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REVIEW

Spinal Cord Stimulation for Pain Treatment After Spinal Cord Injury

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Abstract In addition to restoration of bladder, bowel, and motor functions, alleviating the accompanying debilitating pain is equally important for improving the quality of life of patients with spinal cord injury (SCI). Currently, however, the treatment of chronic pain after SCI remains a largely unmet need. Electrical spinal cord stimulation (SCS) has been used to manage a variety of chronic pain conditions that are refractory to pharmacotherapy. Yet, its efficacy, benefit profiles, and mechanisms of action in SCI pain remain elusive, due to limited research, methodological weaknesses in previous clinical studies, and a lack of mechanistic exploration of SCS for SCI pain control. We aim to review recent studies and outline the therapeutic potential of different SCS paradigms for traumatic SCI pain. We begin with an overview of its manifestations, classification, potential underlying etiology, and current challenges for its treatment. The clinical evidence for using SCS in SCI pain is then reviewed. Finally, future perspectives of pre-clinical research and clinical study of SCS for SCI pain treatment are discussed.

Keywords Pain · Trauma · Spinal cord injury · Spinal cord stimulation · Neuromodulation · Analgesia

Introduction

Patients frequently develop chronic pain after traumatic spinal cord injury (SCI) as a result of maladaptive neurophysiological and neurochemical changes in the somatosensory system [1, 2]. To date, the treatment of SCI pain remains a largely unmet medical need. Since the original "gate control" theory of pain was developed in 1965 [3, 4], spinal cord stimulation (SCS) has been used for over 50 years to manage pathologic pain conditions, especially those with a neurogenic origin [4–8]. Yet, its usefulness and mechanisms of action in SCI pain are still unclear [9, 10]. The purpose of this brief review is to outline SCI pain and the therapeutic potential of different electrical SCS paradigms for its treatment. A literature search was performed in MEDLINE and PubMed on June 1, 2018. No date limits were applied and the search was limited to the English language. Both preclinical and clinical sources were included if they were related to SCI pain and SCS, using key words including pain, SCI, trauma, SCS, and analgesia. The reference lists of the sources selected were also examined to identify additional studies not found in the original search. We used discretion in this process, with preference for clinical and preclinical peer-reviewed articles in indexed medical journals.

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SCI Pain and Treatment

Manifestations of SCI Pain

SCI has devastating consequences, including a high prevalence of chronic pain and altered sensory function. Multiple classification schemes have been developed to define SCI pain in humans based on etiology, anatomical level of injury, or quality of pain. Among them, the International Spinal Cord Injury Pain Data Set [1, 2, 11] and the three-tiered framework proposed by the International Association for the Study of Pain provide general guidelines for the assessment and treatment of SCI pain [12, 13]. It has been estimated that 30%–80% of SCI patients experience chronic pain that develops unilaterally or bilaterally after injury [1, 11, 14, 15]. Strikingly, nearly one-third of SCI patients suffer severe pain [16, 17].

SCI pain can be broadly divided into nociceptive and neuropathic categories. Nociceptive pain, including dull and aching pain, can occur in various body regions and systems, such as in the musculoskeletal system due to muscle spasticity and movement, visceral organs of the abdomen or thorax due to infection or obstruction, and skin due to ulcers [1, 2, 18]. Neuropathic pain may develop in over half of SCI patients and can also occur in various regions [1, 19]. Based on the location of pain from the level of neurologic injury, neuropathic pain can be further categorized into above-level, at-level, and below-level pain [18, 20, 21]. The neuropathic pain component is often described as stabbing, sharp-electrical, shooting, or burning spontaneous pain that occurs in a region of sensory disturbance, and remains the most difficult to treat with current pharmacotherapy [22]. Severe at-level pain is common in SCI patients ($> 50\%$) and is located within the region spanning one dermatome rostral and three dermatomes caudal to the injury [23]. In addition to the common sensations of neuropathic pain, at-level pain is often accompanied by mechanical and thermal hypersensitivity (e.g., allodynia and hyperalgesia). Similar pain manifestations may also occur in dermatomes rostral and caudal to the region of at-level pain, which are classified as above-level and below-level pain, respectively. It has been reported that $\sim$ 34% of patients develop below-level pain within 5 years after injury [21], and the symptoms include both spontaneous and evoked pain. The lower extremities are the most affected by below-level pain, which develops more gradually and is associated with less dysesthesia and allodynia than at-level pain [24, 25].

Etiology

Findings from animal studies and clinical investigations of the pathogenesis of SCI pain have been extensively reviewed [14, 26–30]. Although the details are not yet completely understood, multiple neurochemical and neurophysiological changes at spinal and supraspinal levels and in the peripheral nervous system have been suggested to contribute to SCI pain [29, 31–33]. Increased neuronal excitability and gliosis in the central nervous system are frequent consequences of neurological trauma and lead to the development of persistent pain [34–36].

In animal SCI models, including contusive injuries that represent certain features of SCI in patients [37–39], it is well established that dorsal horn neurons above and below the epicenter develop spontaneous activity and increased responses to peripheral stimulation [40–42]. These neuronal changes may be due to a variety of causes, such as a loss of endogenous GABAergic inhibition, upregulation of ion channels and glutamate receptors in dorsal horn neurons, and enhanced net descending pain facilitation from supraspinal structures [28, 43–49]. Downregulation of K^+-Cl^- co-transporter type 2 (KCC2) has been shown to disinhibit spinal motor neurons and dorsal horn interneurons, and is associated with spasticity after SCI [50, 51]. A recent study demonstrated that selective expression of KCC2 in the inhibitory interneurons around staggered spinal lesions and applying a KCC2 agonist can promote functional recovery after SCI [52]. Downregulation of KCC2 may also contribute to SCI pain, so KCC2 in the spinal cord may be a promising target for pain treatment [53]. Activation of glial cells in the central nervous system also underlies spinal synaptic plasticity, such as the formation of long-term potentiation in dorsal horn neurons [35, 54, 55]. Accumulating evidence suggests that glial cells, such as microglia and astrocytes in the spinal cord, play an important role in the neuronal hyperexcitability underlying SCI pain by releasing pro-inflammatory cytokines and chemokines similar to those in peripheral neuropathic pain [14, 27, 56, 57].

In addition to these central neuronal and non-neuronal mechanisms, mounting evidence has shown that SCI pain may also stem from peripheral mechanisms, such as an increase in the spontaneous activity and excitability of dorsal root ganglia [27, 29, 33, 58, 59]. Recently, epigenetic changes, including histone modifications, DNA methylation, non-coding RNAs, and alteration of chromatin modifiers, were also suggested to contribute to SCI pain [26, 60–62]. Therefore, the etiologies of sensory dysfunction after SCI are likely multifactorial. The affected neurological structure and pathology responsible for different categories (e.g., at-level *versus* below-level pain) and symptoms (e.g., allodynia *versus* burning and ongoing pain) of SCI pain also may differ [14]. Mechanistic studies in different animal models of SCI will help to identify new drug targets and signaling pathways for innovative SCI therapy.

Current Treatment of SCI Pain

The devastating pain associated with SCI impairs quality of life, causes significant suffering, and reduces social interactions. Moreover, the lost productivity and cost of treatment generate a heavy economic burden for patients, their families, and society [1, 2, 14, 18, 63]. Pain may also exacerbate other comorbidities of SCI, as well as delaying wound healing and recovery of motor function. At times, it can lead to depression and even suicide. Accordingly, although the key focus of SCI treatment is the recovery of motor function, improvements in the secondary outcomes, especially pain, are equally important to patients [63]. Both pharmacological and non-pharmacological interventions have been tried for different manifestations of SCI pain. Unfortunately, SCI pain is often refractory to current pharmacological therapies, including opioids, antidepressants, and anticonvulsants [30, 64–67]. In addition, long-term drug treatment often leads to severe dose-limiting side-effects, such as addiction and abuse.

Neurosurgery and functional neuromodulation therapies may become important alternative strategies to alleviate pain symptoms when pharmacotherapies are ineffective or become intolerable [13, 68, 69]. Ablative neurosurgical procedures, such as thermal destruction of the dorsal horn or dorsal root entry zone, can be effective for alleviating debilitating pain in a subgroup of SCI patients. However, neurodestructive procedures are invasive and irreversible, possibly causing additional damage to the spinal cord and permanent loss of function. In addition, such procedures benefit only a small group of patients. Some patients report recurring pain even after these procedures [70, 71]. Since the discovery by Luigi Galvani in the 18th century that electricity can modulate nerve activity, various modes of functional neurostimulation therapies have been developed for improving the primary and secondary outcomes of SCI, such as regaining motor function, alleviating spasticity, triggering cough, assisting breathing, and improving bowel and bladder control [72]. Neurostimulation techniques have also been tested for pain control, including transcranial direct current stimulation, deep brain stimulation, transcranial magnetic stimulation, transcutaneous electrical nerve stimulation, and SCS [73]. Nevertheless, clinical evidence remains insufficient to suggest that "electroceuticals" are highly effective for reducing chronic pain in SCI patients [10, 72, 74, 75].

SCS Paradigms for Pain Inhibition

Conventional SCS

As functional electrical stimulation, SCS has been used to treat a variety of peripheral neurogenic and musculoskeletal pain conditions and to improve the quality of life in patients [76–78]. Currently, three major stimulation paradigms or waveforms have been used for pain management. Conventional SCS was the first developed for pain treatment [79] and was based on the seminal "gate control" theory of pain proposed by Wall and Melzak in 1965 [4, 80]. Conventional SCS delivers mild electrical pulses through epidural electrodes to activate dorsal column fibers at an optimal frequency of 30 Hz–60 Hz [7, 8, 77]. Stimulation of low-threshold afferent fibers (Aβ-fibers) in the dorsal column elicits paresthesia (i.e., supra-sensory threshold). At this intensity, the stimulation activates spinal inhibitory interneurons and other endogenous inhibitory mechanisms to attenuate nociceptive transmission, so-called "closing the gate" [4, 80]. This remains the mainstay of SCS pain therapy, with $>$ 40,000 systems implanted worldwide every year [5, 7, 81, 82]. A large portion of the analgesic effect produced by conventional SCS is mediated through the dorsal column. Conventional SCS produces robust activation in dorsal column nuclei at an intensity that inhibits neuropathic pain after nerve injury in rats [77, 83–85]. In addition to the classical pain gating mechanisms underlying the inhibition by conventional SCS, other spinal mechanisms may also involve the activation of nearby descending pain-inhibitory pathways, inducing inhibitory postsynaptic potentials in dorsal horn neurons by a synchronized antidromic dorsal column volley [86], and the facilitation of primary afferent depolarization, which elicits the presynaptic inhibition of afferent inputs [87]. Thus, the mechanisms of pain inhibition by conventional SCS involve spinal, supraspinal, and, potentially, peripheral mechanisms (Fig. 1).

New SCS Paradigms

The efficacy of conventional SCS for chronic pain has remained suboptimal during the past several decades. Only 50%–60% of patients respond to initial trial stimulation (defined as $>$ 50% pain reduction). Further, only a portion of these selected patients experience pain relief by SCS [88–91]. Burst SCS (bursts of 5 pulses with an internal frequency 500 Hz) applied at 40 Hz was developed as an alternative to conventional SCS [92–94]. Burst SCS can attenuate pain without eliciting paresthesia and may induce better neuropathic pain inhibition than conventional SCS [92–96]. In animal studies, burst SCS was found to be more efficacious than conventional SCS at attenuating visceral nociception [97] and improving the hyperalgesia and physical activity after nerve injury [98]. Nevertheless, clinical evidence to support the use of burst SCS for managing chronic intractable pain is still insufficient [95]. High-frequency, paresthesia-free SCS (10,000 Hz) [83, 99–105] has emerged as another paradigm that has

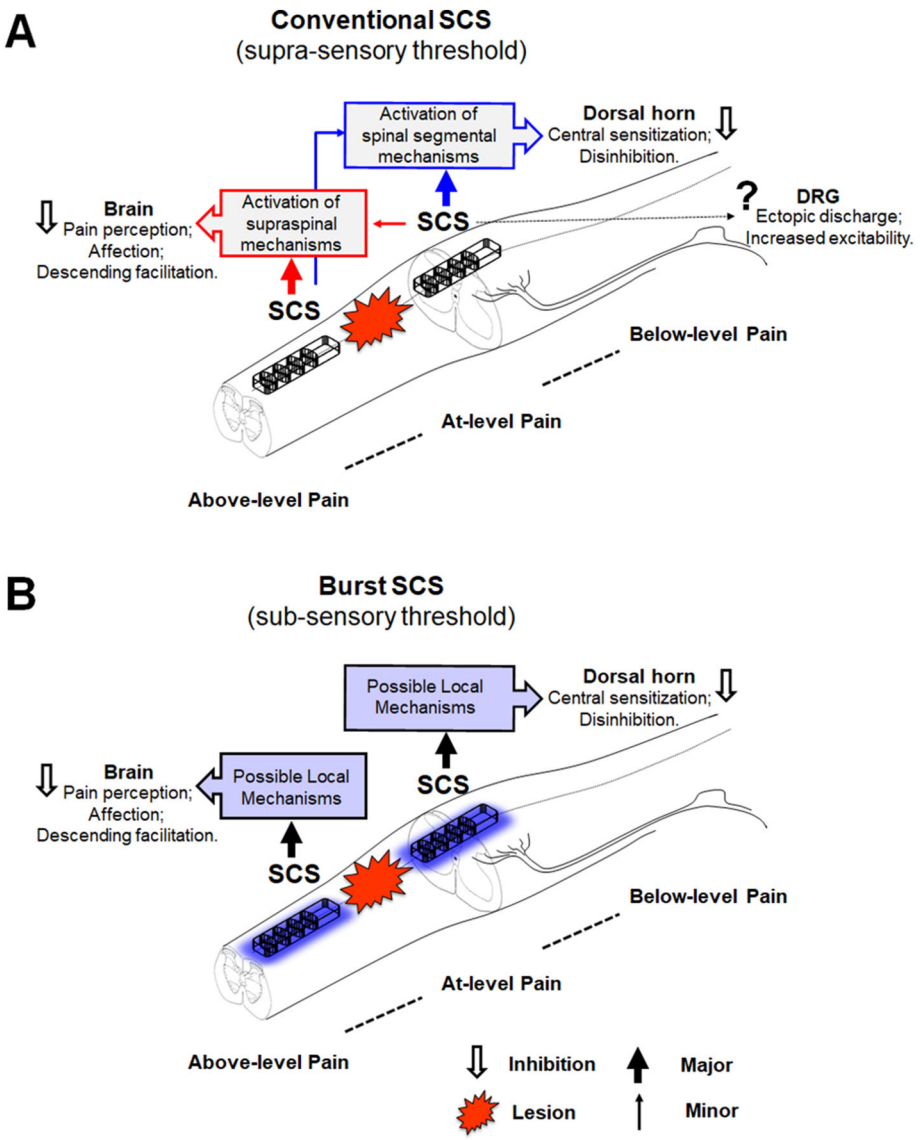

Fig. 1 Schematic illustrating hypothetical mechanisms that may contribute to pain inhibition by spinal cord stimulation (SCS) after spinal cord injury (SCI). **A** Conventional tonic SCS activates Aβ fibers in the dorsal column and induces paresthesia (supra-sensory threshold). The antidromic action potentials trigger a segmental inhibitory mechanism *via* collateral branches. The orthodromic action potentials may activate supraspinal inhibitory mechanisms. Conventional SCS distal (caudal) to the lesion (epicenter) may attenuate below-level and at-level pain rather than above-level pain, primarily by activating segmental mechanisms. The pain inhibition may also involve supraspinal mechanisms if cord transection is incomplete. Conventional SCS proximal (rostral) to the lesion may attenuate above-level and at-level pain by activating supraspinal mechanisms. It remains unclear whether conventional SCS attenuates the increased excitability of peripheral sensory neurons after SCI. **B** Burst SCS at low intensity may not activate dorsal column fibers and induce paresthesia (subsensory threshold). It may progressively generate a weak electrical field that affects the superficial dorsal horn and suppresses sensory information that is integrated and modified at the central terminals of afferent fibers and at the synaptic junctions of dorsal horn neurons, prior to their dispatch to supraspinal centers. Thus, it may attenuate pain without sensory perception. Burst SCS applied distal to the lesion may attenuate below-level and at-level pain, whereas application proximal to the lesion may attenuate above-level and at-level pain, both through unknown local mechanisms.

further improved the clinical outcomes for neuropathic pain. Intriguingly, high-frequency, paresthesia-free SCS can induce pain relief in patients who do not respond well to conventional SCS (non-responders), and its ability to inhibit mechanical hypersensitivity is equal to or greater than that of conventional SCS [78, 83]. At least one clinical trial has shown that 10,000 Hz SCS therapy is superior to conventional SCS in the long-term treatment of back and leg pain [99]. Currently, details about the neuronal substrates and cellular and neurochemical mechanisms that underlie pain inhibition by SCS are only partially understood, especially as they relate to burst and high-

frequency SCS [77, 81, 84, 92]. Importantly, the high-frequency paradigm at the sub-sensory threshold therapeutic intensity may not activate neurons in the dorsal column nuclei [83], and does not activate or change the conduction properties of dorsal column fibers in the same experimental setting, which are in line with findings from recording of single dorsal column axons during high-frequency SCS in rats [106]. Like high-frequency SCS, burst SCS does not increase activity in dorsal column nuclei [97]. Mounting evidence suggests that the modes of action, such as inhibition of pain-processing dorsal horn neurons and activation of endogenous GABAergic inhibition, differ among conventional, burst, and high-frequency SCS [78, 92, 97, 107].

SCS in SCI Pain

Conventional SCS

Conventional SCS has been used for several decades in SCI patients to help them regain motor control below the level of the lesion, improve bone and muscle health, and attenuate spasticity [10, 108–110]. Depending on the parameters and spinal level at which stimulation is applied, SCS may also have other therapeutic actions, including regulating the functions of various organ systems [111–115] and helping to restore cough with cervical SCI [116, 117].

Conventional SCS was the first paradigm applied to control pain in SCI patients [8]. The initial reports from early studies in the 1970s–1990s were encouraging (Table 1). In the first study, which included seven patients with traumatic injury-induced SCI from spinal fractures (5), a gunshot wound (1), and spinal cord contusion (1), 26.7% reported excellent pain relief and 13.3% reported good pain relief after SCS [118]. In a later study, SCS produced good pain relief (mean analgesia 68.2%) in 6 of 15 patients with incomplete traumatic SCI [119], and induced excellent pain inhibition in 6 of 7 paraplegic SCI patients with a 6-year retrospective follow-up [120]. In addition, 43.7% of 16 patients who had paraplegic pain associated with incomplete traumatic SCI reported satisfactory pain relief [121]. In another study of the clinical efficacy of SCS, 9 of 11 SCI patients with painful symptoms benefited from initial trial treatment and proceeded to permanent implants [122]. In a larger cohort of 127 SCI patients, 65% of whom had traumatic SCI, 35 received SCS treatment [123]. In that study, an analysis based on the level and severity of injury showed that conventional SCS may be more effective for reducing pain in patients with incomplete SCI, as 6 of 24 patients who showed good pain relief (decrease in pain of at least 50%) from SCS had incomplete lesions. In contrast, those with complete SCI responded poorly to conventional SCS. Accordingly, the authors suggested that patients with incomplete SCI lesions at low thoracic to upper lumbar levels may benefit from conventional SCS. This notion was supported by findings from a later study, which showed that incomplete SCI at the thoracic level, and paraplegic pain from spasm or contracture are positive prognostic factors for conventional SCS treatment [124]. In a study of pain patients with different etiologies, 55 Hz–60 Hz SCS was found to successfully control pain in 4 of 10 SCI patients [125]. Although the common frequencies of SCS used for pain treatment in these studies ranged from 40 Hz to 60 Hz, low-frequency (1.6 Hz–8 Hz) SCS was also shown to effectively inhibit pain in 5 of 12 SCI patients with lower-extremity pain [126].

In a recent study by Levine *et al.* [127], cervical SCS provided meaningful long-term relief of neuropathic pain in the upper limbs of 15 SCI patients. Permanent SCS leads were implanted above the level of SCI but at the level corresponding to the dermatomal distribution of pain in 11 of these patients, based on a decrease in the pain score on a visual analogue scale. Compared to baseline, patients treated with cervical SCS showed significant improvements in average pain scores at 12 months, with the majority exhibiting pain relief and reduced opioid use. The mechanisms of pain relief by this cervical SCS remain unclear, but modulation of residual spinothalamic tract function may play a role. Pain after traumatic brachial plexus injury (BPI) may share certain features of SCI pain. The pathogenesis of BPI involves central mechanisms and sensitization of superficial dorsal horn neurons secondary to traumatic afferent disconnection of the nerve roots. As with SCI pain, BPI pain is often resistant to pharmacotherapy. Intriguingly, conventional SCS has been shown to produce good pain relief, improve the quality of life, and significantly reduce drug usage in a subgroup of BPI patients [128].

Nevertheless, other clinical studies have suggested that the efficacy of conventional SCS for SCI pain may be suboptimal, and long-term clinical outcomes remain unclear [10]. In general, patients with SCI are much less responsive to conventional SCS than those with failed back surgery pain syndromes or neuropathic pain with a peripheral origin. For example, the results of SCS in 10 SCI patients with intractable pain were unsatisfactory, in contrast to the good outcome of nine patients with intractable post-amputation or post-traumatic neuroma pain [129]. A review of 27 clinical studies conducted in 2009 found the results of conventional SCS treatment for SCI pain to be "disappointing", with only a 30%–40% success rate. The authors further concluded that "there is no significant level of proof to recommend the use of this technique in this indication" [74]. In a large-scale survey

Table 1 Summary of major clinical studies of spinal cord stimulation (SCS) in pain control after spinal cord injury (SCI).

Study	SCI Injury Level	SCI Injury Severity	SCS Parameters	SCS Level	Outcomes and Comments
Nashold Jr. and Friedman, 1972 [118]	Not mentioned	4 complete, 3 transient Pain centered in low back/leg Severe aching or burning pain	15 Hz–200 Hz, 0.2 ms, 0.5–3 V	Thoracic level	26.7% excellent relief of pain 13.3% good relief of pain 16.7% fair result 40 Hz–50 Hz for best outcome
Buchhaas et al., 1989 [120]	T10–11 L1	2 complete 5 incomplete Pain in lower limbs	Not mentioned	Mid-thoracic region (3) Conus and epiconus (4)	6 responders/7 patients Up to 6-year follow-up
Meglio *et al.*, 1989 [121]	Not mentioned	15 incomplete Traumatic injury	85 Hz, 0.21 ms, Cycle on: 64 s; off: 1 min–4 min 20 min–30 min, 2–3 times a day	C6–T1: upper-extremity pain T9–T11: lower-extremity pain	6 responders/15 at initial test period 4 responders/7, 3 months 3 responders/4, 6 months
Tasker *et al.*, 1992 [123]	Cervical T1–9 T10–L2	11 complete 22 incomplete	Not mentioned	Not mentioned	Incomplete SCI: 6/22, good relief of steady pain; 3/22, fair relief of steady pain; 3/22, fair relief of evoked pain Complete SCI: 2/11, fair relief of steady pain Effective for evoked pain in 25% of patients with incomplete lesions and 0% with complete lesions. More benefit for T10–L2 injury
Shimoji *et al.*, 1993 [126]	Not mentioned	Not mentioned Pain in lower extremities	1.6 Hz–8.0 Hz, 0.5 V–5.0 V, adjusted by the patient	Not mentioned	5 responders/12
North *et al.*, 1993 [122]	Not mentioned	Not mentioned	Not mentioned	Not mentioned	9 responders/11 proceeded to permanent implants. Long-term response rate unavailable
Cioni *et al.*, 1995 [124]	C1–7 (5) T1–11 (9) T12–L1 (11)	6 complete 19 incomplete	85 Hz, 0.21 ms, comfortable paresthesia intensity, 30 min, every 3 h	17, above SCI 8, below SCI	9 responders/25 at initial treatment period (all incomplete SCI) Response rate: burning pain (28.6%), painful spasm (75%), constrictive (50%), tearing (33%), allodynia (28.5%) 3-year follow-up responder rate (18%)
Kumar *et al.*, 1998 [125]	Not mentioned	Not mentioned	55 Hz–60 Hz, 0.21 ms–0.3 ms, 1.5 V–6.0 V Cycle on: 1 min; off: 10 min	C5–T1 for upper limb pain T9–T11 for extremity pain	4 responders/10 during trial period 2 responders/4 at long-time follow-up
Levine *et al.*, 2017 [127]	Cervical	Not mentioned	0.25 ms–0.7 ms pulse width, other parameters not mentioned	Cervical	6/9 mean VAS pain score dropped from 7.8 (± 1.2) to 2.7 (± 0.6) at 12-month follow-up (VAS decreased ≥ 50%)
Reck and Landmann, 2017 [135]	T5	Complete Severe pain in both legs and feet	Burst of 40 Hz with intra-burst frequency 500 Hz, each pulse 1 ms	T11–L1 (below lesion)	1 responder/1 at 3 months

VAS visual analogue scale.

of 1100 SCI patients, the improvement in pain scores after SCS (1.67–1.78) was weaker than that reported for opioids (3.08–3.47) or even physical therapy (2.87–3.06) [68]. The long-term outcomes of SCS for SCI pain from the limited number of studies are not promising. In a study by Cioni *et al.* [124] 9 of 25 SCI patients with chronic pain initially reported at least a 50% reduction in pain after SCS, but the success rate decreased to below 20% at 3-year follow-up.

The reasons for the discrepancies between different studies of SCS in SCI pain control are unclear, but it can be postulated that the efficacy of conventional SCS for inhibiting SCI pain may depend on the proximity of SCS to the lesion site and the number of residual fibers and other neuronal substrates within the injured cord (Fig. 1A). Both segmental and supraspinal mechanisms are important to the effectiveness of conventional SCS [7, 77, 84, 130]. Accordingly, conventional SCS-induced pain inhibition requires the activation of dorsal column structures and intact afferent pathways for pain transmission from the peripheral to the central nervous system [77, 84, 131, 132]. However, injury to the spinal cord and subsequent anatomical and pathological changes after a spinal cord lesion may disrupt this anatomical connection and functional integrity [133, 134], in part because the essential neuronal substrates and circuits through which conventional SCS attenuates pain may be damaged or lost. In other words, if the important "pain gating" mechanisms activated by SCS are impaired, the ascending pain signal cannot be prevented, especially when SCS is applied above (rostral) the lesion epicenter (Fig. 1A). This reasoning may also explain why conventional SCS induces better pain relief in patients with an incomplete cord lesion than in those with complete cord transection [123, 124].

New SCS

SCS technology has undergone continuous development and refinement since the 1960s, especially in the past two decades with the development of high-frequency (kilohertz) and burst paradigms. Although the evidence so far suggests only little-to-moderate success of conventional SCS for SCI pain control, the new paradigms may provide an opportunity for SCI pain treatment. A recent case report described a 53-year-old woman with complete paraplegia at T5 who achieved a reduction in below-level pain with the application of burst SCS [135]. When applied at T11–L1, SCS with a burst pattern significantly reduced both the frequency and intensity of severe pain present in both the lower legs and feet. The therapeutic effects lasted for at least 3 months of follow-up. Thus, new paradigms of SCS might be effective for below-level pain, even in cases of complete paraplegia [135]. The mechanism of pain inhibition by burst SCS in SCI pain remains unknown (Fig. 1B). In addition, to our knowledge, no preclinical or clinical study has examined the efficacy of high-frequency, paresthesia-free SCS for SCI pain. Therefore, the utility and selection indications of different SCS paradigms need further investigation in randomized controlled trials with adequate sample sizes and methodology.

Risks and Complications

SCS is considered to be a safe and reversible pain therapy. The associated risks and common complications are generally minor, as suggested by recent reviews of the clinical literature [136, 137]. The common complications of SCS include lead migration, lead fracture and malfunction, implantation and device-related discomfort and pain, dura damage, infection, and skin erosion. Severe complications such as neurological injury, large epidural hematomas, paralysis, and motor deficits are not common [136, 138, 139]. In a recent study that compared 10,000 Hz high-frequency and conventional SCS, the complication rates were comparable in the two groups, and no major neurologic deficit was reported [99]. Because of severe neurological damage to the spinal cord and functional impairment after spinal trauma, SCI patients have a higher risk of the above common complications of SCS compared to other patient populations. Accordingly, extra caution and special care should be taken into consideration for surgical implantation and treatment with SCS in SCI patients. Nevertheless, no major complications or adverse effects have been reported in SCI patients after the treatment [74, 140, 141], supporting its safety and feasibility for pain control.

Future Perspectives

Preclinical Research

Developing effective functional neuromodulatory therapies for alleviating pain in SCI patients requires neurophysiological and neurochemical studies in animal models of SCI pain. SCI neuropathic pain is often referred to as "central pain", which differs from pain caused by injuries to the peripheral nervous system, but our knowledge of the underlying mechanisms is incomplete [14, 61]. The field of SCS is expanding rapidly, with new waveform paradigms that may induce pain inhibition through different mechanisms of action [5, 7, 84]. So far, evidence for the modulation of pain transmission and pain behavior by different paradigms of SCS in animal models of SCI is scarce. Well-designed preclinical studies are essential to provide a rationale for using SCS in the clinic. Emerging technologies, such as *in vivo* high-throughput calcium imaging of sensory neurons [142, 143], optogenetics

[144–146], and computational modeling [147, 148] may help us to gain a better understanding of pain mechanisms after SCI, as well as the biological basis underlying the efficacy of pain inhibition by conventional, burst, and high-frequency SCS.

The correlates of behavioral outcome measures from animal studies of SCI pain with humans need to be better understood. SCI pain-related behavior in animal models has commonly been inferred from observations of evoked reflex withdrawal responses to external tactile and thermal stimulation [38, 149, 150]. However, SCI patients frequently experience ongoing pain, which may have complex underlying mechanisms and require different treatment strategies from those of evoked sensory hypersensitivity [151, 152]. Accordingly, SCS should be studied comprehensively in experimental paradigms that also assess the efficacy by which they inhibit ongoing pain and improve the affective component of chronic pain. Several rodent models have been developed and applied to SCI studies. Among them, the contusion injury model mimics SCI in patients and has been widely used to examine the etiologies of motor and sensory dysfunctions after SCI [37–39, 153]. The effectiveness of SCS on SCI pain shall continue to be explored along with the mechanisms underlying its effect in different animal models. The knowledge gained from future preclinical studies should help researchers to identify the appropriate indications and develop new paradigms and modalities of SCS to manage this difficult pain condition. The hypothetical mechanisms by which conventional and burst SCS inhibit SCI pain are illustrated in Figure 1.

Clinical Studies

Compared to the large number of studies on SCS in the treatment of neuropathic pain with a peripheral origin [154], evidence regarding its efficacy for alleviating central neuropathic pain after SCI remains limited [13, 155]. The criteria and indications for using SCS, and the optimal placement of SCS leads are also not clear for SCI pain. Moreover, it is not fully understood why SCS is effective in some SCI patients but not in others. Improving the technique and selection of patients for treatment will depend on understanding the reasons for both successes and failures. It is also unknown whether different waveforms or paradigms of SCS differentially modify pain manifestations in SCI patients. Because different paradigms of SCS inhibit pain through different mechanisms, they may yield a range of effects for various manifestations and categories of SCI pain. For example, we still need to determine how different SCS paradigms affect the neuropathic and nociceptive components of SCI pain in patients. This knowledge will help us to define the use of each technique and potential applications. The paresthesia-free burst and high-frequency SCS paradigms, if effective, would expand the use of SCS and benefit patients who are not responsive to conventional SCS. The potential side-effect profiles, limitations, loss of efficacy over time, and complications associated with surgical implantation and SCS must also be carefully considered and monitored in SCI patients and will be critical for establishing long-term efficacy and safety.

Owing to the substantial anatomical and pathological changes that occur after traumatic SCI, SCS treatment may need to be tailored for each patient, based on their residual neuronal substrates and functional status, in order to obtain the optimal therapeutic effect. A recent functional magnetic resonance imaging (fMRI) study conducted in traumatic SCI patients with cervical (n = 14) and upper thoracic (n = 2) injuries suggested that the change in pain processing and connectivity between different brain regions varies substantially across different SCI patients. Thus, fMRI imaging may provide sensitive indicators of an individual patient's pain status and perhaps could be used to characterize changes in pain-processing in patients after treatment [156]. In addition to testing different epidural SCS paradigms available for SCI pain, researchers may also determine whether directly targeting the pain generators within the spinal cord, such as by delivering subdural stimulation or intra-spinal stimulation, might be used as an alternative strategy to treat SCI pain [9, 157–159]. Subdural or intra-spinal stimulation may have increased target selectivity and stimulation efficiency compared to epidural stimulation [157, 159] for at-level and below-level pain, when other approaches are ineffective. Other neurostimulation modalities, such as oscillating spinal field stimulation, may also alleviate pain and promote spinal cord healing and neurologic recovery in SCI patients [160].

Conclusions

In light of the tremendous suffering associated with SCI, the development of new non-pharmacologic strategies to alleviate chronic pain and improve the quality of life for SCI patients deserves immediate attention and encouragement. The use of SCS has been shown to reduce opioid use and improve function in patients with other pain conditions, a very important consideration in light of the current epidemic of opioid addiction and abuse [161]. Unlike pharmacotherapy, SCS lacks systemic side-effects, and compared to neuroablation, SCS is adjustable and reversible. These features make SCS promising in the treatment of SCI pain. However, its effectiveness and benefit profiles are not well established, in part because of methodological weaknesses in the available clinical studies, and a lack of

mechanistic studies of SCS for SCI pain. Knowledge gained from studies in experimental animals will provide the rationale for subsequent studies in humans to establish clinical uses of SCS for SCI pain. Accordingly, significant opportunities remain to improve the clinical treatment of SCI pain with different SCS paradigms, but efforts will require multidisciplinary collaborations with clinical, neurophysiological, and biomedical engineering expertise.

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Conflict of interest The authors declare no conflict of interest.

References

1. Widerstrom-Noga E. Neuropathic pain and spinal cord injury: phenotypes and pharmacological management. Drugs 2017, 77: 967–984.
2. Widerstrom-Noga E, Felix ER, Adcock JP, Escalona M, Tibbett J. Multidimensional neuropathic pain phenotypes after spinal cord injury. J Neurotrauma 2016, 33: 482–492.
3. Melzack R, Wall PD. Evolution of pain theories. Int Anesthesiol Clin 1970, 8: 3–34.
4. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965, 150: 971–979.
5. Chakravarthy K, Richter H, Christo PJ, Williams K, Guan Y. Spinal cord stimulation for treating chronic pain: reviewing preclinical and clinical data on paresthesia-free high-frequency therapy. Neuromodulation 2018, 21: 10–18.
6. Geurts JW, Joosten EA, van Kleef KM. Current status and future perspectives of spinal cord stimulation in treatment of chronic pain. Pain 2017, 158: 771–774.
7. Linderoth B, Foreman RD. Conventional and novel spinal stimulation algorithms: hypothetical mechanisms of action and comments on outcomes. Neuromodulation 2017, 20: 525–533.
8. Shealy CN, Mortimer JT, Hagfors NR. Dorsal column electroanalgesia. J Neurosurg 1970, 32: 560–564.
9. Shu B, Yang F, Guan Y. Intra-spinal microstimulation may alleviate chronic pain after spinal cord injury. Med Hypotheses 2017, 104: 73–77.
10. Chari A, Hentall ID, Papadopoulos MC, Pereira EA. Surgical neurostimulation for spinal cord injury. Brain Sci 2017, 7: 18–35.
11. Widerstrom-Noga E, Biering-Sorensen F, Bryce TN, Cardenas DD, Finnerup NB, Jensen MP *et al.* The International Spinal Cord Injury Pain Basic Data Set (version 2.0). Spinal Cord 2014, 52: 282–286.
12. Bryce TN, Ragnarsson KT. Pain after spinal cord injury. Phys Med Rehabil Clin N Am 2000, 11: 157–168.
13. Bryce TN, Budh CN, Cardenas DD, Dijkers M, Felix ER, Finnerup NB, *et al.* Pain after spinal cord injury: an evidence-based review for clinical practice and research. Report of the National Institute on Disability and Rehabilitation Research Spinal Cord Injury Measures meeting. J Spinal Cord Med 2007, 30: 421–440.
14. Shiao R, Lee-Kubli CA. Neuropathic pain after spinal cord injury: challenges and research perspectives. Neurotherapeutics 2018, 15: 635–653.
15. Attal N, Mazaltarine G, Perrouin-Verbe B, Albert T. Chronic neuropathic pain management in spinal cord injury patients. What is the efficacy of pharmacological treatments with a general mode of administration? (oral, transdermal, intravenous). Ann Phys Rehabil Med 2009, 52: 124–141.
16. Dijkers M, Bryce T, Zanca J. Prevalence of chronic pain after traumatic spinal cord injury: a systematic review. J Rehabil Res Dev 2009, 46: 13–29.
17. Widerstrom-Noga E, Biering-Sorensen F, Bryce T, Cardenas DD, Finnerup NB, Jensen MP, *et al.* The international spinal cord injury pain basic data set. Spinal Cord 2008, 46: 818–823.
18. Widerstrom-Noga E, Biering-Sorensen F, Bryce TN, Cardenas DD, Finnerup NB, Jensen MP, *et al.* The International Spinal Cord Injury Pain Extended Data Set (Version 1.0). Spinal Cord 2016, 54: 1036–1046.
19. Burke D, Fullen BM, Stokes D, Lennon O. Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis. Eur J Pain 2017, 21: 29–44.
20. Wieseler J, Ellis AL, McFadden A, Brown K, Starnes C, Maier SF, *et al.* Below level central pain induced by discrete dorsal spinal cord injury. J Neurotrauma 2010, 27: 1697–1707.
21. Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain 2003, 103: 249–257.
22. Siddall PJ, Loeser JD. Pain following spinal cord injury. Spinal Cord 2001, 39: 63–73.
23. Bryce TN, Biering-Sorensen F, Finnerup NB, Cardenas DD, Defrin R, Lundeberg T, *et al.* International spinal cord injury pain classification: part I. Background and description. March 6–7, 2009. Spinal Cord 2012, 50: 413–417.
24. Modirian E, Pirouzi P, Soroush M, Karbalaei-Esmaeili S, Shojaei H, Zamani H. Chronic pain after spinal cord injury: results of a long-term study. Pain Med 2010, 11: 1037–1043.
25. Finnerup NB, Jensen MP, Norrbrink C, Trok K, Johannesen IL, Jensen TS, *et al.* A prospective study of pain and psychological functioning following traumatic spinal cord injury. Spinal Cord 2016, 54: 816–821.
26. Penas C, Navarro X. Epigenetic modifications associated to neuroinflammation and neuropathic pain after neural trauma. Front Cell Neurosci 2018, 12: 158.
27. Walters ET. Neuroinflammatory contributions to pain after SCI: roles for central glial mechanisms and nociceptor-mediated host defense. Exp Neurol 2014, 258: 48–61.
28. Yezierski RP. Spinal cord injury pain: spinal and supraspinal mechanisms. J Rehabil Res Dev 2009, 46: 95–107.
29. Hulsebosch CE, Hains BC, Crown ED, Carlton SM. Mechanisms of chronic central neuropathic pain after spinal cord injury. Brain Res Rev 2009, 60: 202–213.
30. Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine (Phila Pa 1976) 2001, 26: S146–S160.
31. Yezierski RP, Yu CG, Mantyh PW, Vierck CJ, Lappi DA. Spinal neurons involved in the generation of at-level pain following spinal injury in the rat. Neurosci Lett 2004, 361: 232–236.
32. Gwak YS, Hulsebosch CE. Neuronal hyperexcitability: a substrate for central neuropathic pain after spinal cord injury. Curr Pain Headache Rep 2011, 15: 215–222.
33. Carlton SM, Du J, Tan HY, Nesic O, Hargett GL, Bopp AC, *et al.* Peripheral and central sensitization in remote spinal cord regions contribute to central neuropathic pain after spinal cord injury. Pain 2009, 147: 265–276.
34. Gosselin RD, Suter MR, Ji RR, Decosterd I. Glial cells and chronic pain. Neuroscientist 2010, 16: 519–531.

35. Zhou LJ, Liu XG. Glial activation, a common mechanism underlying spinal synaptic plasticity? Neurosci Bull 2017, 33: 121–123.
36. Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? Pain 2013, 154 Suppl 1: S10–S28.
37. Kerasidis H, Wrathall JR, Gale K. Behavioral assessment of functional deficit in rats with contusive spinal cord injury. J Neurosci Methods 1987, 20: 167–179.
38. Vierck CJ Jr, Siddall P, Yezierski RP. Pain following spinal cord injury: animal models and mechanistic studies. Pain 2000, 89: 1–5.
39. Yezierski RP, Liu S, Ruenes GL, Kajander KJ, Brewer KL. Excitotoxic spinal cord injury: behavioral and morphological characteristics of a central pain model. Pain 1998, 75: 141–155.
40. Meisner JG, Marsh AD, Marsh DR. Loss of GABAergic interneurons in laminae I-III of the spinal cord dorsal horn contributes to reduced GABAergic tone and neuropathic pain after spinal cord injury. J Neurotrauma 2010, 27: 729–737.
41. Kalous A, Osborne PB, Keast JR. Spinal cord compression injury in adult rats initiates changes in dorsal horn remodeling that may correlate with development of neuropathic pain. J Comp Neurol 2009, 513: 668–684.
42. Hao JX, Kupers RC, Xu XJ. Response characteristics of spinal cord dorsal horn neurons in chronic allodynic rats after spinal cord injury. J Neurophysiol 2004, 92: 1391–1399.
43. Zhao P, Waxman SG, Hains BC. Modulation of thalamic nociceptive processing after spinal cord injury through remote activation of thalamic microglia by cysteine cysteine chemokine ligand 21. J Neurosci 2007, 27: 8893–8902.
44. Hains BC, Saab CY, Waxman SG. Alterations in burst firing of thalamic VPL neurons and reversal by Na(v)1.3 antisense after spinal cord injury. J Neurophysiol 2006, 95: 3343–3352.
45. Gwak YS, Kim HK, Kim HY, Leem JW. Bilateral hyperexcitability of thalamic VPL neurons following unilateral spinal injury in rats. J Physiol Sci 2010, 60: 59–66.
46. Crown ED, Gwak YS, Ye Z, Johnson KM, Hulsebosch CE. Activation of p38 MAP kinase is involved in central neuropathic pain following spinal cord injury. Exp Neurol 2008, 213: 257–267.
47. Hains BC, Waxman SG. Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. J Neurosci 2006, 26: 4308–4317.
48. Gwak YS, Hulsebosch CE. Upregulation of group I metabotropic glutamate receptors in neurons and astrocytes in the dorsal horn following spinal cord injury. Exp Neurol 2005, 195: 236–243.
49. Hains BC, Saab CY, Klein JP, Craner MJ, Waxman SG. Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury. J Neurosci 2004, 24: 4832–4839.
50. Boulenguez P, Liabeuf S, Bos R, Bras H, Jean-Xavier C, Brocard C, *et al.* Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. Nat Med 2010, 16: 302–307.
51. Liabeuf S, Stuhl-Gourmand L, Gackiere F, Mancuso R, Sanchez Brualla I, Marino P, *et al.* Prochlorperazine increases KCC2 function and reduces spasticity after spinal cord injury. J Neurotrauma 2017, 34: 3397–3406.
52. Chen B, Li Y, Yu B, Zhang Z, Brommer B, Williams PR, *et al.* Reactivation of dormant relay pathways in injured spinal cord by KCC2 manipulations. Cell 2018, 174: 521–535.
53. Tashiro S, Shinozaki M, Mukaino M, Renault-Mihara F, Toyama Y, Liu M, *et al.* BDNF induced by treadmill training contributes to the suppression of spasticity and allodynia after spinal cord injury via upregulation of KCC2. Neurorehabil Neural Repair 2015, 29: 677–689.
54. Filosa A, Paixao S, Honsek SD, Carmona MA, Becker L, Feddersen B, *et al.* Neuron-glia communication via EphA4/ephrin-A3 modulates LTP through glial glutamate transport. Nat Neurosci 2009, 12: 1285–1292.
55. Kronschlager MT, Drdla-Schutting R, Gassner M, Honsek SD, Teuchmann HL, Sandkuhler J. Gliogenic LTP spreads widely in nociceptive pathways. Science 2016, 354: 1144–1148.
56. Gwak YS, Kang J, Unabia GC, Hulsebosch CE. Spatial and temporal activation of spinal glial cells: role of gliopathy in central neuropathic pain following spinal cord injury in rats. Exp Neurol 2012, 234: 362–372.
57. Kim D, Kim MA, Cho IH, Kim MS, Lee S, Jo EK, *et al.* A critical role of toll-like receptor 2 in nerve injury-induced spinal cord glial cell activation and pain hypersensitivity. J Biol Chem 2007, 282: 14975–14983.
58. Hains BC, Waxman SG. Sodium channel expression and the molecular pathophysiology of pain after SCI. Prog Brain Res 2007, 161: 195–203.
59. Bedi SS, Yang Q, Crook RJ, Du J, Wu Z, Fishman HM, *et al.* Chronic spontaneous activity generated in the somata of primary nociceptors is associated with pain-related behavior after spinal cord injury. J Neurosci 2010, 30: 14870–14882.
60. Miranpuri GS, Meethal SV, Sampene E, Chopra A, Buttar S, Nacht C, *et al.* Folic acid modulates matrix metalloproteinase-2 expression, alleviates neuropathic pain, and improves functional recovery in spinal cord-injured rats. Ann Neurosci 2017, 24: 74–81.
61. Schomberg D, Miranpuri G, Duellman T, Crowell A, Vemuganti R, Resnick D. Spinal cord injury induced neuropathic pain: Molecular targets and therapeutic approaches. Metab Brain Dis 2015, 30: 645–658.
62. Descalzi G, Ikegami D, Ushijima T, Nestler EJ, Zachariou V, Narita M. Epigenetic mechanisms of chronic pain. Trends Neurosci 2015, 38: 237–246.
63. Turtle JD, Strain MM, Aceves M, Huang YJ, Reynolds JA, Hook MA, *et al.* Pain input impairs recovery after spinal cord injury: treatment with lidocaine. J Neurotrauma 2017, 34: 1200–1208.
64. Ravenscroft A, Ahmed YS, Burnside IG. Chronic pain after SCI. A patient survey. Spinal Cord 2000, 38: 611–614.
65. Baastrup C, Finnerup NB. Pharmacological management of neuropathic pain following spinal cord injury. CNS Drugs 2008, 22: 455–475.
66. Mehta S, McIntyre A, Janzen S, Loh E, Teasell R. Systematic review of pharmacologic treatments of pain after spinal cord injury: an update. Arch Phys Med Rehabil 2016, 97: 1381–1391.
67. Teasell RW, Mehta S, Aubut JA, Foulon B, Wolfe DL, Hsieh JT, *et al.* A systematic review of pharmacologic treatments of pain after spinal cord injury. Arch Phys Med Rehabil 2010, 91: 816–831.
68. Warms CA, Turner JA, Marshall HM, Cardenas DD. Treatments for chronic pain associated with spinal cord injuries: many are tried, few are helpful. Clin J Pain 2002, 18: 154–163.
69. Cardenas DD, Felix ER. Pain after spinal cord injury: a review of classification, treatment approaches, and treatment assessment. PM R 2009, 1: 1077–1090.
70. Sjolund BH. Pain and rehabilitation after spinal cord injury: the case of sensory spasticity? Brain Res Brain Res Rev 2002, 40: 250–256.
71. Canavero S, Bonicalzi V. Neuromodulation for central pain. Expert Rev Neurother 2003, 3: 591–607.
72. Sadowsky CL. Electrical stimulation in spinal cord injury. NeuroRehabilitation 2001, 16: 165–169.
73. Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, *et al.* Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013, 154: 2249–2261.

74. Lagauche D, Facione J, Albert T, Fattal C. The chronic neuropathic pain of spinal cord injury: which efficiency of neuropathic stimulation? Ann Phys Rehabil Med 2009, 52: 180–187.
75. Siddall PJ. Management of neuropathic pain following spinal cord injury: now and in the future. Spinal Cord 2009, 47: 352–359.
76. Kumar K, Toth C, Nath RK. Spinal cord stimulation for chronic pain in peripheral neuropathy. Surg Neurol 1996, 46: 363–369.
77. Guan Y. Spinal cord stimulation: neurophysiological and neurochemical mechanisms of action. Curr Pain Headache Rep 2012, 16: 217–225.
78. Shechter R, Yang F, Xu Q, Cheong YK, He SQ, Sdrulla A, *et al.* Conventional and kilohertz-frequency spinal cord stimulation produces intensity- and frequency-dependent inhibition of mechanical hypersensitivity in a rat model of neuropathic pain. Anesthesiology 2013, 119: 422–432.
79. Shealy CN. Dorsal column stimulation. Surg Neurol 1977, 7: 192.
80. Costigan M, Woolf CJ. No DREAM, No pain. Closing the spinal gate. Cell 2002, 108: 297–300.
81. Kapural L. Spinal cord stimulation for intractable chronic pain. Curr Pain Headache Rep 2014, 18: 406.
82. Falowski S, Sharan A. A review on spinal cord stimulation. J Neurosurg Sci 2012, 56: 287–298.
83. Song Z, Viisanen H, Meyerson BA, Pertovaara A, Linderoth B. Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. Neuromodulation 2014, 17: 226–234.
84. Foreman RD, Linderoth B. Neural mechanisms of spinal cord stimulation. Int Rev Neurobiol 2012, 107: 87–119.
85. Guan Y, Wacnik PW, Yang F, Carteret AF, Chung CY, Meyer RA, *et al.* Spinal cord stimulation-induced analgesia: electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. Anesthesiology 2010, 113: 1392–1405.
86. Narikawa K, Furue H, Kumamoto E, Yoshimura M. *In vivo* patch-clamp analysis of IPSCs evoked in rat substantia gelatinosa neurons by cutaneous mechanical stimulation. J Neurophysiol 2000, 84: 2171–2174.
87. Shimoji K, Shimizu H, Maruyama Y, Matsuki M, Kuribayashi H, Fujioka H. Dorsal column stimulation in man: facilitation of primary afferent depolarization. Anesth Analg 1982, 61: 410–413.
88. Olsson GL, Meyerson BA, Linderoth B. Spinal cord stimulation in adolescents with complex regional pain syndrome type I (CRPS-I). Eur J Pain 2008, 12: 53–59.
89. Carter ML. Spinal cord stimulation in chronic pain: a review of the evidence. Anaesth Intensive Care 2004, 32: 11–21.
90. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, *et al.* Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 2007, 132: 179–188.
91. Meyerson BA, Linderoth B. Mode of action of spinal cord stimulation in neuropathic pain. J Pain Symptom Manage 2006, 31: S6–S12.
92. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. Neuromodulation 2016, 19: 47–59.
93. de Vos CC, Bom MJ, Vanneste S, Lenders MW, De Ridder RD. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation 2014, 17: 152–159.
94. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg 2013, 80: 642–649.
95. Hou S, Kemp K, Grabois M. A systematic evaluation of burst spinal cord stimulation for chronic back and limb pain. Neuromodulation 2016, 19: 398–405.
96. Van HT, Vancamp T, Van LP, Vanneste S, De Ridder D. Spinal cord stimulation for the treatment of chronic back pain patients: 500-Hz vs. 1000-Hz burst stimulation. Neuromodulation 2015, 18: 9–12.
97. Tang R, Martinez M, Goodman-Keiser M, Farber JP, Qin C, Foreman RD. Comparison of burst and tonic spinal cord stimulation on spinal neural processing in an animal model. Neuromodulation 2014, 17: 143–151.
98. Gong WY, Johanek LM, Sluka KA. A comparison of the effects of burst and tonic spinal cord stimulation on hyperalgesia and physical activity in an animal model of neuropathic pain. Anesth Analg 2016, 112: 1178–1185.
99. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, *et al.* Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: The SENZA-RCT randomized controlled trial. Anesthesiology 2015, 123: 851–860.
100. Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain Med 2014, 15: 347–354.
101. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation 2013, 16: 59–65.
102. Verrills P, Sinclair C, Barnard A. A review of spinal cord stimulation systems for chronic pain. J Pain Res 2016, 9: 481–492.
103. Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, *et al.* Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. Neuromodulation 2013, 16: 363–369.
104. Annemans L, Van Buyten JP, Smith T, Al-Kaisy A. Cost effectiveness of a novel 10 kHz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS). J Long Term Eff Med Implants 2014, 24: 173–183.
105. Wolter T. Spinal cord stimulation for neuropathic pain: current perspectives. J Pain Res 2014, 7: 651–663.
106. Crosby ND, Janik JJ, Grill WM. Modulation of activity and conduction in single dorsal column axons by kilohertz-frequency spinal cord stimulation. J Neurophysiol 2017, 117: 136–147.
107. Crosby ND, Weisshaar CL, Smith JR, Zeeman ME, Goodman-Keiser MD, Winkelstein BA. Burst and tonic spinal cord stimulation differentially activate GABAergic mechanisms to attenuate pain in a rat model of cervical radiculopathy. IEEE Trans Biomed Eng 2015, 62: 1604–1613.
108. Tator CH, Minassian K, Mushahwar VK. Spinal cord stimulation: therapeutic benefits and movement generation after spinal cord injury. Handb Clin Neurol 2012, 109: 283–296.
109. Nagel SJ, Wilson S, Johnson MD, Machado A, Frizon L, Chardon MK, *et al.* Spinal cord stimulation for spasticity: historical approaches, current status, and future directions. Neuromodulation 2017, 20: 307–321.
110. Gater DR Jr, Dolbow D, Tsui B, Gorgey AS. Functional electrical stimulation therapies after spinal cord injury. NeuroRehabilitation 2011, 28: 231–248.

111. Eldabe S, Thomson S, Duarte R, Brookes M, Belder M, Raphael J, *et al.* The effectiveness and cost-effectiveness of spinal cord stimulation for refractory angina (RASCAL Study): A pilot randomized controlled trial. Neuromodulation 2016, 19: 60–70.
112. Saraste A, Ukkonen H, Varis A, Vasankari T, Tunturi S, Taittonen M, *et al.* Effect of spinal cord stimulation on myocardial perfusion reserve in patients with refractory angina pectoris. Eur Heart J Cardiovasc Imaging 2015, 16: 449–455.
113. Kapural L, Cywinski JB, Sparks DA. Spinal cord stimulation for visceral pain from chronic pancreatitis. Neuromodulation 2011, 14: 423–426.
114. Aslan SC, Legg Ditterline BE, Park MC, Angeli CA, Rejc E, Chen Y, *et al.* Epidural spinal cord stimulation of lumbosacral networks modulates arterial blood pressure in individuals with spinal cord injury-induced cardiovascular deficits. Front Physiol 2018, 9: 565.
115. 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.
116. Kowalski KE, Romaniuk JR, Brose SW, Richmond MA, Kowalski T, DiMarco AF. High frequency spinal cord stimulation-New method to restore cough. Respir Physiol Neurobiol 2016, 232: 54–56.
117. DiMarco AF, Geertman RT, Tabbaa K, Polito RR, Kowalski KE. Case report: Minimally invasive method to activate the expiratory muscles to restore cough. J Spinal Cord Med 2018, 41: 562–566.
118. Nashold BS Jr, Friedman H. Dorsal column stimulation for control of pain. Preliminary report on 30 patients. J Neurosurg 1972, 36: 590–597.
119. Meglio M, Cioni B, Rossi GF. Spinal cord stimulation in management of chronic pain. A 9-year experience. J Neurosurg 1989, 70: 519–524.
120. Buchhaas U, Koulousakis A, Nittner K. Experience with spinal cord stimulation (SCS) in the management of chronic pain in a traumatic transverse lesion syndrome. Neurosurg Rev 1989, 12 Suppl 1: 582–587.
121. Meglio M, Cioni B, Prezioso A, Talamonti G. Spinal cord stimulation (SCS) in deafferentation pain. Pacing Clin Electrophysiol 1989, 12: 709–712.
122. North RB, Kidd DH, Zahurak M, James CS, Long DM. Spinal cord stimulation for chronic, intractable pain: experience over two decades. Neurosurgery 1993, 32: 384–394.
123. Tasker RR, DeCarvalho GT, Dolan EJ. Intractable pain of spinal cord origin: clinical features and implications for surgery. J Neurosurg 1992, 77: 373–378.
124. Cioni B, Meglio M, Pentimalli L, Visocchi M. Spinal cord stimulation in the treatment of paraplegic pain. J Neurosurg 1995, 82: 35–39.
125. Kumar K, Toth C, Nath RK, Laing P. Epidural spinal cord stimulation for treatment of chronic pain–some predictors of success. A 15-year experience. Surg Neurol 1998, 50: 110–120.
126. Shimoji K, Hokari T, Kano T, Tomita M, Kimura R, Watanabe S, *et al.* Management of intractable pain with percutaneous epidural spinal cord stimulation: differences in pain-relieving effects among diseases and sites of pain. Anesth Analg 1993, 77: 110–116.
127. Levine AB, Parrent AG, MacDougall KW. Cervical spinal cord and dorsal nerve root stimulation for neuropathic upper limb pain. Can J Neurol Sci 2017, 44: 83–89.
128. Brill S, Aryeh IG. Neuromodulation in the management of pain from brachial plexus injury. Pain Physician 2008, 11: 81–85.
129. Richardson RR, Meyer PR, Cerullo LJ. Neurostimulation in the modulation of intractable paraplegic and traumatic neuroma pains. Pain 1980, 8: 75–84.
130. Barchini J, Tchachaghian S, Shamaa F, Jabbur SJ, Meyerson BA, Song Z, *et al.* Spinal segmental and supraspinal mechanisms underlying the pain-relieving effects of spinal cord stimulation: an experimental study in a rat model of neuropathy. Neuroscience 2012, 215: 196–208.
131. Sdrulla AD, Xu Q, He SQ, Tiwari V, Yang F, Zhang C, *et al.* Electrical stimulation of low-threshold afferent fibers induces a prolonged synaptic depression in lamina II dorsal horn neurons to high-threshold afferent inputs in mice. Pain 2015, 156: 1008–1017.
132. Yang F, Xu Q, Shu B, Tiwari V, He SQ, Vera-Portocarrero LP, *et al.* Activation of cannabinoid CB1 receptor contributes to suppression of spinal nociceptive transmission and inhibition of mechanical hypersensitivity by Abeta-fiber stimulation. Pain 2016, 157: 2582–2593.
133. Zhang H, Xie W, Xie Y. Spinal cord injury triggers sensitization of wide dynamic range dorsal horn neurons in segments rostral to the injury. Brain Res 2005, 1055: 103–110.
134. Hains BC, Willis WD, Hulsebosch CE. Temporal plasticity of dorsal horn somatosensory neurons after acute and chronic spinal cord hemisection in rat. Brain Res 2003, 970: 238–241.
135. Reck TA, Landmann G. Successful spinal cord stimulation for neuropathic below-level spinal cord injury pain following complete paraplegia: a case report. Spinal Cord Ser Cases 2017, 3: 17049.
136. 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: 325–336.
137. Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, *et al.* 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: 515–550.
138. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. J Neurosurg 2004, 100: 254–267.
139. 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 2011, 14: 412–422.
140. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg 1967, 46: 489–491.
141. Franzini A, Ferroli P, Marras C, Broggi G. Huge epidural hematoma after surgery for spinal cord stimulation. Acta Neurochir (Wien) 2005, 147: 565–567.
142. McKinney MC, Kulesa PM. *In vivo* calcium dynamics during neural crest cell migration and patterning using GCaMP3. Dev Biol 2011, 358: 309–317.
143. Anderson M, Zheng Q, Dong X. Investigation of pain mechanisms by calcium imaging approaches. Neurosci Bull 2018, 34: 194–199.
144. Deer TR, Krames E, Mekhail N, Pope J, Leong M, Stanton-Hicks M, *et al.* The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. Neuromodulation Appropriateness Consensus Committee. Neuromodulation 2014, 17: 599–615.
145. Xie YF, Wang J, Bonin RP. Optogenetic exploration and modulation of pain processing. Exp Neurol 2018, 306: 117–121.
146. Rahman MH, Nam Y, Kim JH, Lee WH, Suk K. Optogenetics of the spinal cord: use of channelrhodopsin proteins for interrogation of spinal cord circuits. Curr Protein Pept Sci 2018, 19: 714–724.

147. Ropero Pelaez FJ, Taniguchi S. The Gate Theory of Pain revisited: modeling different pain conditions with a parsimonious neurocomputational model. Neural Plast 2016, 2016: 4131395.
148. Lempka SF, McIntyre CC, Kilgore KL, Machado AG. Computational analysis of kilohertz frequency spinal cord stimulation for chronic pain management. Anesthesiology 2015, 122: 1362–1376.
149. Drew GM, Siddall PJ, Duggan AW. Mechanical allodynia following contusion injury of the rat spinal cord is associated with loss of GABAergic inhibition in the dorsal horn. Pain 2004, 109: 379–388.
150. Krishna V, Andrews H, Jin X, Yu J, Varma A, Wen X, *et al.* A contusion model of severe spinal cord injury in rats. J Vis Exp 2013, 78: e50111.
151. King T, Qu C, Okun A, Mercado R, Ren J, Brion T, *et al.* Contribution of afferent pathways to nerve injury-induced spontaneous pain and evoked hypersensitivity. Pain 2011, 152: 1997–2005.
152. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010, 9: 807–819.
153. Christensen MD, Hulsebosch CE. Chronic central pain after spinal cord injury. J Neurotrauma 1997, 14: 517–537.
154. Meier K. Spinal cord stimulation: Background and clinical application. Scand J Pain 2017, 5: 175–181.
155. Norrbrink BC, Lundeberg T. Non-pharmacological pain-relieving therapies in individuals with spinal cord injury: a patient perspective. Complement Ther Med 2004, 12: 189–197.
156. Stroman PW, Khan HS, Bosma RL, Cotoi AI, Leung R, Cadotte DW, *et al.* Changes in pain processing in the spinal cord and brainstem after spinal cord injury characterized by functional magnetic resonance imaging. J Neurotrauma 2016, 33: 1450–1460.
157. Howell B, Lad SP, Grill WM. Evaluation of intradural stimulation efficiency and selectivity in a computational model of spinal cord stimulation. PLoS One 2014, 9: e114938.
158. Flouty OE, Oya H, Kawasaki H, Reddy CG, Fredericks DC, Gibson-Corley KN, *et al.* Intracranial somatosensory responses with direct spinal cord stimulation in anesthetized sheep. PLoS One 2013, 8: e56266.
159. Flouty O, Oya H, Kawasaki H, Wilson S, Reddy CG, Jeffery ND, *et al.* A new device concept for directly modulating spinal cord pathways: initial *in vivo* experimental results. Physiol Meas 2012, 33: 2003–2015.
160. Walters BC. Oscillating field stimulation in the treatment of spinal cord injury. PM R 2010, 2: S286–S291.
161. Deer T, Kim C, Bowman R, Ranson M, Douglas CS, Tolentino W. Spinal cord stimulation as a method of reducing opioids in severe chronic pain: a case report and review of the literature. W V Med J 2010, 106: 56–59.