Iranian Journal of NEUROSURGERY

2024, Volume 10, E28

Review Paper

# Spinal Cord Injury and Neuroplasticity

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**Citation** Asgari Gashtrodkhani A, Ghorbani Shirkouhi S, Andalib S. Spinal Cord Injury and Neuroplasticity. Iran J Neurosurg. 2024; 10:E28. http://dx.doi.org/10.32598/irjns.10.28

doi: http://dx.doi.org/10.32598/irjns.10.28

**Article info:**
**Received:** 19 Nov 2024
**Accepted:** 04 Dec 2024
**Available Online:** 31 Dec 2024

**Keywords:**
Spinal cord injury (SCI), Neuroplasticity, Corticospinal tract, Rehabilitation, Neuromodulation

## ABSTRACT

**Background and Aim:** Spinal cord injury (SCI) leads to sensory, motor, and autonomic dysfunctions and changes in different nerve fibers that can greatly impact the quality of life of many people. Neuroplasticity is a spontaneous mechanism of the nervous system to adapt to different molecular, physiological, and anatomical changes after SCI.

**Methods and Materials/Patients:** A literature search of relevant articles was made with a focus on recent publications.

**Results:** This narrative review first discusses the definition of neuroplasticity in the nervous system and cellular processes of neuroplasticity in the synapses and their effects on synaptogenesis and neuroplasticity. We describe some of the important central and spinal neuronal pathways and their role in voluntary movements and the regenerative capacity in neuroplasticity and functional recovery. Then this review focuses on the effects of exercise and training programs and different neuromodulation techniques using electrical stimulation (ES) on the development of neuroplasticity. These rehabilitation and neuromodulation techniques accelerate the release of some neurotrophic factors to enhance neuroplasticity and functional sensorimotor recovery.

**Conclusion:** This narrative review emphasizes the importance and capability of neuroplasticity in improving functional recovery and quality of life of the people following SCI. It identifies that different physical rehabilitation and neuromodulation strategies induce significant improvements in sensorimotor recovery and underlines that the combination of rehabilitation and neuromodulation techniques provides greater functional outcomes. There is a need for further investigation using preclinical and clinical studies in the future that should concentrate on the basic molecular and cellular processes of neuroplasticity and investment in enhancing the rehabilitation and neuromodulation techniques and finding new techniques.

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## Highlights

- Neuroplasticity begins spontaneously at the molecular level of synapses after injury.
- Neurotrophic factors have a crucial effect on axonal sprouting and neuroplasticity.
- The corticospinal tract (CST) is the major pathway in voluntary movements.
- Rehabilitation approaches were developed to maximize sensorimotor function recovery.

## Plain Language Summary

Spinal cord injury (SCI) results in multiple difficulties and influences the quality of life of many people worldwide. Injuries can happen at any spinal level and are related to the severity of the trauma, causing many problems in sensation, movement, sex, and independence of their life. These disabilities can also lead to psychosocial disturbances that put them in vulnerable situations. This review focuses on the basic cellular mechanisms of SCI and adaptations and changes in the nervous system related to injury. These changes first happen spontaneously at the molecular level in the nervous system to accelerate the rehabilitation of the body in response to injury. The regeneration and reorganization of the nervous system after injury is called neuroplasticity. Understanding these adaptations and mechanisms is the most important part of treatment strategies and improving the quality of life. Then, we discuss multiple rehabilitation and neuromodulation techniques and their different effects on cellular changes and functional recovery. Exercise and physical activity are the basic parts of the rehabilitation strategies, and besides neuromodulation techniques, using electrical stimulation (ES) to different parts of the body significantly improves the lost functional abilities and the independence of people after spinal cord injury. Overall, this review seeks to consider the different aspects of neuroplasticity and novel treatments in SCI to guide future studies.

## 1. Introduction

The spinal cord is a structure responsible for transmitting and receiving signals between the brain and the rest of the body. Spinal cord injury (SCI) is damage to the spinal cord which can be due to traumatic and non-traumatic causes. It can be complete or incomplete. SCI gives rise to severe sensory, motor, and autonomic impairment by disrupting descending and ascending nerve fibers connecting the spinal cord and supraspinal structures [1]. These structures are necessary for various normal physiological functions, such as autonomic functions, voluntary movement, and sensation. SCI results in partial or complete loss of functions of the lower limbs below the site of injury or all four limbs or even death, depending on the anatomical level and severity of the nerve injury [1, 2]. Inability to voluntary movement, sensory dysfunction, urinary and defecation incontinence, sexual dysfunction, hyperreflexia, spasticity, and psychosocial disturbances are the most important disabilities and consequences following SCI. Due to the limited regenerative capacity of the central nervous system (CNS), the resultant motor and sensory loss in individuals with SCI can severely influence their quality of life [3].

The nervous system's adaptations after SCI are mostly associated with neuroplasticity and spontaneous regeneration in the brain and spinal cord. Preclinical and clinical studies have demonstrated different stages of recovery [4]. Neuroplasticity is the brain and spinal cord's capability to undergo changes and reorganizations to adjust themselves following injury.

These changes can occur in motor cortex structure and function, corticospinal projection pathways, spinal excitability and organization, and afferent input at the cortical and spinal levels [1].

The present narrative review takes account of the effect of neuroplasticity after SCI and highlights neuroplastic changes in the molecular and synaptic level and the major neuronal pathways in the brain and spinal cord. We also discuss the effect of rehabilitation and neuromodulation strategies on neuroplasticity and functional recovery following SCI.

## 2. Methods and Materials/Patients

For this narrative review, a literature search for relevant articles was made with a focus on recent publications.

## 3. Results and Discussion

### Neuroplasticity principles and mechanisms

An important neurophysiological explanation for nervous system neuroplasticity is the strengthening or weakening of the synaptic transmission based on Hebbian learning [5]. High-frequency input at the synaptic level leads to short-term potentiation (STP) by increasing presynaptic neurotransmitter release, however, repetitive high-frequency input results in long-term potentiation (LTP) by increasing synaptic efficacy and synaptogenesis [6, 7]. In addition, a low-frequency input leads to short-term depression (STD) by decreasing presynaptic neurotransmitter release, while repetitive low-frequency input results in long-term depression (LTD) by synaptic pruning [6, 8]. LTP and LTD are two main parts of the brain and spinal neuroplasticity. LTP and LTD are regulated by the two postsynaptic inotropic glutamate receptors, namely N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

NMDA and AMPA receptors play a crucial role at the molecular level in neural plasticity. NMDA receptor numbers rarely change across synapses while the number of AMPA receptors is extremely variable [9].

NMDA and AMPA's mechanism of action begins with releasing the glutamate neurotransmitter from the presynaptic neuron into the synaptic cleft that binds to postsynaptic AMPA and NMDA receptors. Glutamate release induces a structural change in postsynaptic receptors leading to an influx of $Na^+$ which depolarizes postsynaptic neurons. Depolarization results in the influx of $Ca^{2+}$ into the postsynaptic neuron. High numbers influx of $Na^+$ and $Ca^{2+}$ into postsynaptic neurons increases the open time of the AMPA and NMDA receptors [10, 11].

LTP gives rise to the potentiation and growth of the synapses to induce synaptogenesis and neuroplasticity, while LTD decreases the numbers and activity of synapses and the resultant removal of inactive synapses. LTP and LTD are two major components of neuroplasticity and functional recovery following injury.

### Neuroplasticity in spinal cord injury

#### Synaptic remodeling

Synapses are dynamic structures that can have morphological changes in response to injury. The collateral sprouting of intact afferent fibers following injury to the dorsal column of the spinal cord results in notable recovery of lost sensorimotor abilities [12]. Synaptic remodeling in the motor cortex following SCI appears to be accompanied by time-dependent structural changes in dendritic spine density and morphology of postsynaptic connections [13]. Loss of synapses on motor neurons is one of the reasons for motor dysfunction. As shown by a preclinical study, the formation of new synapses has a key role in the regeneration of motor function following SCI [14]. Preservation and generation of synapses rely on protein synthesis. Protein synthesis and the resultant new synapse augmentation lead to functional and structural neuroplasticity and motor cortex map plasticity. The protein synthesis and generation of new synapses in size and number are the fundamental basis of motor map plasticity and motor skill training [15].

#### Motor map plasticity

The sensorimotor cortex is a complex part of the brain in which afferent sensory information from the environment reaches the primary sensory organs, then the primary sensory cortex, to be processed and transferred to the primary motor cortex to induce action. The brain's motor cortex processes information about body movements. This information contains a topographic map of the different parts of the body named motor map that can be shown by transcranial magnetic stimulation (TMS) [16]. The motor map can be used to show different motor cortex sections and their roles in body movements and the exact relationship between them. Motor cortex plasticity is observed during motor skill learning [17]. Motor skill learning arises from the primary motor cortex. It is defined as the repetition-mediated training tasks that increase the speed and accuracy of motor behavior [18, 19]. This process greatly depends on the sensorimotor cortex complex's ability to act precisely.

#### Corticospinal tract plasticity

The corticospinal tract (CST) is a major pathway for skilled voluntary functions in humans and many mammalians and the most regenerative pathway following SCI. CST derives from the primary motor

cortex and then converges in the corpus callosum, passing through the internal capsule, crossing the midline, and descending to the spinal cord [1]. The CST accounts for most of the axons from crossed dorsal parts and fewer of the axons from uncrossed ventral parts [20, 21]. The CST axons in the spinal cord connect with spinal interneurons by lower motor neurons [22]. Spinal interneurons have an important position in regulating motor activity by mediating sensory and motor fibers [23]. Some of the propriospinal interneuron fibers have long projections that connect different parts of the spinal cord and are important in the coordination of the limbs. These propriospinal interneurons take part in neuroplasticity and spontaneous functional improvement through their long descending fibers to bypass the injury site [24].

Although the CST is the most voluntary movement pathway, some other pathways, such as rubrospinal, tectospinal, and reticulospinal tract (RST), also participate in voluntary movements [22]. The RST seems to induce neuroplasticity and axonal sprouting by detouring the site of injury following SCI [24].

The CST neuroplasticity and reorganization result in significant improvements in motor skill actions [1]. Neuroplasticity in the CST leads to axonal sprouting and increasing connectivity with spinal cord motor pathways. These changes are necessary for functional recovery by creating new motor fibers to enhance voluntary movements.

## Rehabilitation in spinal cord injury

### Exercise and programmed training in spinal cord injury

Rehabilitation strategies in patients following SCI improve the quality of life and functional recovery. Exercise and special training in patients after SCI are the first components of the rehabilitation techniques. Given the movement and exercise limitations of SCI patients, the training programs depend on the level and severity of the lesion. These planned activity-based therapies consist of repetitive physical activity on the spinal pathways and skeletal muscles to induce excitation of uninjured and injured neuronal fibers [25]. Repetitive physical activity helps SCI patients prevent muscle atrophy and increase the performance of the body muscles to enhance movements independently.

### Exercise and programmed training induced neuroplasticity in spinal cord injury

Programmed exercise results in considerable molecular and anatomical changes in the synapses [26]. Exercise training was shown to induce the expression of synaptic markers, synaptophysin, and PSD95 in the synaptic field and has a significant effect on axonal sprouting and functional improvement [27]. The increase in the level of these presynaptic proteins leads to strengthening synaptic connectivity and promoting synaptic formation [27].

Exercise and training give rise to neuroplasticity by releasing neurotrophic factors. Neurotrophins are a group of proteins with numerous functions. The neurotrophins bind to tropomyosin receptor kinase (Trk) and pan neurotrophic (P75NRT) to induce their activity [28].

Neurotrophic proteins bind to the two classes of receptors, Trk and P75, with higher affinity to Trk receptors [29]. Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) are among the most important neurotrophins [30]. BDNF is a growth factor that enhances neuroplasticity, neuromodulation, neurodegeneration, and neuronal survival through rubrospinal, reticulospinal, vestibulospinal tracts, and proprioceptive neurons in the spinal cord [30]. BDNF also has a protective effect against glutamate toxicity and glutamate-induced apoptosis following injury by increasing the Bcl-2 protein levels [31]. BDNF results in sprouting and outgrowth of the CST axons in the spinal cord by increasing the TrkB receptors [32]. The CST is the most important pathway in regeneration, axonal growth, and neuroplasticity following SCI [1].

The NGF is another neurotrophic protein with TrkA and P75 receptors that contribute to neuroregeneration and axonal sprouting [33]. The NGF mostly promotes neuroplasticity and axonal growth within the spinal cord by nociceptive fibers and primary sensory neuron stimulation [34].

NT-3 is the third member of the neurotrophic family found in different parts of the body with an important role in the growth and differentiation of sympathetic and sensory neurons [35]. The NT-3 mostly binds to the TrkC receptor with the highest affinity but has a lower affinity to TrkA, TrkB, and P75 receptors [36]. The CST neurons express the TrkC receptors, resulting in the CST's high responsiveness to NT-3 [37]. According to high

regenerative, neuroplasticity, and axonal outgrowth of the CST pathways, the NT-3 plays a key pattern in neurorehabilitation and functional recovery [38].

## Neuromodulation in spinal cord injury

Neuromodulation can improve SCI recovery from basic to skilled functions. Various neuromodulation techniques have been studied in SCI.

## Electrical stimulation (ES) mechanisms and principles

Brain stimulation and neuromodulation affect CST structural neuroplasticity, axonal sprouting, and the organization of more connections with spinal motor pathways [39].

ES refers to a non-invasive regenerative and neuromodulation therapy with different modalities. ES produces an electric field between an anode and a cathode in the target tissue to induce neuronal stimulation and excitation. This electric field generates action potentials in the targeted neurons. ES uses multiple types of electrodes to deliver electrical discharge at different locations of the central and peripheral nervous system, consisting of the brain, spinal cord, peripheral nerves, and skin above the muscle.

## ES and neuroplasticity in SCI

ES augments the expression of neurotrophic factors, such as BDNF, and its receptor TrkB in spinal cord neurons and the Schwann cells of peripheral nerves [40]. ES enhances intracellular calcium levels by voltage-gated calcium channels and extracellular signal-regulated kinase (ERK) dependent signaling pathways to increase the synthesis of neurotrophic factors [40]. ES also enhances the axonal outgrowth in the damaged nerves by increasing the level of cortical and spinal cyclic adenosine monophosphate (cAMP) [41]. The cAMP levels of the cortical and spinal cord decrease after SCI [42].

The acceleration of the neurotrophic factors and their receptors on the spinal cord neurons and peripheral nerves following ES potentiates the regeneration and neuroplasticity of the sensory and motor neuron pathways [43].

## ES and neuroplasticity in CST

Using ES to focus on the motor cortex induces axonal regeneration and sprouting on the CST and plasticity of neuronal pathways [44, 45]. ES applied to the cell body of the corticospinal axons in the cortex has revealed axonal regeneration and sprouting through structural and genetic changes [46]. Considering the downregulation of the intrinsic regeneration capability of the CST axons during development, the recovery of the CST is limited [47]. ES of the motor cortex raises the level of the mammalian target of rapamycin (mTOR) and Janus kinase/signal transducer and activator of transcription proteins (JAK/STAT) signaling activity on the corticospinal pathways [47]. Upregulation of the mTOR and JAK/STAT gene expression and the resultant increased signaling pathways promote CST axonal outgrowth and synaptogenesis [47, 48].

Using ES on the spinal cord and the injury site produces more active signals and connections to neurons. ES leads to axonal growth and plasticity of the neuronal pathways below the injury site to repair damaged neuronal networks and promote functional recovery in SCI patients [44, 49].

## ES techniques in spinal cord injury

TMS, peripheral nerve stimulation (PNS), and vagus nerve stimulation (VNS) are non-invasive neuromodulation techniques that use ES at different anatomical targets [50]. These procedures enhance neuroplasticity and neuronal regeneration in SCI patients [50, 51].

## TMS and neuroplasticity

TMS is a non-invasive method that uses a wired coil probe to produce a magnetic field over the skull. The magnetic field generates an electrical impulse that travels through the scalp to induce neuronal depolarization in the cortical brain area [52]. TMS provides two modalities, that is to say, high-frequency TMS and low-frequency TMS. High-frequency TMS is associated with neuronal and synaptic excitation, resulting in LTP [53]. On the other hand, low-frequency TMS is accompanied by the inhibition of neuronal synapses, resulting in LTD [53]. The LTP caused by repetitive high-frequency TMS has a profound effect on neuroplasticity marker BDNF [53]. TMS is mostly applied to the motor cortex to activate the corticospinal neuronal pathways [54].

Given the neurophysiological and neuromodulation effects of TMS on the motor cortex and CST, using TMS gives rise to neuroplasticity and functional recovery by CST neuron excitation [52, 53].

### PNS and neuroplasticity

PNS transfers ES to the peripheral nerves, neuromuscular junction, and muscles to induce neuroplastic changes in neuronal synapses and also improves muscle power and functional recovery, and prevents muscle atrophy [55]. PNS has mostly been used for pain management; however, it can be useful as a neuromodulation method in rehabilitation and neuroplasticity. PNS is a neuromodulation technique that enhances muscle power and prevents muscle atrophy to promote functional recovery [56]. These electrical impulses turn back to the spinal cord and the brain to induce synaptic neuroplastic changes through sensorimotor neuron pathways [57]. Using PNS in neurorehabilitation programs increases training capability, muscle health, and functional recovery [58].

### VNS and neuroplasticity

VNS is a neuromodulation technique that provokes ES to the vagus nerve. VNS has invasive and non-invasive methods. VNS can increase the level of BDNF in the brain [59]. BDNF has a neuroplastic effect on synaptic area and neuronal pathways [33]. VNS leads to synaptic connectivity, neuroplasticity, and functional motor and sensory recovery after SCI [45]. Using VNS in combination with rehabilitation results in greater functional recovery than rehabilitation alone following SCI [60].

Studies suggest that combining these neuromodulation techniques with physical rehabilitation may provide more significant functional recovery and improvements than using them independently [50, 51].

### Suggestions for future directions

There are multiple molecular and cellular changes such as different molecules, proteins, growth factors, neurotrophic factors, and receptors in the synapses in response to SCI. Therefore, there is a need for further investigation by preclinical and clinical studies in the future that should concentrate on the basic molecular and cellular processes of neuroplasticity. Given the important role in skilled voluntary movements and high capacity in neuroplasticity of the CST, there is also a need for future studies focusing on the CST to elucidate CST's molecular processes of neuroplasticity and the effects of rehabilitation and neuromodulation on the CST's neuroplasticity. Using rehabilitation and neuromodulation techniques together have synergistic effects on accelerating neuroplasticity outcomes. However, exploring the best-combined modalities, time duration, and possible targeted sites for use is challenging and needs further studies.

## 4. Conclusion

There have been numerous progresses in the understanding of the basic molecular mechanisms, important neuronal pathways, and the capacity of neuroplasticity in the individuals following SCI. These cellular and molecular changes are the fundamental mechanism of synaptic sprouting, synaptogenesis, and neuroplasticity. The neurotrophic factors and their receptors are the most important parts of the molecular level of synaptic regeneration and plasticity. From the neuronal pathways, the CSTis the most important voluntary movement pathway and has the greatest regenerative capacity for neuroplasticity and improving functional recovery.

Rehabilitation and neuromodulation approaches enhance the power of neuroplasticity, synaptogenesis, and sensorimotor recovery. Combining these techniques results in significant functional recovery and improvements in the quality of life of people following SCI.

## Ethical Considerations

### Compliance with ethical guidelines

This article is a narrative review with no human or animal sample.

### Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

### Authors' contributions

All authors contributed to preparing this article.

### Conflict of interest

The authors declared no conflict of interest.

## References

[1] Brown AR, Martinez M. From cortex to cord: Motor circuit plasticity after spinal cord injury. Neural Regeneration Research. 2019; 14(12):2054-62. [DOI:10.4103/1673-5374.262572] [PMID] [PMCID]

[2] Kazim SF, Bowers CA, Cole CD, Varela S, Karimov Z, Martinez E, et al. Corticospinal motor circuit plasticity after spinal cord injury: Harnessing neuroplasticity to improve functional outcomes. Molecular Neurobiology. 2021; 58(11):5494-516. [DOI:10.1007/s12035-021-02484-w] [PMID]

[3] Anderson KD. Targeting recovery: Priorities of the spinal cord-injured population. Journal of Neurotrauma. 2004; 21(10):1371-83. [DOI:10.1089/neu.2004.21.1371] [PMID]

[4] Fouad K, Tse A. Adaptive changes in the injured spinal cord and their role in promoting functional recovery. Neurological Research. 2008; 30(1):17-27. [DOI:10.1179/016164107X251781] [PMID]

[5] Brown RE. Donald O. Hebb and the Organization of Behavior: 17 years in the writing. Molecular Brain. 2020; 13(1):55. [DOI:10.1186/s13041-020-00567-8] [PMID] [PMCID]

[6] Walker JR, Detloff MR. Plasticity in cervical motor circuits following spinal cord injury and rehabilitation. Biology. 2021; 10(10):976. [DOI:10.3390/biology10100976] [PMID] [PMCID]

[7] Kusiak AN, Selzer ME. Neuroplasticity in the spinal cord. Handbook of Clinical Neurology. 2013; 110:23-42. [DOI:10.1016/B978-0-444-52901-5.00003-4] [PMID]

[8] Zucker RS, Regehr WG. Short-term synaptic plasticity. Annual Review of Physiology. 2002; 64:355-405. [DOI:10.1146/annurev.physiol.64.092501.114547] [PMID]

[9] Sheng M, Hoogenraad CC. The postsynaptic architecture of excitatory synapses: A more quantitative view. Annual Review of Biochemistry. 2007; 76:823-47. [DOI:10.1146/annurev.biochem.76.060805.160029] [PMID]

[10] Purkey AM, Dell'Acqua ML. Phosphorylation-dependent regulation of Ca2+-permeable AMPA receptors during hippocampal synaptic plasticity. Frontiers in Synaptic Neuroscience. 2020; 12:8. [DOI:10.3389/fnsyn.2020.00008] [PMID] [PMCID]

[11] Diering GH, Huganir RL. The AMPA receptor code of synaptic plasticity. Neuron. 2018; 100(2):314-29. [DOI:10.1016/j.neuron.2018.10.018] [PMID] [PMCID]

[12] Kaas JH, Qi HX, Burish MJ, Gharbawie OA, Onifer SM, Massey JM. Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord. Experimental Neurology. 2008; 209(2):407-16. [DOI:10.1016/j.expneurol.2007.06.014] [PMID] [PMCID]

[13] Kim BG, Dai HN, McAtee M, Vicini S, Bregman BS. Remodeling of synaptic structures in the motor cortex following spinal cord injury. Experimental Neurology. 2006; 198(2):401-15. [DOI:10.1016/j.expneurol.2005.12.010] [PMID]

[14] Li GL, Farooque M, Isaksson J, Olsson Y. Changes in synapses and axons demonstrated by synatophysin immunohistochemistry following spinal cord compression trauma in the rat and mouse. Biomedical and Environmental Sciences. 2004; 17(3):281-90. [Link]

[15] Kleim JA, Bruneau R, Calder K, Pocock D, VandenBerg PM, MacDonald E, et al. Functional organization of adult motor cortex is dependent upon continued protein synthesis. Neuron. 2003; 40(1):167-76. [DOI:10.1016/S0896-6273(03)00592-0] [PMID]

[16] Hallett M. Transcranial magnetic stimulation: A primer. Neuron. 2007; 55(2):187-99. [DOI:10.1016/j.neuron.2007.06.026] [PMID]

[17] Papale AE, Hooks BM. Circuit changes in motor cortex during motor skill learning. Neuroscience. 2018; 368:283-97. [DOI:10.1016/j.neuroscience.2017.09.010] [PMID] [PMCID]

[18] Diedrichsen J, Kornysheva K. Motor skill learning between selection and execution. Trends in Cognitive Sciences. 2015; 19(4):227-33. [DOI:10.1016/j.tics.2015.02.003] [PMID] [PMCID]

[19] Shmuelof L, Krakauer JW. Recent insights into perceptual and motor skill learning. Frontiers in Human Neuroscience. 2014; 8:683. [DOI:10.3389/fnhum.2014.00683] [PMID] [PMCID]

[20] Brösamle C, Schwab ME. Cells of origin, course, and termination patterns of the ventral, uncrossed component of the mature rat corticospinal tract. Journal of Comparative Neurology. 1997; 386(2):293-303. [DOI:10.1002/(SICI)1096-9861(19970922)386:23.0.CO;2-X]

[21] Joosten EA, Schuitman RL, Vermelis ME, Dederen PJ. Postnatal development of the ipsilateral corticospinal component in rat spinal cord: A light and electron microscopic anterograde HRP study. The Journal of Comparative Neurology. 1992; 326(1):133-46. [DOI:10.1002/cne.903260112] [PMID]

[22] Lemon RN. Descending pathways in motor control. Annual Review of Neuroscience. 2008; 31:195-218. [DOI:10.1146/annurev.neuro.31.060407.125547] [PMID]

[23] Courtine G, Song B, Roy RR, Zhong H, Herrmann JE, Ao Y, et al. Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. Nature Medicine. 2008; 14(1):69-74. [DOI:10.1038/nm1682] [PMID] [PMCID]

[24] Filli L, Engmann AK, Zörner B, Weinmann O, Moraitis T, Gullo M, et al. Bridging the gap: A reticulo-propriospinal detour bypassing an incomplete spinal cord injury. The Journal of Neuroscience. 2014; 34(40):13399-410. [DOI:10.1523/JNEUROSCI.0701-14.2014] [PMID] [PMCID]

[25] Ginis KA, Hicks AL, Latimer AE, Warburton DE, Bourne C, Ditor DS, et al. The development of evidence-informed physical activity guidelines for adults with spinal cord injury. Spinal Cord. 2011; 49(11):1088-96. [DOI:10.1038/sc.2011.63] [PMID]

[26] Bilchak JN, Caron G, Côté MP. Exercise-induced plasticity in signaling pathways involved in motor recovery after spinal cord injury. International Journal of Molecular Sciences. 2021; 22(9):4858. [DOI:10.3390/ijms22094858] [PMID] [PMCID]

[27] Goldshmit Y, Lythgo N, Galea MP, Turnley AM. Treadmill training after spinal cord hemisection in mice promotes axonal sprouting and synapse formation and improves motor recovery. Journal of Neurotrauma. 2008; 25(5):449-65. [DOI:10.1089/neu.2007.0392] [PMID]

[28] Blum R, Konnerth A. Neurotrophin-mediated rapid signaling in the central nervous system: Mechanisms and functions. Physiology. 2005; 20:70-8. [DOI:10.1152/physiol.00042.2004] [PMID]

[29] He XL, Garcia KC. Structure of nerve growth factor complexed with the shared neurotrophin receptor p75. Science. 2004; 304(5672):870-5. [DOI:10.1126/science.1095190] [PMID]

[30] Keefe KM, Sheikh IS, Smith GM. Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. International Journal of Molecular Sciences. 2017; 18(3):548. [DOI:10.3390/ijms18030548] [PMID] [PMCID]

[31] Almeida RD, Manadas BJ, Melo CV, Gomes JR, Mendes CS, Grãos MM, et al. Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. Cell Death and Differentiation. 2005; 12(10):1329-43. [DOI:10.1038/sj.cdd.4401662] [PMID]

[32] Hollis ER 2nd, Jamshidi P, Löw K, Blesch A, Tuszynski MH. Induction of corticospinal regeneration by lentiviral trkB-induced Erk activation. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(17):7215-20. [DOI:10.1073/pnas.0810624106] [PMID] [PMCID]

[33] Wood SJ, Pritchard J, Sofroniew MV. Re-expression of nerve growth factor receptor after axonal injury recapitulates a developmental event in motor neurons: Differential regulation when regeneration is allowed or prevented. The European Journal of Neuroscience. 1990; 2(7):650-7. [DOI:10.1111/j.1460-9568.1990.tb00454.x] [PMID]

[34] Romero MI, Rangappa N, Li L, Lightfoot E, Garry MG, Smith GM. Extensive sprouting of sensory afferents and hyperalgesia induced by conditional expression of nerve growth factor in the adult spinal cord. The Journal of Neuroscience. 2000; 20(12):4435-45. [DOI:10.1523/JNEUROSCI.20-12-04435.2000] [PMID] [PMCID]

[35] Rosenthal A, Goeddel DV, Nguyen T, Lewis M, Shih A, Laramee GR, et al. Primary structure and biological activity of a novel human neurotrophic factor. Neuron. 1990; 4(5):767-73. [DOI:10.1016/0896-6273(90)90203-R] [PMID]

[36] Lamballe F, Klein R, Barbacid M. TrkC, a new member of the trk family of tyrosine protein kinases, is a receptor for neurotrophin-3. Cell. 1991; 66(5):967-79. [DOI:10.1016/0092-8674(91)90442-2] [PMID]

[37] Ma YH, Zhang Y, Cao L, Su JC, Wang ZW, Xu AB, et al. Effect of neurotrophin-3 genetically modified olfactory ensheathing cells transplantation on spinal cord injury. Cell Transplantation. 2010; 19(2):167-77. [DOI:10.3727/096368910X492634] [PMID]

[38] Weishaupt N, Mason AL, Hurd C, May Z, Zmyslowski DC, Galleguillos D, et al. Vector-induced NT-3 expression in rats promotes collateral growth of injured corticospinal tract axons far rostral to a spinal cord injury. Neuroscience. 2014; 272:65-75. [DOI:10.1016/j.neuroscience.2014.04.041] [PMID]

[39] Martin JH. Harnessing neural activity to promote repair of the damaged corticospinal system after spinal cord injury. Neural Regeneration Research. 2016; 11(9):1389-91. [DOI:10.4103/1673-5374.191199] [PMID] [PMCID]

[40] Wenjin W, Wenchao L, Hao Z, Feng L, Yan W, Wodong S, et al. Electrical stimulation promotes BDNF expression in spinal cord neurons through Ca(2+)- and Erk-dependent signaling pathways. Cellular and Molecular Neurobiology. 2011; 31(3):459-67. [DOI:10.1007/s10571-010-9639-0] [PMID]

[41] Udina E, Furey M, Busch S, Silver J, Gordon T, Fouad K. Electrical stimulation of intact peripheral sensory axons in rats promotes outgrowth of their central projections. Experimental Neurology. 2008; 210(1):238-47. [DOI:10.1016/j.expneurol.2007.11.007] [PMID]

[42] Pearse DD, Pereira FC, Marcillo AE, Bates ML, Berrocal YA, Filbin MT, et al. cAMP and Schwann cells promote axonal growth and functional recovery after spinal cord injury. Nature Medicine. 2004; 10(6):610-6. [DOI:10.1038/nm1056] [PMID]

[43] Gordon T. Neurotrophic factor expression in denervated motor and sensory Schwann cells: Relevance to specificity of peripheral nerve regeneration. Experimental Neurology. 2014; 254:99-108. [DOI:10.1016/j.expneurol.2014.01.012] [PMID]

[44] Jack AS, Hurd C, Martin J, Fouad K. Electrical stimulation as a tool to promote plasticity of the injured spinal cord. Journal of Neurotrauma. 2020; 37(18):1933-53. [DOI:10.1089/neu.2020.7033] [PMID] [PMCID]

[45] Brus-Ramer M, Carmel JB, Chakrabarty S, Martin JH. Electrical stimulation of spared corticospinal axons augments connections with ipsilateral spinal motor circuits after injury. The Journal of Neuroscience. 2007; 27(50):13793-801. [DOI:10.1523/JNEUROSCI.3489-07.2007] [PMID] [PMCID]

[46] Spencer T, Filbin MT. A role for cAMP in regeneration of the adult mammalian CNS. Journal of Anatomy. 2004; 204(1):49-55. [DOI:10.1111/j.1469-7580.2004.00259.x] [PMID] [PMCID]

[47] Zareen N, Dodson S, Armada K, Awad R, Sultana N, Hara E, et al. Stimulation-dependent remodeling of the corticospinal tract requires reactivation of growth-promoting developmental signaling pathways. Experimental Neurology. 2018; 307:133-44. [DOI:10.1016/j.expneurol.2018.05.004] [PMID] [PMCID]

[48] Lang C, Bradley PM, Jacobi A, Kerschensteiner M, Bareyre FM. STAT3 promotes corticospinal remodelling and functional recovery after spinal cord injury. EMBO Reports. 2013; 14(10):931-7. [DOI:10.1038/embor.2013.117] [PMID] [PMCID]

[49] Moraud EM, Capogrosso M, Formento E, Wenger N, DiGiovanna J, Courtine G, et al. Mechanisms underlying the neuromodulation of spinal circuits for correcting gait and balance deficits after spinal cord injury. Neuron. 2016; 89(4):814-28. [DOI:10.1016/j.neuron.2016.01.009] [PMID]

[50] Evancho A, Tyler WJ, McGregor K. A review of combined neuromodulation and physical therapy interventions for enhanced neurorehabilitation. Frontiers in Human Neuroscience. 2023; 17:1151218. [DOI:10.3389/fnhum.2023.1151218] [PMID] [PMCID]

[51] Cajigas I, Vedantam A. Brain-computer interface, neuromodulation, and neurorehabilitation strategies for spinal cord injury. Neurosurgery Clinics of North America. 2021; 32(3):407-417.[DOI:10.1016/j.nec.2021.03.012] [PMID]

[52] Di Lazzaro V, Rothwell J, Capogna M. Noninvasive stimulation of the human brain: Activation of multiple cortical circuits. Neuroscientist. 2018; 24(3):246-60. [DOI:10.1177/1073858417717660] [PMID]

[53] Gersner R, Kravetz E, Feil J, Pell G, Zangen A. Long-term effects of repetitive transcranial magnetic stimulation on markers for neuroplasticity: Differential outcomes in anesthetized and awake animals. The Journal of Neuroscience. 2011 31(20):7521-6. [DOI:10.1523/JNEUROSCI.6751-10.2011] [PMID] [PMCID]

[54] Di Lazzaro V, Profice P, Ranieri F, Capone F, Dileone M, Oliviero A, et al. I-wave origin and modulation. Brain Stimulation. 2012; 5(4):512-25. [DOI:10.1016/j.brs.2011.07.008] [PMID]

[55] Ragnarsson KT. Functional electrical stimulation after spinal cord injury: Current use, therapeutic effects and future directions. Spinal Cord. 2008; 46(4):255-74. [DOI:10.1038/sj.sc.3102091] [PMID]

[56] Chipchase LS, Schabrun SM, Hodges PW. Peripheral electrical stimulation to induce cortical plasticity: A systematic review of stimulus parameters. Clinical Neurophysiology. 2011; 122(3):456-63. [DOI:10.1016/j.clinph.2010.07.025] [PMID]

[57] Grahn PJ, Lavrov IA, Sayenko DG, Van Straaten MG, Gill ML, Strommen JA, et al. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. Mayo Clinic Proceedings. 2017; 92(4):544-54. [DOI:10.1016/j.mayocp.2017.02.014] [PMID]

[58] van der Scheer JW, Goosey-Tolfrey VL, Valentino SE, Davis GM, Ho CH. Functional electrical stimulation cycling exercise after spinal cord injury: A systematic review of health and fitness-related outcomes. Journal of Neuroengineering and Rehabilitation. 2021; 18(1):99. [DOI:10.1186/s12984-021-00882-8] [PMID] [PMCID]

[59] Follesa P, Biggio F, Gorini G, Caria S, Talani G, Dazzi L, et al. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. Brain Research. 2007; 1179:28-34. [DOI:10.1016/j.brainres.2007.08.045] [PMID]

[60] Ganzer PD, Darrow MJ, Meyers EC, Solorzano BR, Ruiz AD, Robertson NM, et al. Closed-loop neuromodulation restores network connectivity and motor control after spinal cord injury. Elife. 2018; 7:e32058. [DOI:10.7554/eLife.32058] [PMID] [PMCID]