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

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1	Title: Complications of epidural spinal stimulation: Lessons from the past and alternatives	
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4	Running title: Complications of epidural spinal stimulation	
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22 Abstract

23 *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.

30 *Methods*: Systematic analysis of literature, as well as pre-clinical 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.

- 45 **Abbreviations:** spinal cord stimulation (SCS), spinal cord injury (SCI)
- 46
- 47 Keywords: neuromodulation, spinal cord, epidural interface, complications, transcutaneous
- 48 stimulation
- 49

50 Introduction

Recently, spinal stimulation-based neuromodulation has progressed from an "inhibitory" 51 intervention for pain management [1] to become an important modality for reactivating latent 52 53 functions of the underlying processing networks [2]. Between 2008-2017, the United States Food and Drug Administration (U.S. FDA) reported over 600,000 individuals were implanted with 54 spinal cord stimulators (www.apnews.com) [3]. Thirteen percent (78,172) of said individuals 55 56 suffered injuries caused by spinal cord stimulators. These alarming statistics demonstrate why 57 spinal cord stimulators are ranked as the third-highest leading cause of injury among all used medical devices, right after metal hip protheses and insulin pumps. One relevant study was 58 performed recently by Sivanesan et al. [4], where the authors queried the Manufacturer and User 59 Facility Device Experience (MAUDE) database for all entries named 'Dorsal root ganglion 60 61 stimulator for pain relief' between May 1, 2016 and December 31, 2017, verified by the US FDA. There were 979 cases of implantation identified, almost half of which (47%), were categorized as 62 device-related complications, a quarter (28%) as procedural complications, with the remainder as 63 individual complaints (12%), serious adverse events (2.4%), and 'other' complications (4.6%). 64 The authors warn that although the stimulation device has been publicized as a breakthrough in 65 neuromodulation technologies, one must proceed with caution and reevaluate effectiveness as 66 67 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 68 spinal cord stimulators. The implantation itself, especially if it involves laminectomy, can lead to 69 a broad variety of complications associated with invasive procedures, including infection or 70 hematoma, and, depending on the type of the electrodes used for spinal cord stimulation (SCS), 71 can be associated with electrode migration. Still, a health economic assessment of application of 72

73 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 74 [5]. The Incremental Cost Effectiveness Ratio calculated over a 15-year horizon demonstrated high 75 76 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 77 the incidence of complications. At the same time, similar analysis on the benefit to cost ratio from 78 79 the studies recovering motor control using SCS is not available to date, but it would likely show a 80 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 81 ambulation. 82

Spinal stimulation has been shown to have potential for a vast variety of applications in 83 84 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 85 indicate that stimulation of the spinal cord with the use of task-oriented rehabilitation can be 86 87 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 88 various motor tasks including standing [7, 8], stepping [9-11], hand grasping [12], respiration [13], 89 90 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 91 92 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 93 SCS, body-weight load during activity-based training (see 'rules of spinal locomotion' [17]), 94 creates the flow of proprioceptive signals which in turn can facilitate spinal locomotor programs 95

96 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 97 stimulation applied by itself allows regaining of mobility and independence. Most of the papers in 98 99 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 non-functional after SCI, 100 can be engaged by spinal stimulation to produce and modulate motor activities. The fact that 101 102 regaining voluntary motor control can occur within just the first few sessions of epidural spinal 103 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, 104 are highly plastic and prepared for functioning in the presence of spinal stimulation and within 105 106 appropriate somatosensory environment, months or even years following SCI. The fact that when 107 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 108 sensory input can synergize within spinal networks to generate voluntary motor activities. The use 109 110 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 111 phenomena and/or requiring invasive spinal surgeries to overcome adverse side effects. Moreover, 112 113 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 114 procedure, as electrodes are often encapsulated by secondary bony overgrowth and epidural 115 fibrous capsule [26, 27]. For instance, explantation of paddle electrodes is associated with potential 116 risks and postoperative complications which occurred in 12% of surgeries, ranging from minor 117 issues, such as infection (9%), to more serious adverse events, as cerebrospinal fluid leak or 118

epidural bleeding, which causes hematoma and accidental compression of the spinal cord¹⁹. 119 120 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 121 122 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 123 encapsulation and its negative impact on effective and sustainable spinal cord stimulation (SCS). 124

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Complications of implanted electrodes

127 Several large studies [28-30, also see Supplementary Appendix (SA) SA31-34] have documented relatively high complication rates (20 - 75%) following SCS, including hardware 128 129 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 [SA32], and require 130 invasive treatments in approximately half of the cases [26]. 131

Among hardware-related problems, lead migration was previously reported as one of the 132 133 most common risks of SCS, with a variable incidence spanning 13 to 22%, with a higher prevalence for implants in the cervical spine, where the degree of motion of vertebrae is greater 134 [SA35, 36]. Lead migration often requires a new surgical procedure for repositioning or replacing 135 136 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 137 1.4 to 2.1 % of over a hundred of analyzed cases, a much lower incidence rate than previously 138 reported, possibly accounting for hardware and technique improvement, including revised 139 published guidelines by SCS manufacturers on proper fascial anchoring and the use of strain-relief 140 loops [SA37]. Noteworthy, older studies have compared the migration rates of percutaneous leads 141

and paddle array electrodes [SA38, 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. 148 149 Infection is one of the major complications with incidences of 5% and requiring antibiotic 150 treatment and even device removal and reinstallation after healing from sepsis [26, SA32-33]. This is a higher value compared to other implantable electronic devices, such as cardiac pacemakers, 151 152 which have an incidence of infection of about 0.5 to 2.2% [SA40]. For SCS, superficial or 153 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 154 paralysis has been reported [SA41]. Pain in the region around the stimulator has also been 155 156 registered in 5 to 10% [26, SA32-33]. During surgical or blind percutaneous insertion of electrodes, accidental dural puncture, epidural hematoma, as well as blunt trauma to the cord, have 157 been documented, causing the onset of paraplegia in the 30 days following SCS implantation for 158 159 2% of individuals analyzed [42].

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161 **Tolerance to SCS**

Even in the absence of the above mentioned complications, an estimated 10 to 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 [SA34, 165 43, 44]. Although an increase in pulse amplitude might circumvent the problem for a while [SA45-47], the tolerance phenomenon still often mitigates SCS efficacy if therapy is continued. This 166 phenomenon can develop as early as a few months after implantation and as late as 10 to 15 years 167 168 following implantation [29, SA48]. Although, psychological affective factors might also contribute to a tolerance to the analgesic effects of SCS [SA46], there is some evidence that 169 suggests the development of tolerance over time results from dropped charges related to the deposit 170 171 of high impedance biological material progressively encapsulating the electrode after implantation 172 [SA46, 49]. The extent of fibrous tissue growth around the electrode has been positively correlated to impedance increases in studies with cochlear implants [SA50-51]. It is doubtful that tolerance 173 reflects only structural and conductive changes on the surface of the implanted material and can 174 175 be solved by merely substituting the system. Tolerance originates from more profound changes at 176 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 177 mononuclear macrophages and the encapsulation of the device in a collagenous envelope [SA52]. 178 179 The picture can be further worsened by the local toxicity of metal particles dissolved by the longterm corrosion of electrodes [SA53]. All these events can activate fibroblasts, with a consequent 180 fibrotic growth around the electrode that causes a shallow mechanical depression of the spinal cord 181 182 regions under the array [SA52]. 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 183 thickening or even superficial scarring, that eventually alter the charge transfer to the surrounding 184 neural structures [SA54]. 185

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.

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190 Histological Findings in Fibrous Encapsulationsu

Despite the rarity of negative published results in the field of SCS, there have been at least 191 192 20 reported cases of severe spinal compression related to fibrous lead encapsulation developing 3 193 to 17 years after electrode implantation (Table 1, mean onset = 7 ± 5 years) [SA43, 55, 56]. Oftentimes, these cases began as tolerance, eventually resulting in the development of neurological 194 deficits, such as myelopathy [SA43, 57], worsened spasticity [SA45], and increased paralysis 195 196 [SA43, 45, 56, 58]. In all 20 reported cases, delicate surgical procedures on the spinal cord to 197 remove the whole electrode and the scar tissue that surrounded it inside the epidural space were necessary, sometimes in response to tolerance [SA43, 45, 47, 55-57, 59-64]. Also, in some reported 198 cases, analysis of the extracted scar tissue revealed the presence of excessive fibrosis around the 199 200 electrode itself - both for paddle electrodes implanted via laminectomy and those implanted percutaneously into the epidural space [29, SA43, 48]. Still, the vast majority of published clinical 201 reports about failures and complications of SCS unfortunately do not comment on end-term tissue 202 203 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 204 examination of cortical epidural implants has revealed an overgrowth of connective tissue [SA54, 205 206 65] and an aggregation of cortical microglia in a resting state morphology in the first week after implantation [SA52] that is followed in the subsequent week by the accumulation of a layer of 207 astrocytes [SA66]. Further studies have documented the presence of granulomatous tissue and a 208

209 nonspecific chronic inflammatory reaction [SA57] characterized by multinucleate macrophages 210 (giant cells) aggregating in response to the foreign body and engulfing the implant [SA61]. Underlying dural thickening and fibrous implant encapsulation has also been seen in experimental 211 212 animal models within the first month after implantation of cortical epidural arrays [SA54, 65]. This fibrous envelope consists of both fibroblasts and Collagen I, with the "collagenous" tissue 213 located in the distal part of the implanted array mimicking healthy dura mater while the more 214 proximal region contains "cellular" tissue with increased inflammatory cell activity [SA52]. The 215 216 thickness and density of cortical neural tissue, however, does not seem to change appreciably, even with long-term array implantation [SA52]. There has been a number of documented cases of 217 fibrous masses developing in humans in association with SCS, often requiring electrode 218 219 explantation or revision due to some combination of tolerance and/or neurological deficits (Table 220 1). Moreover, many of said cases have reported histological findings similar to those seen in animals, including dense fibroconnective tissue, variable non-specific inflammatory infiltrates, 221 multinucleated giant cells, noncaseating granulomas indicative of a foreign body reaction [SA45, 222 223 55-58, 61, 67]. Furthermore, in a recent clinical report [SA68], histologic examination of the fibrous tissue around the electrode used for SCS revealed granulomatous inflammation and 224 phagocytic reaction of neutrophils and macrophages due to a metallic irritation of the dura mater. 225 226 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 227 electrode. Uncovering of the silicon and urethane coating was likely caused by the micromotion 228 229 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.
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234 Approaches for avoiding fibrous encapsulation

The relevance of epidural electrodes' encapsulation in current practice is supported by the 235 236 many ongoing research efforts underway to reduce encapsulation. One common theory is that the 237 exuberant fibroblastic response may be dependent on the materials used for electrode fabrication [SA45]. Thus, several studies have improved the integration of implanted devices in the central 238 nervous system by modifying the electrode materials in an attempt to minimize the foreign body 239 240 response. These recent approaches include shape alteration of the array substrate [SA54, 65, 69], 241 increased array flexibility [SA70-72], the release of anti-inflammatory drugs through the array itself, either from the substrate or from the electrodes [SA73, 74], and the application of anti-242 fouling or biomimetic surface treatments [SA75, 76], such as different materials and techniques of 243 244 coating and lamination [SA66, 77]. Albeit promising, these approaches require a considerable amount of time and resources both for preclinical development and also for safety and efficiency 245 testing prior to use [SA77], ultimately delaying their availability in the clinic. Interestingly, 246 247 Reynolds and Shetter [SA45] theorized that the fibrotic and inflammatory response associated with implanted electrodes might be related to the electrical stimulation through the electrode; but, 248 249 evidence in support of this is lacking. While intraoperative stimulation is often performed to guide 250 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 251 252 post-surgical rest [8, SA78-79]. Interestingly, research suggests that development of fibrosis and 253 glia around the electrode begins during the initial week of post-surgical rest following implantation [SA66]. These results imply that electrode-associated fibrosis occurs independent of stimulation. 254 However, it is still unclear whether low intensity stimulation in the first week following 255 256 implantation may limit the development of electrode-associated fibrosis. Stimulation amplitudes commonly used to neuromodulate physiological state of the spinal cord [SA79, 80], which are 257 based on previous preclinical studies [SA78], are much greater in magnitude than the amplitudes 258 259 reported in the literature as being endogenous to the nervous system. For example, in vertebrate 260 embryos, glia are sensitive to electrical fields of physiological strength (50-500mV/mm) [SA81]. 261 These electrical fields play a pivotal role not only in retracting and aligning astrocytes processes, thereby leading their orientation perpendicular to the voltage gradient [SA81], but also in 262 promoting and directing neurite growth in the developing central nervous system [SA82-83] where 263 264 endogenous electric fields are generated by a polarized voltage gradient [SA84]. Based on this evidence, we believe that future research could exploit this range of low intensities to create a 265 physiological electrical stimulation to be delivered during the initial days following implantation 266 267 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 268 this could be done without substantial increases in knowledge based on animal experiments. 269 270 Further, a valuable perspective in the field should be the design of neural interfaces in which the 271 delivery of distinct patterns of subthreshold electrical stimulation, that is stimulation at the intensity just below motor threshold [SA85], guides the proliferation of glial cells along a re-272 absorbable array frame eventually leaving only working metal electrodes and connections stably 273 integrated in the epidural connective tissue. These implantable Glio-Electrode Arrays should be 274 considered as a more biocompatible technology for future preclinical research trials. 275

276 In addition to material interface engineering solutions and stimulation protocols to prevent 277 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 278 279 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 [SA86-87]. Development of flexible, 280 microscale electrode arrays that can be inserted as part of a two-component, rigid and flexible, 281 282 delivery system show promise for application in small and large animals [SA88-91]. Optogenetic 283 based flexible optical fibers, especially utilizing tissue penetrating, long-wavelength light, are also being explored to circumvent the problem of decaying electrical current delivery [SA92-94]. Few 284 of these approaches have been either scaled or tested in large animal models. Miniaturization is 285 286 likely to also create design challenges in terms of the long-term durability needed to work over 287 extended periods. Further, implantable, flexible arrays require surgical placement and thereby will inherently lack flexibility for re-positioning or covering multiple sites along a neural pathway. 288 Nevertheless, the future may hold design solutions that bring together material innovations to solve 289 290 scaling, durability and flexibility in the future.

Potentially interesting new approaches come from the technology used in cochlear 291 stimulating implants for treating hearing loss. Here, potent anti-inflammatory glucocorticoids, 292 293 such as triamcinolone or dexamethasone, able to reduce fibrous tissue growth around the electrode, 294 are locally applied as a single dose [SA95] or through micro-osmotic pump delivery [SA96]. In a more recent study, the silicone frame of the electrode array has been used as a carrier to release 295 296 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 297 the device [SA50]. In non-human primates, a non-toxic crystalline formulation for the controlled 298

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 [SA97].

304

305 Transcutaneous SCS

306 Recently, several research groups have demonstrated the feasibility of non-invasive, transcutaneous SCS to neuromodulate excitability at multiple spinal levels, ranging from the 307 cervical to the coccygeal segments, and facilitating both motor [SA98-105] and autonomic 308 309 [SA106-107] 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 310 and non-invasive spinal neurostimulation. Further, they can effectively function even in the lack 311 of supraspinal excitatory drive. Electrophysiological [SA108-110] and computational [SA111-312 313 113] studies demonstrated that the structures, stimulated electrically by epidural or transcutaneous SCS, are primarily afferent fibers of the posterior roots. Additionally, many other neural structures 314 can be directly impacted by the electrical field, including axons, synapses, neuronal cell bodies, 315 316 and glial cells [2]. As such, both invasive and non-invasive spinal neuromodulation may engage spinal interneural networks via synaptic projections, as well as antidromic activation of ascending 317 fibers in the dorsal columns [SA105, 114-116]. Currently, the dominating hypothesis is that the 318 319 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, 320 which were functionally silenced during SCI, and emerging responsiveness of spinal networks to 321

voluntary commands and sensory inputs [2, 6]. Most recently, Hofstoetter et al. (2018) [SA117]
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.

328 At the same time, individual sensorimotor responses to spinal neuromodulation, whether it 329 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 330 effective. To the best of our knowledge, every study utilizing epidural SCS for motor recovery 331 332 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 333 presence of epidural stimulation [9-11, 24]. Although transcutaneous SCS can augment and enable 334 stepping movements [SA98-102, 118] and postural control during sitting [SA104] and standing 335 336 [SA105], the fine and selective voluntary activation of specific agonists (with minimum cocontraction of antagonists) below spinal lesion after clinically diagnosed motor "complete" (but, 337 in fact, discomplete [9, 22]) SCI remains a prerogative of epidural SCS alone. Such difference in 338 339 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, 340 while the current overload over the adjacent motor pools in the case of transcutaneous SCS. 341

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 [SA119]. However, it is unclear if 345 said complications were directly related to the study, especially given the reported findings that transcutaneous SCS can, in fact, decrease spasticity after SCI [SA120, 121]. Potential 346 complications associated with transcutaneous SCS include the variety of events associated with 347 348 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 349 concentration under the electrodes, and muscle contractions caused by the stimulation. Said events, 350 351 in turn, may provoke autonomic dysreflexia in participants with SCI. Thus, although this approach 352 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, 353 including blood pressure monitoring and adjustment of the stimulation parameters to minimize the 354 355 discomfort using SCS. Nevertheless, it is our opinion that the advantages of transcutaneous SCS 356 approach should be recognized in its non-invasiveness, cost-effectiveness, flexibility in delivery, including multi-cite and multi-frequency stimulation, and further, its compatibility with other 357 therapeutic and research techniques. We suggest that transcutaneous SCS can be considered as a 358 359 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 360 training and provide a critical readout prior to invasive SCS, and perhaps even to drive the 361 362 evolution of combinatorial invasive and non-invasive therapies to maximize restorative plasticity.

363

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368 Conflicts of interest statement

No conflicts of interest, financial or personal relationship with other people or organizations thatcould inappropriately influence their work, are declared by the authors.

371

372 Authors' contributions

GT conceptualized the review. GT, SB, PH, HBC, and DS screened potential studies. GT, SB, and DS performed the search. GT prepared the figure and table. GT and DS interpreted results and drafted the manuscript. All authors revised the manuscript, and approved the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

378

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387 **References**

- [1] Verrills P, Sinclair C, Barnard A. A review of spinal cord stimulation systems for chronic pain.
 Journal of pain research. 2016;9:481.
- [2] 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.
- 392 [3] Weiss M, Mohr H. Spinal-cord stimulators help some patients, injure others
 393 https://apnews.com/86ba45b0a4ad443fad1214622d13e6cb2018 [Available from:
 394 https://apnews.com/86ba45b0a4ad443fad1214622d13e6cb.
- [4] 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 Medicine. 2019;44(1):100-6.
- 398 [5] Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of
 399 spinal cord stimulation in the treatment of failed back surgery syndrome. Clin J Pain.
 400 2010;26(6):463-9.
- [6] 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(2):284-94.
- [7] 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.
- [8] 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(4):544-54.
- [9] 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. Nature
 medicine. 2018;24(11):1677-82.
- [10] Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, et al. Recovery of OverGround Walking after Chronic Motor Complete Spinal Cord Injury. The New England journal of
 medicine. 2018;379(13):1244-50.
- [11] 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.
- 417 2018;563(7729):65-71.

- 418 [12] Lu DC, Edgerton VR, Modaber M, AuYong N, Morikawa E, Zdunowski S, et al. Engaging
- Cervical Spinal Cord Networks to Reenable Volitional Control of Hand Function in Tetraplegic 419
- Patients. Neurorehabil Neural Repair. 2016;30(10):951-62. 420
- [13] DiMarco AF, Geertman RT, Tabbaa K, Nemunaitis GA, Kowalski KE. Restoration of cough 421 via spinal cord stimulation improves pulmonary function in tetraplegics. The journal of spinal cord
- 422
 - 423 medicine. 2019:1-7.
 - 424 [14] 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: 425 a case report. Frontiers in physiology. 2018;9:1816. 426
 - 427 [15] 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. 428 429 2018;8(1):8688.
 - [16] Wernig A. No dawn yet of a new age in spinal cord rehabilitation. Brain. 2014;138(7):e362-430 431 e.
 - [17] Wernig A, Müller S, Nanassy A, Cagol E. Laufband therapy based on 'rules of spinal 432 locomotion'is effective in spinal cord injured persons. European Journal of Neuroscience. 433 434 1995;7(4):823-9.
 - 435 [18] Wernig A, Muller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia. 1992;30(4):229-38. 436
 - 437 [19] Wernig A, Nanassy A, Muller S. Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. Spinal cord. 438 1998;36(11):744-9. 439
 - [20] Wernig A, Nanassy A, Müller S. Laufband (treadmill) therapy in incomplete paraplegia and 440 tetraplegia. Journal of neurotrauma. 1999;16(8):719-26. 441
 - 442 [21] 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 443 Clin Neurophysiol. 1998;109(2):140-53. 444
 - 445 [22] Sherwood AM, Dimitrijevic MR, McKay WB. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. Journal of the neurological sciences. 446 1992;110(1-2):90-8. 447

[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(3):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(Pt
5):1394-409.

[25] Darrow D, Balser 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(15):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. Revue neurologique.
2016;172(11):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(5):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(1-2):137-47.

[29] Kumar K, Wilson JR, Taylor RS, Gupta S. Complications of spinal cord stimulation,
suggestions to improve outcome, and financial impact. Journal of Neurosurgery: Spine.
2006;5(3):191-203.

- [30] Pineda A. Dorsal column stimulation and its prospects. Surgical neurology. 1975;4(1):157-63.
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474 Legend

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- 476 Table 1. Reported cases of severe spinal compression related to fibrous lead encapsulation
- 477 developing 3 to 17 years after electrode implantation