Spinal Stimulation for Movement Disorders

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Abstract Epidural spinal cord stimulation (SCS) is currently proposed to treat intractable neuropathic pain. Since the 1970s, isolated cases and small cohorts of patients suffering from dystonia, tremor, painful leg and moving toes (PLMT), or Parkinson's disease were also treated with SCS in the context of exploratory clinical studies. Despite the safety profile of SCS observed in these various types of movement disorders, the degree of improvement of abnormal movements following SCS has been heterogeneous among patients and across centers in open-label trials, stressing the need for larger, randomized, double-blind studies. This article provides a comprehensive review of both experimental and clinical studies of SCS application in movement disorders.

Key Words Spinal cord stimulation · Parkinson's disease · dystonia · painful leg and moving toes · tremor · neuropathic pain

Introduction

Epidural spinal cord stimulation (SCS) has been a well-established, reversible, and adjustable therapy for certain types of neuropathic pain since 1967 [1]. The technique

consists of inserting an epidural lead containing multiple stimulating electrodes (4–16). The leads can be percutaneous or surgical paddle leads. The percutaneous leads are cylindrical insulated catheters. The surgical leads are flat with an insulated backing and need a micro-laminectomy for their placement. The leads are connected to a pulse generator that contains a battery and programmable components of the device. Implantation of the whole SCS system requires a surgical procedure under aseptic conditions. In patients suffering from chronic and intractable neuropathic pain, SCS results in pain relief, improvement in activities of daily living, and a reduction in analgesics dosage [2–5]. Neuroimaging studies using either functional magnetic resonance imaging techniques and positron emission tomography with $H_2^{15}O$ have suggested an activating effect of SCS within the thalamus contralateral to the pain, somatosensory, premotor, anterior cingulate cortex, and prefrontal areas [6, 7].

In 1973, a patient with multiple sclerosis (MS) receiving SCS for pain was reported to have major improvement of some motor aspects of the disease, including amelioration of paraparesis, as well as speech and swallowing impairment, resulting in an overall decrease of disability [8]. Since this preliminary observation, many patients suffering from motor disorders treated with SCS have been reported. Subsequent open-label clinical trials using SCS have emerged in different types of movement disorders, as illustrated by the publication of large series of patients, up to 1336, operated between 1972 and 1997 [9]. More recently, promising studies in animal models of Parkinson's disease (PD) brought SCS up to date in movement disorders [10, 11], followed quickly by case reports in patients suffering from PD [12–17].

SCS generates its therapeutic effect not only through electrophysiological changes at the dorsal horn level but also on deep nuclei structures of the brainstem and the forebrain [7, 10, 18, 19]. Thus, the spinal cord, through its anatomical structure and organization, could facilitate an ascending

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remote effect by modulating the neuronal activities of deep brain structures. This effect might be of interest in diseases associated with basal ganglia dysfunctions. Anatomically, the main dorsal columns convey ascending sensory information from somatic mechanoreceptors to the thalamus and sensory cortex (Fig. 1). This sensory pathway may account for a possible remote effect of SCS as spinal cord leads are surgically implanted inside the epidural space with electrodes facing the dorsal surface of the cord (Fig. 2). Thus, the current delivered by a lead is distributed in the 3-dimensional space within the most dorsal part of the spinal cord through the dura mater. The amount of injected current depends on both the applied voltage of the stimulation pulse and the impedance between 2 stimulator outputs. All these electrical parameters obey Ohm's Law (voltage = current/impedance) and induce isopotential lines that cover variable portions of the spinal cord depending on the voltage or current force [20].

This article provides a comprehensive review of all SCS applications in movement disorders.

Dystonia

Cervical SCS for patients with cervical dystonia was first proposed by Gildenberg in 1971 based on the observation that sensory stimulation ("sensory trick") may reduce the severity of dystonic movements and postures in cases of focal dystonia [21–23]. Twenty patients with spasmodic torticollis were treated with transcutaneous stimulation or underwent surgical implantation of a dorsal column stimulator located at the C1–C2 level. Eleven patients were finally excluded from surgery (most owing to lack of response to percutaneous stimulation). Three had sufficient relief with transcutaneous stimulation only. The remaining 6 patients had surgically implanted cervical stimulators. Therapeutic response was evaluated on head position, comfort, and global disability, and was rated as "excellent" in 1 patient, "good" in 3 patients, "fair" in 1 patient, and "poor" in 1 patient. Two additional patients with generalized dystonia were also evaluated. One patient did not respond to transcutaneous stimulation, but the other was surgically implanted and became less disabled in activities of

Fig. 1 Medullar lemniscal pathway. (a) Schematic representation of the lemniscal track at different levels of the spinal cord: ascending track coming at each level from the dorsal root ganglia and decussating in the lower medulla. (b) Represents the somatotopic arrangement of the ascending medial lemniscal track (in blue, dorsal), the ascending spinothalamic track (in blue, ventral), and the descending lateral

pyramidal track (in red). The epidural electrode is placed along the dorsal aspect of the spinal cord. (c) The somatotopic arrangement has been integrated in the axial computed tomography scan view of a thoracic spine. S = sacral; L = lumbar; Th = thoracic; C = cervical; P = pedicle; TP = transverse process; LA = lamina; SP = spinous process; B = vertebral body

Fig. 2 Thoracic computed tomography (CT) scan. (a) Coronal view; (b) axial view of thoracic spine by CT scan. Red arrow indicates an 8-contact surgical paddle lead located in the dorsal aspect of the epidural space. Ant = anterior; P = pedicle; L = lamina, SP = spinous process; B = vertebral body

daily living after cervical SCS. The best effect on dystonic symptoms was obtained with a frequency of 800–1100 Hz. A second team reported a series of 18 patients suffering from spasmodic torticollis who benefitted from cervical (C2–C4) high-frequency stimulation [24]; 10 patients were surgically implanted with 4-contact electrodes, and 8 with percutaneous electrodes. Half the patients had a very good (disappearance of torticollis in 7 patients) or good (no torticollis at rest in 2 patients) outcome. Five had satisfactory results (subjective and moderate objective improvement or lack of follow-up), and 4 patients had unsatisfactory results, including 3 patients explanted following infection.

Following these initial studies on cervical dystonia, cervical SCS was progressively applied for other types of dystonia, including generalized and secondary dystonias. In 1987, Waltz et al. [25] reported a large series of 129 dystonic patients treated with cervical SCS. Qualitative analysis of dystonic posture, spasms, and functionality showed that up to 79 %

of patients demonstrated some improvement, with 29 % of the patients having a marked improvement. Dystonic patients displaying peripheral, axial, and pseudobulbar manifestations also had reduced incidence of dystonic movements and improvement of dexterity, walking and balance, and dysphagia [25]. Better results were obtained using multilead electrodes (quadripolar) rather than a 2-electrode system (bipolar). In another group of 66 patients undergoing SCS for spasmodic torticollis, and evaluated with the same pattern of multiple qualitative scales, including rating of pain, torticollis, spasm, and function, 77 % demonstrated some improvement, including 38 % having marked improvement [25]. However, the heterogeneity of the population in this study, which included patients with cerebral palsy, spinal cord injury, degenerative diseases, and idiopathic dystonia, in addition to the absence of reproducible stimulation parameter settings, and the descriptive nature of the assessments, preclude any definitive conclusions on the therapeutic value of this procedure.

In 1985, Fahn [26] questioned the beneficial results from cervical SCS and reported negative results, with only 1 patient having a long-lasting benefit among 25 dystonic patients receiving cervical SCS. In this report, the author strongly tempered the positive publicity around the neurological changes following SCS in previous uncontrolled studies. Similarly, a Spanish team [27] also reported 3 dystonic and 2 spasmodic torticollis patients with poor improvement of dystonia except in 1 patient.

Following these controversial results, Goetz et al. [28] designed a double-blind trial in 10 dystonic patients. The patients were implanted with a cervical stimulation device, and the study followed a crossover design with 2 different settings of parameters, 1 improving dystonia and 1 having no effect on dystonia (75 Hz and 1000 Hz, respectively). Despite subjective improvement in 4 patients, objective assessments, including severity of dystonia, time spent in dystonic posture, and severity of spasms, were not significantly improved [28].

Thus, most early studies of dystonic patients undergoing cervical stimulation, summarized in Table 1, showed fair relief with >50 % patients improved (79 % in the largest series). However, it is difficult to determine whether this overall improvement is a result of pain relief or actual alleviation of dystonic movements. Furthermore, the placebo effect may have accounted for a large part of these results [29]. The only double-blind clinical trial had a limited value because of the small sample size, but did not confirm any beneficial effect of SCS in dystonia [28]. Most studies involved patients suffering from spasmodic torticollis with a speculative mechanisms of action, relying on alteration of propriospinal fibers involved in the regulation of tonic reflexes of the neck, thus interrupting the tonic neck reflex pattern [22], or an action on the reticular activating system [30]. Cervical SCS for dystonia was progressively abandoned in the 1990s owing to the emerging successful use of botulinum toxin injection [31, 32].

Table 1 Studies of spinal cord stimulation in dystonia

Reference	Study design	Diagnosis	Stimulation parameters	Follow-up	Evaluation methods	Results
Gildenberg [22]	Open label	Spasmodic torticollis (n=6)	Cervical 800–1000 Hz	4–30 months	Head position, comfort, disability	Excellent (n=1) Good (n=3) Fair (n=1) Poor (n=1)
Dieckmann and Veras [24]	Open label	Generalized dystonia (n=1)	Cervical 1100 Hz	30 months	Disability in activity of daily living	Improvement
		Spasmodic torticollis (n=18)		6–24 months	Head posture (clinical and electrophysiology)	Very good (n=7) Good (n=2)
Waltz et al. [25]	Open label	Dystonia (n=129)	Cervical bipolar or quadripolar	6 months–10 years	Nonofficial multiple subjective and objective parameters scale	Satisfactory (n=5) Unsatisfactory (n=4) Marked (n=38) Moderate (n=43) Mild (n=21)
						Unimproved (n=27) Marked (n=25) Moderate (n=21) Mil (n=5)
Fahn [26]	Retrospective analysis	Focal and generalized dystonia (n=25)	Cervical	Unknown	Subjective improvement	Unimproved (n=15) 4 mild and transient benefit±1 long-lasting
Broseta et al. [27]	Open label	Dystonia (n=3), torticollis (n=2) (and other pathology)	Cervical 200–1400 Hz	22–54 months	Clinical and electrophysiology activities of daily living	Good early results. 1 improvement and 1 slight improvement at late time
Goetz et al. [28]	Randomized, double blind, crossover	Generalized dystonia (n=4), Cervical dystonia (n=5), Foot dystonia (n=1)	Cervical 75–1000 Hz (effective vs ineffective stimulation)	1 month×2 or 4	Subjective improvement Dystonia rating scale, time in dystonic posture, spasms	Subjective improvement (n=4) No objective improvement

Nonparkinsonian Tremors

Only few clinical studies have examined the effect of SCS in patients with nonparkinsonian tremors (Table 2). Clinical beneficial effects of SCS on tremor have been occasionally reported in patients with MS [33]. In the study by Fredriksen et al. [33], 19 patients with MS suffering from tremor (7 of marked and 12 of moderate severity) were implanted with a cervical spinal cord electrode. Primary endpoints included bladder dysfunction and walking abilities, but 11 % of the patients also reported a beneficial effect of SCS on their tremor (none with marked improvement, 68 % with unaltered tremor, and 16 % information lacking). Thoracic SCS has also been investigated in 2 patients suffering from medically intractable orthostatic tremor [34]. Both patients had subjective and objective improvement of unsteadiness within a range of frequencies between 50 to 150 Hz. Electromyographic recordings showed that typical electrical features of orthostatic tremor persisted with a 52 % reduction of the amplitude during SCS. At 1 year, the reported improvement in the length of time patients were able to stand still was maintained, increasing from 2 to >5 min in 1 patient, and from 10 to 102 s in the other. The effect persisted at 3 years for 1 of the patients. In orthostatic tremor, the feeling of instability could be related to a “tremulous disruption” of proprioceptive afferent activity of the legs. SCS could, thus, act by partially masking this pathological disruption, reducing the vicious circle [34]. Beneficial effects of SCS on tremor have also been reported in some patients with dystonia [28].

At present, there are no published reports about SCS in essential tremor. Thus, data concerning the efficacy of SCS in tremor are limited. The positive results in MS associated with tremor and orthostatic tremor have to be confirmed in placebo-controlled studies.

Painful Leg and Moving Toes

Painful Leg and moving toes (PLMT) is a rare syndrome characterized by leg pain, frequently with neurogenic features, associated with involuntary movement of toes [35, 36]; it affects one or both legs and can also involve the upper limbs. The pathophysiology of PLMT entity is unknown. Concomitant neuropathy or radiculopathy is frequently observed, leading to the hypothesis that a peripheral injury induces a central reorganization, with a generator at the spinal cord or brainstem level. When required, treatments are often disappointing [36], with few cases reporting efficacy of some pharmacotherapy, lumbar sympathetic block [37], transcutaneous electrical nerve stimulation and/or vibratory stimulation [38], and nerve root decompression [39]. Dorsal (T10–T11) SCS for 20 min twice a day has also been reported to improve a medically resistant PLMT patient: pain and involuntary movements almost disappeared during stimulation, and recurred between stimulation periods at lower intensity. This effect persisted 6 months after the implantation [37]. In another case, a 59-year-old woman with PLMT experienced substantial improvement of her widespread pain and near disappearance of toe movements following dorsal SCS during a 13-month follow-up period [40]. In contrast, a 75-year-old woman implanted with epidural SCS did not have any beneficial effect on PLMT associated with herpes zoster myelitis [41].

Reported cases are too few to make any firm conclusions about the motor effects of SCS in PLMT. As PLMT is associated with neuropathic pain, it is possible that SCS may act through relieving the pain rather than normalization of abnormal movements in PLMT. SCS may disrupt the vicious circle by stopping the peripheral pain.

Table 2 Studies of spinal cord stimulation in nonparkinsonian tremor

Reference	Study design	Diagnosis	Stimulation parameters	Follow-up	Evaluation methods	Results
Fredriksen et al. [33]	Open label	Multiple sclerosis (n=19)	Cervical 25–100 Hz	2–20 months	Patient's evaluation and questionnaire for tremor	Tremor improvement: 26 % patients at 1 month; 11 % at late control; 6 % on late questionnaire
Krauss et al. [34]	Open label	Resistant orthostatic tremor (n=2)	Thoracic 100–110 Hz bipolar mode	1 year	Clinical and electrophysiology	Increased time from standing to unsteadiness Reduction in tremor amplitude (electromyography)
Goetz et al. [28]	Crossover, double-blind, randomized	Dystonia (n=10)	Cervical 75–1000 Hz	18 months	Incidental observation	1 patient with postural tremor controlled

Parkinson's Disease

PD is a neurodegenerative disease affecting predominantly dopaminergic neurons within the pars compacta of the substantia nigra. Symptomatic medical treatments such as L-dopa and dopaminergic agonists demonstrate a remarkable efficacy on motor symptoms at the initial phases of PD. However, over time, motor symptoms become more difficult to control using dopaminergic treatments alone owing to the development of motor fluctuations and dyskinesias. DBS of the medial pallidum or the subthalamic nucleus (STN) has a beneficial effect on motor symptoms of selected patients with PD [42]. However, DBS is a complex and invasive surgery, and in some instances may worsen dysarthria or gait abnormalities [43]. Potential adverse events may explain why DBS is restricted to a small population of patients, stressing the need to develop new techniques that are more accessible and less invasive to treat the motor symptoms of PD.

Animal Studies

Fuentes et al. [10] stimulated the dorsal column in 2 rodent models of PD with a bipolar platinum electrode chronically implanted epidurally above the dorsal columns of the spinal cord at the upper thoracic level. They evaluated the effect of this intervention in mice before and after an acute pharmacologically induced dopamine depletion by systemic injection of a tyrosine hydroxylase inhibitor, alpha-methyl-para-tyrosine. The result showed that SCS dramatically improved locomotion, particularly at 300 Hz, increasing locomotor activity up to 26-fold of baseline scores. They used control stimulation experiments employing air-puffs or trigeminal nerve stimulation, which led to the absence of locomotor improvement. Both cortical and striatal local field potentials and single-neuron firing patterns were altered during stimulation of the dorsal column, shifting neuronal activity into a state resembling that observed during spontaneous initiation of locomotion [10]. Thus, the authors hypothesized that dorsal column stimulation could induce a brain state permissive of locomotion. They also performed experiments in a model of chronic dopamine depletion using chronic 6-hydroxydopamine (6-OHDA) lesioned rats. Locomotor activity also improved with SCS in these animals. In another study [44], chronic high thoracic SCS prevented the severe body weight loss induced by bilateral intrastriatal 6-OHDA lesions compared with sham operated animals, and restored their motor function, including posture and gait. Strikingly, tyrosine hydroxylase (TH) immunoreactivity in the striatum and substantia nigra pars compacta and TH levels in both structures were significantly preserved in SCS treated 6-OHDA-lesioned rats compared with 6-OHDA-lesioned rats that did not receive SCS. The authors speculated that these results could suggest a neuroprotective

effect possibly related to increased production or delivery of neurotrophic factors [44].

In addition, Fuentes et al. [11] also studied chronic bipolar high thoracic SCS in marmosets with parkinsonism induced by unilateral or bilateral medial forebrain bundle lesions with 6-OHDA. SCS alleviated parkinsonian symptoms and consistently modulated the neuronal firing rate in different structures, mainly in the ventral lateral thalamus, ventral posterior lateral thalamus, and STN. Furthermore, the oscillatory activity observed in the beta range, which is considered one of the hallmarks of parkinsonian electrical abnormalities, was reduced only when SCS was switched on [11].

Human Studies

Recently, clinical observations using electrical SCS yielded conflicting results (Table 3). An initial report of 2 patients with PD treated with SCS did not show any benefit [12]. The patients were 75 and 77 years old, respectively, and had moderate-to-severe motor impairment with poor levodopa responsiveness. Both had a spinal electrode implanted surgically into the high cervical epidural space without any adverse events. They participated in a double-blind crossover study assessing motor function. Patient 1 was stimulated at 130 Hz and patient 2 at 300 Hz in 3 different conditions: OFF stimulation, subthreshold stimulation (without paresthesia), and suprathreshold stimulation (with paresthesia). Stimulation in any condition did not provide acute improvement of Unified Parkinson's Disease Rating Scale (UPDRS)-III scores, gait, or balance.

Our team reported a 74-year-old man who had been treated for lower limb neuropathic pain with a T9–T10 epidural stimulation for 13 years [13]. The patient was diagnosed with PD 8 years after SCS implantation. His parkinsonian symptoms were sensitive to levodopa, with a 50 % improvement of the off-medication UPDRS-III score. Axial signs were not predominant and cognitive function was preserved. The patient had noticed that tremor increased when SCS was off. SCS could improve up to 50 % of the off-medication UPDRS III score when stimulation was switched on at 130 Hz. Motor improvement was mainly observed on tremor of both upper and lower limbs [13]. A similar observation was made in a 68-year-old patient with PD who underwent SCS at the T9–T11 level for postlaminectomy neuropathic pain and whose parkinsonian symptoms, particularly tremor, were improved when the stimulation was switched on [14]. Additionally, a 43-year-old woman with PD who benefited from stimulation at the C2 level for neck and upper extremity neurogenic pain displayed a 40 % improvement in the motor UPDRS-III score following SCS [15]. A larger Japanese study of 15 patients with PD suffering from neuropathic pain and treated with thoracic SCS using percutaneous leads showed some improvement in PD symptoms [16]. Because pain localization

Table 3 Studies of spinal cord stimulation in Parkinson's disease (PD)

Reference	Study design	Diagnosis	Stimulation parameters	Follow-up	Evaluation methods	Results
Thevathasan et al. [12]	Double-blind crossover	2 PD patients aged 75 and 77 years, respectively Dopa response < 50 %	High cervical 300 Hz	Acute testing 10 days postoperatively	UPDRS-III 10-m walk	No improvement
Fénelon et al. [13]	Case report Partial blinding of rater (UPDRS-III rated on video tape)	1 PD patient aged 74 years Dopa response > 50 %	T9-T10 130 Hz	Acute testing several years postoperatively	UPDRS-III rated on video, 7-m walk-back VAS	50 % reduction Off-medication UPDRS-III
Soltani and Lalkhen [14]	Observation	1 PD patient aged 68 years Postlaminectomy syndrome	T9-T11	Unknown	Report by patient and husband	Improvement of parkinsonian symptoms, particularly left-sided tremor
Hassan et al. [15]	Case report	1 PD patient aged 43 years with neuropathic cervical and upper limb pain	Cervical 40 Hz	2 years	VAS UPDRS-III 10-m walking time	Progressive improvement of VAS, UPDRS-III and walk
Agari and Date [16]	Uncontrolled unblinded study	15 PD patients aged 63–69 years with low back and lower limb refractory pain	T7-T12 5–20 Hz	12 months	VAS UPDRS TUG test 10-m walking time	improvement of VAS, UPDRS-II (items 12, 15, 17), UPDRS III (items 28–31), TUG, and 10-m walking time at M3 and M12
Landi et al. [17]	Case report	1 PD patient aged 65 years STN-DBS and lower limb central neuropathic pain	T9-T10 30 Hz; bipolar mode	16 months	VAS; quality of life (Euro quality-VAS) pull test; walk with rapid direction changes; 20-m walking time and pull test	20 % decrease in 20-m walking time; better coordination during walk; no change in UPDRS-III

UPDRS = Unified Parkinson's Disease Rating Scale; STN-DBS = subthalamic nucleus deep brain stimulation; VAS, visual analog scale; TUG = Timed Up and Go

was heterogeneous in these patients, the level of SCS implantation varied from T7 to T12. The mean age of the patients was 71 years, preoperative Hoehn and Yahr score was between 3 and 4, and 7 patients had previously undergone bilateral STN DBS. Twelve months after chronic SCS, a significant improvement compared with baseline was observed on a visual analogue scale for pain, UPDRS-II scores (activity of daily living), and gait.

Despite the increasing number of clinical observations showing motor improvement in PD following SCS, the results presented in these different studies are still a matter of debate. First, the reported studies were small open-label trials, with heterogeneous results. The selection of patients, disease history, and stimulation settings greatly varied among studies. For example, in the first report by Thevathasan et al. [12], which concluded a lack of clinical benefit, the 2 patients were >70 years old, had advanced disease with poor levodopa responsiveness, and 1 had severe gait abnormalities. These clinical features strongly suggest the presence of additional extranigral nondopaminergic lesions. Although the patient reported by our group was >70 years of age, he had an excellent response to levodopa with limited axial motor impairment. Similarly, in the study by Agari and Date [16] the patients displayed limited axial symptoms without any major gait abnormalities. Patients in the 2 other reports [18, 19] were younger (43 and 68 years old, respectively), but their clinical characteristics were less precisely described. All these reports suggest that the quality of levodopa response may account for the level of motor effect following SCS. It is also likely that SCS affects PD symptoms differently, as tremor was the most responsive symptom [13–15].

Second, the methods used were heterogeneous and debatable in some respects. For example, Thevathasan et al. [12] reported a single acute assessment performed as early as 10 days after surgery, the “on-condition” being evaluated only 20 min after switching the stimulator on. However, the patients described by Fénelon et al. [13] underwent 4 acute clinical testing sessions done several years after surgery, with evaluations performed 30–60 min after switching the stimulator on or off. Another important possible bias is the relief of pain observed in the vast majority of patients. Indeed, gait improvement and global well-being induced by reducing pain may have a beneficial influence on symptoms of PD [13–17]. Finally, it should be emphasized that the stimulation in most cases was initially performed to treat neuropathic pain and not PD symptoms. As a result, the level of SCS (cervical vs thoracic) varied, and the leads were different in size and shape among patients, rendering the interpretation of the clinical benefit even more difficult.

Although encouraging, no definite conclusions can be drawn from these few preliminary reports in PD. Randomized double-blind clinical studies are required to prove the motor

effects of SCS on parkinsonian symptoms. Both levodopa-responsive and levodopa-nonresponsive symptoms need to be assessed assuming that SCS may also act through increased somatosensory inputs arising from mechanoreceptors and travelling within the lemniscal pathways to the brain stem.

Pathophysiology

At present, the symptomatic effects of SCS observed in movement disorders are mainly based on the assumption that SCS can modulate the ascending sensory pathways to restore motor abnormalities. This hypothesis has been essentially established from animal models of PD. Thus, the imbalance between the striatal efferent direct and indirect pathways in PD induce inhibition of brainstem and thalamo-cortical pathways. These are responsible for abnormal synchronization of neuronal activation in the cortico-basal ganglia circuit [45], perpetuating the inactive cortical state, and thus preventing the transition to a cortical state permitting initiation of voluntary movements [46, 47]. SCS may induce excitation of dorsal columns [48], increase cortical and thalamic output, and thus activate the thalamo-cortical-pathway, allowing desynchronization of cortico-basal abnormalities observed in PD [49].

In PD, diencephalon–spinal dopaminergic neuronal pathways could be altered [50], and α -synuclein and Lewy bodies have been observed in the spinal cord of patients with PD [51]. However, it is unlikely that SCS could have a direct impact on these neuronal abnormalities to improve motor behavior.

Concluding Remarks

SCS has been assessed as a symptomatic treatment of various neurological conditions. The first recognized clinical application was for neuropathic pain for which clinical efficacy has been fully proven through compelling clinical reports. In the 1970s and 1980s, SCS was reported in open-label clinical trials in a variety of neurological diseases involving motor function (cerebral palsy, Friedreich or other hereditary cerebellar ataxias with spasticity [52], amyotrophic lateral sclerosis, dystonia, multiple sclerosis, etc.) to alleviate spasticity, ataxia, or various movement disorders. More recently, there has been an interest in treating motor symptoms of PD, as well as pain and abnormal movements in some patients suffering from PLMT. Despite these numerous studies, clinical evidence is still insufficient to consider such a neuromodulation technique applicable for abnormal movement symptoms. Indeed, the extent to which the reported improvements in motor function and movement is due to reduction of pain severity is difficult to assess, and the placebo effect can be particularly high in surgical therapies [29]. Randomized, controlled,

double-blind trials are thus mandatory to gain a clear therapeutic picture for SCS.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. 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.
2. 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.
3. Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. *Diabet Med* 2005;22:393-398.
4. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess* 2009;13:1-154.
5. Kunnumpurath S, Srinivasagopalan R, Vadivelu N. Spinal cord stimulation: principles of past, present and future practice: a review. *J Clin Monit Comput* 2009;23:333-339.
6. Stancak A, Kozak J, Vrba I, et al. Functional magnetic resonance imaging of cerebral activation during spinal cord stimulation in failed back surgery syndrome patients. *Eur J Pain* 2008;12:137-148.
7. Kishima H, Saitoh Y, Oshino S, et al. Modulation of neuronal activity after spinal cord stimulation for neuropathic pain; H(2)150 PET study. *Neuroimage* 2010;49:2564-2569.
8. Cook AW, Weinstein SP. Chronic dorsal column stimulation in multiple sclerosis. Preliminary report. *N Y State J Med* 1973;73:2868-2872.
9. Waltz JM. Spinal cord stimulation: a quarter century of development and investigation. A review of its development and effectiveness in 1,336 cases. *Stereotact Funct Neurosurg* 1997;69:288-299.
10. Fuentes R, Petersson P, Siesser WB, Caron MG, Nicoletis MA. Spinal cord stimulation restores locomotion in animal models of Parkinson's disease. *Science* 2009;323:1578-1582.
11. Fuentes R, Petersson P, Santana M, Simplicio H, Palmer T, Nicoletis M. Effects of spinal cord stimulation on the neuronal firing rate and synchronization of the cortico-basal ganglia-thalamic circuit in a primate model of Parkinson's disease. *Neuroscience* 2013 Congress, Poster 241.05/N6.
12. Thevathasan W, Mazzone P, Jha A, et al. Spinal cord stimulation failed to relieve akinesia or restore locomotion in Parkinson disease. *Neurology* 2010;74:1325-1327.
13. Fénelon G, Goujon C, Gurruchaga JM, Cesaro P, Jarraya B, Palfi S, Lefaucheur JP. Spinal cord stimulation for chronic pain improved motor function in a patient with Parkinson's disease. *Parkinsonism Relat Disord* 2012;18:213-214.
14. Soltani F, Lalkhen A. Improvement of parkinsonian symptoms with spinal cord stimulation: consequence or coincidence? *J Neurol Neurosurg Psychiatry* 2013;84:e2:71.
15. Hassan S, Amer S, Alwaki A, Elborno A. A patient with Parkinson's disease benefits from spinal cord stimulation. *J Clin Neurosci* 2013;20:1155-1156.
16. Agari T, and Date I. Spinal cord stimulation for the treatment of abnormal posture and gait disorder in patients with Parkinson's disease. *Neurol Med Chir (Tokyo)* 2012;52:470-474.
17. Landi A, Trezza A, Pirillo D, Vimercati A, Antonini A, Sganzerla EP. Spinal cord stimulation for the treatment of sensory symptoms in advanced Parkinson's disease. *Neuromodulation* 2013;16:276-279.
18. Yakhnitsa V, Linderöth B, Meyerson BA. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. *Pain* 1999;79:223-233.
19. Poláček H, Kozák J, Vrba I, Vrána J, Stancák A. Effects of spinal cord stimulation on the cortical somatosensory evoked potentials in failed back surgery syndrome patients. *Clin Neurophysiol* 2007;118:1291-1302.
20. Holsheimer J. Principles of neuromodulation Electrical stimulation and the relief of pain. *Pain Res Clin Manage* 2003;15:17-36.
21. Gildenberg PL. Treatment of spasmodic torticollis by dorsal column stimulation. *Rev Inst Nal Neurologia* 1976;10:11-15.
22. Gildenberg PL. Treatment of spasmodic torticollis by dorsal column stimulation. *Appl Neurophysiol* 1978;41:113-121.
23. Poisson A, Krack P, Thobois S, Loiraud C, Serra G, Vial C, Broussolle E. History of the 'geste antagoniste' sign in cervical dystonia. *J Neurol* 2012;259:1580-1584.
24. Dieckmann G, Veras G. Bipolar spinal cord stimulation for spasmodic torticollis. *Appl Neurophysiol* 1985;48:339-346.
25. Waltz JM, Andreesen WH, Hunt DP. Spinal cord stimulation and motor disorders. *Pacing Clin Electrophysiol* 1987;10:180-204.
26. Fahn S. Lack of benefit from cervical cord stimulation for dystonia. *N Engl J Med* 1985;313:1229.
27. Broseta J, Garcia-March G, Sánchez-Ledesma MJ, Barberá J, González-Darder J. High-frequency cervical spinal cord stimulation in spasticity and motor disorders. *Acta Neurochir Suppl (Wien)* 1987;39:106-111.
28. Goetz CG, Penn RD, Tanner CM. Efficacy of cervical cord stimulation in dystonia. *Adv Neurol* 1988;50:645-649.
29. Goetz CG, Wu J, McDermott MP. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. *Mov Disord* 2008;23:690-699.
30. Waltz JM, Reynolds LO, Riklan M. Multi-lead spinal cord stimulation for control of motor disorders. *Appl Neurophysiol* 1981;44:244-257.
31. Tsui JK, Eisen A, Mak E, Carruthers J, Scott A, Calne DB. A pilot study on the use of botulinum toxin in spasmodic torticollis. *Can J Neurol Sci* 1985;12:314-316.
32. Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990;40:1213-1218.
33. Fredriksen TA, Bergmann S, Hesselberg JP, Stolt-Nielsen A, Ringkjøb R, Sjaastad O. Electrical stimulation in multiple sclerosis. Comparison of transcutaneous electrical stimulation and epidural spinal cord stimulation. *Appl Neurophysiol* 1986;49:4-24.
34. Krauss JK, Weigel R, Blahak C, et al. Chronic spinal cord stimulation in medically intractable orthostatic tremor. *J Neurol Neurosurg Psychiatry* 2006;77:1013-1016.
35. Reich SG. Painful legs and moving toes. *Handb Clin Neurol* 2011;100:375-383.
36. Hassan A, Mateen FJ, Coon EA, Ahlskog JE. Painful legs and moving toes syndrome a 76-patient case series. *Arch Neurol* 2012;69:1032-1038.
37. Takahashi H, Saitoh C, Iwata O, Nanbu T, Takada S, Morita S. Epidural spinal cord stimulation for the treatment of painful legs and moving toes syndrome. *Pain* 2002;96:343-345.
38. Guieu R, Tardy-Gervet MF, Blin O, Pouget J. Pain relief achieved by transcutaneous electrical nerve stimulation and/or vibratory stimulation in a case of painful legs and moving toes. *Pain* 1990;42:43-48.
39. Miyakawa T, Yoshimoto M, Takebayashi T, Yamashita T. Painful limbs/moving extremities report of two cases. *Clin Orthop Relat Res* 2010;468:3419-3425.

40. Raina GB, Piedimonte F, Micheli F. Posterior spinal cord stimulation in a case of painful legs and moving toes. *Stereotact Funct Neurosurg* 2007;85:307-309.
41. Ikeda K, Deguchi K, Touge T, et al. Painful legs and moving toes syndrome associated with herpes zoster myelitis. *J Neurol Sci* 2004;219:147-150.
42. Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 2010;9:581-591.
43. Hariz MI, Rehncrona S, Quinn NP, Speelman JD, Wensing C. Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years. *Mov Disord* 2008;23:416-421.
44. Yadav AP, Fuentes R, Zhang et al. Chronic spinal cord electrical stimulation protects against 6-hydroxydopamine Lesions. *Sci Rep* 2014;4:3839.
45. Costa RM, Lin SC, Sotnikova TD, et al. Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction. *Neuron* 2006;52:359-369.
46. Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov Disord* 2003;18:357-363.
47. Marceglia S, Foffani G, Bianchi AM, et al. Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease. *J Physiol* 2006;571:579-591.
48. Holsheimer J. Which neuronal elements are activated directly by spinal cord stimulation. *Neuromodulation* 2002;5:6.
49. Fuentes R, Petersson P, Nicoletis MAL. Restoration of locomotive function in Parkinson's disease by spinal cord stimulation: mechanistic approach. *Eur J Neurosci* 2010;32:1100-1108.
50. Sandyk R, Iacono RP. Spinal dopamine mechanisms and primary sensory symptoms in Parkinson's disease. *Int J Neurosci* 1987;32:927-931.
51. Del Tredici K and Braak H. Spinal cord lesions in sporadic Parkinson's disease. *Acta Neuropathol* 2012;124:643-664.
52. Dooley DM, Nisonson I. Treatment of patients with degenerative diseases of the central nervous system by electrical stimulation of the spinal cord. *Appl Neurophysiol* 1981;44:71-76.