# Transcutaneous Spinal Stimulation From Adults to Children: A Review

**_Goutam Singh, PT, PhD,[1,2] Kathryn Lucas, PhD, PT,[2,3] Anastasia Keller, PhD,[4] Rebecca Martin, OTR/L, OTD, CPAM,[5,6] Andrea Behrman, PhD, PT,[2,3] Sergey Vissarionov, PhD,[7] and Yury P. Gerasimenko, PhD[2,8,9]_**

_[1]Kosair Charities School of Physical Therapy, Spalding University, Louisville, Kentucky; [2]Kentucky Spinal Cord Injury Research Center, University of Louisville, Louisville, Kentucky; [3]Department of Neurological Surgery, University of Louisville, Louisville, Kentucky; [4]Department of Neurological Surgery, University of California, San Francisco, San Francisco, California; [5]International Center for Spinal Cord Injury, Hugo W. Moser Research Institute at Kennedy Krieger Institute, Baltimore, Maryland; [6]Department of Physical Medicine and Rehabilitation, The Johns Hopkins University School of Medicine, Baltimore, Maryland; [7]Turner Scientific Research Institute for Children's Orthopedics, St. Petersburg, Russia; [8]Department of Physiology, University of Louisville, Louisville, Kentucky; [9]Pavlov Institute of Physiology Russian Academy of Sciences, St. Petersburg, Russia_

Neuromodulation via spinal stimulation is a promising therapy that can augment the neuromuscular capacity for voluntary movements, standing, stepping, and posture in individuals with spinal cord injury (SCI). The spinal locomotor-related neuronal network known as a central pattern generator (CPG) can generate a stepping-like motor output in the absence of movement-related afferent signals from the limbs. Using epidural stimulation (EP) in conjunction with activity-based locomotor training (ABLT), the neural circuits can be neuromodulated to facilitate the recovery of locomotor functions in persons with SCI. Recently, transcutaneous spinal stimulation (scTS) has been developed as a noninvasive alternative to EP. Early studies of scTS at thoracolumbar, coccygeal, and cervical regions have demonstrated its effectiveness in producing voluntary leg movements, posture control, and independent standing and improving upper extremity function in adults with chronic SCI. In pediatric studies, the technology of spinal neuromodulation is not yet widespread. There are a limited number of publications reporting on the use of scTS in children and adolescents with either cerebral palsy, spina bifida, or SCI. **Key words:** *neuromodulation, motor recovery, pediatric, spinal cord injury, spinal stimulation, transcutaneous spinal cord stimulation*

## Introduction

The spinal cord contains networks of interneurons known as the central pattern generator (CPG)[1] that have the capacity to generate rhythmical reciprocal motor patterns. The CPG can be activated by epidural stimulation (EP) and induce the rhythmic stepping-like movements in persons with motor complete spinal cord injury (SCI).[2] Spinal locomotor-related neuronal circuitry in rats, cats, and humans can be neuromodulated by electrical spinal cord stimulation to regain sensorimotor function after complete paralysis due to SCI.[3] Originally, EP was used as a potential neuromodulatory therapy to manage chronic pain, movement disorders, and spasticity.[4-7] Using the technology of EP and task-specific locomotor training, chronic paralyzed individuals have achieved the ability to walk overground with lumbosacral epidural electrical stimulation.[8,9] These breakthrough studies refute the existing dogma about the impossibility of restoring voluntary control and independent walking in patients with motor complete injuries. Currently, epidural spinal neuromodulation is studied to control locomotor and postural adjustments, voluntary limb movements, and support visceral functions (e.g., cardiovascular, bladder) in adults with SCI and severe paralysis.[10-16] Although EP is an effective tool for regulation of motor functions, the procedure of electrode implantation is invasive and requires bone removal via laminectomy; it involves inherent risk of infection at the site and prolonged recovery post surgery.[17-19] Another limitation of existing epidural devices is that they use a single-plane array of bipolar electrodes applied epidurally on the dorsal spinal cord, which allows for stimulation at one site

*Corresponding author:* Dr. Yury Gerasimenko, 220 Abraham Flexner Way, 1500, Louisville, KY 40202; email: yury.gerasimenko@louisville.edu

*Top Spinal Cord Inj Rehabil* 2023;29(1):16-32

www.asia-spinalinjury.org
doi: 10.46292/sci21-00084

of neuronal networks, for example, across multiple spinal levels.[20]

Gerasimenko and colleagues developed a novel method of noninvasive transcutaneous spinal cord stimulation (scTS) that can modulate the excitability of spinal circuitry via electrodes placed on the skin overlying the spine.[21,22] One of the innovative features is a specific pulse configuration with a carrier frequency of 5 to 10 kHz that minimizes discomfort when used at energies required to transcutaneously reach the spinal networks. In general, electrical spinal cord stimulation counteracts the loss of the tonic supraspinal drive and raises the central state of excitability, enabling reactivation of the neural structures that were otherwise dormant in the persistent state of immobility due to paralysis.[10,23-26] scTS with high carrier frequency is tolerated by participants due to the suppression of the sensitivity of pain receptors.[27] The use of a specific stimulation waveform with high carrier frequency improved muscle strength[28,29] and more effectively regulated the motor functions of upper limbs both in noninjured individuals and in individuals with SCI than scTS without carrier frequency.[30] scTS is thus more readily available to a patient population as compared to EP requiring surgical implantation of the electrodes. This minimizes the risk associated with surgery and is a potential cost-effective alternative to EP. Compared to EP, the ability to shift surface electrode location with scTS is easily accomplished.

Recent studies suggest that scTS produces similar neuromodulatory effects, including reducing spasticity, generating rhythmic leg movements in participants with complete SCI, and facilitating voluntary locomotor activity in participants with motor incomplete SCI, as revealed by the epidural stimulation in participants with SCI.[31-33] In addition, neurophysiological studies have reported that the scTS and the epidural stimulation applied to lumbosacral enlargements activated common neuronal structures, that is, afferent neurons projecting to the locomotor circuitry with identical spinal evoked electromyography (EMG) responses.[34-36] Furthermore, by elevating the spinal network excitability, scTS may activate intraneuronal pathways capable of generating action potentials on motor neurons; it may potentiate the generation of postsynaptic excitatory potentials and bring interneurons and motor neurons closer to motor threshold. This enables the spinal neuronal network to respond to descending drive and increases overall excitability of spinal cord networks and potentially the motor cortex.[37,38]

Similar to adults, children with SCI have paralysis that results in the inability to sit upright, stand, and walk. scTS is a promising, noninvasive technology offering a means of neuromodulation that may be accessible and beneficial to children.[25] Children with SCI may not only benefit from novel neurotherapeutic interventions but also may demonstrate even greater improvements due to inherent plasticity present during development.[39,40] However, children are not small adults and are still undergoing development and maturation. Various factors, such as differences in anatomy (i.e., articular facets are shallow and ligaments are weaker than in adults), ongoing musculoskeletal growth, and developing cognitive abilities (to report a change in sensation like pain),[41] should be addressed before translating scTS as a neurotherapeutic approach from adults to children with SCI. Additional studies on stimulation parameters, sites, and dosage are needed to demonstrate safety, feasibility, and preliminary understanding on potential mechanisms to improve motor function. In this review, we will highlight the scTS studies in adults relative to motor function, potential mechanisms, and stimulation features; ongoing trials in children with SCI; and gaps in our knowledge to extend this approach to pediatrics.

## Neuromodulation Studies in Adults

scTS is thought to modulate the spinal circuitry to a functional state that optimizes the integration of task-specific afferent input to facilitate and enhance motor output. It was originally focused on sitting posture, standing, and stepping, and it has more recently been extended to arm and hand function.[3,42,43]

### Neuromodulation to improve locomotion, standing, and posture

Gerasimenko and colleagues[21] showed that scTS at vertebral level T11 can induce involuntary stepping-like movements in noninjured humans when their legs are placed in a gravity-neutral position. Furthermore, these scientists refined the technology of scTS to involve multisegmental stimulation to further improve the regulation of locomotor activity in humans. Simultaneous independent stimulation at the C5, T11, and L1 vertebrae in noninjured persons induced more coordinated stepping movements with greater amplitude compared to stimulation at T11 alone[22] (**Figure 1**). The synergistic and interactive effects of scTS suggest a multisegmental convergence of descending and ascending and most likely propriospinal effects on the spinal locomotor-related neuronal circuitries. In a study of five adults with complete SCIs between C5 and T4, painless scTS was administered at T11 and the coccyx (Co1) to potentiate and train a locomotor-like stepping response in a gravity-neutral position.[23] Monopolar rectangular 1 ms duration pulses were provided with a carrier frequency of 10 kHz, stimulation frequencies of 30 Hz at T11 and 5 Hz at Co1, and intensities set between 80 and 180 mA.[23] None of the adults could perform a stepping response without stimulation, but they had some voluntary knee movement with stimulation at the first testing session.[23] After four once-a-week training sessions, the participants could create significantly greater voluntary knee motion with stimulation that was further enhanced when buspirone was added.[23] A study of a 29-year-old female with an incomplete SCI, American Spinal Cord Injury Association Impairment Scale (AIS) T9-D, underwent a single session of treadmill stepping with no body weight support or manual assistance at a speed of 0.8 to 1.6 km per hour. Continuous scTS was applied at T11-12 spinous process with anodes over lower anterior abdomen.[44] Stimulation parameters were biphasic rectangular pulses of 2 ms width with a stimulation frequency of 30 Hz.[44] The improved gait mechanics were immediate with improved EMG signals and lower extremity control that responded to changes in speed and step frequency.[44] Noninvasive stimulation technology facilitated functional brain spinal cord connectivity that enabled a participant with complete motor paralysis to move upon volitional intent and perform overground stepping assisted by robotic exoskeletal device.[45] Another

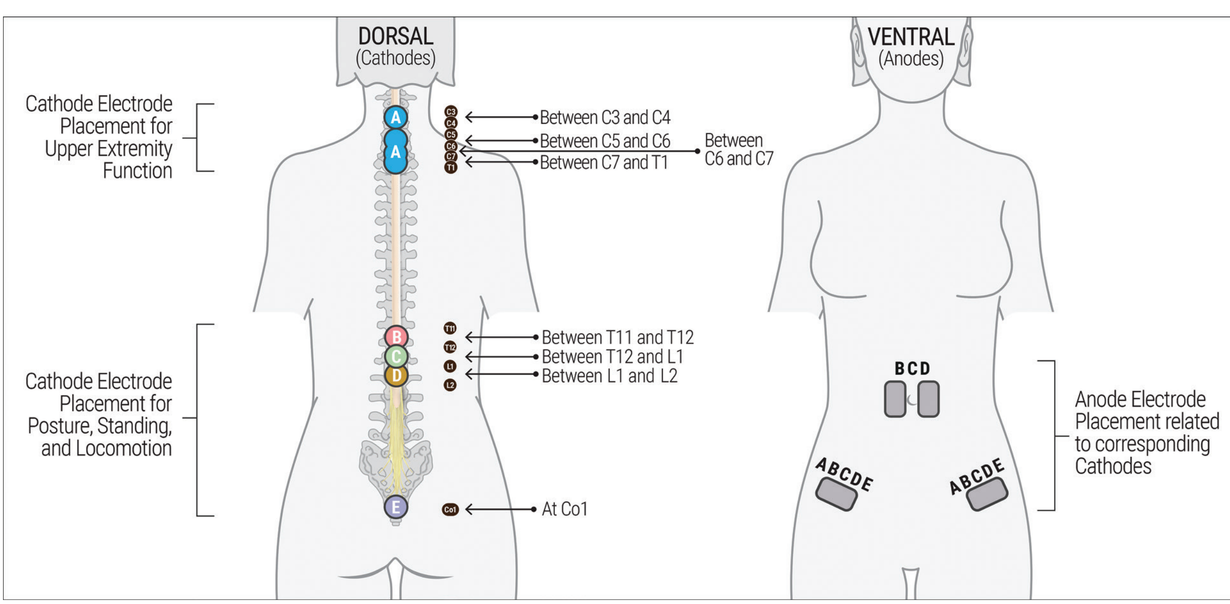


**Figure 1.** Transcutaneous spinal cord stimulation electrodes placement. Schematic of anode and cathode electrode placements used in studies in adult with spinal cord injury. Stimulating electrodes are placed between spinal process of vertebral column. Cathode electrodes labelled as letter A are placed over cervical spinal cord to primarily facilitate upper extremity motor functions. Electrodes B, C, D, and E are placed over thoracolumbar and coccygeal regions of the vertebral column to facilitate posture and locomotion. The anode electrodes are placed bilaterally on the anterior superior iliac crest or on the abdomen, either side of umbilicus.

study using an exoskeleton was carried out on 35 participants with complete or incomplete (AIS A, B, or C) SCI. The results also demonstrated that spinal stimulation may facilitate training and walking in the exoskeleton by activating the locomotor networks and augmenting compensative sensitivity.[46] These studies indicate that stepping-like responses can be potentiated, modulated, and trained, but continued research is needed before identifying whether scTS can result in independent overground walking after complete SCI.

In addition to locomotor-focused studies, investigators studied the use of scTS to promote trunk and postural control. Seated trunk control of eight adults with SCI between C3 and T9 was facilitated using scTS at T11 and L1 set at subthreshold levels based on center of pressure changes and visual postural changes.[47] Monopolar rectangular 1 ms duration pulses were provided with a carrier frequency of 10 kHz, stimulation frequencies of 30 Hz at T11 and 15 Hz at L1, with intensities set between 10 and 150 mA.[47] When asked to sit quietly in an upright posture, participants' trunk extension increased, EMG activity increased, and center of pressure displacement decreased[47] (**Figure 2A-C**). The limits of stability leaning in the forward, backward, and lateral directions all increased.[47] Additionally, the center of pressure displacement decreased when participants were asked to quickly raise their right arm, performing a self-initiated perturbation.[47]

Standing trunk control in 15 participants with SCI between C5 and T12 using two-site (i.e., T11 and L1) simultaneous scTS was examined.[48] Monopolar 1 ms pulses at frequencies of 0.2 to 30 Hz were used at first with both T11 and L1, with a carrier frequency of 10 kHz and stimulation up to 150 mA. Stimulation parameters were set to an intensity whereby knee extension required the least amount of assistance/facilitation. This work demonstrated that postural networks can generate and sustain independent knee and hip extension with the aid of scTS within a single treatment session. The threshold for inducing EMG activity by scTS in leg muscles during sitting versus standing differed and was supported by changes in tonic EMG activity measured using single motor-evoked potentials (**Figure 3A-C**). For training, participants stood for up to 120 minutes (less if the participant fatigued) and worked to extend the limits of stability, controlling the center of pressure based on a force plate center of pressure calculated in real time from the feet.[48] With 12 training sessions, all participants stood with less support, eight of 15 required minimum assistance to stand, and seven of 15 stood without assistance.[48] In some persons, the coupling between postural and locomotor networks was observed. During L1 and T11 scTS, the individual with SCI can stand independently with a rhythmic EMG stepping pattern resembling "stepping in place." Thus, multisegmental scTS delivered at specific parameters of stimulation (at intensities based on motor threshold responses of the trunk and lower limb muscles) facilitates postural and locomotor networks and concurrently enhances generation of motor patterns appropriate for both standing and stepping.

More recently, a new strategy of spinal neuromodulation using scTS continuous stimulation to activate the locomotor circuitry and spatiotemporal scTS to stimulate specific flexor/extensor motor pools during specific phases of the locomotor cycle was introduced.[49] Collectively, these studies indicate that upright posture, standing, and lower extremity muscle strength can improve under experimental conditions with scTS and training in adults with SCI. Despite compelling evidence that scTS improves motor function in people with SCI, these studies had limited knowledge in training approaches necessary for successful translation to clinical practice. In particular, these studies lack clarification on (1) finding optimal scTS parameters (e.g., intensity, frequency, pulse duration) to train patients for greatest improvement and scTS intensity progression across time; (2) identifying the most effective training environment for specific functional goals/tasks (i.e., is sitting, standing, or stepping the optimal position for training trunk and posture control); (3) integrating the role of cognitive effort from the patient during training (does active engagement during scTS play a role and is this to be encouraged throughout training); (4) application of scTS as an early intervention during the acute phase after SCI compared to application in patients with chronic SCI; (5) identifying the durability of scTS on motor improvements (are training effects

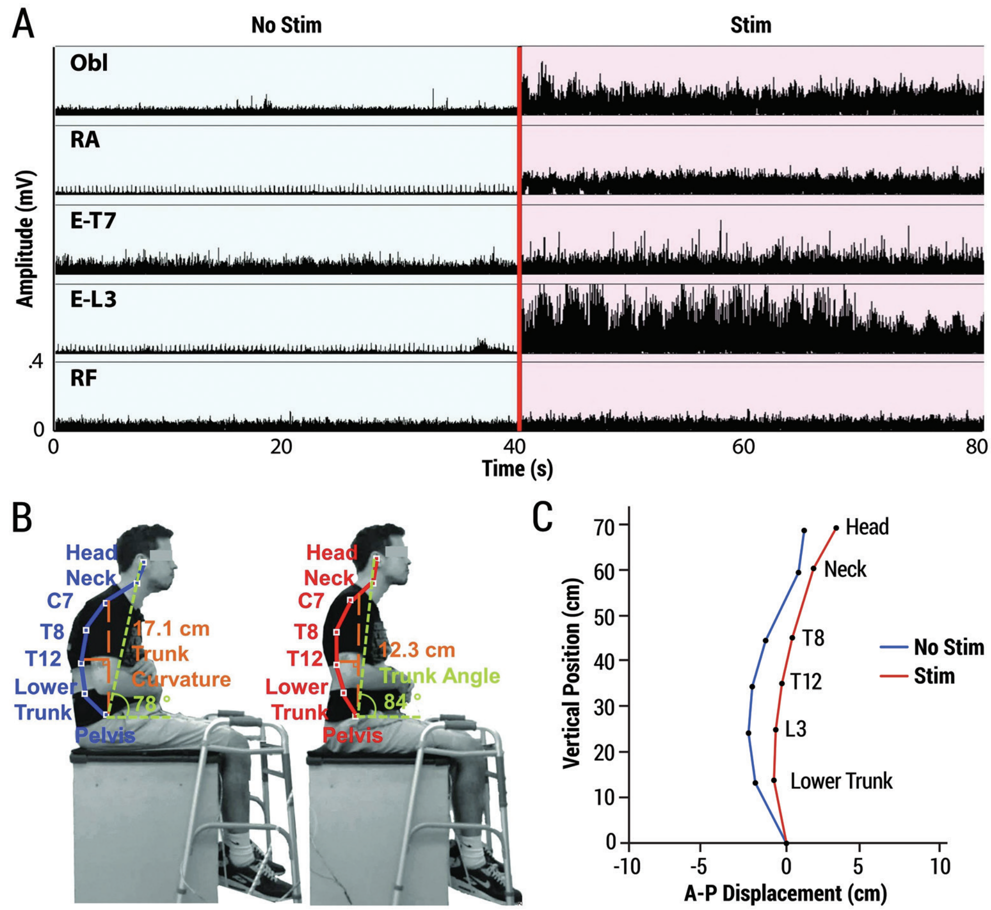


**Figure 2.** Upright sitting postural control enabled by transcutaneous spinal stimulation. (A) Surface electromyography (EMG) recordings of four trunk muscles in a participant during unsupported quiet sitting without (blue) and with (red) submotor threshold stimulation. The external obliques (Obl), rectus abdominis (RA), erector spinae at levels T7 (E-T7) and L3 (E-L3), and rectus femoris (RF) are shown. (B) Upright sitting and trunk curvature of a participant without (left) and with submotor threshold spinal stimulation (right). Note the improvement in trunk angle (green), upright posture and spinal alignment. (C) Spinal alignment during quiet sitting without (blue) and with (red) spinal stimulation from a single participant. Adapted from Rath M, Vette, AH, Ramasubramaniam S, et al. Trunk stability enabled by noninvasive spinal electrical stimulation after spinal cord injury. *J Neurotrauma.* 2018;35(21):2540-2553.

retained after the completion of an intervention); and (6) potentially applying scTS in patients with lower motor neuron injury or identifying whether the effects of scTS on motor recovery are limited to patients with only upper motor neuron lesions. Therefore, additional studies highlighting stimulation training principles, parameters, and clinical decision making are needed to translate this work from research to clinical practice.

**Neuromodulation to improve upper extremity function**

Adults with tetraplegia report that regaining arm and hand function is their highest priority.[50] Current, but limited, clinical therapeutic interventions focus on motor recovery of upper extremity function; most interventions focus on compensation for paralysis and adaptation for daily function.[51] Researchers have recently extended inquiry using scTS to restore volition control of upper extremity motor function after cervical SCI.[42,43] Current developments in noninvasive scTS have demonstrated the efficacy to neuromodulate spinal sensory-motor network above, within, and below the lesion in participants with cervical SCI.[43,52] One study reported recovery of hand grip with one session of scTS at C6-C7 spinal level and following eight training sessions

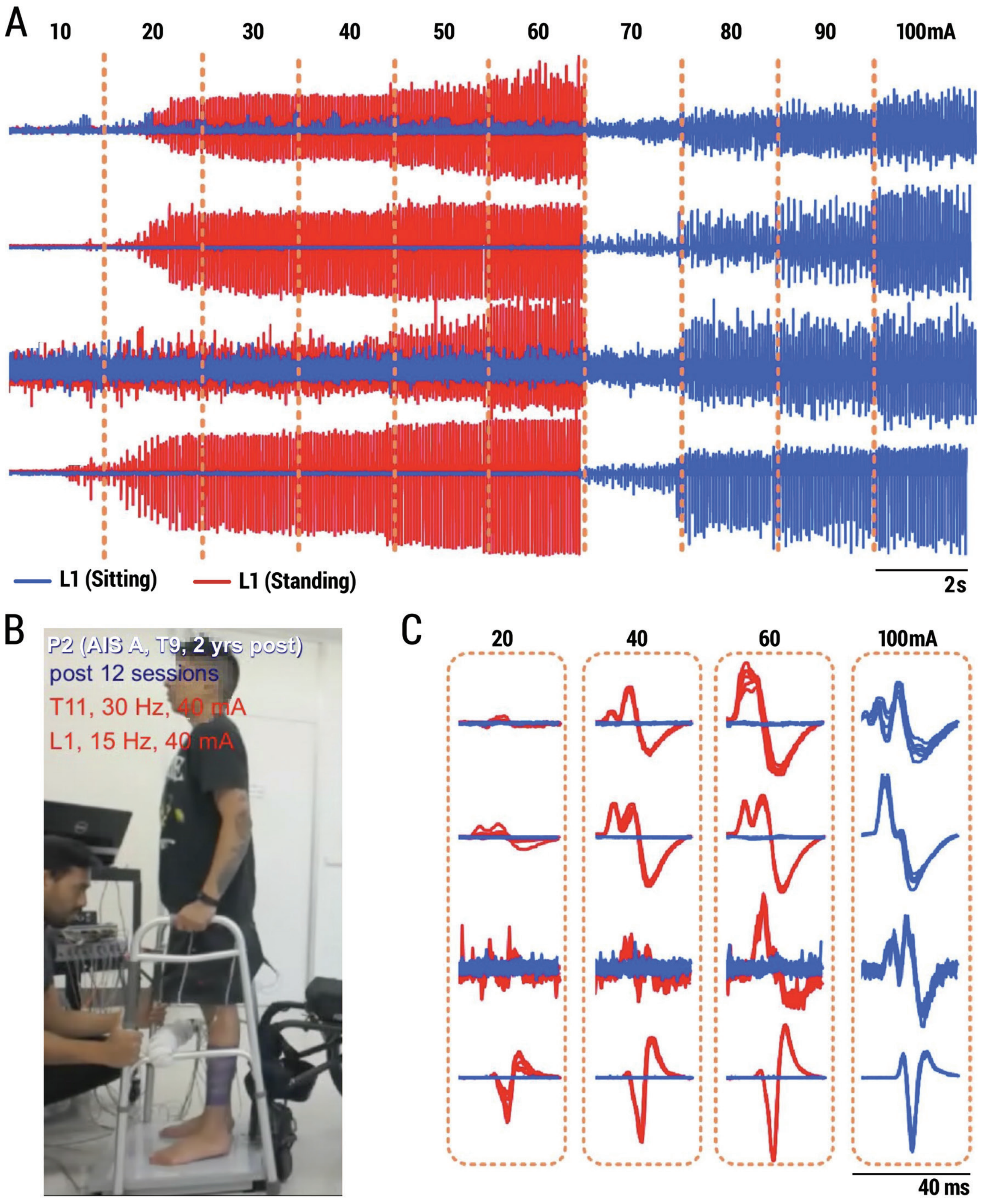


**Figure 3.** Standing posture control enabled by transcutaneous spinal stimulation (scTS). (A) Electromyography (EMG) activity of the left leg muscles during scTS delivered with a frequency of 15 Hz at incremental intensities over L1 during sitting and standing from a single participant. (B) Participant with T9 (AIS A) injury after 20 sessions standing without assistance with stimulation at T11 at 30 Hz at 40 mA and L1 at 15 Hz at 40 mA. (C) Spinally evoked motor potentials recorded during the indicated stimulation intensities at L1 during sitting and standing. Adapted from Sayenko DG, Rath M, Ferguson AR, et al. Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. *J Neurotrauma.* 2019;36(9):1435-1450.

over 4 weeks. These improvements were associated with increased but appropriate activation of distal forearm muscles with decreased activation in proximal muscles.[52] Stimulation parameters were identified for each site, C3-C4 and C6-C7, with fixed frequency of 30 Hz, 1 ms pulse width, and biphasic waveform. In another study, multisite stimulation (C3-C4 and C6-C7) in six participants consistently generated greater hand grip forces with reduction in activation of proximal upper extremity muscles and increased activation of distal muscles to stabilize the wrist during testing. Additionally, four of five cervical-injured participants with upper extremity deficits reported significant improvement in grip force following 2 weeks of hand grip training with scTS at C5 with frequency and intensity range of 5 to 30 Hz and 20 to 100 mA, respectively.[43] Participants reported nonpainful, tingling sensation in the arms at higher intensities with associated tonic contractions of neck paraspinal muscles. Furthermore, functional gains demonstrated by participants were durable and persisted even after 3 months post training with scTS. However, the study investigated a combination of pharmacological agent (buspirone) and scTS on improving upper extremity function. Therefore, independent effects of scTS were not clear. A case study reported improved lateral pinch force, dexterity, and isolated muscle strength in one participant following 5 weeks of intensive physical therapy with cervical scTS.[53] The stimulation was delivered at C3-4 and C6-7 spinal process with biphasic, rectangular waveform of 1 ms pulse, delivered at a frequency of 30 Hz. The stimulation intensities allowed were within a range of 80 to 120 mA. A carrier frequency of 10 kHz was used to minimize pain or discomfort during stimulation. These improvements in motor function were sustained throughout the entire 3 months of follow-up without stimulation or intervention. This work was extended by enrolling an additional six participants to test a combination of intensive upper extremity training with cervical scTS delivered at C3-C4 and C6-7 sites.[54] Participants with cervical SCI underwent activity-based rehabilitation that included bimanual and unimanual gross and isolated movements of upper limbs, pinch, and hand grip performance tasks. Training occurred three times a week with stimulation for up to 120 minutes during each session. The study reported significant improvements in pinch force, strength, and prehension tasks in all six participants with training in the presence of stimulation. In addition, scTS paired with intensive training enabled two participants with complete paralysis to regain digit movements and pinch force. However, these studies reported the combinatorial effects of scTS and activity-based rehabilitation in patients with AIS grade B, C, and D. Therefore, additional scTS studies are needed to investigate the effects of stimulation and training on upper extremity function in patients with motor and sensory complete SCI. In a recent case study, a 38-year-old participant with C5 AIS A received 18 sessions of task-specific hand training combined with scTS at C3-4 and C7-T1 sites simultaneously.[55] Stimulation parameters (intensity) were optimized based on a participant's functional task performance and subjective feedback during training. Instead of a biphasic waveform, as selected in previous UE scTS studies, a monophasic waveform was selected with a frequency of 30 Hz and a carrier frequency of 10 kHz. The participant demonstrated immediate and sustained improvements in bilateral hand grip strength and upper extremity motor control, suggesting the therapeutic potential of scTS in participants with UE motor deficits. More recently, Benavides et al.[30] demonstrated that cervical stimulation with 5 kHz modulated carrier frequency may improve upper limb function via increased intracortical inhibition, which then may result in an improved agonist-antagonist muscle co-activation ratio during a functional task. Consistent with previous findings,[56] the researchers determined that scTS affects motor output of the muscles distal to the applied stimulation sites. The spread of current to the adjacent proximal and distal motor pools is likely mediated via the high degree of propriospinal intersegmental connectivity. The leakage of the current to lower segments due to electrode settings may also contribute to multisegmental effects of single-site scTS stimulation.[30]

These studies provide evidence for scTS applied to the cervical spinal cord to facilitate functional recovery in adult patients with complete and incomplete cervical SCI. The individualized stimulation parameters in combination with task-specific training enabled both short- and long-term recovery of motor functions. These results support the feasibility of the scTS approach to enhance upper extremity function in adults with SCI. In particular, research will need to identify the response(s) to scTS and training parameters for upper limb muscles at baseline (prior to initiation of training) that (1) generate a motor response (e.g., EMG response to stimulation), (2) do not generate a motor response (e.g., no EMG response to stimulation), and (3) demonstrate voluntary muscle activity, yet impaired strength. Furthermore, whether the arm and hand muscles of participants demonstrate upper motor neuron signs (e.g., reflexive activity, spasticity) or lower motor neuron signs (e.g., flaccid tone, atrophy, and absence of reflexes) and the subsequent stimulation parameters and outcomes will be highly relevant for future clinical decision making and should be reported for each muscle identified and trained via scTS. Thus, individual responses may vary depending upon the initial presentation of the muscle, its response to scTS, and the specific training parameters used. Individual injury and sensorimotor presentation variability should be assessed, reported, and understood. Quantitative and physiological tests beyond the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) AIS examination are required to discern such individual differences and inform researchers and ultimately clinicians.

## Mechanisms of Activation of Spinal Networks by Transcutaneous Spinal Stimulation

### Neural structures activated by scTS

Spinal cord stimulation delivers electrical currents in the extracellular compartment surrounding neural tissue. At threshold voltage, electrical stimulation evokes a large change in the membrane potential, resulting in the neuronal depolarization and initiation of the actional potential propagation down the axon.[57,58] In contrast to an action potential generated in response to endogenous stimulus, which is propagated orthodromically, a stimulation-induced action potential travels both orthodromically and antidromically along the nerve fiber.[57] Regardless of the precise mechanism of activation, the neural activity is key for upregulation of immediate early gene expression responsible for morphological and synaptic plasticity underlying neural connectivity.[59-61] Depending on the location, intensity, pulse shape, and frequency, both epidural and transcutaneous stimulation activate various neuronal subtypes along the spinal cord including sensory afferents at the dorsal root entry zone, motor axons, and interneuronal circuitry.[24,34,62,63] Studies also demonstrate that submotor threshold spinal stimulation can increase the central state of excitability of spinal interneuronal networks without direct activation of action potentials that result in a muscle contraction.[24,34,63,64] The rhythmogenesis of EMG stepping pattern induced by spinal cord stimulation is not elucidated completely. Low-intensity stimulation may activate the large-diameter dorsal root afferents (Ia group) that monosynaptically excite the motoneurons[24] (**Figure 4A**). The monosynaptic nature of these responses is confirmed by the fact that vibration of muscle tendons or paired stimulation suppresses the responses.[65] When the intensity of stimulation is gradually increased, in addition to the Ia afferents, the afferents group Ib, group II afferents, flexor afferents group III and IV (FRA), spinal interneurons, and direct motor activation occurs[56] (**Figure 4A**). In addition to the dorsal roots and dorsal columns, the direct stimulation of the spinal cord may also activate the pyramidal and reticulospinal tracts, ventral roots, motor neurons, dorsal horn, and sympathetic tracts.[66,67] In contrast to single pulse stimulation inducing mainly monosynaptic responses in leg muscles, tonic spinal stimulation eliciting involuntary step-like movements activates locomotor-related neuronal networks. Analysis has shown that the genesis of EMG activity accompanying stepping movements differs for extensor and flexor muscles.[3] Gerasimenko et al.[1] reported that in persons with SCI who received epidural spinal cord stimulation, formation of the bursting EMG activity in the extensor muscles is based on the amplitude modulation of monosynaptic responses, whereas in the flexor muscles the main role in this process belongs to the polysynaptic reflex system. It is suggested that the EMG burst in extensor muscles consists of separate monosynaptic responses to activation of Ia afferents and that these responses are modulated in a bursting pattern

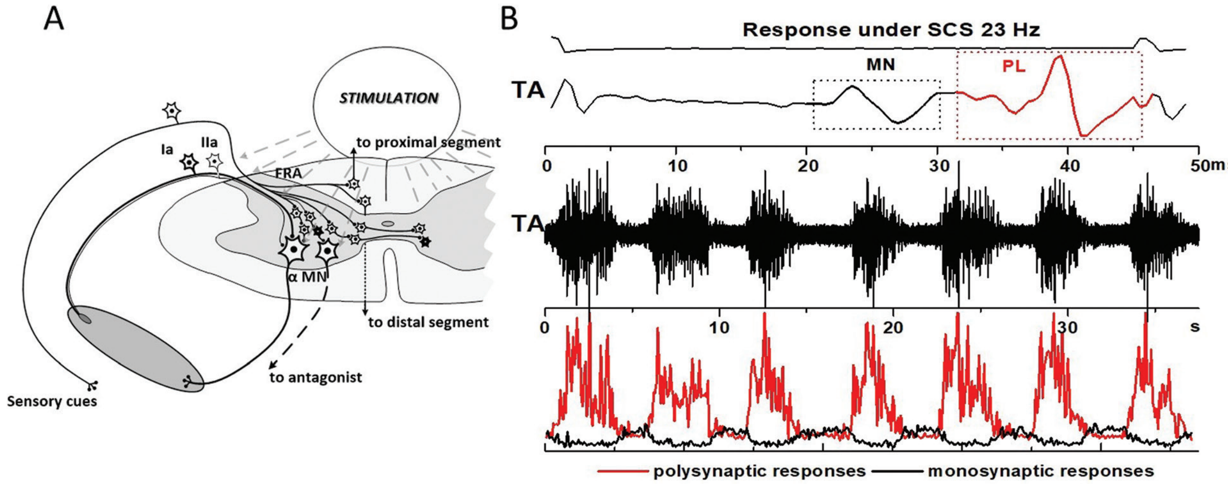


**Figure 4.** Neural structures activated during spinal stimulation. (A) Based on the location, intensity, pulse shape, and frequency, transcutaneous spinal stimulation may activate various neuronal subtypes along the spinal cord including sensory afferents at the dorsal root entry zone, motor axons, and interneuronal circuitry. FRA = flexor reflex afferent neurons; MN = motor neurons. Adapted from Gerasimenko Y, Gorodnichev R, Moshonkina T, Sayenko D, Gad P, Reggie Edgerton V. Transcutaneous electrical spinal-cord stimulation in humans. *Ann Phys Rehabil Med.* 2015;58(4):225-231. (B) Analysis of electromyography (EMG) bursting activity of flexor (tibialis anterior [TA]) muscle using time windows corresponding to the monosynaptic (MN; from 20 to 30 ms) and polysynaptic (PL; from 31 to 45 ms) responses during epidural stimulation at 23 Hz. The response to each stimulus was placed to one of the windows according to its latency. Then successive time windows for each sort of the responses were reassembled into one continuous time curve. Adapted from Gerasimenko Y, Daniel O, Regnaux J, Combeaud M, Bussel B. Mechanisms of locomotor activity generation under epidural spinal cord stimulation. In: Dengler R, Kossev A, eds. *Sensorimotor Control. NATO Science Series, 1: Life and Behavioural Sciences.* 2001;326:164-171.

using the mechanism of presynaptic inhibition. In flexor muscles, the formation of EMG bursting activity is related to polysynaptic activation of the neuronal network due to stimulation of group II afferents. Decomposition of EMG activity of tibialis anterior (TA) to separate mono- and polysynaptic components has revealed that the EMG bursts consist of polysynaptic responses (**Figure 4B**).[1] Using this technique, the reciprocal modulation of mono- and polysynaptic responses in flexor (TA) muscles under EP was established. Monosynaptic responses were inhibited during EMG bursts and were facilitated in inter-burst intervals (**Figure 4B**). One possible explanation of such monosynaptic modulation may be related to the collision of antidromic spikes with orthodromic afferent flow preventing input from Ia afferents to the spinal cord.[1]

### Stimulator features of scTS

Extensive knowledge generated in the research of optimal therapeutic parameters for neuromuscular stimulation laid the foundation for the key engineered features of an experimental stimulation device.[68-71] First, the electrical stimulator can generate either single or repeated rectangular pulses with or without frequency modulation between 4 and 10 kHz. The pulse duration can be set between 0.1 and 1 ms. Repetition frequency settings range from 1 to 99 Hz and can be used with current amplitudes of 0 to 250 mA. The microcontroller software allows the triggering mode and other parameters to be selected independently for each channel. The modulated frequency is a key feature for noninvasive neuromodulation as it allows the safe use of energies (higher current amplitudes) necessary to reach the spinal cord networks that were previously prohibitive due to cutaneous pain perception under the stimulating electrode.[23,24,72] Additionally, up to five channels and thus five sites of stimulation may be employed.

Studies in adults with SCI have investigated responses to scTS also delivered via commercially available stimulators.[73,74] Commercially available devices for spinal stimulation have only one channel with the electrode placed between T11 and T12. In these reports, stimulation is delivered via biphasic 1 ms pulses at 50 Hz. These studies did not discuss pain as a limiting factor in the intervention, and physiologic metrics are equal to those described in studies using stimulation with carrier frequency. With the research to date noting optimal stimulation with multiple sites, a single channel may be a limitation. Successful translation of spinal cord stimulation as a neuromodulation adjunct to rehabilitation for pediatric-onset SCI necessitates a pain-free user experience, highlighting the importance of the noninvasive transcutaneous spinal cord stimulator technology. All scTS studies in pediatrics should monitor and record pain-induced or pain-related events with stimulation and the sensory perception capacity of participants at the site of stimulation. Pain must be eliminated for scTS to be an accessible and effective therapy.

### Neuromodulation With scTS in Children and Adolescents

The impact of scTS on function in children was first reported in children with cerebral palsy (CP) and spina bifida. Although dysfunction in CP is largely attributed to abnormal supraspinal input, imaging confirms immature spinal segments and lack of white matter or track volume, as compared to normal peers, suggesting spinal network involvement.[75] Researchers hypothesize that noninvasive, neuromodulatory inputs of scTS and patient-specific activity-based therapies trigger bidirectional reorganization of brain-spinal cord connections and remediate the abnormal reciprocal inhibition of spinal afferents.[76]

In an examination of 28 children with spastic CP (Gross Motor Functional Classification Scale [GMFCS] III), clinically meaningful improvements in hip and knee function were observed following scTS and step training as compared to children who only received step training.[77] In addition, children who received step training with scTS, a decrease in coactivation index between agonist and antagonist muscles of lower extremity was observed. These mechanical improvements were associated with increased coordination and locomotor performance[77] (**Figure 5A**). Stimulation was provided midline at T11 and L1 with anodes over the iliac crests, as described in adults (**Figure 5B**). A biphasic, rectangular wave at 1 ms and 30 Hz with 10 kHz carrier frequency was used.

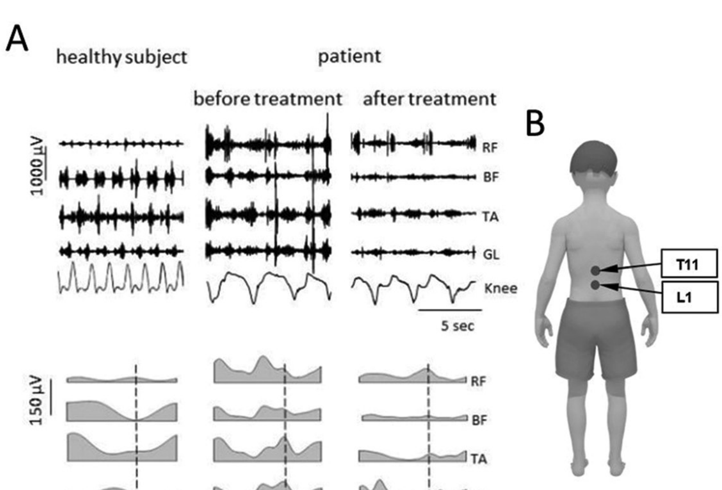


**Figure 5.** Transcutaneous spinal stimulation (scTS) improves motor function in children with cerebral palsy (CP). (A) Patterns of electromyography (EMG) activity during treadmill walking in healthy and in a child with CP before and after scTS with maximal speed and average of 10 movement cycles. The gray filled curves (bottom) represent EMG envelopes of leg muscles in one noninjured participant and in one child with CP before and after treatment. (B) Cathode placement of scTS on the child. Adapted from Solopova IA, Sukhotina IA, Zhvansky DS, et al. Effects of spinal cord stimulation on motor functions in children with cerebral palsy. *Neurosci Lett*. 2017;639:192-198.

A submotor intensity was selected individually and was well tolerated by all the participants.[77] Children participated in 40 minutes of locomotor training via the Lokomat with a total of 20 minutes of scTS for 15 sessions over 3 weeks. Children in the control group received only locomotor training for the same duration.

In another study in children with CP, 12 participants (1 adult) were tested to investigate acute effects of scTS on locomotor function, ability to sit upright, and perform sit to stand.[78] The scTS was applied between T11-T12 and L1-L2 vertebral space as cathode electrodes and two anode electrodes over iliac crest. Findings from the study suggested no significant differences in overall kinetic and kinematics characterized by the change in EMG activity and joint angle excursion without and with scTS (calculated over 15 consecutive step cycles at a same speed and body weight support). However, six out of 12 participants were able to take longer steps with decrease level of co-contraction between antagonistic muscles of lower limb (TA and soleus) with scTS compared to no scTS condition. This represents reduced spasticity and increased levels of coordination between antagonistic muscles. One participant, who was unable to step on treadmill without scTS, demonstrated infrequent and uncoordinated activation in lower limb muscles during stepping attempt on treadmill. Another participant, who was only tested for upright sitting, was able to perform this task for longer periods of time with better control with scTS. In addition, participants reported no pain from scTS.

Other investigators demonstrated the use of scTS and functional electrical stimulation (FES) of lower extremity muscles to improve balance in upright standing for children with CP.[79] Participants underwent 15 daily half-hour sessions of locomotor training via the Lokomat, accompanied by scTS and FES. Children in the experimental group demonstrated a statistically significant improvement in postural stability and normalization of the center of pressure projection compared with participants who received locomotor training alone.

In 2019, a case report was published describing scTS and FES protocols for over 12 months in an infant with spina bifida.[80] Motivated by reports of safe application and restoration of stepping in children with CP, researchers aimed to intervene early in the child's course to capitalize on neural redundancy in children and potentially remediate motor and sensory loss. Initially, scTS was applied midline over T12 to L2 with anodes on the iliac crest. Later, the cathodes were extended C7 to T12 to address upper spinal abnormalities impacting trunk and respiratory function. Authors report the interventions were well tolerated and resulted in improvements in sensation, circulation, and muscle activation.

From the studies of children with CP, it appears that engaging spinal networks may be useful to remediate movement dysfunction via scTS and activity-based therapies.[77,79] scTS has the potential to activate circuitry unavailable to the child's volitional efforts for a more complete recruitment of the nervous system, which, in turn, is shaped by that experience. This modulation of signals is not unlike that experienced by children with SCI undergoing activity-based therapies.[81] Activity-based recovery therapies, such as locomotor training and neuromuscular electrical stimulation, also serve to modulate the physiological state and readiness state of the spinal cord circuitry. In some instances, this training is sufficient for a lasting change in neuromuscular capacity in children[81-85]; in other instances, the neuromodulatory effect of activity-based locomotor training (ABLT) has not been sufficient.[81] This suggests that some additional input is necessary to change the physiological state, to alter motor output, and possibly to produce lasting remediation of movement patterns.

There is limited information in the literature about motor function recovery in pediatric participants with SCI. Proof of physiological change in response to spinal cord stimulation in children with SCI is offered by Shapkova and Schomburg, who demonstrated coordinated, oscillating, rhythmic leg movement following stimulation.[86,87] Recently Baindurashvili et al.[88] reported positive effects of scTS in recovery of motor functions in a 17-year-old individual who sustained an acute injury during roller ski training, and the motor and sensory impairments were subsequently classified as AIS B. The rehabilitation treatment using noninvasive scTS was initiated after 8 postoperative days. Two stimulating round electrodes (LEAD Inc.)

(cathodes) were placed between spinous process of T11-T12 and L1-L2 vertebrae with electrodes (anodes) located symmetrically over iliac crests. The stimulation frequency ranged from 5 to 30 Hz, and the current intensity ranged between 20 and 90 mA. The rehabilitation program included exercise therapies to adapt to vertical loads, stimulation of the foot-bearing surface, unassisted standing, and step training using supporting frame in the presence of scTS. Positive neurologic change, including improved sensations from T6-T7 level and visible contraction of the femoral muscles, were observed after 14 days of treatment. After 21 days of rehabilitation, the participant was able to perform foot dorsiflexion and toe movements. During the next 4 months, the participant had an individualized exercise program to train sitting as well as upright position. The participant was able to walk at a 6-month follow-up using a walker. Finally, at a 12-month follow-up, the participant demonstrated coordinated overground walking using a cane. Even though this outcome is not independent of the potential role of natural recovery, the ambulatory outcome for an individual with an initial classification as an AIS B injury is noteworthy. Owing to the heterogeneity of the population and issues of development both prior and subsequent to injury, studies in the pediatric population can be challenging.

Despite compelling evidence in adults, to date, there has been only one published examination of scTS in children with SCI concerning its safety and feasibility.[89] A clinical trial (NCT03975634) determined the safety and feasibility of scTS to enable upright sitting posture in eight children, age 3 to 15 years, with trunk control impairment due to acquired SCI.[89] Primary safety and efficacy outcomes (pain, hemodynamics stability, skin irritation, and trunk kinematics) and secondary outcomes (center of pressure displacement and compliance rate) were assessed throughout training. As a proof-of-principle, scTS at either T11 (7 out of 7 participants) or L1 (6 out of 7 participants) produced an immediate change from a flexed posture to an upright posture at higher stimulation intensities similar to the outcomes observed in adults.[47] The study demonstrated that lumbosacral scTS is pain-free and well-tolerated in children with SCI whose injury level is at least two segments above the placement of the stimulating electrodes (T11 and L1). Most participants had increased sensitivity in the region of cervical stimulation (C5), as reported by the participant's verbal response of discomfort. Sensitivity was noted both during stimulation in the cervical region and during electrode pad removal. In general, continuous scTS (5-20 minutes) does not adversely affect hemodynamic parameters. However, children should be closely monitored for any signs or symptoms of autonomic dysreflexia during scTS.

In another ongoing clinical trial (NCT04032990), researchers are investigating the safety and feasibility of cervical spinal cord scTS (C3-C4 and C7-T1) in children with upper extremity and trunk deficits. A total of seven out of eight participants with chronic, acquired upper motor neuron SCI; moderate to severe upper extremity deficit as assessed by the Pediatric Neuromuscular Upper Extremity Scale; completion of ≥ 40 sessions of neuromuscular electrical stimulation; and a plateau in neuromuscular recovery have been recruited to investigate the acute effects of cervical scTS to augment arm and hand function. Data collection for this pilot study is under way. In addition to safety feasibility trials, investigators have initiated another clinical trial to (1) investigate (NCT04077346) mechanisms of locomotor specific regulation using single- or multisite scTS in children with chronic SCI and nonambulatory (i.e., unable to stand, initiate a step, or walk); (2) investigate the capacity of the lumbosacral spinal cord for integration of task- specific input (load and speed) during facilitated stepping; and (3) investigate whether nonambulatory children with chronic SCI will demonstrate novel, independent steps after 60 sessions of ABLT in combination with scTS. The team is also initiating a second trial (NCT 04077346) investigating the combined effect of scTS and ABLT on trunk control, measured clinically via the Segmental Assessment of Trunk Control[84] in children ages 4 to 12 years with upper motor neuron injury and new to ABLT and scTS.

The International Center for Spinal Cord Injury (ICSCI) at Kennedy Krieger Institute is undertaking a trial to explore scTS to augment the effects of walking-based therapy in children (ages 6-16) with incomplete

SCI (iSCI). Participants will receive 8 weeks of intensive walking-based therapy with 30 minutes of scTS per session. Strength and walking function will be assessed with clinically relevant outcome measures at multiple time points. The physiological impact of scTS within a single session will be assessed via surface EMG of lower extremity musculature under experimental and sham conditions. This team has previously shown that scTS, delivered via a clinically available, biphasic wave stimulator, in combination with intensive walking-based therapy improves walking capacity, speed, and endurance in adults with iSCI.[73] In addition to gathering data on safety and feasibility, using measures of effort, cost, and adverse events, the team aims to elucidate trends in respondents to better target interventions to particular age, injury, and severity groups.

## Conclusion

The ability to activate spinal neuronal network by means of noninvasive stimulation opens a new possibility for a therapeutic window for children and adolescents with SCI where surgical implantation of a stimulator is not a currently viable option. The application of scTS alone or as an adjuvant to task-specific training rehabilitation in adults with chronic SCI has demonstrated preliminary scientific and clinical evidence to improve motor outcomes. These studies have established the merits of using scTS as a potential neurotherapeutic agent in recovery of voluntary movements after complete and incomplete SCI in adults. There are, however, fundamental anatomical, physiological, and biomechanical differences between adults and children. Such factors may limit direct translation of stimulation parameters from adults to pediatrics. The age at which one may initiate stimulation safely and with a child's capacity to cognitively respond to inquiries and report adverse conditions may also be a consideration. Two aspects of cognitive capacity identified to date by preliminary work[89] and ongoing studies examining locomotor capacity with scTS are the ability to (1) reliably report pain or discomfort and (2) intentionally produce cognitive effort to perform a motor task in muscles and limbs known to be paralyzed below the injury level. Identifying the age at which a child can effectively and safely receive scTS may depend upon their capacity to cognitively respond and participate.[90] Anatomical differences between adults and children relative to spine landmarks and spinal segmental levels may require either sensitive imaging or trial of stimulation sites to arrive at the optimal and viable location for effect.

Children with SCI are underserved as a research population; the predominance of rehabilitation research focuses on adults with SCI. The field is lacking in high-quality empirical investigations that determine optimal neurotherapeutic interventions for children with SCI.[84,91] scTS is a promising, noninvasive technology offering a means of neuromodulation that may be accessible and beneficial to children and adolescents. The translation of scTS from adults with SCI to the pediatric population requires preliminary investigation to establish safety and feasibility[89] (currently ongoing work) and investigation to understand the mechanistic effect of scTS on spinal cord locomotor circuitry in children. The short- and long-term safety and feasibility studies in children with SCI will serve as a foundational step in providing the necessary preliminary data to advance the exploration of scTS as a neurotherapeutic agent for the pediatric population. Completion of these novel studies will establish efficacy and risk likelihood for use of scTS alone and in combination with training to improve motor outcomes. Further studies on optimal parameters, sites, dosage, and electrode placement and training protocols are needed to provide evidence for its safety and efficacy and in the specific domains of potential use, such as upper and lower limb voluntary movements, lower extremity control for standing or stepping, trunk control, or other physiological functions, including bladder control. As with adults with SCI, individual variability among pediatric participants is critical to assess and report, such as upper and lower motor neuron presentation, individual muscle response to stimulation, and specific stimulation parameters and outcomes specific to sensorimotor presentations. Although reporting group differences is the standard for establishing efficacy and effectiveness, research that understands more fully individual differences and the heterogeneity of pediatric SCI will provide a more thorough and complete understanding of specific mechanisms and responders and will guide clinical decision making.

**Financial Support**

This work was funded by the National Institutes of Health (1R01 NS102920-01A1), Kosair Charities (OGMB141540), National Center of Neuromodulation for Rehabilitation (CCDN190765), Jewish Heritage Fund for Excellence (OGMN190574A), and Kentucky Spinal Cord and Head Injury Research Trust (OGMB210076).

**Conflicts of Interest**

Dr. Gerasimenko has a relationship with Cosyma, Ltd, Moscow Russia. He is a founder and Scientific Director of Cosyma and holds a patent on a stimulator used in research. He is funded by National Institutes of Health grant (R01 NS102920-01A1), the Craig H. Neilsen Foundation, and the Kentucky Spinal Cord and Head Injury Research Trust Fund. Dr. Behrman has received support from the Jewish Heritage Foundation for Excellence, National Center for Neuromodulation for Rehabilitation, Kentucky Spinal Cord and Head Injury Research Board, The Craig H. Neilsen Foundation, and Oxford University Press. Kosair Charities made payments to University of Louisville Foundation Inc., and Kosair Charities made payment directly to the institution from 2014-2016. Drs. Lucas and Singh received support from Kosair Charities (OGMB141540), National Center of Neuromodulation for Rehabilitation (NM4R) (CCDN190765), Kentucky Spinal Cord and Head Injury Research Board (OGMB210076), and the Jewish Heritage Foundation for Excellence (OGMN190574A). Dr. Martin received support from Orokawa Foundation, Niche Biomedical, and Kennedy Krieger Institute and research support to the Kennedy Krieger Institute.

## REFERENCES

1. Gerasimenko Y, Daniel O, Regnaux J, Combeaud M, Bussel B. Mechanisms of locomotor activity generation under epidural spinal cord stimulation. In: Dengler R, Kossev A, eds. *Sensorimotor Control. NATO Science Series, 1: Life and Behavioural Sciences*. 2001;326:164-171.
2. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. *Ann NY Acad Sc*. 1998;860:360-376.
3. Gerasimenko Y, Roy RR, Edgerton VR. Epidural stimulation: Comparison of the spinal circuits that generate and control locomotion in rats, cats and humans. *Exp Neurol*. 2008;209(2):417-425.
4. Richardson RR, McLone DG. Percutaneous epidural neurostimulation for paraplegic spasticity. *Surg Neurol*. 1978;9(3):153-155.
5. Siegfried J. Sensory thalamic neurostimulation for chronic pain. *Pacing Clin Electrophysiol*. 1987;10(1 Pt 2):209-212.
6. Krames ES, Peckham PH, Rezai A, Aboelsaad F. What is neuromodulation? In: Krames E, Peckham PH, Rezai A, eds. *Neuromodulation*. Elsevier; 2009:3-8.
7. Vodovnik L, Bowman BR, Hufford P. Effects of electrical stimulation on spinal spasticity. *Scand J Rehabil Med*. 1984;16(1):29-34.
8. Gill ML, Grahn PJ, Calvert JS, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nature Med*. 2018;24(11):1677-1682.
9. Angeli CA, Boakye M, Morton RA, et al. Recovery of over-ground walking after chronic motor complete spinal cord injury. *New Engl J Med*. 2018;379(13):1244-1250.
10. 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 (London, England)*. 2011;377(9781):1938-1947.
11. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*. 2014;137(5):1394-1409.
12. Wagner FB, Mignardot J-B, Le Goff-Mignardot CG, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature*. 2018;563(7729):65-71.
13. Legg Ditterline B, Harkema SJ, Willhite A, Stills S, Ugiliweneza B, Rejc E. Epidural stimulation for cardiovascular function increases lower limb lean mass in individuals with chronic motor complete spinal cord injury. *Exp Physiol*. 2020;105(10):1684-1691.
14. Rejc E, Angeli C, Harkema S. Effects of lumbosacral spinal cord epidural stimulation for standing after chronic complete paralysis in humans. *PloS One*. 2015;10(7):e0133998.
15. 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(77).
16. Megía García A, Serrano-Muñoz D, Taylor J, Avendaño-Coy J, Gómez-Soriano J. Transcutaneous

spinal cord stimulation and motor rehabilitation in spinal cord injury: a systematic review. *Neurorehabil Neural Repair*. 2020;34(1):3-12.
17. Chahoud J, Kanafani Z, Kanj SS. Surgical site infections following spine surgery: Eliminating the controversies in the diagnosis. *Front Med (Lausanne)*. 2014;1:7.
18. Hardman J, Graf O, Kouloumberis PE, Gao WH, Chan M, Roitberg BZ. Clinical and functional outcomes of laminoplasty and laminectomy. *Neurol Res*. 2010;32(4):416-420.
19. Bendersky D, Yampolsky C. Is spinal cord stimulation safe? A review of its complications. *World Neurosurg*. 2014;82(6):1359-1368.
20. Calvert JS, Grahn PJ, Strommen JA, et al. Electrophysiological guidance of epidural electrode array implantation over the human lumbosacral spinal cord to enable motor function after chronic paralysis. *J Neurotrauma*. 2019;36(9):1451-1460.
21. Gorodnichev RM, Pivovarova EA, Pukhov A, et al. Transcutaneous electrical stimulation of the spinal cord: Non-invasive tool for activation of locomotor circuitry in human. *Fiziologiia cheloveka*. 2012;38(2):46-56.
22. Gerasimenko Y, Gorodnichev R, Puhov A, et al. Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. *J Neurophysiol*. 2015;113(3):834-842.
23. Gerasimenko YP, Lu DC, Modaber M, et al. Noninvasive reactivation of motor descending control after paralysis. *J Neurotrauma*. 2015;32(24):1968-1980.
24. Gerasimenko Y, Gorodnichev R, Moshonkina T, Sayenko D, Gad P, Reggie Edgerton V. Transcutaneous electrical spinal-cord stimulation in humans. *Ann Phys Rehabil Med*. 2015;58(4):225-231.
25. Gerasimenko Y, Gorodnichev R, Machueva E, et al. Novel and direct access to the human locomotor spinal circuitry. *J Neurosci*. 2010;30(10):3700-3708.
26. Courtine G, Gerasimenko Y, van den Brand R, et al. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat Neurosci*. 2009;12(10):1333-1342.
27. Ward AR. Electrical stimulation using kilohertz-frequency alternating current. *Phys Ther*. 2009;89(2):181-190.
28. Selkowitz DM. High frequency electrical stimulation in muscle strengthening. A review and discussion. *Am J Sports Med*. 1989;17(1):103-111.
29. Selkowitz DM. Improvement in isometric strength of the quadriceps femoris muscle after training with electrical stimulation. *Phys Ther*. 1985;65(2):186-196.
30. Benavides FD, Jin Jo H, Lundell H, Edgerton VR, Gerasimenko Y, Perez MA. Cortical and subcortical effects of transcutaneous spinal cord stimulation in humans with tetraplegia. *J Neurosci*. 2020:2374-2319.
31. Minassian K, Hofstoetter US, Danner SM, et al. Spinal rhythm generation by step-induced feedback and transcutaneous posterior root stimulation in complete spinal cord-injured individuals. *Neurorehabil Neural Repair*. 2016;30(3):233-243.
32. Estes SP, Iddings JA, Field-Fote EC. Priming neural circuits to modulate spinal reflex excitability. *Front Neurol*. 2017;8:17.
33. Hofstoetter US, McKay WB, Tansey KE, Mayr W, Kern H, Minassian K. Modification of spasticity by transcutaneous spinal cord stimulation in individuals with incomplete spinal cord injury. *J Spinal Cord Med*. 2014;37(2):202-211.
34. Hofstoetter US, Freundl B, Binder H, Minassian K. Common neural structures activated by epidural and transcutaneous lumbar spinal cord stimulation: Elicitation of posterior root-muscle reflexes. *PloS One*. 2018;13(1):e0192013-e0192013.
35. Minassian K, Hofstoetter U, Rattay F. Transcutaneous lumbar posterior root stimulation for motor control studies and modification of motor activity after spinal cord injury (pp. 226-255). In: Dimitrijevic MR, Kakulas BA, McKay WB, Vrbova G, eds. *Restorative Neurology of Spinal Injury*. Oxford University Press; 2012.
36. Minassian K, Persy I, Rattay F, Dimitrijevic MR, Hofer C, Kern H. Posterior root–muscle reflexes elicited by transcutaneous stimulation of the human lumbosacral cord. *Muscle Nerve*. 2007;35(3):327-336.
37. Kumru H, Rodríguez-Cañón M, Edgerton VR, et al. Transcutaneous electrical neuromodulation of the cervical spinal cord depends both on the stimulation intensity and the degree of voluntary activity for training. A pilot study. *J Clin Med*. 2021;10(15).
38. Kumru H, Flores Á, Rodríguez-Cañón M, et al. Cervical electrical neuromodulation effectively enhances hand motor output in healthy subjects by engaging a use-dependent intervention. *J Clin Med*. 2021;10(2).
39. Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: Windows of opportunity in the developing brain. *EurJ Paediatr Neurol*. 2017;21(1):23-48.
40. Parent S, Mac-Thiong J-M, Roy-Beaudry M, Sosa JF, Labelle H. Spinal cord injury in the pediatric population: A systematic review of the literature. *J Neurotrauma*. 2011;28(8):1515-1524.
41. Huelke DF. An overview of anatomical considerations of infants and children in the adult world of automobile safety design. *Annu Proc Assoc Adv Automot Med*. 1998;42:93-113.
42. 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.
43. Freyvert Y, Yong NA, Morikawa E, et al. Engaging cervical spinal circuitry with non-invasive spinal stimulation and buspirone to restore hand function in chronic motor complete patients. *Sci Rep*. 2018;8(1):15546-15546.
44. Hofstoetter US, Hofer C, Kern H, et al. Effects of transcutaneous spinal cord stimulation on voluntary locomotor activity in an incomplete spinal cord injured individual. *Biomed Tech (Berl)*. 2013;58(Suppl 1).

45. Gad P, Gerasimenko Y, Zdunowski S, et al. Weight bearing over-ground stepping in an exoskeleton with non-invasive spinal cord neuromodulation after motor complete paraplegia. *Front Neurosci*. 2017;11:333.
46. Shapkova EY, Pismennaya EV, Emelyannikov DV, Ivanenko Y. Exoskeleton walk training in paralyzed individuals benefits from transcutaneous lumbar cord tonic electrical stimulation. *Front Neurosci*. 2020;14:416.
47. Rath M, Vette, AH, Ramasubramaniam S, et al. Trunk stability enabled by noninvasive spinal electrical stimulation after spinal cord injury. *J Neurotrauma*. 2018;35(21):2540-2553.
48. Sayenko DG, Rath M, Ferguson AR, et al. Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. *J Neurotrauma*. 2019;36(9):1435-1450.
49. Moshonkina T, Grishin A, Bogacheva I, et al. Novel non-invasive strategy for spinal neuromodulation to control human locomotion. *Front Hum Neurosci*. 2020;14:622533.
50. Anderson KD. Targeting recovery: Priorities of the spinal cord-injured population. *J Neurotrauma*. 2004;21(10):1371-1383.
51. Powell A, Davidson L. Pediatric spinal cord injury: A review by organ system. *Phys Med Rehabil Clin N Am*. 2015;26(1):109-132.
52. Gad P, Lee S, Terrafranca N, et al. Non-invasive activation of cervical spinal networks after severe paralysis. *J Neurotrauma*. 2018;35(18):2145-2158.
53. Inanici F, Samejima S, Gad P, Edgerton VR, Hofstetter CP, Moritz CT. Transcutaneous electrical spinal stimulation promotes long-term recovery of upper extremity function in chronic tetraplegia. *IEEE Trans Neural Syst Rehabil Eng*. 2018;26(6):1272-1278.
54. Inanici F, Brighton LN, Samejima S, Hofstetter CP, Moritz CT. Transcutaneous spinal cord stimulation restores hand and arm function after spinal cord injury. *IEEE IEEE Trans Neural Syst Rehabil Eng*. 2021:1-1.
55. Zhang F, Momeni K, Ramanujam A, et al. Cervical spinal cord transcutaneous stimulation improves upper extremity and hand function in people with complete tetraplegia: A case study. *IEEE Trans Neural Syst Rehabil Eng*. 2020:1-1.
56. Sayenko DG, Atkinson DA, Dy CJ, et al. Spinal segment-specific transcutaneous stimulation differentially shapes activation pattern among motor pools in humans. *J Appl Physiol (Bethesda, Md : 1985)*. 2015;118(11):1364-1374.
57. Ramasubbu C, Flagg A, Williams K. Principles of electrical stimulation and dorsal column mapping as it relates to spinal cord stimulation: An Ooverview. *Curr Pain Headache Rep*. 2013;17(2):315.
58. Lodish H BA, Zipursky SL, et al. The action potential and conduction of electric impulses. In: *Molecular Cell Biology*. 4th ed. New York; 2000.
59. Carulli D, Foscarin S, Rossi F. Activity-dependent plasticity and gene expression modifications in the adult CNS. *Front Mol Neurosci*. 2011;4:50-50.
60. Qiu Z, Ghosh A. A calcium-dependent switch in a CREST-BRG1 complex regulates activity-dependent gene expression. *Neuron*. 2008;60(5):775-787.
61. Hogan MK, Hamilton GF, Horner PJ. Neural stimulation and molecular mechanisms of plasticity and regeneration: A review. *Front Cell Neurosci*. 2020;14:271-271.
62. Sayenko DG, Angeli C, Harkema SJ, Edgerton VR, Gerasimenko YP. Neuromodulation of evoked muscle potentials induced by epidural spinal-cord stimulation in paralyzed individuals. *J Neurophysiol*. 2014;111(5):1088-1099.
63. Roy FD, Gibson G, Stein RB. Effect of percutaneous stimulation at different spinal levels on the activation of sensory and motor roots. *Exp Brain Res*. 2012;223(2):281-289.
64. Lavrov I, Gerasimenko YP, Ichiyama RM, et al. Plasticity of spinal cord reflexes after a complete transection in adult rats: Relationship to stepping ability. *J Neurophysiol*. 2006;96(4):1699-1710.
65. Courtine G, Harkema SJ, Dy CJ, Gerasimenko YP, Dyhre-Poulsen P. Modulation of multisegmental monosynaptic responses in a variety of leg muscles during walking and running in humans. *J Physiol*. 2007;582(Pt 3):1125-1139.
66. Barolat G. Epidural spinal cord stimulation: Anatomical and electrical properties of the intraspinal structures relevant to spinal cord stimulation and clinical correlations. *Neuromodulation*. 1998;1(2):63-71.
67. Barolat G. Current status of epidural spinal cord stimulation. *Neurosurgery Quarterly*. 1995;5:98-124.
68. Fukuda TY, Marcondes FB, dos Anjos Rabelo N, de Vasconcelos RA, Junior CC. Comparison of peak torque, intensity and discomfort generated by neuromuscular electrical stimulation of low and medium frequency. *Isokinet Exerc Sci*. 2013;21:167-173.
69. Gorgey AS, Dudley GA. The role of pulse duration and stimulation duration in maximizing the normalized torque during neuromuscular electrical stimulation. *The J Orthop Sports Phys Ther*. 2008;38(8):508-516.
70. Laufer Y, Ries JD, Leininger PM, Alon G. Quadriceps femoris muscle torques and fatigue generated by neuromuscular electrical stimulation with three different waveforms. *Phys Ther*. 2001;81(7):1307-1316.
71. Bickel CS, Gregory CM, Dean JC. Motor unit recruitment during neuromuscular electrical stimulation: A critical appraisal. *Eur J Appl Physiol*. 2011;111(10):2399.
72. Grishin AA, Moshonkina TR, Solopova IA, Gorodnichev RM, Gerasimenko YP. A five-channel noninvasive electrical stimulator of the spinal cord for rehabilitation of patients with severe motor disorders. *Biomed Eng*. 2017;50(5):300-304.

73. McHugh LV, Miller AA, Leech KA, Salorio C, Martin RH. Feasibility and utility of transcutaneous spinal cord stimulation combined with walking-based therapy for people with motor incomplete spinal cord injury. *Spinal Cord Series Cases*. 2020;6(1):104.
74. Estes S, Zarkou A, Hope JM, Suri C, Field-Fote EC. Combined transcutaneous spinal stimulation and locomotor training to improve walking function and reduce spasticity in subacute spinal cord injury: A randomized study of clinical feasibility and efficacy. *J Clin Med*. 2021;10(6).
75. Noble JJ. *Musculoskeletal and spinal cord imaging in bilateral spastic cerebral palsy*. King's College London; 2014.
76. Filloux FM. Neuropathophysiology of movement disorders in cerebral palsy. *J Child Neurol*. 1996;11 (1 Suppl):S5-S12.
77. Solopova IA, Sukhotina IA, Zhvansky DS, et al. Effects of spinal cord stimulation on motor functions in children with cerebral palsy. *Neurosci Lett*. 2017;639:192-198.
78. Edgerton VR, Hastings S, Gad PN. Engaging spinal networks to mitigate supraspinal dysfunction after CP. *Front Neurosci*. 2021;15(409).
79. Nikityuk IE, Moshonkina TR, Gerasimenko YP, Vissarionov SV, Baindurashvili AG. The regulation of balance in the children presenting with severe cerebral palsy following the treatment with the use of the locomotor training in combination with the electrical stimulation of leg muscles and spinal cord. *Vopr Kurortol Fizioter Lech Fiz Kult*. 2016;93(5):23-27.
80. Motavalli G, McElroy J, Alon G. An exploratory electrical stimulation protocol in the management of an infant with spina bifida: A case report. *Child Neurol Open*. 2019;6.
81. Behrman AL, Argetsinger LC, Roberts MT, et al. Activity-based therapy targeting neuromuscular capacity after pediatric-onset spinal cord injury. *Top Spinal Cord Inj Rehabil*. 2019;25(2):132-149.
82. Goode-Roberts M, Bickel SG, Stout DL, Calvery ML, Thompson JE, Behrman AL. Impact of activity-based therapy on respiratory outcomes in a medically complex child. *Children*. 2021;8(1):36.
83. Argetsinger LC, Singh G, Bickel SG, Calvery ML, Behrman AL. Spinal cord injury in infancy: Activity-based therapy impact on health, function, and quality of life in chronic injury. *Spinal Cord Series Cases*. 2020;6(1):13.
84. Argetsinger LC, Trimble SA, Roberts MT, Thompson JE, Ugiliweneza B, Behrman AL. Sensitivity to change and responsiveness of the Segmental Assessment of Trunk Control (SATCo) in children with spinal cord injury. *Dev Neurorehabil*. 2019;22(4):260-271.
85. Behrman AL, Nair PM, Bowden MG, et al. Locomotor training restores walking in a nonambulatory child with chronic, severe, incomplete cervical spinal cord injury. *Phys Ther*. 2008;88(5):580-590.
86. Shapkova E. Spinal locomotor capability revealed by electrical stimulation of the lumbar enlargement in paraplegic patients. *Progr Motor Control*. 2004;3:253-289.
87. Shapkova EY, Schomburg ED. Two types of motor modulation underlying human stepping evoked by spinal cord electrical stimulation (SCES). *Acta Physiol Pharmacol Bulg*. 2001;26(3):155-157.
88. Baindurashvili A, Vissarionov S, Belianchikov S, et al. Comprehensive treatment of a patient with complicated thoracic spine injury using percutaneous electrical spinal cord stimulation (case report). *Genij Ortopedii*. 2020;26:79-88.
89. Keller A, Singh G, Sommerfeld JH, et al. Noninvasive spinal stimulation safely enables upright posture in children with spinal cord injury. *Nature Commun*. 2021;12(1):5850.
90. Pape KE. Developmental and maladaptive plasticity in neonatal SCI. *Clin Neurol Neurosurg*. 2012;114(5):475-482.
91. Grampurohit N, Bell A, Duff S, et al. Highlighting gaps in spinal cord injury research in activity-based interventions for the upper extremity: A scoping review. *NeuroRehabilitation*. 2021;49(1):23-38.