The Effect of Epidural Electrical Stimulation Application in Individuals with Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is a significant cause of disability, affecting both children and adults worldwide. These injuries can arise from various conditions, including traumatic, vascular, tumor-related, infection-related, inflammatory (such as multiple sclerosis), or neurodegenerative (like motor neuron disease) origins. Among these, traumatic spinal cord injuries caused by reasons like falls and traffic accidents stand out, particularly in developed countries. Epidural electrical stimulation (EES) was initially used to inhibit chronic pain. Subsequent studies have shown its effectiveness in individuals with SCI. In research spanning from the past to the present, EES applications have been utilized for activities such as motor function improvement, sensory enhancement, bowel functions, increased sexual functionality, and regulating heart rhythms in people with SCI. However, the exact impact of EES remains inconclusive at present and is still a subject of debate.

Keywords: Spinal cord injury, epidural electrical stimulation, neuromodulation

Spinal Kord Yaralanması Olan Bireylerde Epidural Elektriksel Stimülasyon Uygulamasının Etkisi

Öz

Spinal kord yaralanması (SKY), dünya çapında her yaştan insanı etkileyen ciddi sakatlıklara yol açmaktadır. Travma, damar sorunları, tümörler, enfeksiyonlar, inflamasyon (örn. multipl skleroz) ve nörodejenerasyon (örn. motor nöron hastalığı) gibi çeşitli faktörler bu yaralanmalara neden olabilmektedir. Bunlar arasında, özellikle gelişmiş ülkelerde, düşme ve kazalardan kaynaklanan travmatik SKY öne çıkmaktadır. Başlangıçta kronik ağrı kontrolü için kullanılan epidural elektriksel stimülasyonun (EES), SKY olan bireylerde etkinliği kanıtlanmıştır. Zamanla EES, SKY olan kişilerde motor fonksiyonu geliştirmek, duyu geliştirmek, bağırsak fonksiyonlarını düzenlemek, cinsel yetenekleri geliştirmek ve hatta kalp ritimlerini modüle etmek için kullanılmaktadır. Ancak EES'nin kesin etkisi belirsizliğini korumakta ve devam eden tartışmalara konu olmaktadır.

Anahtar Sözcükler: Spinal kord yaralanması, epidural elektriksel stimülasyon, nöromodülasyon

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Introduction

A spinal cord injury (SCI) is an injury that affects millions of people worldwide. It is often caused by accidents such as traffic collisions, gunshot wounds, and sports accidents[1]. There is currently no known proven treatment for spinal cord injuries. However, recently, the use of Epidural Electrical Stimulation (EES) devices has emerged as an effective method, particularly for motor and sensory functions, in individuals with SCI. Initially, the EES device was utilized for individuals with lower back pain[2]. Nevertheless, studies have shown its effectiveness in individuals with SCI, leading to its application in this population. Currently, research on EES for SCI individuals is rapidly increasing. However, the definitive outcomes of this treatment are yet to be determined. Nonetheless, it is seen as a new hope for treatment in individuals with SCI.

SCI is a condition that affects millions of individuals worldwide and frequently leads to lifelong consequences[1]. This neurological condition leads to physical dependency, psychological stress, disease burden, and fiscal strain. Over the once three decades, the global prevelance of SCI has risen from 236 to 1298 cases per million people. Annually, an estimated 250 000 to 500 000 new cases of SCI occur[3].

These injuries are usually caused by factors such as motor vehicle accidents (constituting 38% of cases), falls (accounting for over 22% of cases), incidents of violence (contributing to 13.5% of cases), and accidents during sports and recreational activities (making up 9% of cases). The impact on functional abilities experienced by individuals depends on factors like the location and severity of the spinal cord injury, as well as the specific anatomical details. Aside from the loss of motor, sensory, and autonomic nervous system functions, additional complications can arise within the affected area. These complications may manifest as issues such as muscle atrophy, chronic pain, urinary tract infections, and pressure ulcers[4].

SCI is categorized as complete or incomplete using the International Standards for Neurological Classification of Spinal Cord Injury and the American Spinal Injury Association Impairment Scale (AIS). In this classification, AIS A corresponds to complete lesions, while AIS B, AIS C, AIS D, and AIS E indicate incomplete lesions. Created in 1982 to replace the previous Frankel system, this classification system offers a more comprehensive assessment, taking into account sensory and motor functions in the S4/5 segments[5].

Normal spinal cord physiology involves interactions between many cell types, such as astrocytes, neurons, microglia, and oligodendrocytes. However, after a spinal cord injury, these multicellular interactions are disrupted and become dysregulated, which may impair spinal cord healing[6].

When autopsies of individuals experiencing SCI are examined, it is seen that there is no standard lesion. Each individual with SCI is different, and therefore no two have a similar neuropathology. That is, the neuropathological difference in individuals with SCI applies to both the vertebral column and spinal cord[7].

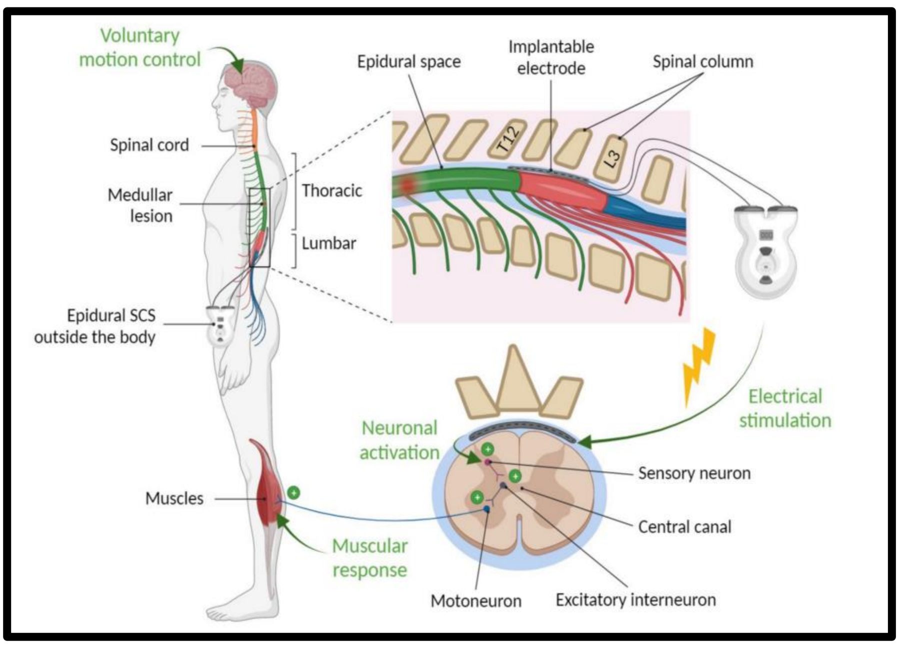
Epidural Electrical Stimulation

EES applied to the spinal cord activates the locomotor centers, enabling a wide range of motor behaviors, like walking in various directions. It also coordinates different systems, including sensation, cardiovascular, pulmonary, bladder, and bowel systems, in cases of paralysis such as paraplegia and quadriplegia[8,9].

When combined with locomotor training (Central Pattern Generator), EES facilitates movement without constant stimulation, aids in bladder and bowel control, restores sensations, and encourages significant rewiring of neural pathways to reinstate cardiovascular and pulmonary functionalities[10]. The EES setup comprises 16 anode-cathode leads in a 5-6-5 configuration[8,11].

Despite being applied to the human spinal cord for many years, the efficacy of EES has shown variation. It can induce rhythmic leg movements in individuals with complete paraplegia or quadriplegia[12,13], and with prolonged application during intensive rehabilitation, it can lead to independent stepping over a year's duration[14,15]. Additionally, EES enables the voluntary activation of paralyzed muscles and initiation of isolated leg movements in those with motor complete paraplegia and quadriplegia[16,17].

Figure 1. Principles of epidural stimulation: Electrode placement and mechanism primarily involve the activation of sensory fibers in the posterior root[10]



History of Epidural Electrical Stimulation

The initial purpose of EES was to manage chronic pain. Neurophysiological studies provided evidence of its pain-inhibiting effects. In 1989, EES received FDA approval specifically for chronic pain management[18]. Subsequent EES trials aimed to regulate neuromotor function restoration.

In 1973, it was first applied to patients with Multiple Sclerosis (MS) to manage chronic pain, but unexpected effects emerged. These effects included enhanced voluntary muscle activation control, increased lower extremity muscle strength, facilitation of sitting, standing, and walking activities[19]. Later studies targeted individuals with upper motor lesions for spasticity management. A long-term cohort study provided evidence of EES effectively managing spasticity[20]. Subsequent investigations focused on individuals with SCI. Although the primary aim was spasticity management, studies also explored its impact on motor function alongside benefits such as improved bowel control and increased sexual function. Results indicated notable enhancement of motor function[21-23].

The General Principle of Epidural Electrical Stimulation

The regulation and control of motor functions in the spinal cord are influenced by the application of electric fields to the spinal cord, eliciting various physiological responses (Figure 1). Electrodes are positioned epidurally, allowing direct contact with the dura mater. With each stimulation pulse, significant ionic currents pass through the protective dural sac surrounding the spinal cord and its roots. This phenomenon is facilitated by the relatively elevated electrical conductivity of the cerebrospinal fluid[24-27].

Specific neural structures within the dural sac depolarize based on the flow, their position, and exposure. The action potentials of these structures are typically generated according to an "all or none" principle. Computational models have been employed to investigate these instantaneous electrical effects. These models can handle complex geometries such as the spinal cord, calculate electric current, and determine its distribution[24-26,28]. However, while these calculations can estimate current and voltage distributions, they do not predict the response of neural tissue to externally applied electric fields.

To address this issue, nerve fiber models using the Hodgkin-Huxley formalism have been developed. These models can calculate membrane properties in response to external currents[29]. Similar models can predict minimum depolarization thresholds and activation points for individual neurons or populations. Neurons triggered by electrical stimulation and involved in motor functions have been investigated through neurophysiological studies in various organisms, ranging from mice to humans. Physiological outcomes arising from these neurons include both local and potentially across-segment circuits. Nevertheless, the precise mechanisms of initiation remain uncertain, and active research on this topic continues[13,23,30-32].

Application of Epidural Electrical Stimulation to People with Spinal Cord Injury

In a study, 15 participants (11 males and 4 females) were included. Individuals had complete SCI between the T3 and T10 levels, classified as AIS A. The average age of the participants was 42.5 years, and the duration since injury was 6.5 years. Customized EES setups with a total of 16 anode-cathode leads (5-6-5 configuration) were implanted between the T11 and L1 levels. Individualized

EES mappings were performed, targeting specific muscle groups (intercostal muscles, rectus abdominis, iliopsoas, rectus femoris, tibialis anterior, extensor hallucis longus, paraspinal, and gastrocnemius) using low-frequency stimulation (2 Hz, 350–450 μs, 0–10 mA). The results showed that cathodal stimulation activated the rectus abdominis, intercostal, paraspinal, iliopsoas, rectus femoris, tibialis anterior, extensor hallucis longus, and gastrocnemius muscles in the transverse plane. Stimulation configurations were evaluated as rostral-caudal dipoles in parallel (vertical configuration), vertical (horizontal configuration), and oblique (diagonal configuration). Caudal cathodal stimulation significantly activated only rectus femoris and extensor hallucis longus muscles. Oblique stimulation activated rectus abdominis, intercostal, paraspinal, iliopsoas, and tibialis anterior muscles in the transverse plane[33].

In another study, 13 participants (9 males and 4 females) with an average age of 27.1 years were included. These individuals had chronic (5.5 years) motor and sensory complete or motor incomplete SCI. Among them, 6 individuals were classified as AIS A and 7 as AIS B. EES was implanted at the lumbosacral level. The study observed spasticity management in 6 participants. Controlled knee flexion and dorsiflexion were observed with EES; however, consistent effects were not observed in all participants[34].

In a study by Pino et al. (2020), 7 participants were included with an average age of 42 years. Among these individuals, 6 were classified as AIS A and 1 as AIS B, with an average time since injury of 7.7 years. The EES coverage spanned from T11 to T12, while the stimulation range was from L2 to S2. The results demonstrated significant voluntary movement improvement in 4 individuals. Additionally, spasticity management paralleled voluntary motor movements. Notably, participants exhibited gait cycles without stimulation as well[35].

In another study, two women aged 48 to 52, with spinal cord injuries spanning five to ten years, were included. Their injury levels were T8 and T4, and they had motor and sensory complete injuries categorized as AIS A. EES was implanted at the T12 level, and participants underwent 60 sessions of EES. The study revealed an increase in voluntary muscle activation and an improvement in autonomous functions, particularly bladder and bowel symptoms[36].

In another study, three distinct individuals with an average age of 36.6 years were included. Their injury levels were C7 (2 individuals) and C4 (1 individual), and two were classified as AIS D and one as AIS C. The time since injury was 4.7 years. EES was placed within the T11 to L1 range, but stimulation was targeted at L1 to S1. Following intensive therapy, voluntary walking control improved, and individuals managed to achieve controlled walking cycles without EES[37].

In yet another study, two individuals with AIS B level injuries at the C5 and C6 levels were included. They exhibited minimal voluntary movement in the shoulder and proximal upper extremities, but not in the hand region. EES was implanted within the C5 to T1 range, and participants underwent intensive EES therapy for 160 sessions. The results showed an increase in voluntary motor control performance and contractions in the hand region[38].

In another study within the literature, a 38-year-old individual with a C5/C6 level injury from a decade ago had previously undergone 5 months of EES. Subsequently, a brain-spine interface (BSI) device, similar to EES but providing brain-spine communication, was implanted at the cortical level. Unlike EES, BSI required only a few minutes of calibration. The study found that BSI enhanced the individual's voluntary lower limb movements and walking. However, the device had to be powered by a backpack worn by the individual, adding extra weight, highlighting the need for further development of this approach[39].

In another study, a 24-year-old female patient with AIS B classification and incomplete T5 level injury received EES within the T8 to S1 range. Pre- and post-therapy urodynamic tests were conducted. The patient underwent EES therapy for 4 weeks, 5 days a week, 2 hours a day. The study revealed that neurological bladder control was achieved and confirmed through urodynamic testing[40].

In another study, a 26-year-old male patient (who had a motor accident 3 years prior) with T6 injury level and AIS A classification was included. EES was integrated at the lumbosacral level. Prior to EES, the patient received 61 sessions of physiotherapy over 22 weeks. After EES surgery, the patient underwent 8 sessions of EES therapy over 2 weeks. The results showed an increase in voluntary motor control of specific muscles. Furthermore, independent (balance-assisted) rhythmic locomotor activities were reported to have increased[41].

In another study involving two participants with AIS A classification, one aged 26 with T6 injury level, and the other aged 37 with T3 injury level. The study observed an increase in urinary incontinence due to worsening bladder function in one participant. In the other participant, an increase in standing and stepping capabilities was observed through EES[42].

Conclusion

When SCI occurs due to various reasons, individuals face physical, economic, and psychosocial challenges, leading to significant problems at both individual and societal levels. As a result of SCI, problems such as motor, sensory, pulmonary, bladder, and bowel impairments emerge. Therapies for individuals with SCI generally aim to optimize anatomical functions as much as possible based on the level of injury and integrate them into their daily activities. However, due to motor function loss or issues like bladder and bowel dysfunction, individuals with SCI often struggle to participate in daily activities and require assistance.

EES is a newly emerging application that involves surgical implantation within the spinal cord. Studies conducted on individuals with SCI primarily focus on voluntary motor movement. However, the literature also covers research on sensory, bladder, bowel, and sexual functions. Despite being a novel approach, EES is not widely known or its effectiveness fully understood.

Given the limited participation in studies in the literature, data remains restricted. Nevertheless, findings from these studies suggest that EES has a significant impact on voluntary motor activity and spasticity management.

With the advancement of EES, we believe it will enhance the participation of individuals with SCI in daily life activities. However, a drawback of EES is its inability to specifically target desired muscle groups during mapping. To address this, Lorach and colleagues at EPFL University applied BSI to an individual with EES, demonstrating real-time cortical-level stimulation and precise targeting of muscle groups[39].

In general, the EES application holds promise as a potential intervention for voluntary motor activity in individuals with SCI. However, more extensive research with larger participant groups is needed to further explore its potential benefits.

Recommendations

EES application is seen as a promising intervention for individuals with SCI. However, the mapping of this newly emerging approach is not well understood. Mapping strategies for this novel application are not widely known. In the literature, mapping is often conducted using electromyography (EMG). Further research is needed to better understand the mapping process of EES and to explore its more effective utilization.

REFERENCES

1. Friedli L, Rosenzweig ES, Barraud Q, et al. Pronounced species divergence in corticospinal tract reorganization and functional recovery after lateralized spinal cord injury favors primates. *Sci Transl Med*. 2015;7(302):302ra134. doi: 10.1126/scitranslmed.aac5811.
2. Sabourin MD, Turpin BA, Head BA, Wu MD, Sharan MD, Hoelscher MD. Spinal cords Stimulation in the 21st century reviewing innovation in neuromodulation. *JHN Journal*. 2019;14(1):5.
3. Khorasanizadeh M, Yousefifard M, Eskian M, et al. Neurological recovery following traumatic spinal cord injury: a systematic review and meta-analysis. *J Neurosurg Spine*. 2019;1-17. doi: 10.3171/2018.10.SPINE18802.
4. Abrams GM, Ganguly K. Management of chronic spinal cord dysfunction. *Continuum (Minneap Minn)*. 2015;21(1 Spinal Cord Disorders):188-200. doi: 10.1212/01.CON.0000461092.86865.a4.
5. Waring WP, Biering-Sorensen F, Burns S, et al. 2009 review and revisions of the international standards for the neurological classification of spinal cord injury. *J Spinal Cord Med*. 2010;33(4):346-352. doi: 10.1080/10790268.2010.11689712.

6. O'Shea TM, Burda JE, Sofroniew MV. Cell biology of spinal cord injury and repair. *J Clin Invest*. 2017;127(9):3259-3270. doi: 10.1172/JCI90608.

7. Dimitrijevic MR, Kakulas BA. Spinal cord injuries, human neuropathology and neurophysiology. *Acta Myol*. 2020;39(4):353-358. doi: 10.36185/2532-1900-039.

8. Van den Brand R, Heutschi J, Barraud Q, et al. Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science*. 2012;336(6085):1182-1185. doi: 10.1126/science.1217416.

9. Capogrosso M, Milekovic T, Borton D, et al. A brain-spine interface alleviating gait deficits after spinal cord injury in primates. *Nature*. 2016;539(7628):284-288. doi: 10.1038/nature20118.

10. Pradat PF, Hayon D, Blancho S, Neveu P, Khamaysa M, Guerout N. Advances in spinal cord neuromodulation: the ıntegration of neuroengineering, computational approaches, and ınnovative conceptual frameworks. *J Pers Med*. 2023;13(6):993. doi: 10.3390/jpm13060993.

11. Asboth L, Friedli L, Beauparlant J, et al. Cortico-reticulo-spinal circuit reorganization enables functional recovery after severe spinal cord contusion. *Nat Neurosci*. 2018;21(4):576-588. doi: 10.1038/s41593-018-0093-5.

12. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci*. 1998;860:360-376. doi: 10.1111/j.1749-6632.1998.tb09062.x.

13. Minassian K, Jilge B, Rattay F, et al. Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. *Spinal Cord*. 2004;42(7):401-416. doi: 10.1038/sj.sc.3101615.

14. Herman R, He J, D'Luzansky S, Willis W, Dilli S. Spinal cord stimulation facilitates functional walking in a chronic, incomplete spinal cord injured. *Spinal Cord*. 2002;40(2):65-68. doi: 10.1038/sj.sc.3101263.

15. Gill ML, Grahn PJ, Calvert JS, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nat Med*. 2018;24(11):1677-1682. doi: 10.1038/s41591-018-0175-7.

16. Harkema S, Gerasimenko Y, Hodes J, et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet*. 2011;377(9781):1938-1947. doi: 10.1016/S0140-6736(11)60547-3.

17. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*. 2014;137(Pt 5):1394-1409. doi: 10.1093/brain/awu038.

18. Krames ES, Hunter Peckham P, Rezai A, Aboelsaad F, Krames ES, Chapter 1 - *What is Neuromodulation*? in: Peckham PH, Rezai AR, (Eds.), Neuromodulation, Academic Press, San Diego, 2009, pp. 3–8.

19. Cook AW, Weinstein SP. Chronic dorsal column stimulation in multiple sclerosis. Preliminary report. *NY State J Med*. 1973;73(24):2868-2872.

20. Siegfried J, Lazorthes Y, Broggi G. Electrical spinal cord stimulation for spastic movement disorders. *Appl Neurophysiol*. 1981;44(1-3):77-92. doi: 10.1159/000102187.

21. Barolat G, Myklebust JB, Wenninger W. Effects of spinal cord stimulation on spasticity and spasms secondary to myelopathy. *Appl Neurophysiol*. 1988;51(1):29-44. doi: 10.1159/000099381.

22. Richardson RR, McLone DG. Percutaneous epidural neurostimulation for paraplegic spasticity. *Surg Neurol*. 1978;9(3):153-155.

23. Waltz JM. Spinal cord stimulation: a quarter century of development and investigation. A review of its development and effectiveness in 1,336 cases. *Stereotact Funct Neurosurg*. 1997;69(1-4 Pt 2):288-299. doi: 10.1159/000099890.

24. Capogrosso M, Wenger N, Raspopovic S, et al. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. *J Neurosci*. 2013;33(49):19326-19340. doi: 10.1523/JNEUROSCI.1688-13.2013.

25. Rattay F, Minassian K, Dimitrijevic MR. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 2. quantitative analysis by computer modeling. *Spinal Cord*. 2000;38(8):473-489. doi: 10.1038/sj.sc.3101039.

26. Greiner N, Barra B, Schiavone G, et al. Recruitment of upper-limb motoneurons with epidural electrical stimulation of the cervical spinal cord. *Nat Commun*. 2021;12(1):435. doi: 10.1038/s41467-020-20703-1.

27. Lempka SF, Zander HJ, Anaya CJ, Wyant A, Ozinga JG, Machado AG. Patient-specific analysis of neural activation during spinal cord stimulation for pain. *Neuromodulation*. 2020;23(5):572-581. doi: 10.1111/ner.13037.

28. Coburn B, Sin WK. A theoretical study of epidural electrical stimulation of the spinal cord--Part I: Finite element analysis of stimulus fields. *IEEE Trans Biomed Eng*. 1985;32(11):971-977. doi: 10.1109/tbme.1985.325648

29. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol.* 1952;117(4):500-544. doi: 10.1113/jphysiol.1952.sp004764.

30. Minassian K, Persy I, Rattay F, Pinter MM, Kern H, Dimitrijevic MR. Human lumbar cord circuitries can be activated by extrinsic tonic input to generate locomotor-like activity. *Hum Mov Sci.* 2007;26(2):275-295. doi: 10.1016/j.humov.2007.01.005.

31. Hofstoetter US, Perret I, Bayart A, et al. Spinal motor mapping by epidural stimulation of lumbosacral posterior roots in humans. *iScience.* 2020;24(1):101930. doi: 10.1016/j.isci.2020.101930.

32. Gerasimenko YP, Lavrov IA, Courtine G, et al. Spinal cord reflexes induced by epidural spinal cord stimulation in normal awake rats. *J Neurosci Methods.* 2006;157(2):253–63.

33. Hoglund BK, Zurn CA, Madden LR, et al. Mapping spinal cord stimulation-evoked muscle responses in patients with chronic spinal cord injury. *Neuromodulation.* 2022;S1094-7159(22)01360-5. doi: 10.1016/j.neurom.2022.10.058.

34. Rejc E, Smith AC, Weber KA, et al. Spinal cord imaging markers and recovery of volitional leg movement with spinal cord epidural stimulation in individuals with clinically motor complete spinal cord injury. *Front Syst Neurosci.* 2020;14:559313. doi: 10.3389/fnsys.2020.559313.

35. Peña Pino I, Hoover C, Venkatesh S, et al. Long-term spinal cord stimulation after chronic complete spinal cord injury enables volitional movement in the absence of stimulation. *Front Syst Neurosci.* 2020;14:35. doi: 10.3389/fnsys.2020.00035.

36. Darrow D, Balser D, Netoff TI, et al. Epidural spinal cord stimulation facilitates immediate restoration of dormant motor and autonomic supraspinal pathways after chronic neurologically complete spinal cord injury. *J Neurotrauma.* 2019;36(15):2325-2336. doi: 10.1089/neu.2018.6006.

37. Wagner FB, Mignardot JB, Le Goff-Mignardot CG, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature.* 2018;563(7729):65-71. doi: 10.1038/s41586-018-0649-2.

38. Lu DC, Edgerton VR, Modaber M, et al. Engaging cervical spinal cord networks to reenable volitional control of hand function in tetraplegic patients. *Neurorehabil Neural Repair.* 2016;30(10):951-962. doi: 10.1177/1545968316644344.

39. Lorach H, Galvez A, Spagnolo V, et al. Walking naturally after spinal cord injury using a brain-spine interface. *Nature.* 2023;618(7963):126-133. doi: 10.1038/s41586-023-06094-5.

40. Özer S, Gündüz S, Akdemir M, Açar G. Investigation of the Effect of Epidural Electrical Stimulation on Neurological Bladder Symptom in a Patient With Spinal Cord Injury: A Case Report. Inovation in Rehabilitation – 1: Balance International Congress. Nov 25-26 2022; Gaziantep, Turkey

41. Grahn PJ, Lavrov IA, Sayenko DG, et al. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. *Mayo Clin Proc.* 2017;92(4):544-554. doi: 10.1016/j.mayocp.2017.02.014.

42. Beck L, Veith D, Linde M, et al. Impact of long-term epidural electrical stimulation enabled task-specific training on secondary conditions of chronic paraplegia in two humans. *J Spinal Cord Med.* 2021;44(5):800-805. doi: 10.1080/10790268.2020.1739894.