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Latest advances in neurointerface-based electrical stimulation for spinal cord injury: a review

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Highlights:

- Emphasizes the critical role of BSCMI systems in restoring brain-spinal cord neural communications.
- Discusses multimodal synergistic therapeutic strategies that integrate electrical stimulation with advanced materials, stem cell transplantation, and AI-driven personalized medicine to promote neural plasticity and axonal regeneration.
- Comprehensively evaluates recent advancements in neuromodulation, flexible electrode materials, and wireless implantable devices, while identifying core challenges for clinical translation such as electrode-tissue interface optimization and long-term device stability.

Abstract: Spinal cord injury (SCI) causes severe damage to neural pathways, leading to substantial motor and sensory deficits that drastically reduce patients' quality of life. In recent years, electrical stimulation technologies rooted in neurointerface research have gained attention as innovative approaches to encourage neural repair and functional recovery after SCI. This article offers a detailed examination of the most recent advancements in electrical stimulation for SCI, focusing on three key areas: multimodal neuromodulation methods, novel neurointerface materials and designs, and the development of wireless and miniaturized neural stimulation devices. A special focus is placed on brain-spinal cord-machine interface (BSCMI) systems, which aim to re-establish communication between the brain and spinal circuits. The review also examines the underlying mechanisms through which electrical stimulation promotes neural plasticity and aids in functional restoration. Notably, it highlights the growing integration of electrical stimulation with other therapies, including neural stem cell transplantation, intelligent rehabilitation techniques, and AI-driven personalized treatment plans. Despite these promising developments, several technical hurdles remain. The article concludes by discussing these challenges and outlining future research directions, with the goal of offering valuable insights for clinical practice and improving outcomes for individuals with SCI. Ultimately, this analysis emphasizes the significant potential of neurointerface-based electrical stimulation in transforming SCI treatment and enhancing patient recovery.

Keywords: spinal cord injury; neurointerface; electrical stimulation; neuromodulation; brain-spinal cord-machine interface; neural repair; functional recovery; neural plasticity

1. Introduction

Spinal cord injury (SCI) inflicts profound damage on the central nervous system (CNS), leading to severe motor, sensory, and autonomic dysfunction. These impairments not only drastically reduce patients' quality of life but also impose significant socioeconomic burdens. The pathological mechanisms of SCI are intricate, involving both immediate mechanical trauma and a series of secondary injury processes, such as inflammation, oxidative stress, excitotoxicity, and glial scar formation. These processes collectively hinder neural repair and functional recovery [1–3]. Traditional treatments, including surgical decompression, medication, and rehabilitation, have shown limited effectiveness in restoring neurological function, especially in severe cases [4]. Consequently, there is a pressing need for innovative strategies to enhance neuroprotection, promote axonal regeneration, and facilitate functional recovery.

Recent years have witnessed promising progress in neural interface technology combined with electrical stimulation, offering new hope for SCI treatment. Neural interfaces act as bioelectronic bridges, enabling bidirectional communication between the nervous system and external devices. This integration allows for targeted neuromodulation and neural signal recording [5,6]. By leveraging electrical stimulation, these interfaces can modulate spinal cord circuits, enhance neuroplasticity, and reactivate dormant neural pathways below the injury site, thereby restoring voluntary motor control and sensory functions [7,8]. This approach marks a shift from purely biological repair strategies to hybrid bioelectronic therapies that integrate material science and neuroengineering principles.

The development of neural interface technology draws on multiple disciplines, including materials science, microfabrication, and neurophysiology. These innovations have led to the creation of wireless, miniaturized, and intelligent devices suitable for chronic implantation. These devices exhibit biocompatibility and mechanical compliance, ensuring long-term functionality [9–12] Breakthroughs in this field include carbon-based electrodes with high electrochemical stability, flexible neural arrays for epidural stimulation, and ultrasound-powered piezoelectric stimulators. These advancements minimize invasiveness while maintaining therapeutic efficacy [9,13,14]. In preclinical and clinical studies, these devices have demonstrated improved motor functions, such as walking, standing, and hand coordination, in SCI models [15,16].

Furthermore, combining neural interfaces with multimodal treatment strategies—such as stem cell transplantation, pharmacological agents, and rehabilitation training—has shown synergistic effects in enhancing neural repair and functional outcomes [6,17,18]. For example, electroactive hydrogels loaded with neural stem cells and neuroprotective drugs create a supportive microenvironment for axonal growth and circuit reconstruction. Concurrently, electrical stimulation promotes synaptic plasticity and motor recovery [19,20]. The emergence of brain-computer interfaces (BCIs) and spinal cord-machine interfaces (SCMIs) expands therapeutic options by enabling direct decoding and modulation of neural activity. This technology aims to restore voluntary control and sensory feedback [21,22].

Despite these advancements, several challenges persist. Key issues include optimizing electrode-tissue interfaces to reduce immune responses, improving long-term device stability, achieving precise targeting of spinal circuits, and customizing stimulation protocols for individual patients [23–25]. Translating preclinical successes into clinical applications requires rigorous validation, standardized stimulation parameters, and the development of closed-loop systems that adaptively modulate neural activity based on real-time feedback [10,26]. Addressing these challenges demands continued interdisciplinary collaboration among neuroscientists, engineers, clinicians, and material scientists.

Spinal cord injuries can be broadly classified based on injury severity and temporal stage. According to the American Spinal Injury Association (ASIA) classification, SCI can be categorized as complete or incomplete depending on the preservation of sensory or motor function below the injury level. In addition, the pathological progression of SCI includes acute, subacute, and chronic phases, each characterized by distinct cellular and molecular processes. The therapeutic strategies and effectiveness of electrical stimulation may vary across these injury types and stages. Therefore, when discussing neuromodulation strategies and clinical applications in this review, particular attention is given to studies involving chronic incomplete SCI, which currently represents the most common target population in clinical neuromodulation trials.

In summary, the integration of neural interface technologies and electrical stimulation represents a transformative approach to SCI treatment, opening new avenues for neuroregeneration and functional restoration. This multidisciplinary field harnesses advancements in biomaterials, device engineering, stem cell biology, and neurophysiology to overcome the limitations of traditional therapies. Ongoing refinements in neural interfaces, coupled with multimodal therapeutic strategies, hold great promise for improving outcomes for SCI patients. This review systematically examines the latest progress in neural interface-based electrical stimulation for SCI, elucidates underlying mechanisms, and explores future directions for clinical translation.

2. Neural regulation mechanisms and multimodal treatment strategies of electrical stimulation for spinal cord injury

2.1. Mechanisms of neuromodulation promoting neural regeneration and plasticity

Electrical stimulation (ES) has become a cornerstone in neuromodulation strategies aimed at promoting neural regeneration and plasticity following SCI. By influencing neural network activity and cellular behavior, ES plays a transformative role in restoring functional connectivity within damaged neural circuits.

A key mechanism involves the regulation of neural network excitability, which triggers the sprouting of collateral branches from surviving axons. This process fosters new synapse formation and enhances neural plasticity, both of which are critical for rebuilding functional connections. For instance, low-frequency spinal cord electrical stimulation can modulate the excitability of spinal neurons, reinstating intrinsic rhythmic motor control and improving locomotor function. By reactivating dormant pathways, this approach facilitates coordinated motor outputs through the modulation of spinal interneurons and motor neurons.

Beyond its effects on neuronal activity, ES also impacts neural stem cells (NSCs). It promotes their differentiation and migration, contributing to neural tissue regeneration. Research indicates that neuromodulatory interventions activate intracellular signaling pathways, such as the Akt/mTOR/p70S6K cascade, which enhance NSC survival, differentiation into neurons and glial cells, and synaptic development under ischemic or injury conditions. These pathways also upregulate the expression of synaptic proteins—including BDNF, synaptophysin, and PSD95—that are essential for synapse formation and plasticity.

Additionally, ES induces the release of neurotrophic factors and modulates the inflammatory microenvironment, further supporting regenerative processes. Recent advances in biomaterials have enabled the integration of electrical cues with topographical guidance. For example, magnetoelectric nanochains embedded in hydrogels synergistically enhance neural regeneration by activating voltage-gated ion channels and promoting synaptic remodeling.

Collectively, these mechanisms highlight how ES facilitates neural repair by orchestrating network-level activity modulation, stem cell-mediated regeneration, and microenvironmental remodeling. This multifaceted approach holds promise for fostering functional recovery after SCI [27–29].

2.2. Neural stem cells combined with electrical stimulation for repair potential

The combination of exogenous neural stem cell (NSC) transplantation and ES has emerged as a highly promising strategy for enhancing SCI repair. This integrated approach addresses key challenges in SCI treatment by improving cell survival, promoting neuronal differentiation, and facilitating functional neural network reconstruction. Exogenous NSCs often struggle in the hostile microenvironment of the injured spinal cord, where low survival rates and inefficient differentiation limit their therapeutic potential. Electrical stimulation offers a solution by actively modulating the local cellular environment and behavior.

For instance, electrical cues delivered through conductive biomaterials or wireless stimulation systems have demonstrated remarkable effects. These systems enhance NSC differentiation into mature neurons, accelerate neuronal maturation, and promote synaptic connectivity, all of which contribute to functional recovery. innovative approaches like piezoelectric nanoparticles and magnetoelectric hydrogels generate localized electrical signals in response to external stimuli such as ultrasound or magnetic fields. These signals activate critical intracellular pathways, including the PI3K/Akt/GSK-3β/β-catenin cascade, which are essential for neuronal differentiation and survival [30–32].

Wireless electrical stimulation platforms, based on conductive hydrogels or MXene films, represent another significant advancement. These systems enable noninvasive, *in situ* electrical modulation, overcoming the limitations of traditional wired systems and reducing risks of inflammation and infection [33–35]. The synergistic effects of NSC transplantation and ES extend beyond neurogenesis. This combination also modulates the immune microenvironment, reduces glial scar formation, and supports axonal regeneration, as evidenced in various rodent SCI models [36].

Electrical stimulation further optimizes the NSC microenvironment by enhancing neurotrophin release—such as nerve growth factor (NGF)—improving mitochondrial function in muscle tissue, and activating central pattern generator circuits. These actions collectively enhance motor function [37–39]. When combined with conductive biomaterial scaffolds, NSCs can be integrated into “active” artificial dura mater or injectable hydrogels. These materials provide both structural support and electrical conductivity, improving cell integration and survival [40,41]. Additionally, these biomaterials can be engineered to release growth factors and exosomes in synergy with electrical stimulation, further boosting neurogenesis and immunoregulation [31,42].

The convergence of NSC transplantation, electrical stimulation, and advanced biomaterials represents a multifaceted approach with great potential to overcome current barriers in SCI repair. By enhancing cell survival, directing neuronal lineage commitment, and reconstructing functional neural circuits, this integrated strategy offers a transformative path forward. However, translating these promising preclinical findings into clinical therapies requires further large-scale trials and optimization of stimulation parameters to ensure safety and efficacy for patients with spinal cord injury.

2.3. Preclinical and clinical applications of multimodal treatment strategies

Multimodal treatment strategies combining electrical stimulation with rehabilitation training, robotic assistance, and BCIs have emerged as a transformative approach for enhancing neural functional recovery after SCI. Preclinical research indicates that electrical epidural stimulation (EES) of the spinal cord can activate sensorimotor circuits to facilitate locomotion and standing, though the underlying mechanisms require further investigation [43]. When paired with pharmacological agents, EES demonstrates synergistic effects in modulating spinal networks, suggesting that multimodal interventions may amplify motor recovery [44].

Integrating electrical stimulation with rehabilitation exercises promotes neuroplasticity by encouraging new synaptic connections and collateral sprouting of residual nerve fibers, thereby improving motor function [45]. The development of innovative neural interfaces, such as ultrasound-powered piezoelectric stimulators, offers wireless, minimally invasive options for chronic neuromodulation, potentially enhancing the clinical feasibility of multimodal therapies [14]. BCIs have been incorporated into rehabilitation frameworks, enabling patients to translate brain signals into commands for electrical stimulation or robotic-assisted movement, which may augment motor recovery [46].

Clinical evidence supports the efficacy of personalized rehabilitation programs combining electrical stimulation and task-specific training. For instance, a 12-week multimodal pelvic rehabilitation program integrating electrical stimulation, muscle training, and biofeedback resulted in significant improvements in urinary and fecal continence, pelvic floor muscle strength, and quality of life [47]. Similarly, interventions combining functional electrical stimulation during exercise with pharmacotherapy have shown promise in enhancing aerobic capacity, musculoskeletal health, and metabolic function in SCI patients [48,49].

Despite these promising findings, translating multimodal strategies into clinical practice requires large-scale, rigorous trials to validate safety, efficacy, and long-term benefits. Key challenges include optimizing stimulation parameters, timing, and integration of diverse technologies to tailor interventions to individual patient needs. Advances in biomaterials, nanotechnology, and artificial intelligence offer potential solutions by improving neural interface biocompatibility, enabling closed-loop control, and enhancing data-driven personalization [50,51].

In summary (Figure 1), the convergence of electrical stimulation with rehabilitation, robotics, and BCIs represents a paradigm shift in SCI treatment, with preclinical and early clinical data supporting enhanced functional recovery. Future research must prioritize systematic clinical validation and technological optimization to fully realize the potential of these multimodal therapeutic approaches.

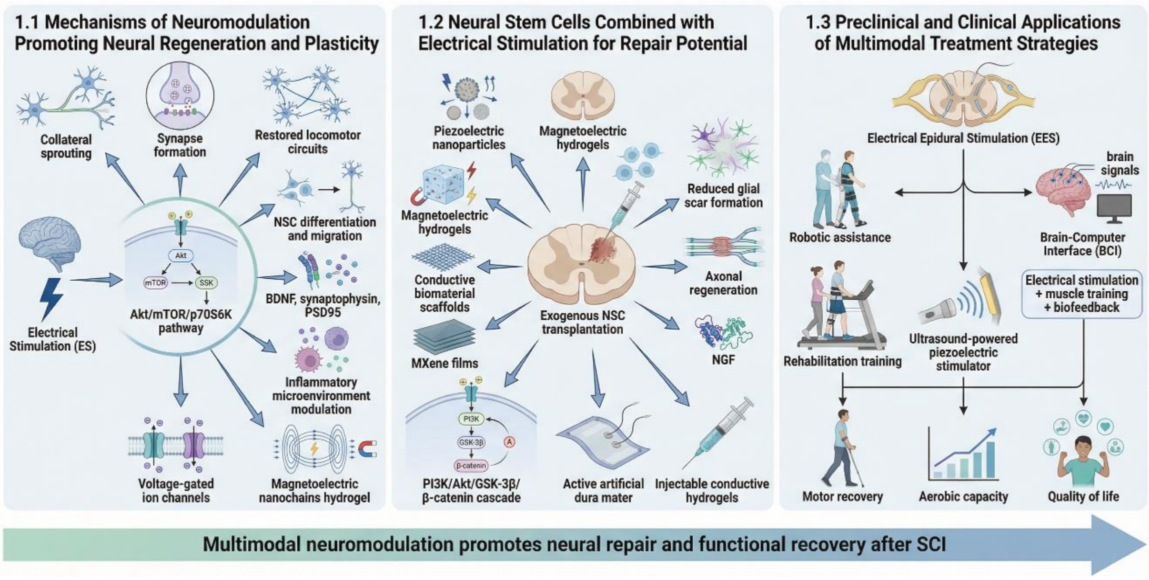

Figure 1. Neural regulation mechanisms and multimodal treatment strategies of electrical stimulation for spinal cord injury. Diagram created with Gemini Nano Banana Pro.

3. Latest advances in neural interface materials and design

3.1. Carbon-based materials and flexible electrode technology

Carbon-based electrodes, including glassy carbon variants, have become frontrunners in neural interface development for SCI applications. These materials combine exceptional biocompatibility with electrochemical stability, making them ideal for long-term implantation. Their favorable electrical characteristics—such as high conductivity and low impedance—are essential for efficient neural stimulation and recording. For example, carbon nanotube (CNT)-modified microelectrode arrays exhibit reduced impedance and enhanced stability, resulting in improved signal-to-noise ratios for chronic neural interfacing [52]. Similarly, glassy carbon electrodes used in cervical epidural implants have demonstrated stable stimulation performance and impedance over weeks in rat SCI models, underscoring their durability and biocompatibility [9].

The inherent flexibility of carbon-based fibers and films enables the fabrication of electrodes that closely conform to the spinal cord's intricate anatomy. This design minimizes mechanical mismatch and reduces foreign body reactions. Flexible carbon nanotube-embroidered graphene film electrode arrays, for instance, showcase ultraflexibility and mechanical robustness, facilitating stable neural recordings over extended periods [53]. Such flexibility is critical for accommodating spinal cord movements during daily activities.

Flexible electrode designs, often incorporating polymer substrates with carbon-based conductive materials like graphene or CNTs, offer enhanced mechanical compliance and electrochemical performance [54,55]. Composite electrodes—integrating carbon nanomaterials with conductive polymers or metal compounds—further synergize flexibility, conductivity, and charge injection capacity. An example is carbon nanotube/nickel/nickelous hydroxide composites, fabricated via single-side printing technology for wearable electrodes [56]. These electrodes withstand bending and stretching during spinal cord motion, reducing mechanical strain and improving chronic implantation outcomes.

To ensure durability and safety, mechanical load testing and finite element analysis (FEA) are employed. For instance, FEA of carbon-based neural arrays confirms their ability to endure physiological mechanical loads with minimal stress concentrations, preserving mechanical integrity during implantation and *in vivo* movements [9]. Experimental testing, including tensile and bending assessments, validates robustness under cyclic deformation, which is vital for maintaining electrical performance over time [57]. Additionally, inorganic barrier layers integrated into polymer insulation films enhance electrode insulation stability without sacrificing flexibility, extending lifespan [58].

The high surface area and tunable porosity of carbon-based nanomaterials also contribute to superior electrochemical properties. These features enhance charge storage capacity and reduce impedance, which are pivotal for effective neural stimulation. Heteroatom-doped lignin-based carbon materials and nitrogen-doped coal-based activated carbon electrodes, for example, exhibit high specific capacitance and cycling stability, indicating potential for long-term neural interfaces [59,60]. The nanostructured morphology of carbon electrodes—comprising carbon nanotubes, graphene, and graphene oxide—facilitates ion transport and electron transfer, as evidenced by their excellent capacitance retention and mechanical flexibility under bending loads [61].

In summary, carbon-based materials paired with flexible electrode designs provide a robust solution for spinal cord neural interfaces. Their superior biocompatibility, electrochemical stability, and mechanical compliance enable long-term implantation with reduced inflammatory responses and improved interface stability. Mechanical load testing and FEA offer critical validation of durability and safety, supporting their translational potential for SCI therapies. Ongoing advancements in material engineering and flexible electrode fabrication are poised to further enhance performance and longevity in SCI applications.

3.2. Applications of nanomaterials and wide bandgap semiconductors in neural interfaces

The incorporation of nanomaterials and wide bandgap semiconductors into neural interface systems has marked a transformative leap in creating durable, stable, and multifunctional platforms for neural stimulation. Emerging materials like silicon carbide (SiC) and silicon-carbon nanomembranes have shown exceptional promise in developing long-lasting neural interfaces that maintain performance over extended periods. These materials are characterized by their superior chemical stability, biocompatibility, and mechanical resilience—attributes that are indispensable for chronic implantation and minimizing adverse tissue reactions [62].

Silicon carbide, for instance, leverages its wide bandgap properties to offer outstanding thermal stability and electrical insulation. This enables reliable neural stimulation without the risk of excessive heating or material degradation, thereby enhancing device longevity and safety *in vivo* [62]. Meanwhile, nanostructured coatings—such as conductive polymers integrated with carbon-based nanomaterials like graphene and carbon nanotubes—have revolutionized the electrode-neural tissue interface. These coatings improve electrical conductivity and mechanical compliance while increasing the effective surface area for better neural tissue contact. This leads to reduced impedance and enhanced signal fidelity for both recording and stimulation tasks [54,63].

Recently, emerging neuromodulation technologies based on nanoscale devices and soft bioelectronic materials have attracted increasing attention for spinal cord injury therapy. Nanosized neuromodulators enable minimally invasive neural stimulation through remote activation mechanisms such as magnetic or sound fields. These nanoscale systems can interact with neuronal membranes and modulate neural activity with high spatial precision, offering a promising strategy for noninvasive neuromodulation[64,65].

Flexible electronics technologies have further bolstered these advancements by enabling conformal electrode arrays that closely mimic the soft, dynamic nature of neural tissues. This design minimizes mechanical mismatch and lowers inflammatory responses, addressing a critical challenge in chronic neural interfacing [66]. The integration of nanomaterial coatings with flexible substrates has paved the way for multifunctional neural interfaces capable of simultaneous electrophysiological recording, chemical sensing, and targeted neuromodulation. A key innovation lies in the development of multi-channel and programmable neural stimulation systems. These systems can deliver spatially and temporally precise electrical stimuli, addressing the complexity of neural networks. For example, nanomaterial-enhanced microelectrode arrays with integrated drug delivery and optoelectronic capabilities enable closed-loop neuromodulation strategies tailored to specific neural circuits [67,68]. Wide bandgap semiconductors like gallium nitride (GaN) and SiC also play a pivotal role in miniaturizing neural stimulators while improving energy efficiency. These materials support high-voltage operation with low conduction losses and fast switching speeds, which are essential for advanced implantable devices with extended battery life and reduced thermal footprint [69].Collectively, the synergy between nanomaterials and wide bandgap semiconductor technologies is driving neural interfaces toward highly stable, biocompatible, and versatile platforms. These innovations meet the rigorous demands of complex neural network modulation and long-term clinical applications. By enabling precise, durable, and programmable neural stimulation, these advancements hold significant promise for enhancing therapeutic outcomes in spinal cord injury and other neurological disorders [24,70].

3.3. Wireless power supply and miniaturized neural stimulation devices

The evolution of wireless power delivery and miniaturized neural stimulators marks a pivotal shift in neurotechnology, driven by the goals of minimizing surgical intrusion, enhancing biocompatibility, and improving the long-term stability and practicality of implantable devices. Among the various strategies under investigation, ultrasound-driven piezoelectric stimulators have gained considerable attention. These systems operate by converting externally applied ultrasound energy into localized electrical charges, thereby enabling effective neural stimulation without relying on percutaneous wires or bulky integrated batteries. For instance, a system leveraging aluminum nitride (AlN)-based piezoelectric micromachined ultrasonic transducers (PMUTs) has demonstrated efficient wireless power transfer, achieving an output sufficient for operating low-power implantable biomedical devices, including neural stimulators, while maintaining excellent biocompatibility and compatibility with standard CMOS processes [71]. This methodology facilitates energy transmission through biological tissues, substantially mitigating the risks associated with repeated explanation surgeries, and adheres to established safety limits on ultrasound intensity, such as those set by the FDA.

Complementing ultrasound-based approaches are lightweight magnetic coupling systems designed for non-invasive neural stimulation and recording. Wearable transmitter coils, engineered for inductive wireless power transfer, can deliver substantial power (e.g., simulated outputs of 50 mW) to deeply implanted devices. This capability supports precise functional measurement and control of endovascular and neural implants [72]. These head-worn setups strive to balance high power transfer efficiency with user comfort for daily application. Furthermore, the integration of magnetoelectric (ME) materials has enabled the development of highly compact, dual-band smart nanoelectromechanical systems (NEMS). Such ME antennas, with dimensions on the order of hundreds of micrometers, achieve wireless power transfer efficiencies one to two orders of magnitude higher than conventional micro-coil devices, while rigorously adhering to specific absorption rate (SAR) safety limits [73]. This integrated technology supports simultaneous wireless powering and neural magnetic signal recording, thereby significantly expanding the functional capabilities of miniaturized neural interfaces.

In studies using animal models, the miniaturization of neural stimulation devices has become indispensable for chronic experiments involving freely moving subjects. Researchers have successfully engineered fully implantable, rechargeable platforms based on open-source, wirelessly powered microcontrollers. These systems can be flexibly customized with miniature sensors and actuators, enabling continuous nerve stimulation over multiple weeks in freely behaving rats. These platforms exhibit minimal thermal effects and are designed for straightforward assembly [74]. Their compact dimensions and cable-free operation not only lessen the invasiveness of implantation procedures but also promote animal welfare, thereby strengthening the translational value of preclinical findings.

Continuing this trajectory of innovation, recent developments include biodegradable miniaturized neurostimulators that employ capacitive-coupling for wireless power transfer. These devices incorporate molybdenum electronic elements sealed within self-healing, biodegradable polyurethane elastomers. This design supports stable neural interfaces that receive power wirelessly via capacitive coupling from wearable transmitters. The therapeutic potential of such systems has been validated in models of pediatric inflammatory bowel disease, where they effectively modulated vagus nerve activity [75]. By combining biodegradability with wireless power delivery, this approach simultaneously addresses safety issues related to device explanation and the pressing requirement for device downsizing.

Another noteworthy direction involves the creation of miniaturized spinal cord stimulators fabricated on biocompatible substrates such as liquid crystal polymer (LCP). These devices feature monolithic encapsulation and utilize inductive wireless power transfer. Compared to traditional implants housed in metal packages, these LCP-based stimulators are markedly lighter and more compact, and they have already demonstrated successful pain suppression in rat models [76].

Parallel to these advances, magnetoelectric-powered bio-implants (ME-BITs) have proven capable of delivering wireless neural stimulation at frequencies relevant to clinical practice, all within a millimeter-scale form factor. This miniaturization permits their complete implantation and operation in freely moving animals [77]. Importantly, the ME-BIT system also incorporates digital programmability and supports bidirectional communication. These features significantly improve the precision and adaptability of stimulation protocols [78].

In addition, soft and wireless neural electrodes fabricated from stretchable polymers and conductive nanomaterials have demonstrated improved mechanical compatibility with neural tissues, thereby reducing inflammatory responses and enhancing long-term recording and stimulation stability. These advances represent an important step toward the development of next-generation neural interfaces for SCI treatment [79].

Collectively (Figure 2), the ongoing drive toward wireless power and device miniaturization is primarily motivated by three objectives: to minimize surgical invasiveness, to reduce the physical footprint of the implant, and to enhance long-term stability and functional performance. Leading this technological push are ultrasound-driven piezoelectric stimulators, magnetically coupled wearable transmitters, and magnetoelectric nanoantennas. Together, these technologies are pushing the field toward neural interfaces that are safer, more effective, and broadly applicable. These collective innovations not only empower more physiologically relevant long-term studies in animal models but also create a clearer pathway toward clinical translation. They open up promising possibilities for treating complex neurological conditions and spinal cord injuries through minimally invasive, wirelessly controlled neurostimulation systems.

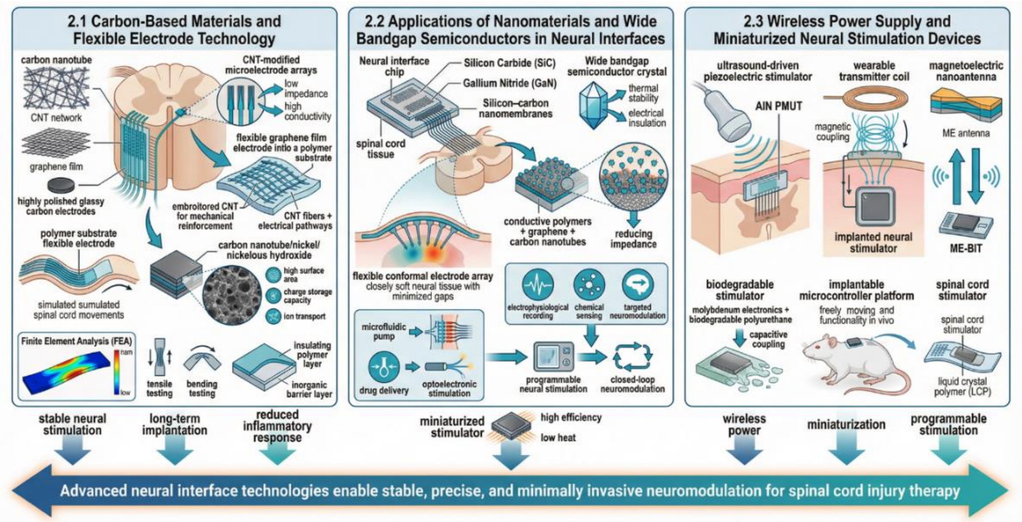

Figure 2. Latest advances in neural interface materials and design. Diagram created with Gemini Nano Banana Pro.

4. Brain-spinal cord-machine interface and its application in spinal cord injury

4.1. Bidirectional neural interface technology

Bidirectional neural interface systems are reshaping rehabilitation paradigms for SCI by creating dynamic communication channels between the nervous system and external devices. These systems utilize implanted microelectrode arrays (MEAs) to both record neural signals and deliver precisely targeted stimulation to spinal cord axonal bundles. The technology capitalizes on the exceptional spatial resolution of MEAs to capture compound action potentials (CAPs) from specific spinal pathways like the dorsal columns, which process sensory information. In one illustrative application, MEAs positioned in the lumbar dorsal column successfully mapped somatotopic representations of tactile stimuli from various lower body areas, while also registering proprioceptive signals influenced by joint positioning, including hip abduction [21]. This precise detection capability is fundamental for interpreting the neural signatures of motor and sensory processes, establishing the groundwork for responsive neuromodulation platforms.

The incorporation of feedback control mechanisms within these bidirectional interfaces enables closed-loop regulation, substantially improving the precision of motor recovery. By perpetually tracking neural activity and automatically fine-tuning stimulation parameters, these adaptive systems can modulate spinal circuits in real-time to reinstate volitional movement. For instance, researchers have engineered closed-loop spinal cord-machine interfaces (SCMIs) that administer electrical pulses bidirectionally along ascending and descending neural tracts. This configuration permits selective engagement of lower limb musculature while intercepting propagating signals through recording electrodes [22]. Such closed-loop designs significantly enhance movement quality by integrating sensory feedback—an indispensable element for refined motor control and adaptive learning.

Growing experimental evidence solidly affirms the capacity of bidirectional interfaces to mediate interactions between sensory and motor pathways. Clinical investigations with tetraplegic participants have revealed that dual implantation of intracortical microelectrode arrays in sensorimotor regions alongside extraneural peripheral nerve electrodes can facilitate selective peripheral nerve stimulation guided by decoded cortical signals, consequently restoring both motor capacity and tactile perception [80]. These bidirectional brain-machine interfaces (BMIs) permit instantaneous interpretation of intended motor commands while providing somatosensory feedback through microstimulation. This creates an efficient communication cycle that approximates natural sensorimotor integration—a bidirectional exchange vital for achieving intuitive neuroprosthetic control that drives muscle activation while reestablishing the sensory awareness required for dexterous tasks.

Recent technological progress has substantially upgraded bidirectional neural interfaces through innovations in electrode composition and architecture. Graphene-based intraneural electrodes, for example, demonstrate superior stimulation efficiency with diminished current requirements, while consistently recording compound nerve action potentials throughout prolonged implantation durations [81]. Parallel developments in microelectronic circuitry now allow synchronous high-voltage stimulation and low-noise neural recording within highly compact implantable units [82]. These hardware refinements work in concert with advanced signal processing algorithms that filter noise, categorize patterns, and interpret peripheral nerve signals, collectively boosting the functional performance of bidirectional interface systems [5].

In essence, bidirectional neural interface technology employs implanted microelectrode arrays to accomplish high-fidelity sensing and stimulation of spinal cord axonal bundles. When paired with closed-loop feedback control, these systems markedly improve the accuracy of motor rehabilitation. The successful interplay between sensory and motor pathways—validated across both animal studies and human trials—highlights their promise in reinstating sophisticated sensorimotor capabilities following spinal cord injury. Ongoing refinements in materials engineering, device design, and computational techniques promise to further evolve these interfaces, enhancing their adaptability, longevity, and clinical applicability for holistic neurorehabilitation.

4.2. Brain-computer interface (BCI) combined with spinal cord stimulation

The convergence of BCI and spinal cord stimulation (SCS) is rapidly emerging as one of the most promising strategies for restoring volitional motor control after spinal cord injury. By interpreting neural activity related to movement intention, BCIs can initiate precisely timed stimulation of spinal circuits below the injury level. This integrated method takes advantage of remaining neural connections and the nervous system's inherent capacity for adaptation and reorganization.

A growing number of experimental and clinical investigations have validated this combined approach. In rodent models of cervical SCI, for instance, a brain-computer-spinal interface (BCSI) accurately decoded forelimb movement plans from sensorimotor cortex signals, subsequently activating epidural spinal stimulation to successfully restore functional forelimb movements [83]. Human trials have yielded similarly encouraging outcomes: BCI-triggered functional electrical stimulation therapy (BCI-FEST) demonstrated both technical feasibility and meaningful clinical improvements in subacute SCI patients recovering reaching and grasping functions. Participants exhibited enhanced scores on functional independence measures following repeated training sessions [84]. Further evidence comes from a clinical case study, where combining BCI-based motor priming with transcutaneous spinal cord stimulation (tSCS) led to measurable gains in motor strength and sensory perception in an individual with chronic cervical SCI, suggesting that cortical preconditioning may amplify the rehabilitative effects mediated by spinal stimulation [85].

An important strength of certain advanced BCI systems lies in their bidirectional capability—they not only decode motor commands but also deliver sensory feedback through targeted neural stimulation, thereby completing the control loop in a more physiological manner. For example, integrated bidirectional BCIs have been developed to operate robotic exoskeletons for walking assistance, while simultaneously providing corresponding tactile sensations through intracortical microstimulation (ICMS). Such sensory input has been reported to produce tactile perceptions congruent with hand movements, thereby facilitating sensory feedback integration within BCI-controlled neuroprosthetics [21,86].

Interestingly, spinal cord stimulation itself appears to modulate cortical networks involved in sensorimotor processing. Electroencephalography (EEG) studies indicate that applying tSCS can alter functional connectivity within the cerebral cortex. This observed neural modulation may represent a core mechanism through which combined BCI-SCS therapies enhance neuroplasticity and promote motor recovery [87,88].

On the clinical translation front, this integrated approach has shown encouraging results in terms of safety, feasibility, and functional restoration. Notably, a fully implanted BCI system was used to drive hand functional electrical stimulation in individuals with complete cervical SCI. The system achieved a high degree of decoding accuracy and contributed to improved hand function over an extended treatment period [89–91]. Similarly, systems like KITE-BCI—which integrate a single-channel BCI with functional electrical stimulation—have demonstrated clinically acceptable setup times and sensitivity across both subacute and chronic SCI populations [92].

Despite these advancements, several hurdles remain. Key challenges include ensuring the long-term stability of neural signal decoding, minimizing the invasiveness of the technology, optimizing stimulation parameters for individual patients, and seamlessly integrating artificial sensory feedback into closed-loop control systems [93].

Future progress in this area will likely focus on several priorities: the development of embedded, modular BCI systems suitable for home-based rehabilitation, and the development of comprehensive strategies that orchestrate BCI, spinal stimulation, and robotic exoskeletons. By concurrently engaging efferent motor pathways and afferent sensory channels, such multi-modal interventions could synergistically enhance neural plasticity and drive functional recovery [94].

Overall, the synergistic integration of BCI and SCS technologies holds substantial promise for re-establishing voluntary motor control and sensory feedback in people living with SCI, potentially reshaping the landscape of neurorehabilitation.

4.3. Advances in brain-spinal cord-machine interface research in animal models

Animal models have been indispensable in establishing the scientific foundation for brain-spinal cord-machine interfaces (BSCMIs), with studies across species providing critical insights into interface functionality, durability, and clinical translation potential. In non-human primate models, particularly macaque monkeys, epidural spinal cord stimulation has proven effective in reactivating volitional upper extremity movements. These investigations reveal not only the functional capacity of such systems but, more importantly, the remarkable adaptive potential preserved within the corticospinal circuitry following injury. These findings offer a solid experimental basis for developing next-generation neuroprosthetic systems [95,96].

Parallel developments in rabbit models have demonstrated how electrocorticography (ECoG)-recorded brain signals can be translated into precise intraspinal stimulation patterns. Through nonlinear autoregressive exogenous (NARX) neural network modeling, researchers have established robust correlations between cortical activity and spinal stimulation parameters, leading to substantial recovery of natural leg movements in sedated SCI rabbits [97].

Rodent models, especially rats, have significantly contributed to our understanding of long-term interface stability. Implanted epidural or intraparenchymal electrode arrays, particularly those employing carbon-based materials like glassy carbon, have maintained stable electrochemical characteristics and elicited consistent motor evoked potentials over several weeks. This sustained performance highlights their viability for chronic neuromodulation research [9]. Furthermore, sophisticated electrode designs featuring integrated active electronics and high-density configurations—initially validated in larger animal models—have shown excellent durability while enabling complex spatial stimulation and recording configurations that remain fully compatible with rodent experimental setups.

Recent technological innovations now enable simultaneous recording from multiple neural sites—cortical, spinal, peripheral nerve, and muscular electrodes in freely behaving rats. This multisite approach yields comprehensive data on motor pathway dynamics across diverse behaviors, significantly enriching our comprehension of neural plasticity and the fundamental mechanisms underlying functional recovery [98].

Together, these cross-species investigations validate a fundamental principle: BSCMIs can effectively utilize residual neural pathways and inherent neuroplasticity to regain motor functions after spinal cord damage. These studies consistently underline several critical factors: the essential role of electrode biocompatibility, the necessity of long-term functional stability, and the critical importance of advanced computational algorithms for optimizing stimulation protocols.

The implications for clinical translation are substantial. These collective findings lay the groundwork for creating patient-specific, adaptive neuroprosthetic devices. By re-establishing volitional movement through integrated brain-spinal interfaces, this technology offers genuine potential for enhancing quality of life in individuals living with SCI (Figure 3).

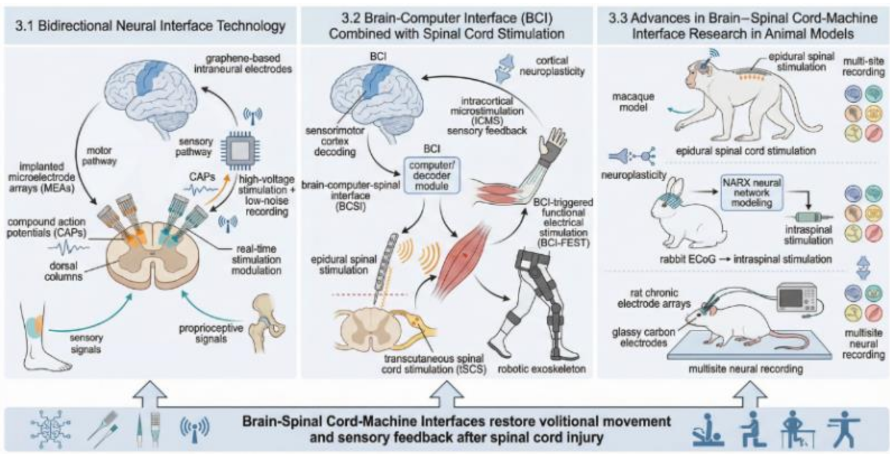

Figure 3. Overview of brain–spinal cord–machine interfaces (BSCMIs), including bidirectional neurointerfaces, BCI–SCS integration, and multi-site neural recording in animal models. Diagram created with Gemini Nano Banana Pro.

5. Clinical and cutting-edge research on electrical stimulation promoting neural function recovery

5.1. Surface and epidural spinal cord stimulation techniques

Among the diverse neuromodulation strategies being explored for spinal cord injury rehabilitation, transcutaneous spinal stimulation (TSS) and epidural spinal cord stimulation (eSCS) stand out as two pivotal modalities, each bringing distinct technical features and therapeutic potentials to the table.

TSS delivers electrical currents noninvasively through the skin surface to modulate spinal and cortical networks. This external approach improves patient acceptance and allows repeated application without surgical intervention. Mechanistically, TSS modulates the excitability of neural circuits within both cortical and spinal cord networks, thereby facilitating sensorimotor integration and functional gains. Electroencephalographic (EEG) recordings indicate that this technique engages motor-related cortical areas, implying it strengthens descending motor commands and fosters the neuroplastic changes necessary for restoring motor functions [99]. Moreover, studies involving individuals with chronic motor complete SCI reveal that TSS effectively reduces muscle hypertonus—an effect attributed to the activation of proprioceptive afferents and recruitment of inhibitory spinal interneurons [100]. This finding points to its utility in managing spasticity and supporting the recovery of voluntary movement.

In contrast, eSCS requires surgical placement of electrodes within the epidural space overlaying targeted spinal segments. This invasive method offers precise control over spinal circuits governing motor activity. By directing electrical stimulation to the dorsal aspect of the spinal cord, eSCS can selectively stimulate large-diameter proprioceptive afferents within the dorsal roots, which subsequently modulates spinal interneuronal networks to enhance motor output. Supporting clinical data shows that eSCS leads to improved motor capacity—including standing, stepping, and trunk stability—in people with chronic SCI [101,102]. The spatial accuracy of electrode positioning proves critical here; emerging paradigms like orientation-selective stimulation have been devised to optimize the distribution of the electrical field, boosting both the selectivity and overall effectiveness of the stimulation [103]. Functional MRI investigations in animal models further validate that eSCS activates distributed brain networks participating in motor and sensory processing [104]. This evidence reinforces its contribution to regaining functional abilities.

When comparing the two, TSS emerges as a safer and more accessible option than eSCS, with the added benefit of engaging both cortical and spinal networks while avoiding surgery. However, TSS is inherently constrained in its stimulation depth and spatial precision compared to the epidural approach. While invasive, eSCS provides superior targeting precision and has consistently yielded strong recovery in motor and autonomic functions—encompassing bladder and sexual performance—across various species and in human trials [105,106]. The use of EEG alongside TSS has shed light on the neural underpinnings of its effects, showing increased engagement of motor cortical regions that likely contribute to functional improvements [99]. Additionally, progress in wearable and implantable systems, exemplified by large-area epidermal electronics for EMG monitoring, aids in honing and customizing stimulation parameters for both TSS and eSCS [107].

Typical stimulation parameters vary depending on the modality and therapeutic objectives. For transcutaneous spinal stimulation (TSS), frequencies typically range from 5 to 150 Hz with pulse widths between 200 and 1000 μs and stimulation intensities between 20 and 100 mA ([100], see [108] for review]. Epidural spinal cord stimulation (eSCS) commonly employs frequencies of 20–50 Hz and pulse widths of

200–500 μs, with stimulation amplitudes ranging from 0.1–10 mA depending on electrode placement and patient tolerance (see [101, 102] for review). Functional electrical stimulation (FES) used for rehabilitation training generally operates at frequencies of 20–50 Hz with pulse widths of approximately 200–400 μs to achieve effective muscle activation ([109], for review see [47, 110], Table 1). Optimizing these parameters is critical for maximizing therapeutic outcomes while minimizing adverse effects. The parameter ranges shown represent commonly reported values across preclinical and clinical studies rather than standardized protocols.

To sum up, both surface-level and epidural spinal cord stimulation methods present synergistic pathways for influencing spinal and cortical networks to aid recovery post-SCI. TSS serves as a noninvasive tool to heighten neural excitability and plasticity via skin-surface application, as confirmed by EEG studies. Epidural stimulation achieves precise engagement of spinal segments through accurate electrode implantation, leading to better motor control and autonomic regulation. Continued innovation in stimulation protocols, electrode architecture, and neuroimaging techniques is poised to further refine these tools, amplifying their therapeutic value and expanding their role in clinical neurorehabilitation practice.

Table 1. Electrical stimulation parameters used in SCI studies.

Modality	Frequency	Pulse width	Intensity	Duration	Application
TSS	5–150 Hz	200–1000 μs	20–100 mA	30–60 min	locomotion
eSCS	20–50 Hz	200–500 μs	0.1–10 mA	continuous	motor recovery
FES	20–50 Hz	200–400 μs	adjustable	task-based	muscle activation

5.2. Functional improvement by combining electrical stimulation with rehabilitation training

Electrical stimulation, when paired with structured rehabilitation training, has established itself as a powerful combined therapy for functional restoration after SCI. This integrated strategy works by strengthening activation along preserved neural pathways and supporting motor skill acquisition. The synergy between targeted electrical neuromodulation and task-oriented practice helps engage and refine functional neural circuits more effectively than either approach could accomplish independently.

For example, in individuals with chronic tetraplegia, the simultaneous application of TSS and task-specific rehabilitation (TSR) led to marked gains in trunk stability and sitting balance. This combination boosted electromyographic activity in postural muscles and expanded movement ranges—evidence suggesting that electrical stimulation can amplify the contribution of residual pathways that often remain underutilized during standard rehabilitation [111]. Parallel findings come from stroke rehabilitation, where combining FES with Brunnstrom hand training produced better hand motor function outcomes compared to physiotherapy alone. These improvements, reflected in higher Fugl-Meyer Assessment scores and better functional test results, imply that carefully timed stimulation assists motor relearning by reinforcing neural circuits needed for voluntary control [112].

Mechanistic insights reveal that even low-intensity, subthreshold stimulation can regulate spinal network dynamics by fine-tuning neuronal firing patterns—affecting both randomness and rhythmicity [110]. This influence helps improve motor performance by optimizing the responsiveness and coordination of spinal interneurons.

Technological progress has been pivotal. Multi-channel electrical stimulation platforms can now elicit intricate movement synergies by selectively stimulating multiple muscles or spinal segments. One compelling example is an automated multi-channel FES-assisted gait training system. Using a wearable suit integrated with embedded electrodes and motion sensors, this setup enhanced walking speed, step length, and rhythm in people with incomplete SCI [109]. Such capabilities highlight how distributed stimulation sites can promote coordinated locomotion.

Taken together, current evidence indicates that electrical stimulation effectively boosts residual pathway activity and modulates spinal network function, thereby creating a foundation for improved motor learning and functional gains. The ability to adjust spinal excitability and evoke complex motor patterns via multi-site stimulation contributes to better functional outcomes and enhanced quality of life for those living with SCI and similar neurological conditions. Future investigations should prioritize refining stimulation protocols, embedding real-time neurofeedback, and tailoring interventions to individual patient profiles to maximize rehabilitation outcomes.

5.3. Electrical stimulation combined with artificial intelligence and intelligent rehabilitation technologies

The convergence of electrical stimulation with artificial intelligence (AI) and smart rehabilitation technologies marks a pivotal evolution in SCI care, unlocking new potential for customized and resource-efficient neurorehabilitation. AI-aided neuromodulation approaches enhance therapy personalization by systematically evaluating intricate physiological datasets, which supports the design of patient-specific intervention plans aligned with individual neural and functional profiles. Advanced computational techniques, such as machine learning and deep neural networks, contribute to the real-time refinement of stimulation parameters, thereby boosting treatment precision while curbing unwanted side effects. For example, by integrating multimodal inputs—ranging from electromyographic readings and neural activity traces to biomechanical metrics—AI frameworks help calibrate stimulation timing, amplitude, and localization to maximize gains in motor recovery [51,113,114].

Furthermore, pairing electrical stimulation with intelligent robotic devices and exoskeletons has substantially elevated the effectiveness of motor restoration therapies. Robotic exoskeletons used alongside FES offer complementary assistance by promoting voluntary motion and reinforcing muscle activation rhythms, thereby encouraging neuroplastic changes and functional rewiring in the spinal cord and brain. This cooperative interaction advances gait and upper extremity rehabilitation through repeated, task-oriented practice augmented by instantaneous performance feedback—an essential component for successful motor skill reacquisition post-SCI. Empirical evidence confirms that such integrated systems not only elevate locomotor outcomes but also alleviate demands on clinical staff and heighten patient involvement throughout the rehabilitation process [70,113].

Predictive modeling, driven by advanced algorithms, plays a key role in enhancing precision rehabilitation by forecasting treatment outcomes and adjusting neural network activity to optimize recovery. These predictive models analyze large clinical and neurophysiological datasets to identify biomarkers and patterns that suggest a patient's potential responsiveness to electrical stimulation, allowing clinicians to personalize interventions more effectively. Closed-loop systems that incorporate these models can continuously monitor neural activity and adjust stimulation parameters in real time, ensuring that spinal circuits remain in an optimal state of excitability, which contributes to improved functional outcomes. For instance, BCIs integrated with such algorithms can interpret cortical signals to control stimulation devices or robotic assistive technologies, enabling even patients with severe paralysis to restore voluntary movement [46,114–116]. Furthermore, AI supports multimodal rehabilitation approaches that combine electrical stimulation with virtual reality and neurofeedback, creating immersive environments that enhance both sensorimotor integration and cognitive engagement (Figure 4).

However, despite these promising advancements, several challenges persist, particularly in data acquisition, the generalizability of algorithms, and ethical issues surrounding privacy and data security. High-quality, large-scale clinical datasets are crucial for developing robust AI models that can handle the variability found in SCI presentations. Collaborative efforts between clinicians, engineers, and data scientists are necessary to address these challenges and to implement AI-enhanced electrical stimulation technologies into routine clinical use [51,113]. Moving forward, there is a strong focus on developing adaptive, multimodal neuromodulation systems that integrate electrical stimulation with biochemical and biomechanical signals, guided by AI, to provide personalized, autonomous therapies. This integrated approach holds significant potential to transform neurorehabilitation, offering more effective and sustainable restoration of motor functions for individuals with spinal cord injuries.

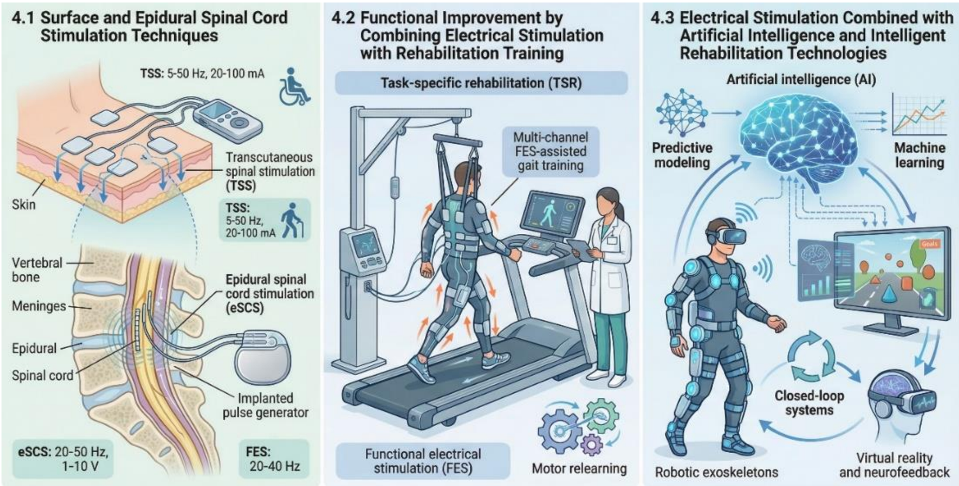

Figure 4. Clinical and cutting-edge research on electrical stimulation promoting neural function recovery. Diagram created with Gemini Nano Banana Pro.

6. Conclusion

In conclusion, the development of neurointerface-based electrical stimulation technologies for SCI represents a promising frontier in neurorehabilitation, with significant potential to support neural repair and functional recovery. This review highlights the progress made by combining multimodal therapeutic approaches, advancements in materials science, and sophisticated neuromodulation systems. While the role of electrical stimulation in modulating neural network activity and promoting neuroplasticity is well-understood, its clinical effectiveness is enhanced when used in combination with neural stem cell therapies and structured rehabilitation programs. This synergy creates a more favorable environment for axonal regeneration and synaptic reorganization, leading to meaningful improvements in both motor and sensory functions in SCI patients.

A key factor driving these advancements is the innovation of flexible carbon-based electrodes, wireless power delivery systems, and the application of nanomaterials. These breakthroughs address long-standing challenges related to the stability, biocompatibility, and precision of neural interfaces, ensuring that neuromodulation can be both sustained and safe. The advent of brain-spinal cord-machine interfaces further exemplifies progress by allowing closed-loop control of stimulation, driven by a patient's intentions. This technology effectively bridges the gap between voluntary neural commands and functional output, leading to more precise and adaptable restoration of lost functions. These systems showcase the integration of neuroscience, bioengineering, and computational intelligence, underscoring the need for collaborative work across multiple disciplines.

While preclinical studies have provided valuable insights into the mechanisms involved and have validated proof-of-concept, clinical application remains a significant challenge. The diversity of SCI pathology, differences in patient responses, and the complexity of neuromodulatory effects call for carefully designed, large-scale clinical trials. These trials must focus on optimizing stimulation parameters, timing, and combined approaches to maximize therapeutic efficacy while minimizing adverse effects. Additionally, ethical concerns and patient-centered outcome measures must guide the development and application of these technologies to ensure that they address real-world challenges effectively.

Despite the encouraging progress in neurointerface-based electrical stimulation technologies, several critical challenges remain before widespread clinical translation can be achieved. First, long-term stability of implanted neural interfaces remains a major concern, as chronic inflammatory responses and electrode degradation can compromise stimulation efficacy. Advances in soft bioelectronic materials, conductive hydrogels, and biointegrated electrodes may help address these limitations. Second, stimulation parameters are often optimized empirically and vary significantly among patients, highlighting the need for adaptive closed-loop neuromodulation systems capable of dynamically adjusting stimulation patterns. Finally, increasing evidence suggests that electrical stimulation alone may not be sufficient for optimal neural regeneration. Integrating neuromodulation with biomaterial scaffolds, stem cell therapies, and drug delivery systems may provide a more favorable microenvironment for axonal regeneration and circuit reconstruction [117,118].

Looking ahead, the future of SCI electrical stimulation lies in the continued integration of expertise from multiple fields, including materials science, neurobiology, biomedical engineering, and clinical sciences. Personalized neuromodulation, guided by real-time neural feedback and adaptive algorithms, offers the potential to tailor treatments to individual patients. Expanding research to include long-term functional outcomes and quality-of-life assessments will also be crucial for evaluating the true impact of these interventions. Ultimately, ongoing investment in translational research and collaborative efforts will be essential for bridging the gap between laboratory discoveries and their clinical applications.

In summary, neurointerface-based electrical stimulation technologies have introduced a new era of possibilities for SCI treatment, characterized by advanced device engineering and integrated therapeutic approaches. By synthesizing various research findings and addressing existing challenges through rigorous clinical evaluation and cross-disciplinary innovation, this field is on track to achieve its goal of maximizing functional recovery for individuals with spinal cord injuries. These advances not only contribute to scientific progress but also have significant implications for improving patient autonomy and quality of life.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools to improve language and readability and used Gemini Nano Banana Pro in order to generate the figures. After using this tool, the author reviewed and edited the content as needed. The authors take full responsibility for the content of the manuscript and the figures.

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Authors' contribution

Conceptualization, YRL; investigation, YRL; resources, HZP; writing—original draft preparation, HZP; writing—review and editing, YRL; visualization, HZP; supervision, YRL; funding acquisition, YRL. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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