivity. Guo et al. demonstrated that atmospheric pressure plasma jet (APPJ) treatment of PLA/polyaniline solutions improves their viscosity and electrical conductivity. Separately, scaffolds fabricated via electrospinning and treated with nitrogen dielectric barrier discharge (DBD) exhibited significantly improved surface wettability while incorporating C–N and N–C=O functional groups onto nanofibers; these plasma-modified neural electrospun scaffolds subsequently subjected to APPJ treatment promoted neural synapse extension and neuronal network formation among PC-12 cell clusters [38]. This technique offers operational simplicity without chemical introduction and broad material applicability, though its effects may diminish with temporal decay.

Surface coating enhances material biocompatibility and cell affinity through deposition of bioactive molecules (e.g., collagen, hyaluronic acid, chitosan). Pi et al. fabricated novel aligned conductive PCL/CNT scaffolds via electrospinning, then modified surfaces with polydopamine (PDA) and loaded brain-derived neurotrophic factor (BDNF) to create PCL/CNT-PDA-BDNF fiber scaffolds capable of sustained BDNF release for 28 days. In vitro and in vivo experiments confirmed that these scaffolds effectively promoted sciatic nerve regeneration and functional recovery [39]. This technique enables highly flexible introduction of diverse bioactive molecules, though coatings may exhibit inhomogeneous deposition and potential instability.

Physical adsorption is a simple surface modification technique where a biomaterial substrate is immersed in a solution containing ECM proteins or other biomolecules. These biomolecules bind to the substrate via non-covalent interactions—such as electrostatic forces, hydrophobic bonds, van der Waals interactions, or hydrogen bonding—immobilizing biologically active molecules (e.g., growth factors, peptides) on the material surface [40]. Chen et al. demonstrated this method by using a laminin solution to physically adsorb onto electrostatically spun silica nanofiber scaffolds (SNF2), also employing covalent attachment; they confirmed that laminin incorporation lengthened PC12 cells upon stimulation, benefiting nerve growth and repair [41]. While physical adsorption applies to a wide range of biomolecules, adsorbed molecules may be susceptible to shedding.

3.2.2 | Chemical Modifications

Surface grafting chemically attaches functional molecules (e.g., poly(ethylene glycol), peptides, polysaccharides) to material surfaces to enhance biocompatibility and bioactivity. Wang et al. prepared chitosan/gelatin porous scaffolds incorporated with conductive poly(3,4-ethylenedioxythiophene) nanoparticles (PEDOT-NPs) through interfacial static polymerization: chitosan/gelatin hydrogels were submerged in aqueous ammonium persulfate solution, followed by immersion in cyclohexane containing EDOT monomer. During polymerization, PEDOT-NPs formed in situ via hydrogen bonding and grafted onto the substrate surface, resulting in scaffolds with improved hydrophilicity,

thermal stability, electrical conductivity, and mechanical properties that promoted PC12 cell adhesion and differentiation [42]. While surface grafting provides stable modification and enables diverse functionalization, its reaction conditions can be complex and may require additional chemical reagents.

Chemical cross-linking enhances material surface stability, mechanical properties, and bioactivity. In one study, a double-crosslinked hydrogel (o-CSMA-E) was developed by combining porcine tendon extracellular matrix (ECM) biocompatibility with quaternary ammonium methacrylate chitosan's antimicrobial/conductive properties, creating a matrix that promotes axon growth and neural signaling. This hydrogel was incorporated into nanofiber PLLA-ZnO sheath scaffolds (ZnO@PLLA) to mimic natural nerve architecture, guiding cell growth and promoting nerve regeneration. In vivo studies demonstrated that the ZnO@PLLA/o-CSMA-E nerve conduit's core-sheath collaboration enhanced Schwann cell migration, myelin sheath formation, and motor function recovery in sciatic nerve-defect rats [43]. While chemical cross-linking significantly improves material stability and mechanical properties, most cross-linking agents exhibit cytotoxicity.

4 | Design and Construction of Neural Electrospinning Scaffolds

Neural electrospinning scaffolds enable tailored structural and functional properties through precise modulation of spinning parameters—including solution concentration, applied voltage, and collection distance—combined with post-treatments such as cross-linking or surface modification. These scaffolds must replicate the hierarchical organization of native nerves to provide essential topographical cues for axonal guidance and nutrient diffusion pathways, with common architectures including porous fiber matrices, hollow cores, and multichannel configurations.

Nanofiber surface topology critically regulates cell-substrate biointerfacial interactions through synergistic effects of interfacial roughness and specific surface area, particularly when engineered with porous architectures. This design modulates cellular adhesion stability and persistence [44], thereby influencing proliferation, migration, and differentiation dynamics. Liu et al. developed a porous electrospun PLGA nerve guidance conduit (NGC) with conductive coating optimization for enhanced peripheral nerve regeneration under electrical stimulation. Characterization of conductivity, surface morphology, and mechanical properties demonstrated that porous aligned fiber scaffolds significantly outperform non-porous aligned controls in neuroregenerative capacity, facilitating cellular signaling and promoting adsorption of neurite-promoting surface proteins [45].

Electrospun nerve guidance conduits (NGCs) serve as critical bridges across nerve gaps while stabilizing the regenerative microenvironment against inflammatory infiltration [46]. Without such topographical guidance, axons fail to regenerate across large defects despite permissive substrates and neurotrophic support. Early-generation hollow NGCs thus underwent biological modifications and structural optimizations to enhance

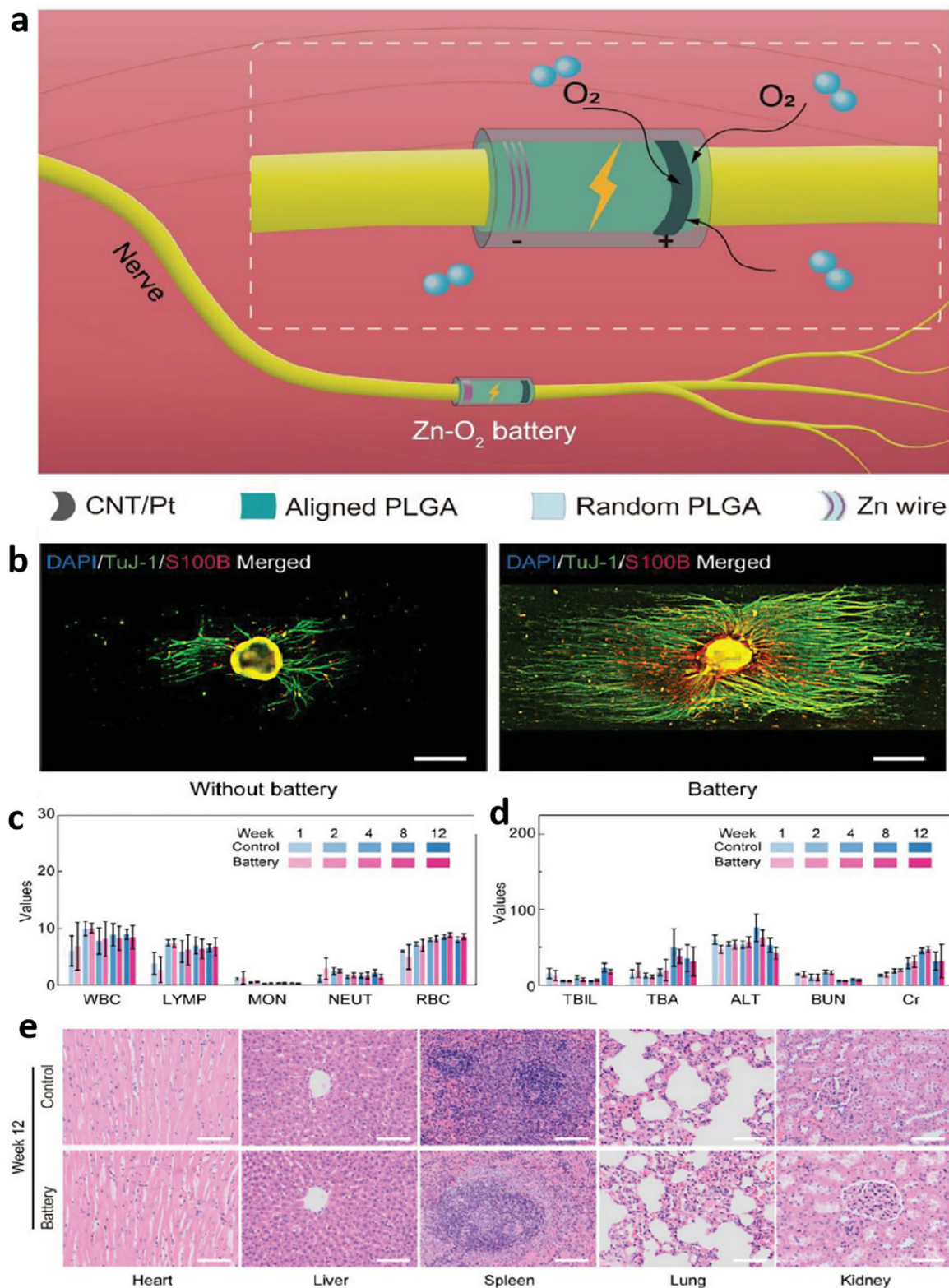


FIGURE 2 | Zn-O₂ battery integrated with conductive PLGA/ PPy electrospun scaffolds' introduction and related experiments. (a) Schematic illustration of tubular Zn-O₂ battery wrapping around nerve as an in vivo power supplier. (b) Confocal laser scanning microscopy images of cultured with common nerve conduit (without battery group) and Zn-O₂ battery-based nerve conduit (battery group) for 7 days, respectively. DAPI: blue, TuJ-1: green, S100B: red. Scale bar: 500 μm. (c,d) Blood routine test and blood chemical analysis of rats. $n = 6$. (e) H&E staining of Heart, Liver, Spleen, Lung, and Kidney from control and battery groups after 12 weeks. Scale bar, 100 μm. $n = 6$. Reproduced with permission [1]. Copyright 2023, Wiley.

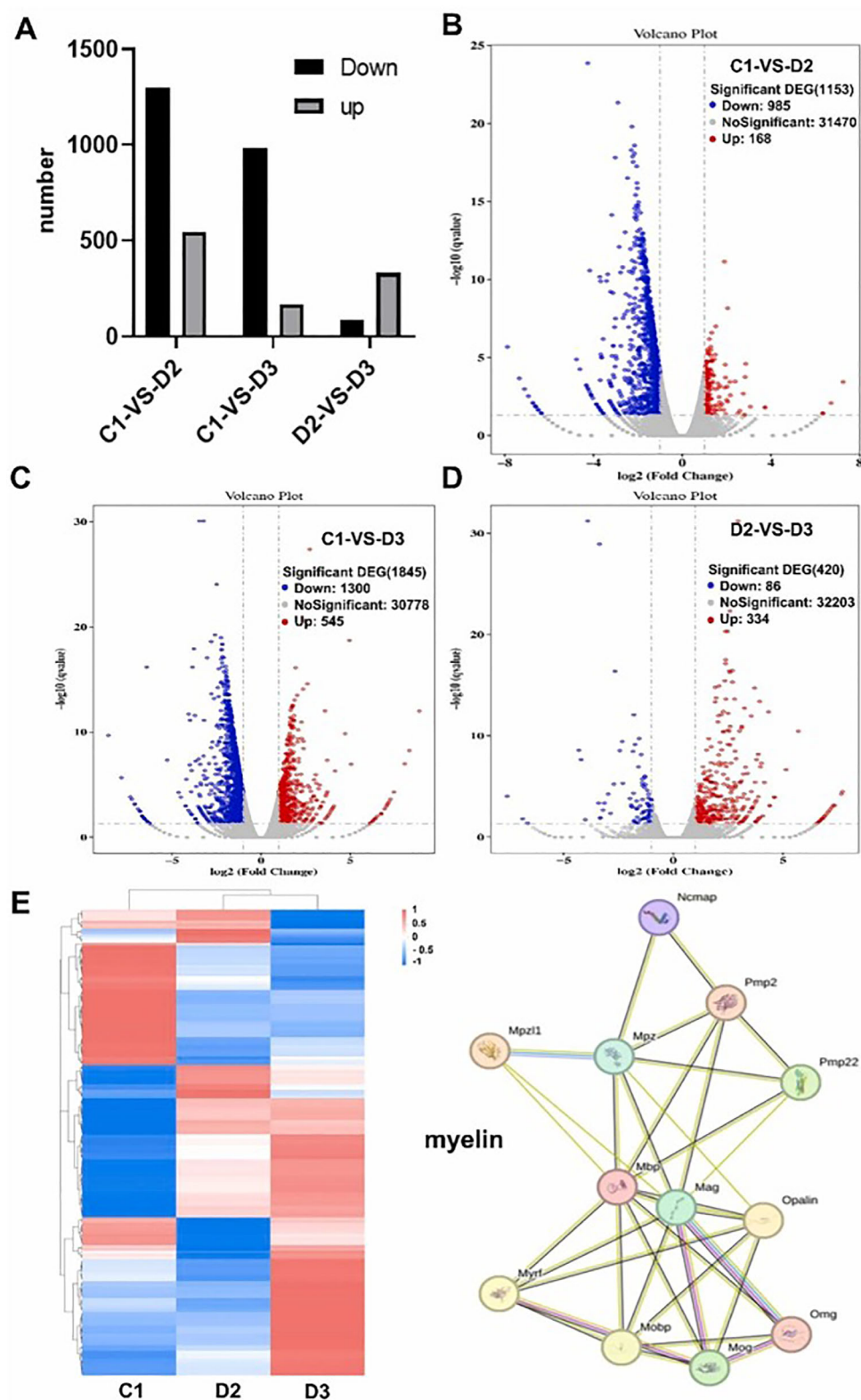


FIGURE 3 | Gene expression changes in Schwann cells under different magnetic field strengths and conditions were investigated using transcriptome sequencing analysis. (a) Number of upregulated and downregulated differentially expressed genes expression in samples with different conditions. C1-small round slide group, D2-no magnetic field with 3D scaffolding group, and D3-with magnetic field 3D scaffolding group. (b–d) Differential gene volcano plots. Red dots indicate up-regulated genes and blue dots indicate down-regulated genes. Significant differences in gene expression between C1 vs D2 (b), C1 vs D3 (c), and D2 vs D3 (d) groups are shown, respectively. (e) Differential gene clustering map with protein interaction network diagram. Expression clustering maps and protein interactions network maps of myelin formation-related genes are shown. Red color indicates highly expressed genes, and blue color indicates lowly expressed genes. The protein interaction network diagram shows the interactions between gene products. Reproduced with permission [2]. Copyright 2026, Elsevier.

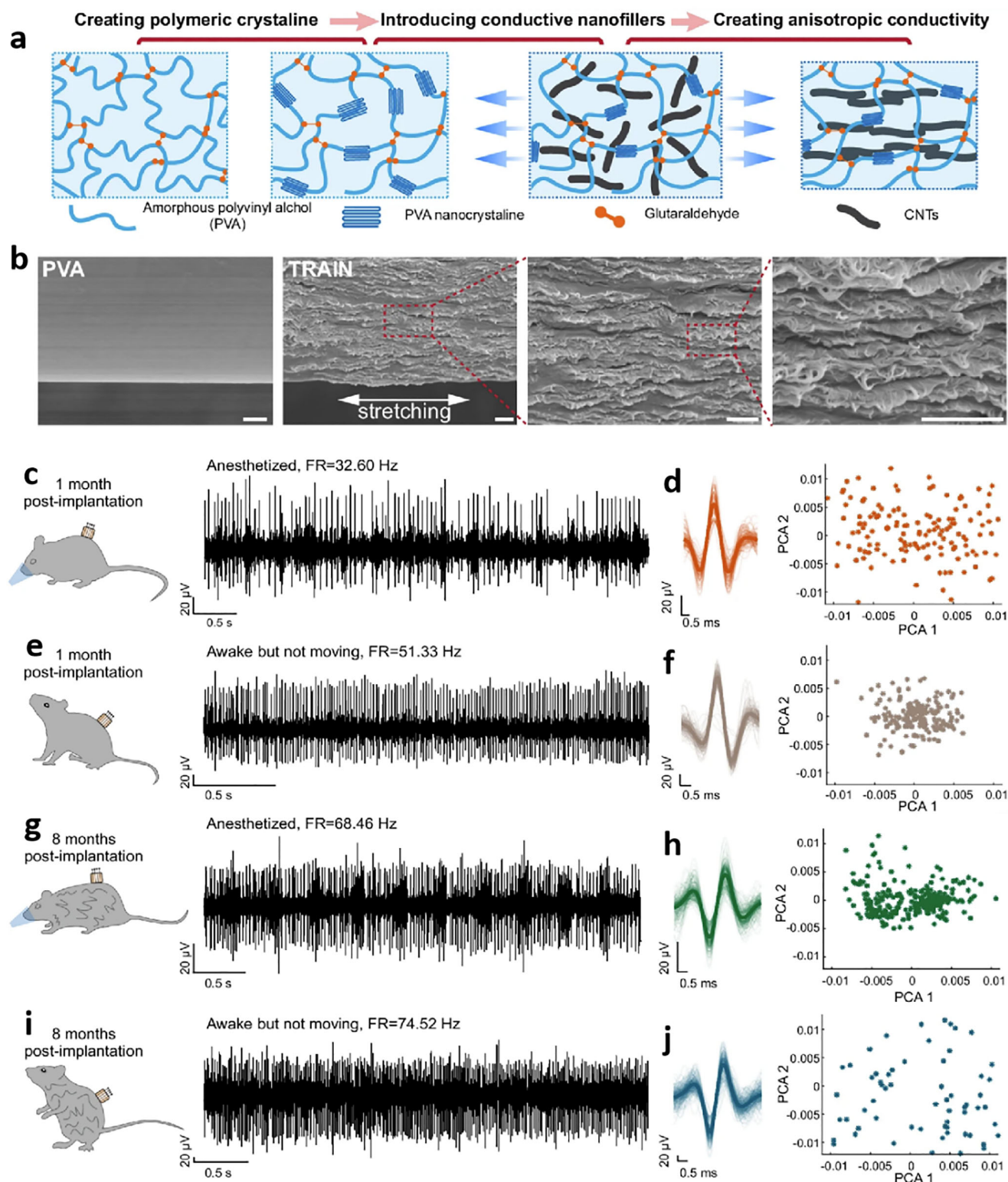


FIGURE 4 | PVA hydrogels can activate voltage-gating to promote calcium influx and the secretion of neurotrophic factors. (a) Schematics of microstructures in PVA hydrogels under different phases: chemical cross-linking, nanocrystalline growth, cyclic training after incorporation of CNTs in PVA, and realignment of CNTs in PVA hydrogel matrix. (b) Representative SEM images at the cross-section of untrained PVA hydrogel film and TRAIN CNTs (0.24 wt%)-PVA hydrogel film. Scale bars: 2 μ m. (c) Endogenous spinal cord neural activity recorded from a mouse 1-month post-implantation under anesthesia. Implantation under anesthesia. (d) Overlaid waveforms of single neuron spiking from (c) and principal component analysis (PCA) from (c) showing a cluster of single waveform is presented as mean $\pm$ s.d. (e) Spontaneous spinal cord neural activity recorded from an awake mouse 1-month post-implantation. (f) Overlaid waveforms of single neuron spiking from (c) and PCA from (c) showing a cluster of overlaid waveforms. Single waveform is presented as mean $\pm$ s.d. presented as mean $\pm$ s.d. (g) Spontaneous spinal cord neural activity recorded from another

TABLE 2 | Comparison of multi-technology synergistic restoration.

Cooperative technology	Dominance	Malpractice	Reference
Electrical stimulation	Activates ion channels, promotes neurotrophic factor secretion, and guides axon-directed growth	Conductive materials (e.g., CNT) may trigger a foreign body reaction, and prolonged electrical stimulation may lead to tissue polarization	[82–84]
Drug Loading and Sustained Release	Sequential controlled release of anti-inflammatory drugs and growth factors, reduction of scarring	Sudden release problems (e.g., PLGA fibers release 50% of drug in 24 h), drug loading limited by material adsorption capacity	[85, 86]
Hydrogel filler	Biomimetic ECM microenvironment, supports cell migration and nutrient infiltration, injectable for minimally invasive surgery	Low mechanical strength (requires composite fiber reinforcement), complex preparation of dynamically responsive materials (e.g., pH-sensitive)	[81, 87, 88]
3D printing technology	Multi-scale structural design (e.g., multi-channel, gradient porosity), personalized adaptation of damage patterns	Printing precision is limited (micron-scale structures are difficult to achieve), biocompatibility of light-curing materials needs to be optimized	[89, 90]

peripheral nerve regeneration. Precise micro/nano-topographical design of NGC luminal surfaces significantly increases effective contact area, providing high-density bio-anchorage sites for Schwann cells and axonal growth cones to systematically support cellular adhesion, directional migration, and functional differentiation [47]. Building on this, researchers fabricated bilayer electrospun NGCs using PCL and PLGA substrates-featuring aligned inner fibers and random outer fibers-with hollow cathode discharge (HCD) plasma surface modification. In cellular assays, PC12 cells cultured on these conduits exhibited dense neurite outgrowth with contact guidance along the underlying fiber alignment, ultimately forming neural network-like architectures that demonstrate significant regenerative potential [48]. However, conventional hollow nerve guidance conduits (NGCs) exhibit topological mismatches with regenerating nerve fibers due to insufficient axon growth-orienting structures, resulting in disorganized synaptic connections. Quantitative histology confirms that this disorganization correlates negatively with nerve bundle microstructural order [49]. Consequently, multi-channel NGC designs have emerged to better mimic the peripheral nerve's 'multi-fascicular' organization [50]. This biomimetic approach increases internal conduit density, providing enhanced adhesion sites for nerve cells while improving bioactive modification capacity through greater specific surface area. Crucially, when conduit dimensions match native nerve fiber topology, interfacial adhesion site density increases two-

three-fold. This creates spatial constraints that direct neuronal process extension via contact guidance, enabling precise axonal topological reconnection across injury gaps-effectively resolving neurological deficits from traditional repair mismatches [51, 52]. Demonstrating this principle, Wang et al. engineered radially/longitudinally oriented 3D fiber scaffolds via coaxial electrospinning and gas-foaming, integrated with shape-memory conduit to form micro/nanostructured multi-channel NGCs [53]. These scaffolds' grooved fiber surfaces significantly enhanced cellular guidance, promoting directional Schwann cell migration from peripheral to central regions and from base to apex.

5 | Multi-Technology Synergistic Repair Combined With Neural Electrospinning Scaffolds

While electrospinning offers exceptional maneuverability for neural scaffold fabrication, single-component electrospun scaffolds exhibit significant limitations. Degradable polyesters represented by polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers (PLGA), their degradation products (acidic oligomers or monomers) will change the pH value of the local microenvironment. This acidic microenvironment not only may cause toxicity to the surrounding cells, but also further intensifies the inflammatory response, forming a vicious cycle

mouse 8 months post-implantation under anesthesia. (h) Overlaid waveforms of single neuron spiking from (g) and PCA from g showing a cluster of the overlaid waveforms. The single waveform is presented as mean $\pm$ s.d. (i) Spontaneous spinal cord neural activity recorded from a conscious mouse 8 months after implantation. (j) Overlaid single neuron spike waveforms from (i) with PCA from i illustrating a cohesive cluster. The single waveform is presented as mean $\pm$ s.d. Reproduced with permission [3] Copyright 2025, Springer.

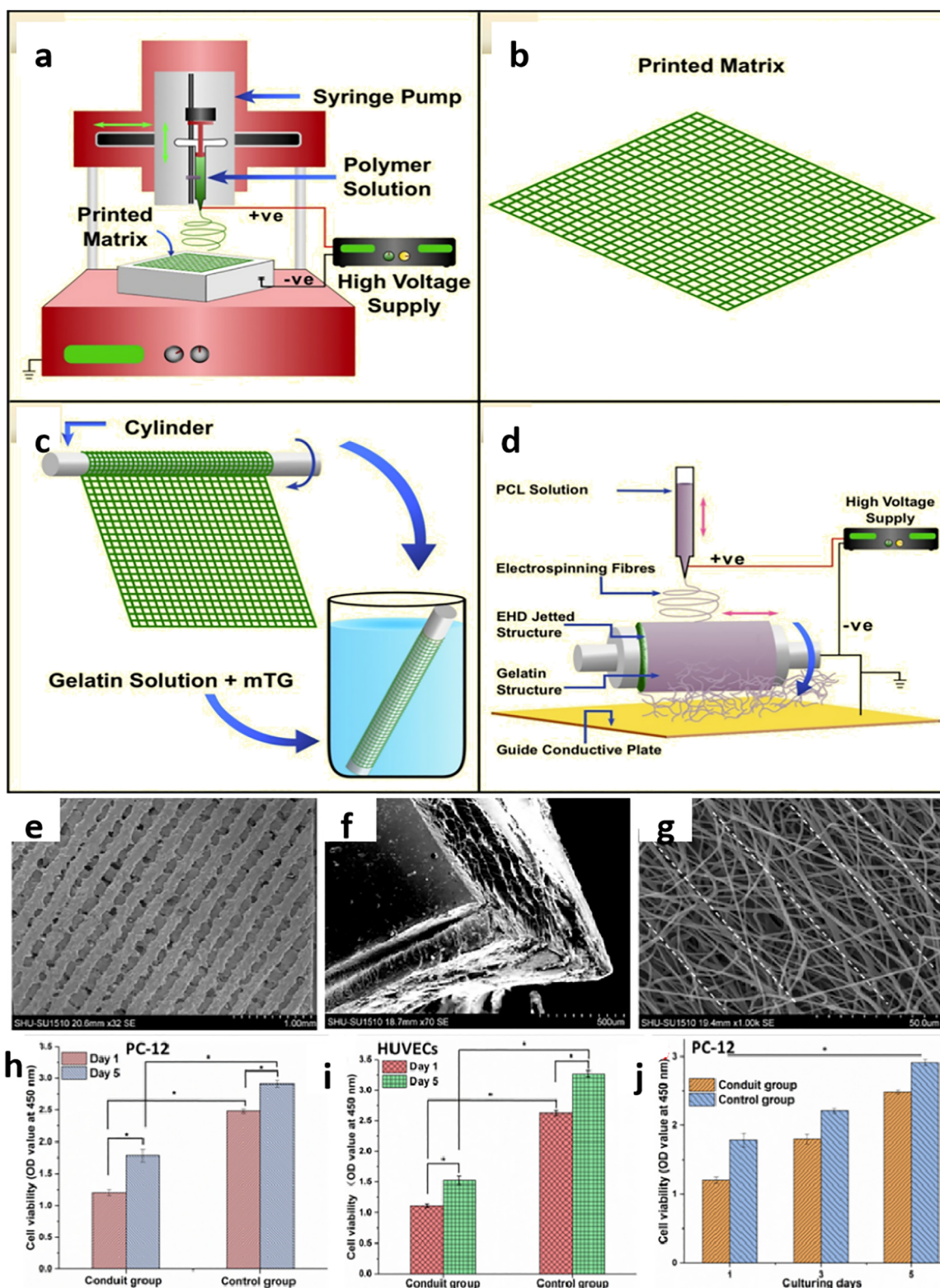


FIGURE 5 | Morphology and biocompatibility evaluation of 3D-printed PCL conduit with gelatin hydrogel coating. (a) Schematic for the EHD jet printing system. (b) Fabrication of the microfiber porous 3D structure. (c) The formation of the inner layer and middle layer. (d) The schematic diagram for the fabrication of the outer layer. C 1 s spectrum of the C-NFO@GDY membrane. (e–g) The corresponding SEM micromorphologies. CCK-8 assay data analysis after culturing 1 and 5 days for h PC-12 cells and i HUVECs (the error bars represent the standard deviation ($n = 6$), and the value of $*p \leq 0.05$ was considered statistically significant). (j) The CCK-8 assay data analysis of PC-12 cells after culturing for 1, 3, and 5 days to correspond with the cells' fluorescent staining experiment (the error bars represent the standard deviation ($n = 6$), and the value of $*p \leq 0.05$ was considered statistically significant). Reproduced with permission [4]. Copyright 2021, Elsevier.

of “degradation-inflammation”. Many synthetic polymers (such as PCL and PLGA) have natural hydrophobicity, which not only hinders the adhesion and spread of hydrophilic cells but also promotes the adsorption of non-specific proteins, making it more likely to trigger intense foreign body reactions. In addition, electrospun fibers have an extremely high specific surface area. Although this is beneficial for cell interactions and drug loading, it also means that the surface area for the material to come into contact with and react with the host tissue increases significantly, which may amplify the aforementioned effects of protein adsorption, inflammatory responses, and the release of degradation products. Consequently, researchers have systematically investigated synergistic combinations with complementary technologies—extending beyond drug/growth factor loading—to explore how integrated stimuli (e.g., electrical fields) and advanced techniques (e.g., hydrogel integration, 3D printing) can positively modulate cellular behavior and enhance functional tissue regeneration, and it effectively compensates for the relevant defects of electrospinning [22].

5.1 | Combination of Electrical Stimulation and Neural Electrospinning Scaffolds

Electrical stimulation promotes nerve repair through three primary mechanisms: first, by activating voltage-gated ion channels to induce calcium influx, which triggers calmodulin-dependent kinase II (CaMKII) activation and enhances neuronal synaptogenesis; second, by modulating neurotrophic factor secretion, specifically upregulating brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) expression in Schwann cells—as demonstrated by a three-fold increase in BDNF secretion from NGF-loaded PCL fibers under electrical stimulation [54]; and thirdly, by promoting directional axonal growth through contact guidance along the orientational alignment of conductive fibers (parallel or radial) in the applied electric field.

Electrospun nerve conduit materials must balance biocompatibility, electrical conductivity, and mechanical properties. Conductive polymers (e.g., PPy, PANI) form conductive interfaces when spun with biodegradable substrates like PCL or PLGA. Wang et al. developed Ni-doped PAN/PANI electrospun scaffolds that accelerated Schwann cell proliferation 2.1-fold under 100 mV/cm electrical stimulation (5 hr daily $\times$ 5 days), demonstrating conductivity’s critical role in neuroregeneration [55]. Carbon-based materials (e.g., CNTs, graphene) significantly enhance conductivity when composited with synthetics; a graphene/CNT/poly(vinyl alcohol)/sodium alginate (PVA/SA/Gr/CNT) electrospun membrane exhibited high conductivity suitable for scalable nerve conduit production. Piezoelectric materials (e.g., PVDF, PLLA) generate endogenous electrical signals under mechanical stress to simulate neural activity [56]. Shan et al. engineered a biodegradable PLLA/BaTiO₃ (BTO) piezoelectric sensor (PBPS) with sandwich architecture: PCL encapsulation layer, Mo electrode layer, and PLLA/BTO fiber core. This design demonstrated exceptional piezoelectric performance and responsiveness, enabling motor function assessment during nerve recovery [57].

Electrical stimulation implementation primarily utilizes three modalities: external power systems, self-powered systems, and wireless modulation. External systems deliver continuous stim-

ulation to implanted electrospun neural scaffolds via external generators; Liu et al. [58] demonstrated this by implanting poly(L-lactic acid)/multi-walled carbon nanotube/agarose conductive multichannel scaffolds in nerve-injured rats, with subsequent 20 Hz external stimulation promoting significant axonal growth and myelination after 12 weeks. Self-powered systems convert biomechanical energy into electricity using biological batteries, piezoelectric materials, or triboelectric nanogenerators (TENGs). Li et al. [59] developed a novel tubular zinc-oxygen (Zn-O₂) battery integrated with conductive PLGA/polypyrrole (PPy) electrospun scaffolds, enabling wire-free in situ electrical stimulation that directly wraps nerves to enhance Schwann cell migration, neurotrophic factor secretion, and axonal growth (Figure 2). Wireless modulation employs near-field communication (NFC) technology for remote parameter adjustment; Borah et al. [60] reviewed capacitive coupling in conductive polymer-based neural scaffolds, where electrodes at opposing ends of culture systems establish electric fields without direct contact, optimizing electrochemical interactions between scaffolds and neural tissues.

5.2 | Drug Loading and Biofactor Retardation

Conventional drug delivery systems face limitations, including initial burst release, limited drug-loading efficiency, short in vivo half-life, and off-target loss. Electrospun fibrous drug carriers address these challenges through their highly porous topology and large specific surface area, enabling efficient drug loading while regulating release kinetics via fiber-drug interactions (e.g., hydrogen bonding, π - π stacking). This extends the therapeutic window for maintaining local drug concentration to 14–28 days [61, 62]. Furthermore, the biomimetic ECM morphology of electrospun fibers activates integrin receptor-mediated endocytosis on cell membranes, enhancing drug uptake efficiency by 1.5–2.3-fold [63]. Importantly, externally applied stimuli can trigger controlled drug release from these platforms, enabling precise spatiotemporal regulation critical for tissue regeneration. Demonstrating this paradigm, Xu et al. [64] incorporated barium titanate piezoelectric nanoparticles (BTNPs) into poly(vinylidene fluoride-co-hexafluoropropylene) [BTNPs/P(VDF-TrFE)] via electrospinning, yielding aligned nanofibers with enhanced β -phase crystallinity. They integrated a thermo-responsive poly(N-isopropylacrylamide) (pNIPAM)-hybridized hydrogel and NGF onto the scaffold. This neurospun construct simultaneously guides neuronal directional elongation and utilizes ultrasound (US) stimulation to: (1) generate wireless electrical stimulation (ES) promoting neurite outgrowth and differentiation, and (2) induce localized heating causing pNIPAM hydrogel contraction for controlled NGF release, further accelerating neurite extension.

To address the distinct requirements of different tissue repair phases, drug-carrying platforms enabling continuous or spatiotemporally controlled multi-drug release were fabricated [65]. Among these, emulsion electrospinning utilizes a water/oil emulsion system to encapsulate hydrophilic drugs and is more widely applied. Demonstrating its utility in peripheral nerve regeneration, Xia et al. [66] engineered a PLLA scaffold via emulsion electrospinning, loading VEGF on the fiber surfaces and NGF within the fiber core. In vitro studies revealed rapid VEGF release alongside sustained NGF elution persisting over one

month; in vivo assessments after three months demonstrated that scaffold treatment significantly enhanced neovascularization and nerve healing. Conversely, coaxial electrospinning facilitates time-sequential release kinetics through deliberate core-shell structural design, as shown in the figure, it is the transcriptome analysis result of Schwann cells. This result to some extent, indicates that the neural scaffolds used can promote the recovery of Schwann cells' nerves at the genetic level (Figure 3). Illustrating this approach, Cheng et al. [67] fabricated core-shell SF/PCL/PVA nanofiber mats via coaxial electrospinning, incorporating bone morphogenetic protein-2 (BMP-2) within the core while attaching connective tissue growth factor (CTGF) to the surface, thereby achieving sustained BMP-2 release concurrent with rapid CTGF delivery.

Among therapeutic agents loaded for nerve repair applications, NGF, proteins, and small-molecule drugs are most widely utilized. Illustrating NGF delivery, Mays et al. [68] combined gelatin microspheres (GMS) encapsulating NGF with methacrylated hyaluronic acid via electrospinning to form GMS-functionalized fibers, demonstrating effective NGF release. Further demonstrating immunomodulatory strategies, Lv et al. [69] investigated collagen VI-regulated macrophage polarization on axonal regeneration and functional recovery. Their results showed that locally delivering collagen VI within electrospun PCL conduits significantly increased macrophage recruitment and polarization toward a pro-regenerative (M2) phenotype. Consequently, axonal regeneration and neurological recovery in PCL/collagen VI conduits matched autograft performance, indicating that sustained collagen VI release enhances nerve regeneration by promoting M2 macrophage polarization. In a combinatorial pharmacotherapy approach, Haidar et al. [70] incorporated α -lipoic acid (ALA) and atorvastatin (ATR)-loaded chitosan nanoparticles into PLGA electrospun nanofibers. Using comprehensive functional assessments-sciatic nerve function index (SFI), extensor postural thrust (EPT), withdrawal reflex latency (WRL), and Basso, Beattie, and Bresnahan (BBB) locomotor scoring-in a rat sciatic nerve crush model, they confirmed that this nanocomposite fiber formulation promotes significant recovery of motor/sensory functions and nerve regeneration.

5.3 | Hydrogel Filling and Bionic Microenvironment Construction

Hydrogel-based neural repair strategies leverage critical biomimetic properties, their 3D network structure replicates the structural microenvironment of natural neural ECM to facilitate cell migration and nutrient infiltration [71]. Furthermore, hydrogels offer tunable mechanical properties where elastic modulus is precisely regulated via crosslinking density to match neural tissue compliance [72].

Integrating hydrogel filling with bionic microenvironment construction significantly enhances nerve conduit repair efficacy. Hydrogels establish dynamic microenvironments when infused into conduit lumina or applied as functional coatings [73]. Zheng et al. [74] engineered an advanced neural scaffold comprising longitudinally aligned electrospun PLLA nanofibers encapsulated within porcine decellularized neural matrix hydrogel (pDNM). This composite design demonstrated synergistic in vitro enhance-

ment of oriented axonal extension and Schwann cell migration, providing concurrent topographical and biochemical cues to potentiate axonal pathfinding, myelination, and functional recovery. Beyond structural guidance, hydrogels enable controlled spatiotemporal delivery of neurotrophic factors (e.g., BDNF), anti-inflammatories, or genetic payloads [71]. Wang et al. [75] fabricated a multilayer conduit via electrospinning, featuring an anti-adhesive PCL outer sheath and an alginate-based ECM-mimetic inner hydrogel loaded with melatonin. In vivo studies confirmed the scaffold's sustained melatonin release attenuated neuroinflammation and oxidative stress, significantly improving sciatic functional indices (SFI) and electrophysiological recovery. Furthermore, conductive hydrogels incorporating materials like polypyrrole or carbon nanotubes accelerate neuroelectrophysiological pathway restoration [76]; their combined conductivity with aligned fiber topology activates voltage-gated calcium influx and neurotrophic factor secretion, dually accelerating axonal regeneration (Figure 4). Hydrogel-electrospinning-3D printing hybridization achieves macro-micro structural synergy: printed frameworks provide mechanical integrity while hydrogel infills optimize nutrient diffusion and cellular migration. Song et al. [77] exemplified this by functionalizing electrospun PCL scaffolds with 3D-printed spinal cord ECM hydrogel microfibers and supramolecular oxidized matricellulose (OMT)-loaded hydrogel. This hierarchical construct demonstrated biocompatibility, controlled OMT release, and enhanced neuronal differentiation in vitro, while in vivo it reduced glial scarring and improved motor function recovery by guiding directional axon growth.

5.4 | 3D Printing and Multi-Technology Synergy

3D printing enables rapid fabrication of arbitrarily complex architectures via CAD-guided, layer-by-layer material deposition. This technology offers precise control over design parameters, facilitating the creation of oriented multi-lumen conduits with tailored geometries critical for axonal guidance. Complementarily, nanoscale fibrous membranes fabricated by electrospinning exhibit interconnected 3D microporous networks that ensure efficient nutrient diffusion and metabolite exchange-addressing key limitations of traditional nerve conduit fabrication methods while enabling high-fidelity neural repair [78]. The synergistic integration of 3D printing (capable of constructing complex scaffold architectures like multi-channel systems and gradient pore spaces) with electrospinning technology significantly advances precision engineering strategies for neural tissue regeneration after injury [79].

3D printing technology synergizes with multiple modalities to enhance neural electrospun scaffolds for nerve regeneration. When combined with conductive materials (e.g., PPy), this approach restores electrophysiological signaling to promote voltage-gated calcium influx and neurotrophic factor secretion. Researchers fabricated PLCL/PLGA scaffolds via 3D-Bioplotter extrusion, applied electrospun PLCL/PLGA coatings, and deposited PPy to enhance biocompatibility [33]. These constructs demonstrated optimized architecture and electrical conductivity conducive to neuronal signaling, showing significant potential for peripheral nerve applications. Furthermore, 3D printing integrates with hydrogels to create microenvironments enhancing neuronal attachment and growth. Liu et al.

[80] engineered a hierarchically structured conduit using EHD-jet 3D printed aligned PCL fibers (inner layer) with gelatin hydrogel coating, and electrospun PCL nanofiber membranes as outer sheath. This biomimetic design exhibited neuromimetic structural features validated through mechanical, porosity, and biocompatibility assessments (Figure 5). Similarly, Fan et al. [81] fabricated aligned PLGA inner scaffolds via E-jet printing with electrospun PCL NGC outer layers, filling lumens with umbilical cord dECM hydrogel and extracellular vesicles (EVs) to modulate the regenerative microenvironment. This system enhanced sciatic nerve reconstruction through improved motor function recovery and myelination (Table 2).

6 | Summary and Outlook

Electrospun neural scaffolds have emerged as a transformative platform for nerve regeneration, leveraging their biomimetic fibrillar architecture, tunable degradation profiles, and multi-functional payload capacity to overcome limitations of conventional approaches. This technology has evolved from standalone constructs to convergent regenerative systems integrating 3D bioprinting, electrostimulation, spatiotemporal drug delivery, and hydrogel matrices. Such synergy enables unprecedented control over the structural hierarchy through fiber diameter/orientation/porosity engineering to direct axonal extension; the bioactivity modulation via loading of neural progenitor cells, neurotrophins, and anti-inflammatory agents to potentiate adhesion/proliferation/differentiation; and functional recovery through surface-functionalized conductive polymers and hydrophilic coatings that restore electrophysiological microenvironments and accelerate neurite outgrowth. Collectively, these integrated platforms recapitulate native neural tissue's structural, biochemical, and electromechanical complexity—establishing a new paradigm for comprehensive neural repair.

The long-term biocompatibility of neural electrospun scaffolds necessitates precise degradation matching. Acidic degradation byproducts from synthetic polymers (e.g., PLGA) can induce chronic neuroinflammation, demanding buffer systems or novel copolymers to neutralize local microenvironments. Natural materials require controlled crosslinking to decelerate rapid degradation rates. Scaling manufacturing remains critical, as traditional electrospinning suffers from low throughput, incompatible with clinical demands. There are still strict regulatory obstacles for the electrospinning stent to become a mature implantable medical device. Traditional biocompatibility evaluation standards (such as the ISO 10993 series) are designed for conventional medical devices and may not be able to fully assess the unique high specific surface area effect of nanofiber structures, the local immunotoxicity of long-term degradation products, and the complex impacts brought about by active immune regulation functions. While 3D printing enables architectural precision, resolution limitations persist; electrical stimulation potentiates regeneration but faces material stability constraints; and drug-loaded hydrogels combat burst release and mechanical integrity challenges. Apart from rodent models, clinical translation also faces the challenge of insufficient translation validation, especially the lack of systematic data in large animal models (such as pigs or non-human primates), which limits the advancement of the technology into clinical practice. In addition, future research

should focus on the following specific directions: (1) Develop a new generation of intelligent biomaterial systems and construct “intelligent scaffolds” that can dynamically respond to external stimuli (such as electrical signals, temperature changes, mechanical environments or specific biomolecules), thereby achieving dynamic regulation of the neural regeneration microenvironment; (2) Promote the innovation and application of high-throughput manufacturing technologies, integrating 3D printing, microfluidics, and bioassembly technologies to establish a process platform for the large-scale preparation of nerve conduits with bionic structures, providing customizable and reproducible implantable devices for clinical use. (3) Deepen the multi-modal integrated treatment strategy and explore the combination of gene therapy technology and scaffold functionalization, such as constructing matrix materials that can encode or non-viral gene vectors, while integrating functional components like electrical stimulation modules and optogenetic regulatory units, to form an integrated platform that can precisely regulate the neural regeneration microenvironment in time and space, promote the directional growth and functional remodeling of axons.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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