REVIEW

Electrical Stimulation of the Dorsal Columns of the Spinal Cord for Parkinson's Disease

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ABSTRACT: Spinal cord stimulation has been used for the treatment of chronic pain for decades. In 2009, our laboratory proposed, based on studies in rodents, that electrical stimulation of the dorsal columns of the spinal cord could become an effective treatment for motor symptoms associated with Parkinson's disease (PD). Since our initial report in rodents and a more recent study in primates, several clinical studies have now described beneficial effects of dorsal column stimulation in parkinsonian patients. In primates, we have shown that dorsal column stimulation activates multiple structures along the somatosensory pathway and desynchronizes the pathological cortico-striatal oscillations responsible for the manifestation of PD symptoms. Based on recent evidence, we argue that neurological disorders such as PD can be broadly classified as diseases emerging from abnormal neuronal timing, leading to pathological brain states, and that the spinal cord could be used as a "channel" to transmit therapeutic electrical signals to disrupt these abnormalities. © 2017 International Parkinson and Movement Disorder Society

Key Words: spinal cord stimulation; Parkinson's disease; neuronal oscillations; deep brain stimulation; dopamine

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease[1-3] resulting from the loss of dopamine-producing brain cells in the substantia nigra pars compacta.[4] Patients suffering from PD experience progressive motor impairments,[1] which include tremor, rigidity, bradykinesia, and gait instability. It is estimated that approximately 0.4 to 1 million Americans live with PD.[5,6] Although dopamine replacement therapy, through administration of the dopamine precursor L-3,4-dihydroxyphenylalanine (L-dopa), effectively ameliorates PD symptoms in the early stages of the disease,[7] prolonged use of the drug results in dose-limiting side effects,[8,9] reduced efficacy,[10,11] and complications such as L-dopa–induced dyskinesia.[12,13] In this context, additional therapeutic strategies, such as deep brain stimulation (DBS), that have proven to be effective for treating the main PD motor symptoms have attracted considerable attention in the past few decades.[14-17]

Despite its unquestionable success, there are some disadvantages associated with DBS. First, it requires a highly invasive and expensive surgical procedure, which targets a very small structure deep in the brain.[18,19] Because of this, the neurosurgical procedure for DBS comes associated with a 1.1% risk of death during the operation and 1.2% to 15.2% risk of other major complications.[20-23] This means that only very experienced functional neurosurgeons can perform the procedure. Altogether, these factors, in particular the procedure's invasiveness, limit the procedure to just a small fraction of severely ill PD patients: 1.6% to 4.5%.[24-26]

Another important issue is that, although DBS produces a very significant improvement of the patient's tremor and rigidity, it is less effective in treating those

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who suffer primarily from bradykinesia or gait instability and "freezing."[14,27,28] Thus, although DBS greatly improves the quality of life in patients with advanced PD by addressing the disease's cardinal motor symptoms while reducing levodopa-induced dyskinesias, locomotion impairment can be extremely disabling and severely affect the quality of life of PD patients, even when the primary symptoms are controlled by this surgical therapy. Furthermore, if one considers that standard treatments for bradykinesia and freezing, such as physical therapy, are often ineffective in PD, it becomes clear that novel therapeutic approaches are required to address postural instability and gait disturbance in PD patients.[24,29,30]

In this context, a significantly less invasive method—epidural dorsal column stimulation (DCS)—has been suggested by our laboratory as an alternative approach for symptomatic treatment of PD. DCS is a well-established therapy for the treatment of chronic neuropathic pain. In the United States, DCS has been approved by the Food and Drug Administration for treating chronic low back and limb pain.[31] Back in 2009, our laboratory reported on the initial experimental demonstrations of the potential therapeutic benefit of DCS in multiple rodent models of PD.[32] Initially, we demonstrated an acute effect of DCS on akinesia and bradykinesia in rodents.[32] Later, the same effect was reproduced in nonhuman primate models.[33] Further studies revealed both a long-term motor improvement and a neuroprotective effect on the rat nigrostriatal dopaminergic system of rodents, following chronic DCS.[34]

Following these initial studies, other laboratories have independently validated our animal findings.[35,36] In parallel, during the past 7 years, several independent clinical studies in PD patients with abnormal posture and gait disturbances have demonstrated positive results with DCS.[37-43]

The central goal of this short review is to cover the recent literature that supports our initial contention that DCS can become a useful new therapy for PD, particularly for those patients who cannot benefit from DBS because their main symptoms are related to gait dysfunction.

Spinal Cord Stimulation

Electrical stimulation of the dorsal funiculus of the spinal cord was first used for the treatment of chronic pain by Shealy and colleagues at Case Western Reserve University in 1967.[44] Since then it has become a treatment for different pain syndromes such as pain from failed back surgery syndrome or intractable low back pain[31,45,46] and also investigated for numerous novel pain syndromes.[47-49] The rationale for using DCS in pain treatments was initially provided by the classic gate control theory of pain proposed originally by Melzack and Wall.[50] According to the theory, by activating the large diameter, myelinated, nonnociceptive fibers of the dorsal funiculus of the spinal cord, DCS would produce a closing of the "gate" at the dorsal horns, leading to suppression of the noxious stimuli carried by the much smaller unmyelinated C fibers that transmit nociceptive information that contributes to the genesis of pain. Subsequently, other potential mechanisms for the suppression of pain by DCS were uncovered, including the following:

1. Paresthesia triggered by the activation of supraspinal circuits produced by orthodromic activation of dorsal columns (DCs),[51,52]
2. Changes in the local transmitter systems and the suppression of dorsal horn neurons in the case of neuropathic pain,[53,54] and
3. The balance of the oxygen supply and demand by inhibition of sympathetic activity in the case of ischemic pain.[51,55]

Interestingly, over the years and in parallel with the growing use of this approach for chronic pain, several reports of the potential therapeutic effects of DCS in improving motor symptoms in patients suffering from various motor disorders, such as dystonia,[56-59] multiple sclerosis,[60] nonparkinsonian tremor,[61,62] and painful leg and moving toes syndrome,[63,64] have appeared in the literature.[65]

Although the exact neurophysiological mechanisms involved in relieving the symptoms in these motor disorders by DCS have not been elucidated, computational modeling studies have shown that epidural electrical stimulation of the spinal cord, when applied within the therapeutic range, usually activates DC fibers and the dorsal roots in the vicinity of the stimulating cathode.[66] In addition, functional magnetic resonance imaging during DCS application in patients revealed clear modulation of activity in cortical structures, such as primary and secondary somatosensory cortices (S1 and S2), prefrontal cortex, cingulate cortex, insula, and thalamus.[67-69]

DCS has also been shown to cause changes in c-fos expression in supraspinal structures, which in turn may lead to long-term sustained effects.[70,71] Both of these findings are consistent with the neurophysiological and immunohistochemical results obtained in our animal studies with DCS, which show that this approach disrupts pathological oscillations around the cortical-basal ganglia circuitry while inducing a neuroprotective effect on the dopaminergic neurons of the nigrostriatal system.[34]

Low-Frequency Neuronal Oscillations Are Correlated With PD Symptoms

The basal ganglia is involved in the execution of goal-directed behavior in conjunction with the cortex

via an extensive circuitry formed by multiple structures that share feedforward and feedback pathways.[72] Multiple clinical studies in parkinsonian patients have detected the presence of pathologically high levels of synchronous oscillatory neuronal and local field potential activity in the basal ganglia, which is particularly prominent in the beta frequency range of 15 to 30 Hz.[73-75] Animal models of PD also exhibit similar pathological activity. For example, monkeys treated with the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) show a significant increase in the fraction of basal ganglia neurons with oscillatory frequency in the 3 to 8 Hz and 8 to 15 Hz ranges. Often this neuronal activity is correlated with the animal's tremor.[76,77] Multiple reports using the MPTP model have identified neuronal synchronous oscillatory activity in the subthalamic nucleus (STN), internal globus pallidus, external globus pallidus, and substantia nigra pars reticulata neurons.[76,78] Similarly, studies involving the 6-hydroxydopamine (6-OHDA) rat model have also demonstrated the presence of beta frequency (15-30 Hz) oscillations in STN and substantia nigra pars reticulata.[79-81]

Sharott and colleagues[80] demonstrate that the power of beta frequency oscillations and their coherence between the STN and cortex was significantly reduced after the administration of apomorphine (a dopamine agonist) in rats, shifting the peak coherence to higher frequencies, a phenomenon we have also observed after L-dopa administration in dopamine-depleted mice.[82] This effect coincides with previous observations in the basal ganglia areas of parkinsonian patients after dopaminergic medication.[83,84] In monkeys, dopamine replacement therapy[85] and STN inactivation through DBS[86] significantly ameliorate MPTP-induced tremor while reducing prominent 8 to 20 Hz oscillations in the basal ganglia. DBS has shown to effectively improve PD symptoms in humans while attenuating synchronous beta band activity in the cortico-basal ganglia network.[87-90] It is, however, important to note that the reduction in beta band activity after medication as well as DBS is often correlated with the improvement in motor performance, suggesting that the attenuation of oscillatory and synchronous neural activity has a therapeutic effect on PD symptoms.[91-93]

Spinal Cord Stimulation Mechanism for PD

For the past 7 years, our laboratory has studied the effects of DCS on PD symptoms in rodents and nonhuman primates. Based on previous evidence that electrical stimulation of the peripheral afferents of a major somatosensory pathway could be used to induce potent cortical desynchronization,[94] we proposed that high-frequency synchronous activation of the DC fibers could lead to cortico-striatal desynchronization, thereby causing the alleviation of PD symptoms. Our studies revealed that DCS treated animals exhibited much higher levels of locomotion than dopamine-depleted mice, 6-OHDA lesioned rats, and 6-OHDA lesioned marmosets.[32-34] Increased oscillatory power in the 1.5 to 4 Hz and 10 to 15 Hz bands and decreased power in 25 to 55 Hz bands was observed during the dopamine-depleted state in mice.[32] DCS created a shift in spectral power from lower to higher frequencies (Fig. 1) and produced a neuronal firing pattern similar to the one observed prior to locomotion initiation.[32] The fraction of neurons in the M1 and striatum that were entrained to the Local Field Potential (LFP) activity also dropped considerably after the application of DCS. Although the onset of locomotion on DCS application was delayed by a few seconds, the changes in neuronal activity were almost spontaneous. These findings suggested that DCS created a brain state permissible for locomotion onset.

Thereafter, our study using a marmoset monkey model of PD revealed that DCS indeed alleviates akinesia and restores the pathological brain state, defined by abnormal neuronal bursting and oscillatory activity, to normalcy by altering the functional coupling between multiple areas in the cortico-basal ganglia-thalamic loop.[33] During the induced PD state, we observed a significant increase in functional coherence, in the 8 to 15 Hz range, between multiple neural structures that belong to the cortical-basal ganglia circuitry. During DCS, however, this enhanced coherence—which can also be seen as enhanced functional connectivity—was reduced, an effect similar to what was observed after L-dopa administration. DCS resulted in the suppression of 8 to 20 Hz beta band LFP power as well as the beta rhythmicity of neurons

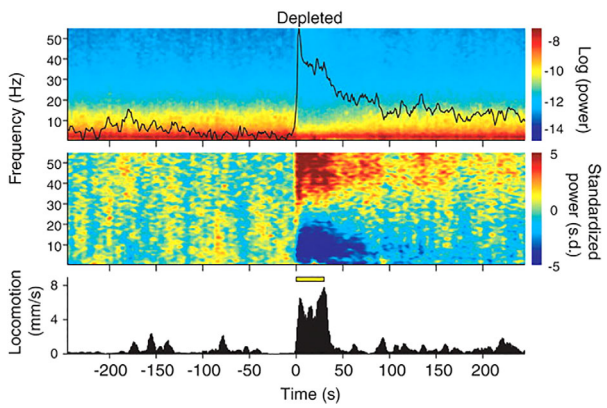

FIG. 1. Dorsal column stimulation (DCS) restores locomotion and desynchronize corticostriatal activity (reprinted with permission; originally published in Fuentes et al.[32]). Average spectrograms of striatal local field potentials (LFP) (in dopamine-depleted mice) recorded around 300-Hz stimulation events (yellow bar) shown in top row indicates the spectral power (denoted by black trace) shifting to higher frequencies, middle row showing LFP power standardized to first 240 seconds demonstrates desynchronization, whereas the bottom row shows increased locomotion during stimulation "ON" period.

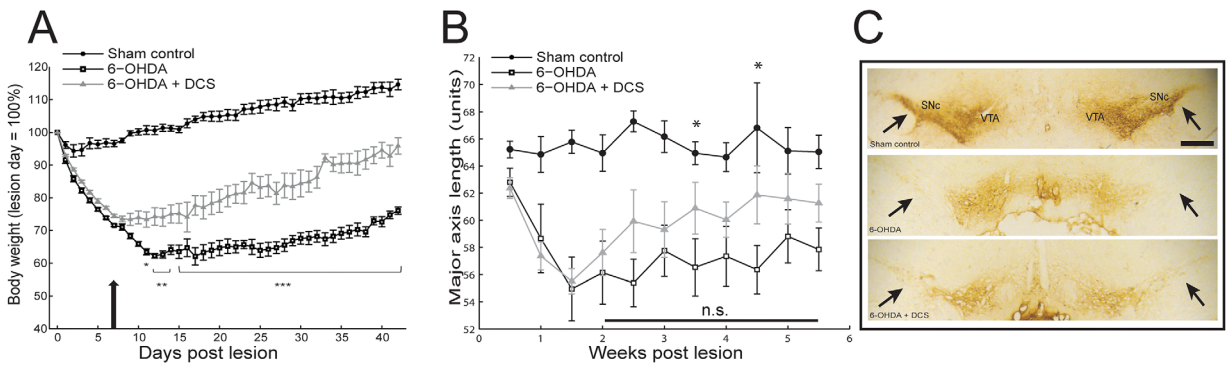

FIG. 2. Dorsal column stimulation (DCS) reverses weight loss, restores motor function, and protects dopaminergic neurons in a 6-hydroxydopamine (6-OHDA) model of Parkinson's disease (reprinted with permission; originally published in Yadav et al.[34]). (**A**) Changes in body weight after bilateral intrastriatal 6-OHDA lesion with or without DCS treatment. Lesioned, nontreated rats (n = 8) suffered sustained weight loss with little to no recovery. Lesioned rats with DCS treatment (n = 7, 30 minutes, 333 Hz continuous DCS during 30 minutes twice a week, starting 7th day, black arrow) recovered body weight significantly faster than nontreated rats. (**B**) Lesioned rats develop crouched posture resulting in shorter major axis length. DCS treatment restores posture significantly faster than nontreated rats. (**C**) Representative immunostaining for tyrosine hydroxylase in substantia nigra pars compacta (SNc); scale bar = 500 um. There was a significant difference between the tyrosine hydroxylase (TH) levels of 6-OHDA and 6-OHDA+DCS groups in the SNc. VTA, ventral tegmental area.

in the cortico-basal ganglia-thalamic loop. Detailed analysis revealed that DCS activation of the primary somatosensory cortex via the ventral posterolateral nucleus of the thalamus induces a potent disruption of beta oscillations in multiple cortical and subcortical neural structures via a phase reset mechanism, where the LFP oscillations get phase locked to the incoming DCS pulses.[33] This finding corroborated our original hypothesis that DCS desynchronizes corticostriatal oscillations, following the activation of the DC–medial lemniscal pathway.

Preliminary Evidence of Neuroprotection

In a subsequent series of experiments (Fig. 2), we investigated the long-term effects of DCS on animal body weight, motor symptoms, and survival of nigrostriatal dopaminergic neurons in a chronic rat model of PD using 6-OHDA lesioning.[34] This study revealed that the application of DCS at regular intervals led to a progressive improvement in the observed motor impairment, such as gait and postural instability, and an accelerated recovery from weight loss. When compared with untreated control animals, motor improvement was accompanied by a higher density of dopaminergic innervation in the striatum and higher neuronal cell counts in the substantia nigra pars compacta (SNc) of DCS-treated rats. These results suggest that DCS applied in 6-OHDA-treated rats induced both a functional and structural recovery in the nigrostriatal circuitry. Remarkably, such a neuroprotective effect was achieved by delivering DCS for 30 minutes, twice a week only, suggesting that better effects could be produced by more frequent therapy. These results have now been replicated independently by another laboratory,[36] which reported that 1 hour/day of DCS, delivered for 16 consecutive days, resulted in the improvement of PD symptoms and the significant preservation of tyrosine hydroxylase (TH) fibers in the striatum and TH-positive neurons in the SNc. Although the cellular mechanism underlying this putative long-term neuroprotective action of DCS remains to be investigated, Shinko and colleagues[36] also reported that DCS treatment upregulated the levels of vascular endothelial growth factor, a finding that could account, at least partially, for the observed neuroprotective effects. Support for this idea comes from studies in which intrastriatal injections of glial-derived nerve growth factor (GDNF) and brain-derived neurotrophic factor (BDNF) have shown significant protection or restoration following 6-OHDA or MPTP lesions.[95-98] Comparative analysis revealed that GDNF was more effective than BDNF for correcting behavioral deficits and protecting nigrostriatal DA neurons.[99] Spieles-Engemann and colleagues[100] have shown that STN DBS also exerts a neuroprotective effect on the SN neurons in a 6-OHDA rodent model of PD. A follow-up study from the same group revealed that this effect could be mediated by the increased levels of BDNF in the nigrostriatal system and the primary motor cortex.[101] Shinko and colleagues note that upregulation of vascular endothelial growth factor may protect the nigrostriatal dopaminergic system by improving microcirculation in the striatum as a result of enhanced glial proliferation and angiogenesis.[36] Although the results showing neuroprotection in animal models using DCS or DBS are promising, there is no clinical evidence supporting this claim, suggesting that further investigation using DCS in parkinsonian humans is necessary.[102]

TABLE 1. Clinical studies of spinal cord stimulation for Parkinson's disease

Study	No. of patients	Patients' age, y	Disease duration, y	Diagnosis	Stimulation		Evaluation method	Follow-up	Results
					Location	Frequency (Hz)			
Thevathasan et al, 2010[103]	2	75-77	NA	PD with moderate to severe motor impairments	High cervical	130 and 300	Motor UPDRS, timed 10 meter walk, timed hand-arm movement test, timed lower limb tapping	10 days	No improvement
Weise et al, 2010[43]	1	72	17	PD (Hoehn/Yahr stage IV) with chronic back pain	Cervicothoracic		NAS, UPDRS III, up and go test	NA	Improvement in NAS score but not UPDRS
Fenelon et. al. 2011[39]	1	74	5	PD with lower back neuropathic pain	T9-T10	130	VAS for pain, UPDRS and 7 meter walk and back	4 sessions two to five weeks apart	>50 improvement in UPDRS scores
Agari et al, 2012[37]	15	63-79	7-31	PD (Hoehn/Yahr stage III and IV) with low back and lower limb pain	T7-T12	5-20	VAS for pain, UPDRS ADL and motor, TUG, 10 meter walk test	12 months	Improvement >50% for VAS, improvement in TUG at 3 months, and 10 metre walk at 3 and 12 months, improvement in UPDRS II (items 12,15) and III (items 28,29,30,31)
Landi et al, 2012[41]	1	65	8	Advanced PD with chronic intractable leg pain	T9-T10	30	VAS for pain, quality of life, 20 meter walk and UPDRS III	16 months	Improvement of 70% in VAS score for pain, 20% in 20 meter walk time, 60% in quality of life, No change in UPDRS III
Hassan et al, 2013[40]	1	43	8	PD with chronic neuropathic pain in neck and upper extremities	C2	40	VAS for pain, UPDRS and timed 10 meter walk test	2 years	Improvement in VAS pain score throughout follow-up and timed 10 meter walk, UPDRS score: 28 (early post-operative), 22 (1 year) and 16 (2 year)
Soltani & Lalkhen 2013[42]	1	68	NA	PD with post-laminectomy syndrome pain	T9-T11	60	Patient observation	NA	Improvement in leg pain and left sided resting tremor

(Continued)

TABLE 1. *Continued*

Study	No. of patients	Patients' age, y	Disease duration, y	Diagnosis	Stimulation		Evaluation method	Follow-up	Results
					Location	Frequency (Hz)			
Mitsuyama et al, 2013[104]	2	NA	07-10	Chronic low back pain associated with PD Hoehn/Yahr stage II	Midthoracic	NA	VAS for pain, walking posture and bradykinesia	NA	>50% pain relief, improvement in walking posture, no change in bradykinesia
Arii et al, 2014[38]	37	50-85	NA	PD (Hoehn/Yahr stage III and IV) with camptocormia (anterior flexion of thoracolumbar spine $\geq$ 45%)	Lower thoracic to upper lumbar	5 Hz rTSMS	thoracolumbar spine flexion angle in standing and seated position	acute	Significant improvement in thoracolumbar spine flexion angle in both standing (10.9°) and seating (8.1°) positions
Nishioka & Nakajima 2015[107]	3	67-80	05-10	PD with severe intractable lower back and lower limb pain	T8-L1	5-65	VAS and WPI for pain, UPDRS and Hoehn/Yahr for PD	1 year	Improvement in VAS pain score, and UPDRS score
de Souza et al, 2016[108]	4	56-69	NA	Advanced idiopathic PD with significant PIGD after bilateral STN DBS	Upper thoracic (T2-T4)	300	TUG, TUG-DT, 20 minute walking with/without obstacles, PDQ-39, UPDRS III	6 months	Improvement of 63.2% for TUG, 54% TUG-DT, 63.3%/58% 20-minutes walking with/without obstacle, 44.7% for PDQ-39, 38.3% for UPDRS III

NAS, Numeric Analog Scale; VAS, Visual Analog Scale; WPI, Widespread Pain Index; ADL, Activities of Daily Living; TUG, Timed-Up-Go; TUG-DT, Timed-Up-Go with Dual Task; PDQ, Parkinson's Disease Questionnaire; PIGD, postural instability and gait disturbance; UPDRS, Unified Parkinson's Disease Rating Scale; rTSMS, Repetitive Trans-Spinal Magnetic Stimulation; NA, not available.

Clinical Studies in PD Patients

Following our original report showing that high-frequency DCS alleviated akinesia and bradykinesia in rodent models of PD, Thevathasan and colleagues[103] investigated the effect of DCS on motor function in 2 patients with advanced PD in a double-blind cross-over study. Patient 1 was stimulated at 130 Hz, whereas patient 2 received 300 Hz, and the following assessments were made 10 days postoperatively (see Table 1) using the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, timed 10-meter walk, timed hand-arm movements, and timed lower limb in 3 different conditions (off-stimulation, suprathreshold stimulation, and subthreshold stimulation). In this study, DCS failed to provide improvement in all of the assessments. However, after closely analyzing the experimental design of this study, we argued that this clinical study failed to show significant improvements in PD symptoms mainly because of major differences in both the geometry of stimulation electrodes used and the chosen location of the implant along the spinal cord.[105] Support for our contention followed soon after, when several clinical groups around the world began to report positive results with DCS in PD patients. For example, a 74-year-old man who had originally been implanted with a DCS electrode in the T9-T10 epidural area for treating back pain because of failed back surgery syndrome, reported increased tremor when the stimulator was turned off.[39] Clinical examination revealed that the patient had developed PD-related tremor 8 years after the implantation of DCS. When DCS stimulation was turned on and a 130-Hz stimulus was employed, the patient's UPDRS-III scores (evaluated during 4 separate sessions) improved by almost 50%. Tremor in the upper and lower limbs showed significant improvement during the stimulation-on condition while axial symptoms of gait and posture were also improved.

In another case report, a 68-year-old woman implanted with DCS electrodes for postlaminectomy syndrome exhibited dramatic clinical improvements in her parkinsonian tremor in concurrence with relief from leg pain when DCS stimulation was delivered at 60 Hz.[42] Another 43-year-old woman with a PD history was implanted with DCS electrodes at the C2 level for neuropathic pain in her neck and upper extremities.[40] After years 1 and 2 of DCS treatment, using a stimulation frequency of 40 Hz, her motor UPDRS scores showed significant progressive improvements, leading to a significant reduction in tremor, rigidity, gait imbalance, and neuropathic pain.

A total of 15 patients (5 men and 10 women), ranging in age from 63 to 79 years (mean 71.1 years), with complaints of low back and leg pain received DCS implants in the thoracic area T7 to T12, depending on pain localization.[37] Overall, 7 of these patients had previously undergone DBS in the STN. At 1 year after surgery, the pain scores and the UPDRS scores were significantly improved. There was a clear relief of gait disorder and postural instability, indicating that DCS had a remarkable effect on the axial symptoms associated with advanced PD. Another study by Arii and colleagues[38] involving 37 PD patients with camptocormia (a treatment-resistant postural abnormality) demonstrated an immediate effect using repetitive trans-spinal magnetic stimulation in the lower thoracic to upper lumbar vertebral area. Landi and colleagues[41] also reported significant improvement in gait and postural stability in a patient with advanced PD who had previously undergone STN DBS. Another advanced PD patient implanted with DCS electrodes for chronic back pain showed no improvement in UPDRS scores or locomotion.[43] Mitsuyama and colleagues[104] reported pain relief as well as significant improvement in walking posture in 2 patients with chronic lumbar pain and PD symptoms of abnormal posture, sagittal imbalance, and difficulty in locomotion. Similarly, 3 PD patients, who also suffered from intractable pain as a result of failed back surgery syndrome and lumbar canal stenosis, showed remarkable improvement in pain as well as rigidity and tremor reflected in their UPDRS III scores.[107] Finally, in a more recent study[108] conducted by a neurosurgical team at the University of São Paulo, Brazil, in 4 long-term PD patients who had been subjected to DBS 7 to 8 years prior but still exhibited serious problems in locomotion including freezing, at the time of testing, 300 Hz DCS was found to induce a significant improvement in patient gait (Timed-Up-Go [TUG], 50%-65%) and the 20-minute walking test (50%-60% on time and 65%-70% on the number of steps). A significant improvement in UPDRS III (38% OFF meds; $P = .017$), Freezing of Gait (FOG) (56%; $P = .04$), and Parkinson's Disease Questionnaire (PDQ)-39 (mobility 57%, $P = .003$; Activities of Daily Living (ADL) 28%, $P = .02$) was also documented.

Based on the data described in the previous paragraph, it is fair to say that, 7 years after our initial report in rodents, a beneficial clinical effect of DCS on alleviating multiple parkinsonian symptoms has been consistently reported by several independent groups. These preliminary clinical studies validated our original proposal that DCS should be further examined as a potential new therapy for PD, particularly in cases involving gait problems and freezing. Encouraging as they are, however, it is important to emphasize that these initial clinical results involved a small and heterogeneous number of patients, tested in an open-label and heterogeneous fashion. For example, in 1 case the patients were >70 years old, whereas in 2 other cases they were aged 43 and 68 years.[40,42,103] Studies varied

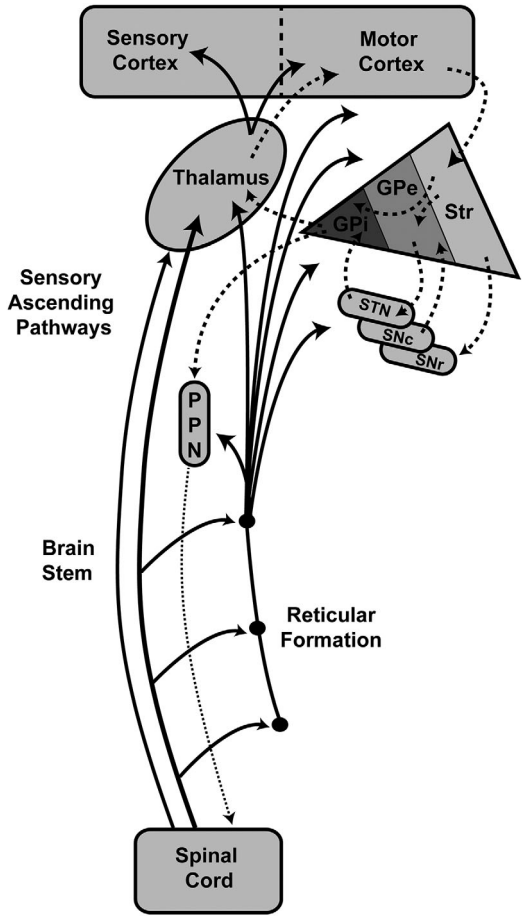

FIG. 3. Illustrative model of the motor circuitry involving the direct and indirect pathways of basal ganglia, thalamus, and cortex and also the pathways from the postural and gait control with projections from the basal ganglia to the pedunculopontine nucleus and the spinal cord. (adapted with permission; originally published in de Andrade et al.[106]). PPN, pedunculopontine nucleus; Str, striatum; GPe, globus pallidus external segment; GPi, globus pallidus internal segment; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulate.

in the type of electrodes used, stimulation parameters selected, number of sessions performed, and timeline of symptom evaluation. Moreover, most patients also exhibited a broad range of pain symptoms in addition to PD symptoms. Although most patients had relief from symptoms of pain, Thiriez and colleagues[65] argue that the effect of DCS on PD motor symptoms in these multiple studies might depend on the patients' initial quality of response to L-dopa therapy. Thus, although the initial human results seem promising (summarized in Table 1), large, randomized, double-blind, clinical studies need to be performed to truly assess the potential therapeutic effects of DCS in PD and other motor disorders.

It is also important to highlight that the effect of DCS on axial symptoms of PD was noticeable in more recent clinical studies.[37,39,40] The role of the pedunculopontine nucleus (PPN)—a part of the mesencephalic locomotor region in the brain stem in the pathophysiology of PD—has gained considerable interest in recent times. Similar to striatal lesions, PPN lesions in rhesus monkeys have resulted in parkinsonian symptoms of bradykinesia, hypokinesia, and flexed posture.[109,110] Stimulation of the PPN in PD patients has resulted in significant improvements in axial symptoms, such as gait imbalance and postural instability, suggesting that DCS may also exert its clinical effect by modulation of PPN activity.[111-113] Alternatively, other studies have highlighted the moderate response to PPN-DBS during longer evaluation periods and its inadequacy as an alternate target for DBS when not used in conjunction with STN-DBS.[27,114,115] However, the fact that PPN has reciprocal connections with the cortex, thalamus, basal ganglia, and spinal cord[116] implies that modulation of PPN either by ascending pathways from the DCs or by indirect descending pathways from the cortex might play a crucial role in the alleviation of PD symptoms (Fig. 3).

The Spinal Cord as a Potential Common Neural Pathway for Treating Multiple Brain Disorders With Electrical Stimulation

The spinal cord serves as a true "neural information highway" transmitting non-noxious as well as nociceptive sensory information from various parts of the body to supra-spinal structures in the brain. Although spinal cord stimulation has been used for the treatment of chronic pain for decades, its role as a channel to deliver therapeutic electrical signals to the cortex and other subcortical targets has never been explored.[31] Traditionally, it has been assumed that, to cause cortical or subcortical neuronal modulation, the electrical stimulation has to be applied at the target site, which is evident in earlier approaches where intracortical microstimulation of areas 3b and 3a of the somatosensory cortex was used for creating artificial sensation of flutter and proprioception, respectively.[117-119] However, more recently, thalamic stimulation or even peripheral nerve innervation have been used for the same purpose, suggesting that multiple locations along a neural pathway can be used for modulating the activity of the target of interest.[120,121] Consistent with this argument, we had previously used electrical nerve stimulation to treat epileptic seizures.[94] Recently we reported that closed-loop DCS can also be used to reduce the frequency and duration of seizures in a Pentylenetetrazol (PTZ) rat model of epilepsy, primarily by modulating the theta frequency oscillations in the somatosensory cortex.[122]

DCS has also been used for the remodeling of corticospinal projections in spinal cord injured rats, leading

to partial recovery of locomotion.[123] As mentioned previously, although functional magnetic resonance imaging studies revealed distinct modulation of cortical structures on the administration of DCS, it is also known to cause gene expression changes in upstream pathways.[69,71] This suggests that the stimulation of the DCs does indeed result in the electrical signal being transmitted to multiple cortical and subcortical areas of great interest, from a therapeutic point of view, in the human brain.

In addition, research on PD patients undergoing tango lessons has shown that the asymmetrical movements involved in this type of dancing could be providing the sensory feedback necessary for improvement in symptoms of balance and gait.[124,125] Because proprioceptive signals run primarily through some of the largest myelinated axons that comprise the DC of the spinal cord, the observations that increased proprioceptive feedback is correlated with improvements in PD symptoms strongly support our claim that high-frequency electrical stimulation of the dorsal funiculus of the spinal cord could provide therapeutic effects for PD. Accordingly, future implementation of a closed-loop DCS, which allows intermittent and not only continuous DCS, may provide a better strategy to maximize this beneficial effect.

Pathological Brain States as Neuronal Timing Disorders

Synchronization of neuronal oscillations is representative of the temporally precise interactions necessary for neural communication to occur between multiple areas in a neural circuit.[126] High-frequency oscillations are observed in local neuronal areas, whereas slow oscillations recruit large networks. The relation between neural circuit architecture and oscillatory patterns is responsible for the dynamic establishment of normal brain operations carried out across spatial and temporal scales.[127] Earlier work in human patients using EEG emphasized the role of neural synchrony in cognitive functions, such as attention dependent stimulus selection and working memory tasks that require integration of distributed neural activity.[128,129] Although EEG recordings showed that synchronization of rhinal and hippocampal oscillations takes place during memory formation,[130] using multielectrode recordings we have demonstrated that hippocampal and prefrontal cortical oscillations synchronize during spatial-cognitive processes.[131] Ulhass and colleagues[132,133] observed impaired neural synchrony in schizophrenia patients performing a cognitive task particularly reduced phase synchrony in the beta band (20-30 Hz), suggesting the relation between impaired neuronal synchrony and cognitive deficits associated with schizophrenia. Previous work in our laboratory has shown that, although cross-structural synchronization of oscillations in the limbic circuit plays an important role in the manifestation of anxiety-related behaviors in healthy animals, deficits in the neuronal oscillations can lead to the development of behaviors that are typically characterized as bipolar mania disorder.[134] We show that the nucleus accumbens–ventral tegmental area synchrony and nucleus accumbens–amygdala synchrony increases during specific phases of the elevated zero-maze task and that the correlation between synchrony and anxiety-related behaviors changes between healthy and diseased mice.[134]

EEG and functional magnetic resonance imaging studies of autistic children have also revealed reduced neural synchronization, characterized by a decreased functional connectivity between neural areas,[135,136] particularly in the cortical language system during comprehension of sentences[137] or between frontal and parietal areas during an executive task.[138] Similarly, the reduction of alpha and beta band synchronization has been implicated in patients with Alzheimer's disease during the resting state,[139,140] and the reduction is correlated with the severity of the cognitive deficits.[141] Pijnenburg and colleagues[142] showed that in Alzheimer's disease patients, alpha and beta band synchronization decreased during a working memory task when compared with controls. Moreover, our research has demonstrated that neuronal synchronization increases between the amygdala and medial prefrontal cortex circuits in a mouse model of depression.[143] Likewise, an increase in mesolimbic cross-structural coherence was correlated with hyperactivity and stereotyped behaviors in a model of hyponoradrenergia.[144]

These results suggest that many neurological disorders are characterized by pathological levels of neuronal synchronization, occurring in distinct neural circuits involved in key brain functions. In fact, in our decade-long survey of transgenic mice models of neurological/psychiatric disorders, we have always identified a particular brain circuit in which pathological levels of neuronal oscillations or synchronization can be identified and found to correlate with the behavior abnormalities exhibited by each mouse strain. This led us to postulate that, independent of their specific etiology (eg, genetic, specific cellular degeneration, etc.), a large number of intrinsic brain disorders may produce abnormal motor, sensory, cognitive, and emotional outcomes as a result of fundamental disturbances in neuronal timing, taking place in specific brain circuits. Based on this view, we propose that any technique that can reset the pathological neuronal timing of a given neural circuit, bringing it close to a normal dynamic state, may be capable of ameliorating the symptoms, and hence the brain pathology, created by

such electrophysiological disturbance. Support for this contention came from the observation that neuronal activity recorded in both PD animal models and parkinsonian patients often resembles the type of pathological neuronal hyper-synchronization that is prominent during epileptic seizures.[145,146] Our results with animal PD models and, more recently in an animal model of epilepsy,[122] indicate that DCS may achieve its major therapeutic effects by disrupting ongoing supraspinal pathological synchronization by simultaneous activation of DC fibers in the spinal cord.

Based on a decade of experimental work in animal models of brain disorders, we envision that the spinal cord "neural super highway" may become an optimal route to deliver different types of electrical, optical, and even noninvasive magnetic stimulation to manipulate or even abolish pathological neuronal activity in supraspinal structures. This approach could trigger the establishment of a complete new repertoire of non-pharmacological, low-cost, and less invasive, neurophysiologically inspired therapeutic options for treating a variety of neurological and even psychiatric diseases for which we have very few efficient treatments available today.

Concluding Remarks

After the original experimental findings in animal models of PD carried out in the late 2000s, multiple preliminary studies have reported the beneficial clinical effects of DC stimulation in PD patients. DCS effects are not only significant in motor symptoms such as akinesia, bradykinesia, and tremor, but they also provide significant alleviation of axial symptoms, gait and posture impairment, and "freezing," a range of problems that are difficult to treat with current therapeutic options, such as DBS. Current experimental evidence from our laboratory suggests that DCS modulates activity of subcortical and cortical structures by activating ascending DC fibers of the spinal cord. Although the precise mechanism is not yet clear, high-frequency continuous DCS appears to disrupt the pathological low-frequency hypersynchronized neuronal firing observed in the basal ganglia and motor cortex, which has been associated with PD. Indeed, the neurophysiological effects observed with DCS in experimental animals mimic those observed during dopamine-replacement therapy. In addition, in rodents, DCS also has produced a long-term protective effect on the degeneration of dopaminergic neurons, making it a promising treatment option for early-stage PD along with traditional levodopa therapy. Because of its semi-invasive nature, we propose that in the future DCS may become a potential therapeutic alternative for DBS. ■

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