REVIEW ARTICLE

Reconstructing Structure and Function Post Spinal Cord Injury by Facilitating Novel Integration Therapy and Neuromodulation

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Abstract: Spinal cord injury (SCI) has been a research hotspot for its poor prognosis and limited effects in current treatment methods. Consistent hostile responses in damaged regions and functional incapabilities can lead to major complications. Most approaches focus on either structural or functional reconstruction. For restoring function, facilitating innate neuroplasticity and neuromodulation showed promising potentials, including rehabilitation therapy and various forms of electrical stimulation, examples include epidural electrical stimulation (EES), functional electrical stimulation (FES), transcutaneous electrical neural stimulation (TENS), and deep brain stimulation (DBS). Recent advances in treatments for SCI include integrating conventional methods and installing interfaces, such as brain-computer interface (BCI) and brain-spine interface (BSI).
Keywords: Spinal Cord Injury; Neuromodulation; Electrical Stimulation; Rehabilitation Therapy; Functional Reconstruction.

1. INTRODUCTION

Spinal cord injury (SCI) is a serious central nervous system (CNS) disease, commonly caused by trauma [1]. According to the 2019 Global Burden of Disease, approximately 20.6 million people suffer from different levels of SCI [2]. SCI results in a loss of sensory and motor functions from below the damaged region. Complications in multiple systems can occur as an aftermath of SCI, severely decreasing patients' quality of life and burdening families and communities. Though there is no effective method currently in clinical use that can achieve a complete restoration of spinal cord functions, explorations and advances are being made, for the restoration of spinal cord function is essential in better outcomes for patients, including lower incidence rates of secondary traumas, higher life qualities, etc. [3]

Anatomically, incomplete SCI is more common in humans. Though clinically, complete SCI is defined by no detection of motor or sensory response from below the lesion level, spared connections remain [4]. Consistently induced neuronal loss in the region caused by hostile environment and growth-inhibitory factors can lead to secondary injury post the primary SCI. Therefore, retaining adverse responses (such as immune responses) is ideal for preserving spared cells and tissue to maintain remnant structure and function [5].

The pathophysiologic mechanism of secondary SCI differs in sequential phases: acute, sub-acute and chronic. Spinal ischemia, ionic imbalance, vasogenic edema and glutamate excitotoxicity were

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mostly responsible for acute damages, while sub-acute changes are characterized by neuroinflammation, mitochondrial phosphorylation, higher levels of nitric oxide synthase (NOS), apoptosis and necrosis, axonal degeneration, remyelination and remodeling, also glial scar formation [6]. If adverse factors persistently exist, the injury will progress into the chronic phase, with cystic cavity formation, glial scar maturation and axonal dieback [7, 8]. In the acute and sub-acute phases, the main goal for medical interventions is to preserve neurons and surrounding tissues (i.e. neuroprotection), to prevent future cascades of neuronal loss [7]. For example, pressured and isobaric oxygen treatment in the acute phase can reduce the inflammatory response, potentially inducing tissue survival [9]. Therapeutic hypothermia is reported to be more effective with an earlier application to patients [10]. In the chronic phase, interventions focus more on the prevention of prolonged trauma caused by long-term inflammatory response and persistent oxidative stress [8]. Strategies include reducing inflammation, anti-oxidation, revascularization, modifying micro-environments of damaged regions, etc. [11]

2. RECONSTRUCTING NORMAL STRUCTURES IN DAMAGED REGIONS OF SCI

Structural repair involves mainly the restoration of the anatomical structures (such as nerve cells, axons, and supporting tissues) and the re-establishment of the natural physiology of the micro-environment in the regions affected by SCI, such as modulation of immune factors and growth factors, usually through molecular, cellular, and tissue-level interventions. This type of repair aims to recover the physical integrity of SCI, which can facilitate functional recovery [4].

2.1. Pharmaceutical agents and molecular intervention

Molecular agents can provide nutrients to the damaged area, impede inflammation, and reduce scarring while inducing neuroprotection, cell repair, and axonal regeneration. They can be administered in various ways. Common clinical approaches include systemic administration via oral or intravenous routes, intrathecal administration targeting the CNS, or direct regional administration through surgical implantation near the injured spinal cord.

2.1.1. Anti-inflammatory factors

Anti-inflammatory drugs reduce inflammatory responses, thereby minimizing secondary damage and promoting repair. Commonly used anti-inflammatory drugs, such as methylprednisolone sodium succinate (MPSS), can decrease inflammation, reduce free radicals, enhance blood supply, and elevate the secretion of neurotrophic factors, thus lowering the risk of secondary injury [10, 12]. However, recent studies suggest that methylprednisolone has limited efficacy for acute spinal cord injury [5, 8, 12]. AO Spine practice guideline in 2017 suggested a weak recommendation for the use of methylprednisolone sodium succinate in the acute phase [13].

Glial scarring can impede axonal regeneration across damaged tissue, therefore reducing scar tissue formation may facilitate axonal regeneration and functional recovery [8]. In neonatal mouse models, microglia secrete fibronectin to synthesize extracellular matrix and bridge spinal cord transections; meanwhile expressing high levels of protease inhibitors and anti-inflammatory substances, creating a scar-free environment that supports axonal regeneration. Chemical protease inhibitors such as E64 and serpin A3N have shown similar beneficial effects [14].

2.1.2. Neuroprotection strategies

Neuroprotective strategies involving molecular interventions can be separated according to the different hostile pathways intended to be modulated, including neurotransmitter modulators, channel blockers, anti-apoptotic drugs, etc. [7]

Neurotransmitter modulators include agonists and antagonists. For alpha 2-adrenergic (A2A) receptors, both the up regulation and down regulation of its expression have been reported to have neuroprotective effects [15-17], with beneficial effects on tissue preservation, locomotor functions, pain management [15], and inflammation control [16]. Blockade of A2A receptors may suppress the release of excitable transmitters that activate excitotoxicity to healthy nearby neurons [17]; while receptor agonists are reported to have anti-inflammatory effects, including reducing pro-inflammatory cytokines, impeding apoptotic processes, and potentially promoting axonal regeneration [16]. Channel blockers regulate cellular activity through ion modulation. In acute phases of SCI, the increase of intracellular influx of sodium and calcium cultivates cell death [18]. Sodium channel blockers hinder this process

and inhibiting neurons from releasing high concentrations of glutamate [19], similar to glutamate receptor antagonists, which cause toxicity to healthy neurons nearby, resulting in magnified damage [20]. Anti-apoptosis modulators can function in various stages of intrinsic and extrinsic pathway cascades, such as inhibitors of caspases and calpains [7].

Certain drugs that have contributed to other diseases in neural repair, enhancing neural plasticity, and managing complications such as muscle spasms or neuropathic pain, have been explored for their potential to indirectly aid spinal cord functional recovery. Examples include neuroprotective drugs such as riluzole [18] and immunosuppressants such as minocycline [10]. However, research findings reported inconsistent efficacy [8, 12, 21], highlighting an urgent need for the development of novel clinical drugs for spinal cord injury.

2.1.3. Bioactive factors

Growth factors are essential for supporting neural development and enhancing neuronal survival. Brain-derived neurotrophic factor (BDNF) promotes axonal regeneration, neuroprotection, synaptic remodeling, and enhancing synaptic connectivity, facilitating neural plasticity and repair following injury. Fibroblast growth factor (FGF) stimulates axonal growth, promotes angiogenesis, and exerts effects on inflammatory cells, thereby providing both anti-inflammatory and neuroprotective benefits. Neurotrophin-3 (NT-3) has been shown to support oligodendrocyte proliferation, thereby promoting myelination and neuroprotection without inducing unwanted side effects, such as pain or spasms, which are often associated with other neurotrophic factors [8].

2.2. Cellular repair or replacement as structural restoration

On cellular levels, structural restoration can be achieved by repairing damaged neurons and supporting cells, or by replacing unhealthy tissue with stem cells in the injured site, ultimately reconstructing a natural environment.

2.2.1. Repairing damaged neurons or promoting axonal regrowth

Axonal growth can present as the regrowth and reconnection of the freshly cut proximal segment in injured axons, and (or) as the newly extended axons from uninjured neurons [5]. Axon regeneration is often unsuccessful. The main theories for this incapability include 1) extrinsic inhibitor, 2) neuron intrinsic, and 3) growth factor theory. More research in the area is emerging with increasing evidence for the first two theories. Extrinsic inhibitor theory suggests a tendency of the CNS to inhibit growth and regeneration post injury, with related factors including myelin inhibitors, axon guidance molecules, etc. A regulation or deletion in protein translation pathways of neurons, such as PTEN-mTOR, and transcriptional pathways such as SOCS3, JAK2-STAT3, can generate axon regrowth, evidencing the neuron intrinsic theory [5].

New theories are being presented in the discussion of neuroregeneration. Studies using stem cell therapy have established evidence for several hypotheses. If presented with environments enabling growth, neurons are able to revert into an immature state, allowing the regeneration of axons, albeit with disadvantages or inhibitors [5]. This reversion can be initiated by the injury itself, presenting as a regenerative transcriptome in neurons. With homologous neural progenitor cell grafting, this effect can be sustained [22].

Single-cell genomic technologies were widely used for classification and identification among neuron cells [23]. Using this method, researchers were able to identify specific subpopulations of neurons, some of which are essential in the functional restoration of incomplete SCI [24]. A recent study has shown that targeted regeneration of a specific neuronal subpopulation to its original distribution or projection site resulted in substantial improvements in walking abilities in mice with complete SCI, whereas broad neuron regeneration failed to achieve such effect [25], indicating the need for a more targeted approach in axon regeneration for functional restoration.

2.2.2. Stem Cell Transplantation Assists Neural Repair in Spinal Cord Injury

With the limitations of the regenerative ability of the CNS, explorations into multipotent stem cell replacement therapy have been made [10]. Mesenchymal stem cells (MSCs) and neural stem cells (NSCs) have demonstrated the capacity to replace damaged cells and/or facilitate the repair of surrounding spinal cord tissues through the secretion

of various molecular factors [26, 27]. Induced pluripotent stem cells (iPSCs) are capable of differentiating into various neural and glial cell types at the site of injury, enabling the reconstruction of normal tissue architecture [28]. While preclinical studies in animal models highlighted the potential efficacy of stem cell therapies, their clinical translation remains challenging, with limited therapeutic benefits due to factors such as high susceptibility to adverse environmental conditions [29] and low long-term survival rates of transplanted cells [30]. To address these limitations, combined therapeutic approaches are increasingly explored for their potential to yield superior outcomes [31]. For example, incorporating trophic factors into NSC transplantation [5] or integrating molecular regulatory interventions [29] represents a promising direction for enhancing therapeutic efficacy.

2.3. Facilitating Structural Repair of Spinal Cord Injury Using Advanced Biomaterials

Spinal cord injury often results in the formation of cystic cavities [7], which not only cause structural disruption but also harbor necrotic tissue and fluid devoid of the bioactive factors necessary for neuronal growth. These pathological changes significantly impede neural regeneration [32]. Biomaterials, characterized by their excellent biocompatibility and biodegradability, offer a promising solution. They serve as structural scaffolds to bridge damaged tissues and can also deliver anti-inflammatory agents, molecular regulators, and/or stem cells, thereby promoting neural regeneration and spontaneous tissue reconstruction [11].

Categories of biomaterials include natural-origin materials, synthetic materials, nanomaterials, and composite materials. Natural-origin materials, such as collagen, fibrin, hyaluronic acid, chitosan, alginate, polysialic acid, and gelatin, are noted for their low toxicity, high biocompatibility, and degradability. For instance, the long-term safety and efficacy of collagen-based scaffolds have been well-documented [33]. Compared to natural materials, synthetic materials offer more selectivity over degradability and physical properties due to the diversity of raw material sources and customizable characteristics [11]. Examples include synthetic peptides and polymers, such as conductive materials like polyaniline and polypyrrole. Advanced fabrication techniques, including hydrogel synthesis, electrospinning, decellularization, and 3D printing, enhance the versatility and applicability of biomaterials [34].

3. FACILITATING NEUROPLASTICITY OF THE CNS

Neuroplasticity refers to the dynamic capacity of the nervous system to modulate its connections in response to changes following neurological impairment [35]. This process involves self-modifications at the structural and functional levels, which are influenced by a spectrum of factors such as experiential learning, traumatic events, environmental conditions, and memory [36, 37]. The plasticity inherent in the nervous system is crucial for the organism's ability to adapt its behavior to fluctuations in both internal and external environmental stimuli. This adaptability is facilitated through mechanisms such as dendritic and axon regeneration, stem cell transplants, and interface connections for neuromodulation [38, 39].

Structural plasticity can be divided into four different ways: nerve regeneration, nerve germination, synapticplasticity, and myelin plasticity, which can achieve partial or ideally whole structural restoration through new neural connection routes [40].

Nerve regeneration is the process of axon regrowth, involving construction, reconstruction, metabolism, and repair. It requires a viable cell body and glial cell support. The process is challenging due to inhibitory factors in the CNS, such as myelin debris and glial scars, which hinder axon growth and synaptic reconnection [41].

Nerve sprouting can be divided into regenerative sprouting, collateral sprouting and compensatory sprouting. They mainly manifested in peripheral nerves and innervated targeted muscles [42, 43].

Synapticplasticity encompasses changes in synapse structure and function post-neuronal injury, including two types. The first type is synaptic combination plasticity, involving long-lasting morphological changes and the creation of new synapses with transmission functions. The second type is synaptic transmission plasticity, which is the modulation of synaptic efficiency through increased or decreased activity [44]. Most synaptic plasticity forms investigated thus far fall under the standard autonomous correlative Hebbian

category, and this includes practically all types of spike timing-dependent plasticity (STDP). They follow the quintessential Hebbian protocol, meaning if two neurons are frequently active simultaneously, the synaptic connection becomes stronger [45].

Myelin plasticity has been considered to be the contributions of myelin to neural circuit function, the dynamic influences of experience on myelin microstructure, and the role that plasticity of myelin may play in cognition [46].

Functional restoration can be achieved by preserving and enhancing the function of spared regions, such as strengthening synaptic connections or elevating the sensitivity of neurons.

Neuroplasticity allows the CNS to reallocate functions to undamaged areas when other parts are injured, compensating for lost capabilities. This involves nearby neurons, the healthy contralateral side, and behavioral adjustments [8]. With applicable treatment, like chemical or electrical stimulation or rehabilitative training, dormant nerve cells can be activated to take over the roles of damaged pathways. Some neurons can regain their activity and function, potentially restoring lost abilities with no significant findings of anatomical change [7].

4. NEURAL-NETWORK-BASED MODULATION AND FUNCTIONAL RECONSTRUCTION

Spontaneous repair and restoration occur after SCI due to the innate structural and functional plasticity of the CNS, making it possible for the neurons to reroute and deliver information by alternative circuits [5, 24]. Neuroplasticity allows the nervous system to reorganize and form new neural connections to bypass damaged areas. Functional restoration can be achieved by 1) preserving and enhancing the function of spared regions (such as strengthening synaptic connections or elevating sensitivity of neurons) through chemical or electrical stimulation or rehabilitative training with no significant findings of anatomical change, or 2) achieving partial or ideally whole structural restoration, creating new neural connection routes through axon regeneration, stem cell transplants, or interface connections for neuromodulation.

Clinically, enhancing peripheral sensory input and central reflexes through neuromuscular promotion techniques in rehab is vital for boosting brain and spinal plasticity in patients with neurological impairments [47]. This approach can lead to functional recovery and improved quality of life. Neuroplasticity provides a physiological basis in the rehabilitation of patients with SCI. Understanding the mechanism of neuroplasticity and its influencing factors provides a guiding method for the remodeling of nerve function in patients with nerve injury [48].

Explorations of facilitating neuroplasticity are constantly being made, ranging in multiple aspects such as rehabilitation therapies, electrical stimulation, and constructing alternative pathways. Examples of functional restoration therapies applied in clinical trials [49-60] are included in Table 1. These clinical studies highlight the translational potential of bridging foundational research to real-life applications. For example, López-Larraz *et al.* (2016) [49] proved EEG-based brain-machine interfaces (BMI) successful in triggering exoskeleton-assisted gait initiation in 3 of 4 participated SCI patients. Comino-Suárez *et al.* (2025) [60] demonstrated that combining transcutaneous spinal cord stimulation (tSCS) with robotic-assisted gait training (RAGT) significantly improved lower extremity motor scores (LEMS) and gait recovery in subacute incomplete spinal cord injury (iSCI) patients compared to sham stimulation, highlighting the potential of non-invasive neuromodulation. On the other hand, invasive strategies also presented promising results. Ajiboye *et al.* (2017) [50] demonstrated a groundbreaking implanted FES + intracortical BCI system that enabled a tetraplegic participant to regain volitional control of reaching and grasping. Lorach *et al.* (2023) [58] pioneered a fully implanted brain-spine interface (BSI), restoring natural walking in a chronic cervical SCI patient through cortical signal-driven epidural stimulation, enabling adaptive locomotion across complex terrains and triggered neurological recovery, allowing the participant to walk with crutches even when the system was off. These studies exemplify the translational spectrum from non-invasive adjunct therapies to invasive neuroprosthetics, bridging cortical intent to functional restoration.

Study (Author, Year)	Design	Participants	Intervention(s)	Outcome Measures	Duration
López-Larraz 2016 [1]	Non-RCT	3 healthy subjects, 4 SCI patients (ASIA C or D, iSCI, undergoing gait rehabilitation)	BMI-controlled ambulatory exoskeleton (no weight/balance support); EEG-based movement intention decoding to trigger exoskeleton movement; 3 healthy subjects for system validation, 4 SCI patients for clinical testing	Average decoding accuracy; Gait initiation detected via EEG (ERD, MRCP); Exoskeleton successfully triggered in 3 of 4 SCI patients; exertion and fatigue levels; QUEST user satisfaction scale	1-day experiment for healthy subjects; 3-day protocol for SCI patients (1 familiarization, 2 BMI sessions)
Ajiboye 2017 [2]	Non-RCT	1 male; ASIA-A, C4 SCI	Implanted FES; intracortical BCI (iBCI)	Cortically commanded single-joint and multi-joint arm movements (point-to-point target acquisition in virtual/own arm animated by FES)	2 years
Hoffman 2017 [3]	Non-RCT	17 chronic, stable cervical SCI; AIS: A (n=12), B (n=1), C (n=2), D (n=2)	MediSens handgrip device; weekly handgrip-based ABT	MVC, MAA, and SCIM (MVC: 4.1 N to 21.2 N [NS]; MAA: 9.01% to 21.7% [p=0.02]; SCIM unchanged)	~21.3 weeks
Akkurt 2017 [4]	RCT	33 SCI patients (Intervention: n=17; Control: n=16)	Arm ergometer exercise (3 days/week; 1.5 h/week at 50-70% pVO2) plus general exercise (2 sessions/day; 5 days/week)	pVO2 and PO levels; no significant changes in functional status, QoL, psychological state, disability level, or metabolic parameters	12 weeks
Edwards 2022 [5]	RCT	25 chronic iSCI; groups: 9 [Ekso], 10 [Active Ctrl], 6 [Passive Ctrl]	Exoskeleton-based robotic gait training	Self-selected gait speed; 6MWT; TUG; clinical ambulation category	12 weeks
Rowald 2022 [6]	Non-RCT	3 chronic iSCI	EES plus overground robot-assisted rehabilitation training	Recovery of independent ambulation (standing, walking, cycling, swimming, trunk control)	Pre-implant (6-8 wks), implant/stimulation optimization (6-8 wks), rehab training (~5 months; total starting 8-12 months post-injury)
Nicolelis 2022 [7]	RCT	8 males; traumatic SCI (thoracic), AIS-A; complete paraplegia; >6 wks post-injury	Locomotion training with BMI: LOC vs. L+B; using Lokomat and ZeroG	ISNCSCI: Mean Lower Extremity Motor, Pinprick, and Tactile scores	14 wks training with 8 wks follow-up

Study (Author, Year)	Design	Participants	Intervention(s)	Outcome Measures	Duration
Mitchell 2023 [8]	Non-RCT	4 patients with severe bilateral upper-limb paralysis	Fully implanted endovascular BCI (Stentrode with thought-controlled digital switch)	Successful computer control using the BCI	12 months follow-up
Jo 2023 [9]	RCT	20 chronic SCI participants	20 sessions of 30-min multisite Hebbian or sham stimulation targeting corticospinal-motoneuronal synapses of multiple leg muscles; 60-min exercise training	10 MWT walking speed; MEPs, MVCs; GRASSP; ISNCSCI sensory and function scores	4-7 weeks
Lorach 2023 [10]	Non-RCT	1 patient; incomplete cervical (C5/C6) SCI	BSI integrated with neurorehabilitation: walking, single-joint movement, balance training with standard physiotherapy	Natural gait with stimulation; volitional hip flexion (without stimulation); sensory/motor scores; WISCI-II scores	Calibration: 6 wks; neurorehabilitation: 15 wks; follow-up: 3 years
Moritz 2024 [11]	Non-RCT	60 SCI patients	ARCEX Therapy (surface ES via ARCEX device) plus rehabilitation	Primary: Strength (ISNCSCI-UEMS, GRASSP) and function (CUE-T/GRASSP); Secondary: responder rates (ARCEX vs. rehab-alone)	25 sessions (60 min each) over 4 months
Comino-Suárez 2025 [12]	RCT	27 iSCI participants	tSCS combined with RAGT (standard Lokomat protocol: 5 familiarization, 20 sessions with active/sham tSCS, 15 sessions standard Lokomat)	Primary: LEMS and dynamometry; Secondary: 10MWT, TUG, 6MWT, SCIM III, WISCI-II, and MEP (via TMS)	40 sessions with 3-week follow-up

Table 1. Summarized Table of Functional Restoration Clinical Studies. **Abbreviations:** ABT: Activity-Based Therapy; AIS: ASIA Impairment Scale; BCI: Brain-Computer Interface; BMI: Brain-Machine Interface; BSI: Brain-Spine Interface; CUE-T: Clinical Upper-Extremity Evaluation Tool; EES: Epidural Electrical Stimulation; ES: Electrical Stimulation; FES: Functional Electrical Stimulation; GRASSP: Graded Redefined Assessment of Strength, Sensibility and Prehension; iBCI: Intracortical Brain-Computer Interface; iSCI: Incomplete Spinal Cord Injury; ISNCSCI: International Standards for Neurological Classification of Spinal Cord Injury; LEMS: Lower Extremity Motor Score; LOC: Locomotion Only; L+B: Locomotion plus Brain-Machine Interface; MAA: Mean Absolute Accuracy; MEP: Motor Evoked Potential; MRCP: Movement-Related Cortical Potentials; MVC: Maximum Voluntary Contraction; Non-RCT: Non-Randomized Controlled Trial; pVO2: Percentage of Peak VO2; QUEST: Quebec User Evaluation of Satisfaction with Assistive Technology; RAGT: Robotic-Assisted Gait Training; RCT: Randomized Controlled Trial; SCI: Spinal Cord Injury; SCIM: Spinal Cord Independence Measure; tSCS: Transcutaneous Spinal Cord Stimulation; TMS: Transcranial Magnetic Stimulation; TUG: Timed Up and Go; 6MWT: 6-Minute Walk Test; 10MWT: 10-Meter Walk Test.

However effective the studies have reported their methods, limitations and challenges persist. Key concerns include 1) surgical complexity leading to major financial costs and limited application criteria, such as BSI surgery which consists of dual cortical implants; 2) accessibility as most of the procedures require special equipment or environments, including non-invasive approaches; 3) limited generalizability as most pioneered studies are focused on small cohorts with strict eligibility criteria or even single participant (Ajiboye *et al.* 2017, Lorach *et al.* 2023). For future advances, cost-efficient and accessibility-enhancing innovations could be prioritized, also longitudinal studies investigating the long-term effects of interventions could be carried out to assess durability, such as prospective sessions (Jo *et al.* 2023 [57]), and continued follow-ups and monitoring (for example 8 weeks in Nicolelis *et al.* 2022 [55], 12 months in Mitchell *et al.* 2023 [56], and 3 years in Lorach *et al.* 2023).

To better review current existing approaches, we have categorized them into 1) rehabilitation therapies, which are mostly more conventional and non-invasive, 2) electrical stimulations, including invasive and non-invasive, and 3) installing interfaces, which are comparatively more effective and have been a recent research hotspot. Detailed discussions are as follows.

4.1. Rehabilitation therapies

Rehabilitation therapy is a strategy like exercise or physical training, which appears to have multiple applications and benefits for an acute or chronic SCI. It seems logical to address the need for neuroprotection, regeneration and rehabilitation will require different treatment strategies applicable to varied stages of the post-injury response [61]. Long-term outcomes are expected differently for varied injury levels. The current guidelines recommend tailored rehabilitation degrees. For higher-level injuries, low-intensity rehabilitation (such as strengthening specific undamaged muscles) to perform adaptive movements such as call bells is recommended. As for lower-level injuries, the goal for rehabilitation is to gain complete independence in self-care, therefore training interventions are more complex and demanding, with examples such as motor training and balance training [62].

Muscle atrophy occurs after spinal cord injury as an aftermath of muscle disuse and denervation. This effect is magnified especially in injuries of higher levels [63]. This may barricade the rebuild of function as muscles remain consistently atrophied, in which case neural repair alone could not grant effective function reconstruction ideally [64]. Exercise and electrical stimulation are the main methods for the prevention of muscle atrophy, regardless of disease mechanisms [65]. In consideration of muscle atrophy, weak and inconsistent contraction may limit therapeutic choices [66]. Careful musculoskeletal measurements should be taken pre-regimens for optimal benefits (such as muscle structure, fiber type composition, muscle loads, etc.) [63, 66]. Some studies have found benefits in the prevention of muscle loss through exercise with (or without) electrical stimulation [67-69]. Exercise therapies combined with pharmaceutical interventions also showed potential benefits for muscle recovery [70, 71].

Rehabilitation therapy has been demonstrated to be advantageous at cellular and biochemical levels and beneficial for the whole animal or human subject [72].

Activity-based therapy (ABT) can assist brain and spinal cord adaptation and has proven effective in past studies in restoring functionality in SCI patients [73]. However, some recent researchers believe ABT lacks efficacy in SCI [74]. Rehabilitative training such as passive exercise, task-specific motion repetitive exercises assisted by exoskeleton and other devices [75], or active exercise with some voluntary control and use of neuroprosthetics, can enhance sensorimotor recovery after SCI by promoting adaptive structural and functional plasticity while mitigating maladaptive changes at multiple levels of the neuroaxis. It is always suitable for rehabilitation training of patients after stroke, spinal cord injury, myelitis, craniocerebral injury, coma and joint replacement surgery [72, 75]. Repetitive exercises in particular have shown a positive correlation: the higher the intensity of repetition, the better the outcome [75].

Rehabilitation training for SCI has shifted in its main focus from a compensatory purpose to restoring motor functions, with multiple approaches such as robotic-assisted locomotor training, gait training, sometimes combined with functional electrical stimulation (FES), and repetitive transcranial magnetic stimulation (rTMS) devices [74]. In later sections, we will be focusing on granting extremity locomotion training programs for SCI patients.

4.1.1. Exoskeleton-Assisted Training

Wearable powered robotic exoskeletons are a developing technology of wearable orthoses that can serve as assistive devices to enable non-ambulatory individuals with spinal cord injuries to maintain muscle volume, stand and walk, or as rehabilitation tools to enhance walking ability in ambulatory individuals with SCI [76]. The exact physiology mechanism is still unclear, but it can be seen in the clinic that the success of walking with these powered exoskeletons depends on how well the user senses and controls the device and how smoothly the kinematic control of the lower limbs of the exoskeleton is [77]. These are key factors to facilitate human-robot interaction and to increase the walking abilities of the subject [78]. Robotic-assisted locomotor training is proven effective in providing non-ambulatory individuals with thoracic-level motor-complete SCI the ability to walk at modest speeds. This speed is related to level of injury as well as training time [79]. The exoskeleton devices also perform well in a home-like environment and are safe and well-tolerated, which can be convenient for SCI patients to do long-term stable training [76].

4.1.2. Gait Training

Gait is a crucial requirement for the rehabilitation of patients with spinal cord injuries. Robot-assisted gait training (RAGT) after SCI induces several different neurophysiological mechanisms to restore walking ability, including the activation of central pattern generators, task-specific stepping practice and massed exercise [80]. A systematic review found that RAGT improves mobility-related outcomes to a greater degree than conventional overground training (OGT) for patients with incomplete SCI, particularly during the acute stage [81]. Gait training is a promising method to restore walking and improve mobility in SCI patients, helping them maintain a healthy lifestyle and increase physical activity. However, the specific dosages and guidelines are still unsure, and more research is urgently needed [82].

4.1.3. Combined therapy

Currently, rehabilitation robot technology combining functional electrical stimulation (FES), and repetitive transcranial magnetic stimulation (rTMS) devices is a hot research topic. This strategy controls the lower extremity movements through a real-time-feedback system [83]. FES refers to the use of a certain intensity of low-frequency pulse current to stimulate one or more groups of muscles through a pre-set program to induce muscle movement or simulate normal autonomous movement [84]. High-intensity rTMS can generate excitatory postsynaptic potentials, resulting in abnormal excitation of nerves at the stimulation site. In contrast, low-intensity rTMS has the opposite effect. Through bidirectional regulation of brain excitation and inhibition functions, local nerves interact with each other through the connection between neural networks [85]. Through long-term rehabilitation training and combined with the robot exoskeletons, it can utilize neuroplasticity and stimulate the input of nerve signals in sensory and motor pathways, and promote the reorganization of brain and spinal cord functions [86]. A meta-analysis demonstrated that RAGT therapy in combination with non-invasive brain stimulation was effective in patients with SCI [87].

4.2. Electrical stimulation

Electrical stimulation (ES) can induce connections between synapses and assist in remodeling, sequentially activating muscles, which is essential in spinal cord functional restorations [88].

Epidural electrical stimulation (EES) stimulates the spinal cord with electrical impulses, helping patients regain complex motor functions even if they have a complete injury [54]. Functional electrical stimulation (FES) uses electrical currents to stimulate paralyzed muscles, promoting movement and recreating spinal cord function [67]. A combined stimulation is ideal to mimic the afferent and efferent signals in the pathways, leading to better functional enhancement [89]. Integrating electrical stimulation and exercise training has promising beneficial results. FES-assisted cycling has been widely used for attenuating muscle loss and improving conditions of neurological impairments, though the responsiveness for FES differs in varied injury levels due to anatomical characteristics (for example, damage to the final pathway of muscle activation would barricade the effects) [90].

Transcutaneous electrical neural stimulation (TENS) is an alternative non-invasive electrical stimulation to activate neural circuits below the level of injury, elevating excitability and sensitivity in neurons [91], and is often used in settings of pain

management [92, 93]. Studies involving stimulation in different regions of the spinal cord showed varied levels of mobility enhancement, including locomotion, standing, and posture [91]. Better results were obtained with combined exoskeleton assistance or other activity-based training, in upper [94] and lower extremity mobility [95].

Deep brain stimulation (DBS) is a neurosurgical technique in which electrodes are implanted into specific brain regions to modulate nerve activity and has been conventionally and successfully used in treatments of movement disorders such as Parkinson's disease and essential tremor [96]. Currently, DBS therapy is being actively investigated as a potential new approach to the treatment of SCI, for it may counteract the interference of SCI, and repair the disrupted projection of neurons from the brain to the spinal cord regions that regulate walking [4]. A recent study has reported its efficacy in restoring walking abilities in rodent models as well as in human participants. Researchers located glutamatergic neurons in the lateral hypothalamus (LH) as the piloting region relating to the recovery of lower extremity locomotion in incomplete SCI, with the aid of a time-space brain-mapping analytical framework. After delivering DBS towards LH, patients with incomplete SCI and different degrees of gait deficits reported immediate sensation in paralyzed lower extremities, along with a direct increase in muscle activity. Patients' motor scores increased significantly, along with their gait balance and endurance. This effect is prolonged even when DBS is deactivated [97].

Traumatic SCI results in severed communication pathways between the brain and motor or sensory neurons, and beneficial effects for electrical stimulations are magnified by the existence of spared neurons in the injury site [69], which is not the case for paralysis caused by neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and neuromuscular diseases such as spinal muscular atrophy (SMA) [98], where upper and/or lower motor neurons deteriorate consistently due to genetic or unknown causes [99]. ES may have temporary benefits in earlier stages of neurodegenerative diseases[100], but for later stages, brain-computer interfaces could be more effective, as they provide a complete alternative route for functional realization [101]. For ischemic changes such as anterior spinal artery stroke (ASAS), as it affects the anterior two-thirds of the spinal cord predominantly responsible for motor function [102], some natural structures remain intact. Therefore, ES may be more beneficial for ASAS than for SCI. ES-integrated methods proven effective for SCI can be adapted for ASAS, such as transcranial magnetic stimulation, FES and RAGT [103].

4.3. Brain-computer interface (BCI)

Also referred to as a brain-machine interface (BMI), the brain-computer interface (BCI) leverages various methodologies to decode brain electrical signals and interpret user intent. By connecting to external devices functioning as effectors, BCIs facilitate daily activities for individuals with partial or complete paralysis, thereby significantly enhancing patient autonomy. When integrated with electrical stimulation, BCIs enable bidirectional information exchange, which is instrumental in establishing a closed-loop signal circuit [104]. This allows devices to not only receive upstream motor signals but also provide feedback through downstream somatosensory signals. Implantable electrodes enable the monitoring of cortical motor area signals. When interfaced with an exoskeleton, patients can voluntarily control paralyzed limbs and achieve functional movements. Similarly, when connected to a computer, patients can operate a cursor and perform complex tasks [105]. Signal acquisition technology is often separated into categories of non-invasive, embedded, or intracranial [106]. Subcortical electrodes, though more invasive, demonstrate superior performance compared to extracranial electrodes [107]. BCIs can also be installed through neurointerventional procedures, which are considered to be less invasive and present with positive effects similar to BCIs implanted by surgical open-brain procedures in patients with varied degrees of paralysis [56]. Additionally, BCIs have been shown to exert positive effects on memory and cognitive functions, underscoring their wide-ranging applications and transformative potential [108].

4.4. Brain-spine interface (BSI)

The brain-spine interface (BSI) is an innovative technology that restores functional connectivity by recreating neural connections between cortical intention signals and epidural stimulation targeting spinal regions associated with locomotion. This approach integrates BCI technology with epidural electrical stimulation to facilitate spinal functional restoration. The BSI operates by decoding brain

signals, bypassing the injured site, and delivering them to motor effectors via an artificial neural pathway. By comparing instant cortical signals with pre-recorded motor intention signals, the BSI identifies motion intentions and generates preconfigured epidural electrical stimulation targeting spinal cord motor regions, effectively restoring a complete descending signal transmission pathway. Following quick calibrations, the BSI can seamlessly couple intention recognition with motor reproduction, enabling robust brain-spinal communication [58].

With the BSI activated, the participant achieved natural and independent walking, even in complex settings, suggesting its high utility in real-world scenarios. Remarkably, some degree of locomotor ability was retained even after the device was deactivated, indicating long-term therapeutic benefits [58].

5. CONCLUSION

Restoration of function in SCI patients is crucial not only for preventing severe complications but also for elevating overall quality of life. Current strategies focused on natural structural reestablishment include pharmaceutical interventions, tissue repair, and stem cell therapy, all aimed at regenerating damaged neural tissues and reestablishing functional connectivity. In parallel, neuromodulation approaches (with improvements to conventional methods and integration with new techniques) such as rehabilitation training and electrical stimulation provide additional methods for improving motor function and sensory perception. While these strategies can induce varying degrees of structural repair or functional recovery, the benefits are still limited in many instances. Consequently, more advanced therapeutic methods are being actively explored, including novel pharmaceutical agents and integrated multi-modal treatments that combine stem cell therapy with other regenerative technologies. Recently, brain-computer interfaces (BCIs) and their variations have emerged as promising new interventions in restoring functional needs in SCI patients, showing significant potential for more precise and targeted therapeutic outcomes.

In conclusion, current biological and functional repair strategies for SCI are characterized by multifaceted approaches and the integration of diverse therapeutic modalities. Though demonstrating varying degrees of efficacy, these strategies offer substantial improvements in the prognosis and quality of life for individuals with spinal cord injuries.

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Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

Not applicable. ♦

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