



Complications of epidural spinal stimulation: lessons from the past and alternatives for the future

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Abstract

Study design Systematic review.

Objectives Over the past decade, an increasing number of studies have demonstrated that epidural spinal cord stimulation (SCS) can successfully assist with neurorehabilitation following spinal cord injury (SCI). This approach is quickly garnering the attention of clinicians. Therefore, the potential benefits of individuals undergoing epidural SCS therapy to regain sensorimotor and autonomic control, must be considered along with the lessons learned from other studies on the risks associated with implantable systems.

Methods Systematic analysis of literature, as well as preclinical and clinical reports.

Results The use of SCS for neuropathic pain management has revealed that epidural electrodes can lose their therapeutic effects over time and lead to complications, such as electrode migration, infection, foreign body reactions, and even SCI. Several authors have also described the formation of a mass composed of glia, collagen, and fibrosis around epidural electrodes. Clinically, this mass can cause myelopathy and spinal compression, and it is only treatable by surgically removing both the electrode and scar tissue.

Conclusions In order to reduce the risk of encapsulation, many innovative efforts focus on technological improvements of electrode biocompatibility; however, they require time and resources to develop and confirm safety and efficiency. Alternatively, some studies have demonstrated similar outcomes of non-invasive, transcutaneous SCS following SCI to those seen with epidural SCS, without the complications associated with implanted electrodes. Thus, transcutaneous SCS can be proposed as a promising candidate for a safer and more accessible SCS modality for some individuals with SCI.

Introduction

Recently, spinal stimulation-based neuromodulation has progressed from an “inhibitory” intervention for pain management [1] to become an important modality for reactivating latent functions of the underlying processing networks [2]. Between 2008 and 2017, the United States Food and Drug Administration reported over 600,000 individuals were implanted with spinal cord stimulators (www.apnews.com) [3]. Thirteen percent (78,172) of said individuals suffered injuries caused by spinal cord stimulators. These alarming statistics demonstrate why spinal cord stimulators are ranked as the third-highest leading cause of injury among all used medical devices, right after metal hip prostheses, and insulin pumps. One relevant study was performed recently by Sivanesan et al. [4], where the authors queried the Manufacturer and User Facility Device Experience database for all entries named ‘Dorsal root ganglion stimulator for pain relief’ between May 1, 2016

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and December 31, 2017, verified by the US FDA. There were 979 cases of implantation identified, almost half of which (47%), were categorized as device-related complications, a quarter (28%) as procedural complications, with the remainder as individual complaints (12%), serious adverse events (2.4%), and ‘other’ complications (4.6%). The authors warn that although the stimulation device has been publicized as a breakthrough in neuromodulation technologies, one must proceed with caution and reevaluate effectiveness as information becomes available. These outcomes may serve as a representation for a single year and may present a perspective of the rate of complication and adverse events related to implanted spinal cord stimulators. The implantation itself, especially if it involves laminectomy, can lead to a broad variety of complications associated with invasive procedures, including infection or hematoma, and, depending on the type of the electrodes used for spinal cord stimulation (SCS), can be associated with electrode migration. Still, a health economic assessment of application of spinal stimulation as chronic neuropathic pain management performed in the United Kingdom’s National Institute of Health and Clinical Excellence, has shown that the therapy is cost-effective [5]. The Incremental Cost Effectiveness Ratio calculated over a 15-year horizon demonstrated high economic benefits mostly referred to the improved health and productivity of the subjects, that have been quantified as 35 times more significant than the cost of the therapy itself, even including the incidence of complications. At the same time, similar analysis on the benefit to cost ratio from the studies recovering motor control using SCS is not available to date, but it would likely show a smaller ratio given that the recovery of independent motor function is rather small, requires intensive therapy, and is limited so far by a person’s need for continuous assistance during ambulation.

Spinal stimulation has been shown to have potential for a vast variety of applications in motor and autonomic function recovery, given its high capacity to modulate neural activity in neurorehabilitation of individuals with spinal cord injury (SCI) [2, 6]. The latest available data indicate that stimulation of the spinal cord with the use of task-oriented rehabilitation can be applied to modulate the adaptive activity coming from the spinal cord segments located below the lesion, in order to enhance excitability from spinal networks and regain some voluntary control of various motor tasks including standing [7, 8], stepping [9–11], hand grasping [12], respiration [13], and bladder voiding [14, 15]. From some of these studies, it is difficult to say with certainty whether the intensive training paradigm, spinal stimulation parameter adjustments, or (the most likely case) both variables, play a key role in achieving minimized assistance during standing or stepping in the presence of stimulation [16]. Indeed, previous

work has shown that even without SCS, body-weight load during activity-based training (see ‘rules of spinal locomotion’ [17]), creates the flow of proprioceptive signals which in turn can facilitate spinal locomotor programs and—after weeks of training—enable individuals with severe but incomplete SCI to carry their own body weight over ground [17–21]. As such, it would be incorrect to state that epidural spinal stimulation applied by itself allows regaining of mobility and independence. Most of the papers in this field should be considered as observations toward better understanding to what extent the spinal networks below the injury, which were previously thought to be nonfunctional after SCI, can be engaged by spinal stimulation to produce and modulate motor activities. The fact that regaining voluntary motor control can occur within just the first few sessions of epidural spinal stimulation in practically all participants with clinically diagnosed motor complete paralysis (most likely discomplete [8, 22–25]), indicates that spared neural connections spanning the site of SCI, are highly plastic and prepared for functioning in the presence of spinal stimulation and within appropriate somatosensory environment, months or even years following SCI. The fact that when the stimulator was turned OFF, most of the participants were not able to perform these movements, indicates that epidural spinal stimulation, descending signals through the injury, and extrinsic sensory input can synergize within spinal networks to generate voluntary motor activities. The use of this technology will undoubtedly grow consistently in the coming years, and it is likely that there will also be a concomitant increase in the number of individuals experiencing tolerance phenomena and/or requiring invasive spinal surgeries to overcome adverse side effects. Moreover, albeit SCS is considered a fully reversible treatment, removal of epidural electrodes, and especially the paddle electrodes, is not uncommon (5–35%). However, it is a quite challenging surgical procedure, as electrodes are often encapsulated by secondary bony overgrowth and epidural fibrous capsule [26, 27]. For instance, explantation of paddle electrodes is associated with potential risks and postoperative complications which occurred in 12% of surgeries, ranging from minor issues, such as infection (9%), to more serious adverse events, as cerebrospinal fluid leak or epidural bleeding, which causes hematoma and accidental compression of the spinal cord [19]. Research into the underlying causes and risk factors for adverse effects of invasive SCS is therefore paramount to maintain high levels of therapeutic efficiency, decrease complication rates, reduce the need for costly surgeries for electrode revision or scar removal, and improve clinical and functional outcomes. The current perspective paper focuses on the implanted electrode encapsulation and its negative impact on effective and sustainable SCS.

Complications of implanted electrodes

Several large studies [28–34] have documented relatively high complication rates (20–75%) following SCS, including hardware failure, infection, and even more severe neurological consequences, such as SCI. Side effects may occur both intraoperatively and in the early or late postoperative period [32], and require invasive treatments in approximately half of the cases [26].

Among hardware-related problems, lead migration was previously reported as one of the most common risks of SCS, with a variable incidence spanning 13–22%, with a higher prevalence for implants in the cervical spine, where the degree of motion of vertebrae is greater [35, 36]. Lead migration often requires a new surgical procedure for repositioning or replacing the electrode. However, two recent retrospective studies, analyzing SCS systems implanted from 2008 to 2011, found that lead migration requiring repositioning of the systems occurred in only in 1.4–2.1% of over a hundred of analyzed cases, a much lower incidence rate than previously reported, possibly accounting for hardware and technique improvement, including revised published guidelines by SCS manufacturers on proper fascial anchoring and the use of strain-relief loops [37]. Noteworthy, older studies have compared the migration rates of percutaneous leads and paddle array electrodes [38, 39] and reported markedly lower migration rates with paddle electrodes. This is one of the most commonly cited advantages for choosing the paddle-type systems over percutaneous leads. However, because the cited above rate of clinically significant migration is similar to the published rates for paddle electrodes' migration, this argument requires revision. A head-to-head prospective trial comparing revision rates for lead migration between percutaneous leads and paddle electrodes is warranted.

Additional complications originate from an acute biological response to the implant. Infection is one of the major complications with incidences of 5% and requiring antibiotic treatment and even device removal and reinstallation after healing from sepsis [26, 32, 33]. This is a higher value compared with other implantable electronic devices, such as cardiac pacemakers, which have an incidence of infection of about 0.5–2.2% [40]. For SCS, superficial or subcutaneous infections at the incision site are more common than deep tissue infections with abscesses over the spine. Although meningitis rarely occurred, an intradural abscess resulting in paralysis has been reported [41]. Pain in the region around the stimulator has also been registered in 5–10% [26, 32, 33]. During surgical or blind percutaneous insertion of electrodes, accidental dural puncture, epidural hematoma, as well as blunt trauma to the cord, have been documented, causing the onset of paraplegia in the 30 days following SCS implantation for 2% of individuals analyzed [42].

Tolerance to SCS

Even in the absence of the above mentioned complications, an estimated 10–29% of subjects implanted with epidural electrodes developed tolerance to SCS, defined as the loss of the therapeutic effect over time, even in the presence of fully-functioning stimulating systems [34, 43, 44]. Although an increase in pulse amplitude might circumvent the problem for a while [45–47], the tolerance phenomenon still often mitigates SCS efficacy if therapy is continued. This phenomenon can develop as early as a few months after implantation and as late as 10 to 15 years following implantation [29, 48]. Although, psychological affective factors might also contribute to a tolerance to the analgesic effects of SCS [46], there is some evidence that suggests the development of tolerance over time results from dropped charges related to the deposit of high impedance biological material progressively encapsulating the electrode after implantation [46, 49]. The extent of fibrous tissue growth around the electrode has been positively correlated to impedance increases in studies with cochlear implants [50, 51]. It is doubtful that tolerance reflects only structural and conductive changes on the surface of the implanted material and can be solved by merely substituting the system. Tolerance originates from more profound changes at the interface between the contact electrode and the underlying tissues. An immune-mediated foreign body response is determined by the implant's materials and causes both the aggregation of mononuclear macrophages and the encapsulation of the device in a collagenous envelope [52]. The picture can be further worsened by the local toxicity of metal particles dissolved by the long-term corrosion of electrodes [53]. All these events can activate fibroblasts, with a consequent fibrotic growth around the electrode that causes a shallow mechanical depression of the spinal cord regions under the array [52]. Moreover, perturbations on the surface of the cord result both in the localized activation of glial cells, and in epidural fibrosis, which can be associated with dural thickening or even superficial scarring, that eventually alter the charge transfer to the surrounding neural structures [54].

Epidural electrode encapsulation has been documented in numerous reports (Table 1), and can lead not only to tolerance, but occasionally also to severe spinal cord compression and neurological deficits.

Histological findings in fibrous encapsulations

Despite the rarity of negative published results in the field of SCS, there have been at least 20 reported cases of severe spinal compression related to fibrous lead encapsulation

Table 1 Reported cases of severe spinal compression related to fibrous lead encapsulation developing up to 17 years after electrode implantation.

Time after implant (years)	N of cases	Complications	Cause	Action	References
Missing	3	Motor deficits	Unknown	Surgical removal of the electrode	Nashold and Friedman [59]
2	1	Spinal and radicular compression symptoms	Severe tissue reaction at the site of implant	Surgical removal of the electrode	Krainick et al. [60]
0.25	1	Mild spastic quadripareisis	Exuberant fibroblastic response with a dense scar surrounding the electrode	Surgical removal of the electrode and scar microdissection	Reynolds and Shetter [45]
5 and 16	2	Myelopathy	Epidural fibrosis with a scar tissue surrounding the electrode and compressing the spinal cord	Surgical removal of both scar tissue and the electrode	Dam-Hieu et al. [43]
5	1	Motor deficits	Severe spinal cord compression around the epidural electrode	Surgical removal of both scar tissue and the electrode	Wada and Kawai [55]
9	1	Worsening left upper extremity pain	Epidural mass with significant cervical stenosis and spinal cord compression at the site of the electrode	Surgical removal of both epidural mass and the electrode	Lennarson and Guillen [61]
1	1	Progressive paraparesis	Fibrous scar tissue around the epidural electrode	Surgical removal of both scar tissue and the electrode	Cicunendez et al. [56]
17	1	Cervical myelopathy	Epidural mass surrounding the electrode and compressing the spinal cord	Surgical removal of both electrode and fibrous scar tissue (via hemilaminectomy)	Wloch et al. [62]
5	1	Clinical signs of spinal cord compression	Hard and thickened fibrosis at the level of the electrode	Microsurgical removal of fibrous tissue, while the electrode was replaced at the same place.	Fransen et al. [47]
7	1	Progressive paresthesia along the spine and the limbs, gait ataxia with sensation of weakness in the legs, increased muscle tone, and tendon reflexes in the lower extremities	Fibrotic epidural mass at the level of lead	Surgical removal of both scar tissue and the electrode	Guzzi et al. [63]
0.75	1	Gait instability, spasticity, neck and shoulder pain, upper extremity weakness	Dorsal epidural mass, C2–T1 causing spinal cord compression	Surgical removal of spinal cord stimulators and scar tissue	Scranton et al. [58]
7	1	Dyesthesias of the lateral three fingers of the left hand	Severe spinal cord compression by an epidural soft tissue mass	Surgical removal of the electrode which was embedded in a thick and solid fibrotic mass	de Eulade-Beramendi et al. [64]
10	1	Neck pain, upper extremity numbness, tingling, and weakness	Dorsal epidural mass, C2–C4 with spinal cord compression and associated bony osteolysis	Removal of spinal cord stimulators and scar tissue followed by spinal instrumentation and fusion	Dimar et al. [67]
10	1	Progressive paraplegia	Spinal cord central canal stenosis at the level of electrodes with increased dorsal epidural soft tissue around the leads	Removal of the fibrotic tissue and electrodes albeit with minimal neurologic and functional return	Benfield et al. [122]

Table 1 (continued)

Time after implant (years)	N of cases	Complications	Cause	Action	References
“Several years”	1	Progressive neck pain in addition to increased limb pain, paresthesia, and weakness in extremities	An epidural mass at the level of the electrode due to fibrosis with granulomatous tissue and a nonspecific chronic inflammatory reaction	Surgical removal of both scar tissue and the electrode	Tamimi et al. [57]
8	1	Bilateral lower extremity weakness, and myelopathic symptoms	Epidural fibrosis around the paddle lead with compression of the spinal cord	Surgical removal of the lead and the surrounding fibrosis	Aoun et al. [123]
10	1	Severe cervical pain, numbness in both arms, weakness in both legs, and gait disturbance	Metallic irritation of the dura mater and fibrosis at the site of the lead with cord compression	Laminectomy, debridement of metallosis, and adhesiolysis of epidural fibrosis	Kim et al. [68]

developing up to 17 years after electrode implantation (Table 1, mean onset = 7 ± 5 years) [43, 55, 56]. Often-times, these cases began as tolerance, eventually resulting in the development of neurological deficits, such as myelopathy [43, 57], worsened spasticity [45], and increased paralysis [43, 45, 56, 58]. In all 20 reported cases, delicate surgical procedures on the spinal cord to remove the whole electrode and the scar tissue that surrounded it inside the epidural space were necessary, sometimes in response to tolerance [43, 45, 47, 55–57, 59–64]. Also, in some reported cases, analysis of the extracted scar tissue revealed the presence of excessive fibrosis around the electrode itself—both for paddle electrodes implanted via laminectomy and those implanted percutaneously into the epidural space [29, 43, 48]. Still, the vast majority of published clinical reports about failures and complications of SCS unfortunately do not comment on end-term tissue and array conditions. Rather, a more detailed exploration of electrode-associated fibrous tissue comes primarily from the few animal studies that have explored this issue. Notably, histological examination of cortical epidural implants has revealed an overgrowth of connective tissue [54, 65] and an aggregation of cortical microglia in a resting state morphology in the first week after implantation [52] that is followed in the subsequent week by the accumulation of a layer of astrocytes [66]. Further studies have documented the presence of granulomatous tissue and a nonspecific chronic inflammatory reaction [57] characterized by multinucleate macrophages (giant cells) aggregating in response to the foreign body and engulfing the implant [61]. Underlying dural thickening and fibrous implant encapsulation has also been seen in experimental animal models within the first month after implantation of cortical epidural arrays [54, 65]. This fibrous envelope consists of both fibroblasts and collagen I, with the “collagenous” tissue located in the distal part of the implanted array mimicking healthy dura mater while the more proximal region contains “cellular” tissue with increased inflammatory cell activity [52]. The thickness and density of cortical neural tissue, however, does not seem to change appreciably, even with long-term array implantation [52]. There has been a number of documented cases of fibrous masses developing in humans in association with SCS, often requiring electrode explantation or revision due to some combination of tolerance and/or neurological deficits (Table 1). Moreover, many of said cases have reported histological findings similar to those seen in animals, including dense fibroconnective tissue, variable nonspecific inflammatory infiltrates, multinucleated giant cells, non-caseating granulomas indicative of a foreign body reaction [45, 55–58, 61, 67]. Furthermore, in a recent clinical report [68], histologic examination of the fibrous tissue around the electrode used for SCS revealed granulomatous inflammation and phagocytic reaction of

neutrophils and macrophages due to a metallic irritation of the dura mater. Putatively, metallosis due to the deposition of metal debris on the dura mater was secondary to the corrosion of the protective silicon and urethane coating around the lead of the SCS paddle electrode. Uncovering of the silicon and urethane coating was likely caused by the micromotion and friction between the electrode and the dura mater.

Although, an invasive histological examination of paddles is not always recommended in clinics, in case of electrode failure one should always carefully consider lead encapsulation and epidural fibrotic mass formation, especially if associated to mild neurological symptoms.

Approaches for avoiding fibrous encapsulation

The relevance of epidural electrodes' encapsulation in current practice is supported by the many ongoing research efforts underway to reduce encapsulation. One common theory is that the exuberant fibroblastic response may be dependent on the materials used for electrode fabrication [45]. Thus, several studies have improved the integration of implanted devices in the central nervous system by modifying the electrode materials in an attempt to minimize the foreign body response. These recent approaches include shape alteration of the array substrate [54, 65, 69], increased array flexibility [70–72], the release of anti-inflammatory drugs through the array itself, either from the substrate or from the electrodes [73, 74], and the application of anti-fouling or biomimetic surface treatments [75, 76], such as different materials and techniques of coating and lamination [66, 77]. Albeit promising, these approaches require a considerable amount of time and resources both for pre-clinical development and also for safety and efficiency testing prior to use [77], ultimately delaying their availability in the clinic. Interestingly, Reynolds and Shetter [45] theorized that the fibrotic and inflammatory response associated with implanted electrodes might be related to the electrical stimulation through the electrode; but, evidence in support of this is lacking. While intraoperative stimulation is often performed to guide electrode placement, both in research and in clinics, continuous stimulation is seldom delivered right after implantation. Rather, stimulation begins in a delayed fashion, after an initial week of post-surgical rest [8, 78, 79]. Interestingly, research suggests that development of fibrosis and glia around the electrode begins during the initial week of postsurgical rest following implantation [66]. These results imply that electrode-associated fibrosis occurs independent of stimulation. However, it is still unclear whether low intensity stimulation in the first week following implantation may limit the

development of electrode-associated fibrosis. Stimulation amplitudes commonly used to neuromodulate physiological state of the spinal cord [79, 80], which are based on previous preclinical studies [78], are much greater in magnitude than the amplitudes reported in the literature as being endogenous to the nervous system. For example, in vertebrate embryos, glia are sensitive to electrical fields of physiological strength (50–500 mV/mm) [81]. These electrical fields play a pivotal role not only in retracting and aligning astrocytes processes, thereby leading their orientation perpendicular to the voltage gradient [81], but also in promoting and directing neurite growth in the developing central nervous system [82, 83] where endogenous electric fields are generated by a polarized voltage gradient [84]. Based on this evidence, we believe that future research could exploit this range of low intensities to create a physiological electrical stimulation to be delivered during the initial days following implantation that would help to not only orient glia and neurite regrowth, but also repel fibrosis from the electrode without damaging the recovering spinal cord. At the same time, it is difficult to see how this could be done without substantial increases in knowledge based on animal experiments. Further, a valuable perspective in the field should be the design of neural interfaces in which the delivery of distinct patterns of subthreshold electrical stimulation, that is stimulation at the intensity just below motor threshold [85], guides the proliferation of glial cells along a re-absorbable array frame eventually leaving only working metal electrodes and connections stably integrated in the epidural connective tissue. These implantable Glio-Electrode Arrays should be considered as a more biocompatible technology for future preclinical research trials.

In addition to material interface engineering solutions and stimulation protocols to prevent gliosis and encapsulation, mechanical design may be an important option for advancing the success of implanted electrodes. Theorized designs based on matching the elastic modulus of tissue surrounding the implant or micro-scaling of electrodes is a growing trend for the prevention of scar formation and increasing the working cycle of electrodes [86, 87]. Development of flexible, microscale electrode arrays that can be inserted as part of a two-component, rigid and flexible, delivery system show promise for application in small and large animals [88–91]. Optogenetic based flexible optical fibers, especially utilizing tissue penetrating, long-wavelength light, are also being explored to circumvent the problem of decaying electrical current delivery [92–94]. Few of these approaches have been either scaled or tested in large animal models. Miniaturization is likely to also create design challenges in terms of the long-term durability needed to work over extended periods. Further, implantable, flexible arrays require surgical placement and thereby will inherently lack flexibility for repositioning or covering multiple sites along a neural pathway.

Nevertheless, the future may hold design solutions that bring together material innovations to solve scaling, durability and flexibility in the future.

Potentially interesting new approaches come from the technology used in cochlear stimulating implants for treating hearing loss. Here, potent anti-inflammatory glucocorticoids, such as triamcinolone or dexamethasone, able to reduce fibrous tissue growth around the electrode, are locally applied as a single dose [95] or through micro-osmotic pump delivery [96]. In a more recent study, the silicone frame of the electrode array has been used as a carrier to release the previously incorporated drug. The continuous release of dexamethasone over an observational period of 91 days, largely attenuated the electrode impedance, yet exploiting the performance of the device [50]. In nonhuman primates, a nontoxic crystalline formulation for the controlled delivery of the antifibrotic agent GW2580, prevented cellular infiltration and collagen deposition on implanted biocompatible materials for more than a year. Moreover, this crystalline formulated drug can be mixed into polydimethylsiloxane or loaded for surface coatings of other materials, including plastic composites and metal alloys, becoming one of the best candidates for improving the long-term performance of multicomponent stimulating devices [97].

Transcutaneous SCS

Recently, several research groups have demonstrated the feasibility of non-invasive, transcutaneous SCS to neuromodulate excitability at multiple spinal levels, ranging from the cervical to the coccygeal segments, and facilitating both motor [98–105] and autonomic [106, 107] functions. These findings provide some evidence that human spinal networks feature the critical level of motor task-specific automaticity, which can be exploited using both invasive and non-invasive spinal neurostimulation. Further, they can effectively function even in the lack of supraspinal excitatory drive. Electrophysiological [108–110] and computational [111–113] studies demonstrated that the structures, stimulated electrically by epidural or transcutaneous SCS, are primarily afferent fibers of the posterior roots. In addition, many other neural structures can be directly impacted by the electrical field, including axons, synapses, neuronal cell bodies, and glial cells [2]. As such, both invasive and noninvasive spinal neuromodulation may engage spinal interneural networks via synaptic projections, as well as antidromic activation of ascending fibers in the dorsal columns [105, 114–116]. Currently, the dominating hypothesis is that the mechanisms through which invasive and non-invasive SCS can improve motor function after paralysis include activation of residual, longitudinal fibers across and

below the level of injury, which were functionally silenced during SCI, and emerging responsiveness of spinal networks to voluntary commands and sensory inputs [2, 6]. Most recently, Hofstoetter et al. [117] directly compared spinally evoked motor potentials using transcutaneous and epidural electrodes and confirmed the activation of common neural input structures by both techniques. However, a direct comparison of the functional neuromodulatory effects using each approach has yet to be performed. As such, it is important to establish the relative effectiveness of transcutaneous SCS versus the invasive epidural SCS in restoration of sensorimotor function.

At the same time, individual sensorimotor responses to spinal neuromodulation, whether it be transcutaneous or epidural, vary significantly across participants, making it difficult to determine which research subject will benefit and which stimulation paradigm will be the most effective. To the best of our knowledge, every study utilizing epidural SCS for motor recovery after motor complete SCI has been successful so far in regaining muscle-specific control below the lesion, and executing voluntary tasks with selectivity of appropriate motor pools, in the presence of epidural stimulation [9–11, 24]. Although transcutaneous SCS can augment and enable stepping movements [98–102, 118] and postural control during sitting [104] and standing [105], the fine and selective voluntary activation of specific agonists (with minimum co-contraction of antagonists) below spinal lesion after clinically diagnosed motor “complete” (but, in fact, discomplete [9, 22]) SCI remains a prerogative of epidural SCS alone. Such difference in engagement of specific muscles can be not at least because of the difference in stimulating electrodes’ size and focal stimulation of the particular motor pool in the case of epidural SCS, while the current overload over the adjacent motor pools in the case of transcutaneous SCS.

The adverse events during or following transcutaneous SCS are currently unknown, except one known report wherein an individual with SCI began experiencing spasms and pain in his lower body following the repeated sessions of transcutaneous SCS [119]. However, it is unclear if said complications were directly related to the study, especially given the reported findings that transcutaneous SCS can, in fact, decrease spasticity after SCI [120, 121]. Potential complications associated with transcutaneous SCS include the variety of events associated with any non-invasive electrical stimulation, including discomfort or pain due to activation of nociceptors in the skin beneath the stimulating electrodes, skin irritation, or breakage due to current concentration under the electrodes, and muscle contractions caused by the stimulation. Said events, in turn, may provoke autonomic dysreflexia in participants with SCI. Thus, although this approach is non-invasive, it may be premature to translate into home-based training programs without

supervision of clinicians. Both researchers and clinicians must exercise standard precautions, including blood pressure monitoring and adjustment of the stimulation parameters to minimize the discomfort using SCS. Nevertheless, it is our opinion that the advantages of transcutaneous SCS approach should be recognized in its non-invasiveness, cost-effectiveness, flexibility in delivery, including multi-site and multi-frequency stimulation, and further, its compatibility with other therapeutic and research techniques. We suggest that transcutaneous SCS can be considered as a tool for mechanistic research to delineate the underlying mechanisms and effects of either SCS. For instance, transcutaneous SCS can be utilized to guide research subject selection as well as training and provide a critical readout prior to invasive SCS, and perhaps even to drive the evolution of combinatorial invasive and noninvasive therapies to maximize restorative plasticity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

- Verrills P, Sinclair C, Barnard A. A review of spinal cord stimulation systems for chronic pain. *J Pain Res.* 2016;9:481.
- Taccola G, Sayenko D, Gad P, Gerasimenko Y, Edgerton VR. And yet it moves: recovery of volitional control after spinal cord injury. *Prog Neurobiol.* 2018;160:64–81.
- Weiss M, Mohr H. Spinal-cord stimulators help some patients, injure others. 2018. <https://apnews.com/86ba45b0a4ad443fad1214622d13e6cb>.
- Sivanesan E, Bicket MC, Cohen SP. Retrospective analysis of complications associated with dorsal root ganglion stimulation for pain relief in the FDA MAUDE database. *Regional Anesthesia Pain Med.* 2019;44:100–6.
- Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. *Clin J Pain.* 2010;26:463–9.
- Minassian K, McKay WB, Binder H, Hofstoetter US. Targeting lumbar spinal neural circuitry by epidural stimulation to restore motor function after spinal cord injury. *Neurotherapeutics.* 2016;13:284–94.
- 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:e0133998.
- Grahn PJ, Lavrov IA, Sayenko DG, Van Straaten MG, Gill ML, Strommen JA, et al. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. *Mayo Clin Proc.* 2017;92:544–54.
- Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nat Med.* 2018;24:1677–82.
- Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, et al. Recovery of over-ground walking after chronic motor complete spinal cord injury. *N Engl J Med.* 2018;379:1244–50.
- Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature.* 2018;563:65–71.
- Lu DC, Edgerton VR, Modaber M, AuYong N, Morikawa E, Zdurowski S, et al. Engaging cervical spinal cord networks to reenact volitional control of hand function in tetraplegic patients. *Neurorehabil Neural Repair.* 2016;30:951–62.
- DiMarco AF, Geertman RT, Tabbaa K, Nemunaitis GA, Kowalski KE. Restoration of cough via spinal cord stimulation improves pulmonary function in tetraplegics. *J Spinal Cord Med.* 2019;1–7. <https://doi.org/10.1080/10790268.2019.1699678>. Online ahead of print.
- Walter M, Lee AH, Kavanagh A, Phillips AA, Krassioukov AV. Epidural spinal cord stimulation acutely modulates lower urinary tract and bowel function following spinal cord injury: a case report. *Front Physiol.* 2018;9:1816.
- Herrity AN, Williams CS, Angeli CA, Harkema SJ, Hubscher CH. Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. *Sci Rep.* 2018;8:8688.
- Wernig A. No dawn yet of a new age in spinal cord rehabilitation. *Brain.* 2014;138:e362–e.
- Wernig A, Müller S, Nanassy A, Cagol E. Laufband therapy based on 'rules of spinal locomotion' is effective in spinal cord injured persons. *Eur J Neurosci.* 1995;7:823–9.
- Wernig A, Müller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. *Paraplegia.* 1992;30:229–38.
- Wernig A, Nanassy A, Müller S. Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. *Spinal Cord.* 1998;36:744–9.
- Wernig A, Nanassy A, Müller S. Laufband (treadmill) therapy in incomplete paraplegia and tetraplegia. *J Neurotrauma.* 1999;16:719–26.
- Dietz V, Wirz M, Colombo G, Curt A. Locomotor capacity and recovery of spinal cord function in paraplegic patients: a clinical and electrophysiological evaluation. *Electroencephalogr Clin Neurophysiol.* 1998;109:140–53.

22. Sherwood AM, Dimitrijevic MR, McKay WB. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. *J Neurol Sci.* 1992;110:90–8.
23. McKay WB, Lim HK, Priebe MM, Stokic DS, Sherwood AM. Clinical neurophysiological assessment of residual motor control in post-spinal cord injury paralysis. *Neurorehabil Neural Repair.* 2004;18:144–53.
24. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain.* 2014;137:1394–409.
25. Darrow D, Balsler D, Netoff TI, Krassioukov A, Phillips A, Parr A, 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;36:2325–36.
26. Kleiber J-C, Marlier B, Bannwarth M, Theret E, Peruzzi P, Litre F. Is spinal cord stimulation safe? A review of 13 years of implantations and complications. *Rev Neurologique.* 2016;172:689–95.
27. Maldonado-Naranjo AL, Frizon LA, Sabharwal NC, Xiao R, Hogue O, Lobel DA, et al. Rate of complications following spinal cord stimulation paddle electrode removal. *Neuromodulation: technology at the Neural. Interface.* 2018;21:513–9.
28. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain.* 2004;108:137–47.
29. Kumar K, Wilson JR, Taylor RS, Gupta S. Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact. *J Neurosurg Spine.* 2006;5:191–203.
30. Pineda A. Dorsal column stimulation and its prospects. *Surgical Neurol.* 1975;4:157–63.
31. Pineda A. Complications of dorsal column stimulation. *J Neurosurg.* 1978;48:64–8.
32. Bendersky D, Yampolsky C. Is spinal cord stimulation safe? A review of its complications. *World Neurosurg.* 2014;82:1359–68.
33. Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: a review of the literature. *Pain Med.* 2016;17:325–36.
34. Shamji MF, Westwick HJ, Heary RF. Complications related to the use of spinal cord stimulation for managing persistent post-operative neuropathic pain after lumbar spinal surgery. *Neurosurg Focus.* 2015;39:E15.
35. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg Spine.* 2004;100:254–67.
36. Mekhail NA, Mathews M, Nageeb F, Guirguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. *Pain Pract.* 2011;11:148–53.
37. Gazelka HM, Freeman ED, Hooten WM, Eldrige JS, Hoelzer BC, Mauck WD, et al. Incidence of clinically significant percutaneous spinal cord stimulator lead migration. *Neuromodulation: technology at the Neural. Interface.* 2015;18:123–5.
38. North RB, Lanning A, Hessels R, Cutchis PN. Spinal cord stimulation with percutaneous and plate electrodes: side effects and quantitative comparisons. *Neurosurg Focus.* 1997;2:E5.
39. Villavicencio AT, Leveque J-C, Rubin L, Bulsara K, Gorecki JP. Laminectomy versus percutaneous electrode placement for spinal cord stimulation. *Neurosurgery.* 2000;46:399–406.
40. Sandoe J, Barlow G, Chambers J, Gammage M, Guleri A, Howard P, et al. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). *J Antimicrob Chemother.* 2015;70:325–59.
41. Levy R, Henderson J, Slavin K, Simpson BA, Barolat G, Shipley J, et al. Incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads. *Neuromodulation: technology at the neural. Interface.* 2011;14:412–22.
42. Petraglia FW III, Farber SH, Gramer R, Verla T, Wang F, Thomas S, et al. The incidence of spinal cord injury in implantation of percutaneous and paddle electrodes for spinal cord stimulation. *Neuromodulation: technology at the Neural. Interface.* 2016;19:85–90.
43. Dam-Hieu P, Magro E, Seizeur R, Simon A, Quinio B. Cervical cord compression due to delayed scarring around epidural electrodes used in spinal cord stimulation: report of 2 cases. *J Neurosurg Spine.* 2010;12:409–12.
44. Hayek SM, Veizi E, Hanes M. Treatment-limiting complications of percutaneous spinal cord stimulator implants: a review of eight years of experience from an academic center database. *Neuromodulation.* 2015;18:603–8.
45. Reynolds AF, Shetter AG. Scarring around cervical epidural stimulating electrode. *Neurosurgery.* 1983;13:63–5.
46. Deer T, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, et al. Neuromodulation appropriateness consensus committee: the appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. *Neuromodulation.* 2014;17:515–50.
47. Fransen P. Reversible late thoracic myelopathy and neurostimulation tolerance caused by fibrous scar tissue formation around the spinal cord stimulation electrode. *Neuromodulation.* 2015;18:759–61.
48. Lang P. The treatment of chronic pain by epidural spinal cord stimulation—a 15 year follow up; present status. *Axone.* 1997;18:71–3.
49. Henle C, Raab M, Cordeiro J, Doostkam S, Schulze-Bonhage A, Stieglitz T, et al. First long term in vivo study on subdurally implanted micro-ECOG electrodes, manufactured with a novel laser technology. *Biomed Microdevices.* 2011;13:59–68.
50. Wilk M, Hessler R, Mugridge K, Jolly C, Fehr M, Lenarz T, et al. Impedance changes and fibrous tissue growth after cochlear implantation are correlated and can be reduced using a dexamethasone eluting electrode. *PLoS ONE.* 2016;11:e0147552.
51. Lin DP-Y, Chen JK-C, Tung T-H, Li LP-H. Differences in the impedance of cochlear implant devices within 24 hours of their implantation. *PLoS ONE.* 2019;14:e0222711.
52. Degenhart AD, Eles J, Dum R, Mischel JL, Smalianchuk I, Endler B, et al. Histological evaluation of a chronically-implanted electrocorticographic electrode grid in a non-human primate. *J Neural Eng.* 2016;13:046019.
53. Wissel K, Brandes G, Pütz N, Angrisani GL, Thieleke J, Lenarz T, et al. Platinum corrosion products from electrode contacts of human cochlear implants induce cell death in cell culture models. *PLoS ONE.* 2018;13:e0196649.
54. Schendel AA, Nonte MW, Vokoun C, Richner TJ, Brodnick SK, Atry F, et al. The effect of micro-ECOG substrate footprint on the meningeal tissue response. *J Neural Eng.* 2014;11:046011.
55. Wada E, Kawai H. Late onset cervical myelopathy secondary to fibrous scar tissue formation around the spinal cord stimulation electrode. *Spinal Cord.* 2010;48:646.
56. Cicuendez M, Munarriz PM, Castaño-Leon AM, Paredes I. Dorsal myelopathy secondary to epidural fibrous scar tissue around a spinal cord stimulation electrode: case report. *J Neurosurg.* 2012;17:598–601.
57. Al Tamimi M, Aoun SG, Gluf W. Spinal cord compression secondary to epidural fibrosis associated with percutaneously

- placed spinal cord stimulation electrodes: case report and review of the literature. *World Neurosurg.* 2017;104:1051. e1–e5.
58. Scranton RA, Skaribas IM, Simpson RK Jr. Spinal stimulator peri-electrode masses: case report. *J Neurosurg Spine.* 2015;22:70–4.
 59. Nashold BS Jr, Friedman H. Dorsal column stimulation for control of pain. Preliminary report on 30 patients. *J Neurosurg.* 1972;36:590–7.
 60. Krainick J-U, Thoden U, Riechert T. Pain reduction in amputees by long-term spinal cord stimulation: long-term follow-up study over 5 years. *J Neurosurg.* 1980;52:346–50.
 61. Lennarson PJ, Guillen FT. Spinal cord compression from a foreign body reaction to spinal cord stimulation: a previously unreported complication. *Spine.* 2010;35:E1516–9.
 62. Wloch A, Capelle HH, Saryyeva A, Krauss JK. Cervical myelopathy due to an epidural cervical mass after chronic cervical spinal cord stimulation. *Stereotact Funct Neurosurg.* 2013;91:265–9.
 63. Guzzi G, Volpentesta G, Chirchiglia D, Della Torre A, Lavano F, Lavano A. Cervical spinal cord compression from delayed epidural scar tissue formation around plate lead for SCS. *J Neurosurg Sci.* 2019;63:337–43.
 64. de Eulate-Beramendi SA, Santamarta-Liebana E, Leon RF, Saiz-Ayala A, Seijo-Fernandez FJ. Cervical cord compression secondary to epidural fibrous scar tissue around the spinal cord stimulation electrode. *Neurology.* 2016;64:1363–5.
 65. Schendel AA, Thongpang S, Brodnick SK, Richner TJ, Lindevig BD, Krugner-Higby L, et al. A cranial window imaging method for monitoring vascular growth around chronically implanted micro-ECoG devices. *J Neurosci Methods.* 2013;218:121–30.
 66. Sridar S, Churchward MA, Mushahwar VK, Todd KG, Elias AL. Peptide modification of polyimide-insulated microwires: Towards improved biocompatibility through reduced glial scarring. *Acta Biomater.* 2017;60:154–66.
 67. Dimar JR II, Endriga DT, Carreon LY. Osteolysis and cervical cord compression secondary to silicone granuloma formation around a dorsal spinal cord stimulator: a case report. *J Neurol Surg Rep.* 2016;77:e67–e72.
 68. Kim JE, Yang JH, Lee MK, Suh SW, Kang SW. Cervical myelopathy secondary to metallic irritation of the dura mater following insertion of a spinal cord stimulator in a patient with ossification of posterior longitudinal ligament. *Pain Med.* 2017;19:631–4.
 69. Yamakawa T, Yamakawa T, Aou S, Ishizuka S, Suzuki M, Fujii M. Subdural electrode array manipulated by a shape memory alloy guidewire for minimally-invasive electrocorticogram recording. *IEEE, World Automation Congress, Kobe, 2010.* p. 1–6.
 70. Yeager JD, Phillips DJ, Rector DM, Bahr DF. Characterization of flexible ECoG electrode arrays for chronic recording in awake rats. *J Neurosci Methods.* 2008;173:279–85.
 71. Rubehn B, Bosman C, Oostenveld R, Fries P, Stieglitz T. A MEMS-based flexible multichannel ECoG-electrode array. *J Neural Eng.* 2009;6:036003.
 72. Kim JJ, Gean AD. Imaging for the diagnosis and management of traumatic brain injury. *Neurotherapeutics.* 2011;8:39–53.
 73. Norton L, Tegnell E, Toporek S, Reichert W. In vitro characterization of vascular endothelial growth factor and dexamethasone releasing hydrogels for implantable probe coatings. *Biomaterials.* 2005;26:3285–97.
 74. Weaver CL, LaRosa JM, Luo X, Cui XT. Electrically controlled drug delivery from graphene oxide nanocomposite films. *ACS Nano.* 2014;8:1834–43.
 75. Collier TO, Anderson JM, Brodbeck WG, Barber T, Healy KE. Inhibition of macrophage development and foreign body giant cell formation by hydrophilic interpenetrating polymer network. *J Biomed Mater Res Part A.* 2004;69:644–50.
 76. Kolarcik CL, Bourbeau D, Azemi E, Rost E, Zhang L, Lagenaur CF, et al. In vivo effects of L1 coating on inflammation and neuronal health at the electrode–tissue interface in rat spinal cord and dorsal root ganglion. *Acta Biomater.* 2012;8:3561–75.
 77. Vallejo-Giraldo C, Krukiewicz K, Calaresu I, Zhu J, Palma M, Fernandez-Yague M, et al. Attenuated glial reactivity on topographically functionalized poly (3, 4-ethylenedioxythiophene): P-toluene sulfonate (PEDOT: PTS) neuroelectrodes fabricated by microimprint lithography. *Small.* 2018;14:1800863.
 78. Lavrov I, Dy CJ, Fong AJ, Gerasimenko Y, Courtine G, Zhong H, et al. Epidural stimulation induced modulation of spinal locomotor networks in adult spinal rats. *J Neurosci.* 2008;28:6022–9.
 79. Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, 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;377:1938–47.
 80. Calvert JS, Manson GA, Grahn PJ, Sayenko DG. Preferential activation of spinal sensorimotor networks via lateralized transcutaneous spinal stimulation in neurologically intact humans. *J Neurophysiol.* 2019;122:2111–8.
 81. Borgens RB, Shi R, Mohr TJ, Jaeger CB. Mammalian cortical astrocytes align themselves in a physiological voltage gradient. *Exp Neurol.* 1994;128:41–9.
 82. Alexander JK, Fuss B, Colello RJ. Electric field-induced astrocyte alignment directs neurite outgrowth. *Neuron Glia Biol.* 2006;2:93–103.
 83. Pelletier SJ, Lagacé M, St-Amour I, Arsenault D, Cisbani G, Chabrat A, et al. The morphological and molecular changes of brain cells exposed to direct current electric field stimulation. *Int J Neuropsychopharmacol.* 2015;18:pyu090.
 84. Metcalf MM, Shi R, Borgens RB. Endogenous ionic currents and voltages in amphibian embryos. *J Exp Zool.* 1994;268:307–22.
 85. Taccola G, Gad P, Culaclii S, Ichiyama RM, Liu W, Edgerton VR. Using EMG to deliver lumbar dynamic electrical stimulation to facilitate cortico-spinal excitability. *Brain Stimul.* 2020;13:20–34.
 86. Pancrazio JJ, Deku F, Ghazavi A, Stiller AM, Rihani R, Frewin CL, et al. Thinking small: progress on microscale neurostimulation technology. *Neuromodulation: technology at the neural interface.* 2017;20:745–52.
 87. Lecomte A, Descamps E, Bergaud C. A review on mechanical considerations for chronically-implanted neural probes. *J Neural Eng.* 2018;15:031001.
 88. Sohal HS, Jackson A, Jackson R, Clowry GJ, Vassilevski K, O'Neill A, et al. The sinusoidal probe: a new approach to improve electrode longevity. *Front Neuroeng.* 2014;7:10.
 89. Du ZJ, Kolarcik CL, Kozai TD, Luebben SD, Sapp SA, Zheng XS, et al. Ultrasoft microwire neural electrodes improve chronic tissue integration. *Acta Biomater.* 2017;53:46–58.
 90. Canales A, Park S, Kiliyas A, Anikeeva P. Multifunctional fibers as tools for neuroscience and neuroengineering. *Acc Chem Res.* 2018;51:829–38.
 91. Garcia-Sandoval A, Pal A, Mishra AM, Sherman S, Parikh AR, Joshi-Imre A, et al. Chronic softening spinal cord stimulation arrays. *J Neural Eng.* 2018;15:045002.
 92. Park SI, Brenner DS, Shin G, Morgan CD, Copits BA, Chung HU, et al. Soft, stretchable, fully implantable miniaturized optoelectronic systems for wireless optogenetics. *Nat Biotechnol.* 2015;33:1280.
 93. Nguyen H, Arnob MMP, Becker AT, Wolfe JC, Hogan MK, Horner PJ, et al. Fabrication of multipoint side-firing optical fiber by laser micro-ablation. *Opt Lett.* 2017;42:1808–11.

94. Chang S-Y, Naganuma K, Kanazawa H, Sekino M, Onodera H, Kuniyoshi Y, editors. *Applying Multichannel Optogenetic System for Epidural Spinal Cord Stimulation in Rats*. 2018 40th Annual International Conference of the IEEE. EMBC. ThCT10.5, 2018.
95. Braun S, Ye Q, Radeloff A, Kiefer J, Gstoettner W, Tillein J. Protection of inner ear function after cochlear implantation: compound action potential measurements after local application of glucocorticoids in the guinea pig cochlea. *ORL*. 2011;73:219–28.
96. Van De Water TR, Dinh CT, Vivero R, Hoosien G, Eshraghi AA, Balkany TJ. Mechanisms of hearing loss from trauma and inflammation: otoprotective therapies from the laboratory to the clinic. *Acta Oto-laryngologica*. 2010;130:308–11.
97. Farah S, Doloff JC, Müller P, Sadraei A, Han HJ, Olafson K, et al. Long-term implant fibrosis prevention in rodents and non-human primates using crystallized drug formulations. *Nat Mater*. 2019;18:892.
98. Hofstoetter US, Hofer C, Kern H, Danner SM, Mayr W, Dimitrijevic MR, et al. Effects of transcutaneous spinal cord stimulation on voluntary locomotor activity in an incomplete spinal cord injured individual. *Biomed Tech Biomed Eng*. 2013;58 (Suppl 1):<https://doi.org/10.1515/bmt-2013-4014>.
99. Hofstoetter US, Krenn M, Danner SM, Hofer C, Kern H, McKay WB, et al. Augmentation of voluntary locomotor activity by transcutaneous spinal cord stimulation in motor-incomplete spinal cord-injured individuals. *Artif Organs*. 2015;39:E176–86.
100. Minassian K, Hofstoetter US, Danner SM, Mayr W, Bruce JA, McKay WB, et al. Spinal rhythm generation by step-induced feedback and transcutaneous posterior root stimulation in complete spinal cord-injured individuals. *Neurorehabil Neural Repair*. 2016;30:233–43.
101. Gerasimenko YP, Lu DC, Modaber M, Zdurowski S, Gad P, Sayenko DG, et al. Noninvasive reactivation of motor descending control after paralysis. *J Neurotrauma*. 2015;32:1968–80.
102. Gad P, Gerasimenko Y, Zdurowski S, Turner A, Sayenko D, Lu DC, 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.
103. 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 transactions on neural systems and rehabilitation engineering: a publication of the IEEE engineering in medicine and biology. Society*. 2018;26:1272–8.
104. Rath M, Vette AH, Ramasubramaniam S, Li K, Burdick J, Edgerton VR, et al. Trunk stability enabled by noninvasive spinal electrical stimulation after spinal cord injury. *J Neurotrauma*. 2018;35:2540–53.
105. Sayenko DG, Rath M, Ferguson AR, Burdick JW, Havton LA, Edgerton VR, et al. Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. *J Neurotrauma*. 2019;36:1435–50.
106. Gad PN, Kreydin E, Zhong H, Latack K, Edgerton VR. Non-invasive neuromodulation of spinal cord restores lower urinary tract function after paralysis. *Front Neurosci*. 2018;12:432.
107. Phillips AA, Squair JW, Sayenko DG, Edgerton VR, Gerasimenko Y, Krassioukov AV. An autonomic neuroprosthesis: noninvasive electrical spinal cord stimulation restores autonomic cardiovascular function in individuals with spinal cord injury. *J Neurotrauma*. 2018;35:446–51.
108. Hunter JP, Ashby P. Segmental effects of epidural spinal cord stimulation in humans. *J Physiol*. 1994;474:407–19.
109. Maertens de Noordhout A, Rothwell JC, Thompson PD, Day BL, Marsden CD. Percutaneous electrical stimulation of lumbosacral roots in man. *J Neurol Neurosurg Psychiatry*. 1988;51:174–81.
110. 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;35:327–36.
111. 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;38:473–89.
112. Ladenbauer J, Minassian K, Hofstoetter US, Dimitrijevic MR, Rattay F. Stimulation of the human lumbar spinal cord with implanted and surface electrodes: a computer simulation study. *IEEE Trans Neural Syst Rehab*. 2010;18:637–45.
113. Danner SM, Hofstoetter US, Ladenbauer J, Rattay F, Minassian K. Can the human lumbar posterior columns be stimulated by transcutaneous spinal cord stimulation? A modeling study. *Artif Organs*. 2011;35:257–62.
114. Jilge B, Minassian K, Rattay F, Dimitrijevic MR. Frequency-dependent selection of alternative spinal pathways with common periodic sensory input. *Biol Cybern*. 2004;91:359–76.
115. 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;26:275–95.
116. 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;111:1088–99.
117. 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:e0192013.
118. Minassian K, Hofstoetter US. Spinal cord stimulation and augmentative control strategies for leg movement after spinal paralysis in humans. *CNS Neurosci Ther*. 2016;22:262–70.
119. Willyard C. How a revolutionary technique got people with spinal-cord injuries back on their feet. *Nature*. 2019;572:20–5.
120. 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;37:202–11.
121. Hofstoetter US, Freundl B, Danner SM, Krenn MJ, Mayr W, Binder H, et al. Transcutaneous spinal cord stimulation induces temporary attenuation of spasticity in individuals with spinal cord injury. *J Neurotrauma*. 2020;37:481–93.
122. Benfield J, Maknojia A, Epstein F. Progressive paraplegia from spinal cord stimulator lead fibrotic encapsulation: a case report. *Am J Phys Med Rehab*. 2016;95:e30–e3.
123. Aoun SG, El Ahmadieh T, Johnson ZD, Connors SW, Al Tamimi M. Reversible thoracic myelopathy after surgical decompression and removal of paddle neurostimulator lead and encasing fibrosis: technical video case report. *Interdisciplinary. Neurosurgery*. 2018;11:29–30.