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Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms

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ABSTRACT

Background: Deep brain stimulation (DBS) is an established and effective treatment for Parkinson's disease (PD). After surgery, a number of extensive programming sessions are performed to define the most optimal stimulation parameters. Programming sessions mainly rely only on neurologist's experience. As a result, patients often undergo inconsistent and inefficient stimulation changes, as well as unnecessary visits.
Objective/hypothesis: We reviewed the literature on initial and follow-up DBS programming procedures and integrated our current practice at Toronto Western Hospital (TWH) to develop standardized DBS programming protocols. We propose four algorithms including the initial programming and specific algorithms tailored to symptoms experienced by patients following DBS: speech disturbances, stimulation-induced dyskinesia and gait impairment.
Methods: We conducted a literature search of PubMed from inception to July 2014 with the keywords "deep brain stimulation", "festination", "freezing", "initial programming", "Parkinson's disease", "postural instability", "speech disturbances", and "stimulation induced dyskinesia". Seventy papers were considered for this review.
Results: Based on the literature review and our experience at TWH, we refined four algorithms for: (1) the initial programming stage, and management of symptoms following DBS, particularly addressing (2) speech disturbances, (3) stimulation-induced dyskinesia, and (4) gait impairment.
Conclusions: We propose four algorithms tailored to an individualized approach to managing symptoms associated with DBS and disease progression in patients with PD. We encourage established as well as new DBS centers to test the clinical usefulness of these algorithms in supplementing the current standards of care.

Introduction

Deep brain stimulation (DBS) is an established and effective treatment for Parkinson's disease (PD). Three brain nuclei are on-label targets for DBS in PD: subthalamic nuclei (STN), globus pallidus pars interna (GPi) and ventral intermediate (Vim) nucleus of the thalamus [1]. After electrode(s) implantation, connection wires are internalized and connected to an implantable pulse generator (IPG) in the upper chest. Patients then participate in a number of extensive programming sessions to define the best stimulation parameters for optimal symptom management. Programming mainly relies on neurologist's personal experience, as no programming guidelines have been provided so far, with the exception of algorithms proposed by experts for the initial programming of PD patients [2–5]. Other sessions are very often organized during the follow-up visits in order to manage stimulation-induced side effects [e.g., speech problems and stimulation-induced dyskinesias] or the worsening of the underlying parkinsonism. While the usefulness of these reprogramming sessions is well established [6], no guidelines are available and most of these changes rely on the results of few open-label studies [1,7]. Indeed, although DBS has been in use for almost

Abbreviations: CCS, current-constant stimulation; DBS, deep brain stimulation; FOG, freezing of gait; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; IPG, implantable pulse generator; MRI, magnetic resonance imaging; PD, Parkinson's disease; SNr, substantia nigra pars reticulate; STN, subthalamic nuclei; TEED, total energy delivered; TWH, Toronto Western Hospital; VCS, voltage-constant stimulation; Vim, ventral intermediate nucleus of the thalamus.

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three decades, systematic programming protocols are still lacking, thus leading to inconsistent and inefficient stimulation adjustments, as well as numerous or unnecessary patients' visits. These issues compelled us to find ways to improve the efficiency of our programming sessions aimed at quality improvement of the process, thereby enhancing the patient's quality of care.

Here, we reviewed the literature on initial and follow-up DBS programming procedures and integrated it with our current practice at Toronto Western Hospital (TWH), in order to develop standardized DBS programming protocols to be shared with the scientific and medical community.

Methods

We searched published data in English language on the following topics: (1) initial programming; and (2) follow-up stimulation adjustments (for speech difficulties, stimulation-induced dyskinesias, freezing, festination and postural instability) from inception to July 2014 on PubMed. Keywords included "deep brain stimulation", "festination", "freezing", "initial programming", "Parkinson's disease", "postural instability", "speech disturbances", and "stimulation induced dyskinesia". Six hundred and sixty (660) papers were retrieved. Additional articles were recovered from recent reviews and reference lists of relevant publications. In total, 70 papers were taken into account for this review after excluding those not focused on movement disorders, preclinical studies and duplicated data. Results from the studies related to STN DBS management and considered to build the algorithms are summarized in Table 1.

Initial programming

Available data and recommendations

The only systematic evaluation of the impact of stimulation parameters on cardinal appendicular signs of PD was performed by the Grenoble group in 2002 [27]. The authors evaluated several combinations of settings, including pulse width (from 60 to 450 μs), frequency [from 5 to 185 Hz (Itrel II, Medtronic, Minneapolis, MN, USA) or 250 Hz (Kinetra, Medtronic)], and amplitude (from 1 V up to the highest tolerated value) and concluded that voltage followed by frequency was the most important factor in ameliorating parkinsonian signs [27].

Few papers – mainly driven by authors' own experience – detailed the basic algorithm for initial programming of DBS in PD [2–5].

The goal of the first programming visit after surgery is to determine the therapeutic window for each electrode contact, thus the lowest amplitude threshold for clinical benefits and the lowest amplitude threshold eliciting unwanted side effects [28]. It has been suggested that the initial programming visit should be performed off medication (MED OFF) after an overnight dopaminergic washout to assess the effects of DBS without the interference of medications [28].

Currently, there is debate on the timing of the first programming visit and practice among centers varies [28]. For instance, some teams initiate stimulation 2–3 or 4–5 weeks after hospital discharge [29,30] while others perform the initial programming during the hospitalization period [31]. Although this fast postoperative programming may be more cost-effective and convenient for patients, two important factors may bias the estimation of thresholds when programming is performed soon after surgery: (1) the effect of stimulation on motor symptoms may be covered by the insertional effect (i.e., the transient improvement induced by the mechanical placement of the electrode mimicking a lesion effect), especially after STN DBS [32]; (2) although strong evidence is still lacking, it is conceivable that the threshold for determining the therapeutic window may be biased due to the fluctuation of impedances in the early post-operative period (i.e., impedances are lower after electrode insertion due to the local edema and then higher over the first few days/weeks) [33]. The latter may have important clinical implications when using voltage-constant stimulation (VCS) whereby the current delivered to the tissue is inversely proportional to the electrode impedance [33]. Conversely, current-constant stimulation (CCS), which dynamically adjusts the current to adapt to changes in impedances of the tissue–electrode interface, might offer a more stable stimulation and thus preferred when performing the programming soon after surgery [34].

Indeed, the clinical effect of any programming algorithm is closely related to the electrode location and exclusion of surgical complications (i.e., bleedings, infections). Thus, post-operative neuroimaging is recommended possibly using approved magnetic resonance imaging (MRI) protocols [35]. Before initiating the programming, the impedances for each of the four electrode contacts should also be recorded under standard stimulation parameters to detect any hardware problems immediately following the implantation and to use as a reference for troubleshooting future hardware problems [4]. Then, the therapeutic window for each contact is determined keeping both the pulse width (60 μs) and frequency constant (130 Hz) and applying stepwise increase in amplitude (0.5 V) using a monopolar configuration (i.e., having the IPG as the anode and the contact as the cathode) [2,3].

Rigidity is the most useful sign to determine the benefit of stimulation because its severity does not fluctuate, it responds quickly to stimulation adjustments and it can be reliably examined, even if patient's cooperation is poor [2]. If rigidity is not present then bradykinesia or rest tremor may be used. Unfortunately, the time course of the stimulation response for bradykinesia is longer and is biased by fatigue and the patient's discomfort or expectations, and rest tremor may spontaneously fluctuate [2,3].

Focusing on one of these symptoms, amplitude is increased to determine the threshold for side effects, which can be *somatosensorial* (paresthesia), *motor* (muscle spasms, eye/gaze deviation, stimulation-induced dyskinesias or dystonia), *dysautonomic*, *behavioral* (depression, mania), or *unspecific* (confusion, malaise). Somatosensorial side effects are usually transient but may become permanent with high voltages. Unspecific side effects are only transient and may last few hours after the programming session. Remaining side effects demonstrate no habituation and are usually permanent at a certain threshold. Of note, stimulation-induced dyskinesias rarely occur during parameter adjustments, as they present with a latency of several hours. Finally, the contact with the largest therapeutic window is chosen to start the chronic stimulation, which is typically undertaken with a low amplitude (1.0 or 1.5 V) and slowly titrated in increments of 0.2–0.5 or more during the following days to reduce the risk of stimulation-induced dyskinesias and behavioral side effects [2,3].

There is considerable evidence that the active electrode contacts located either in proximity to the dorsal border of the STN or further dorsal within the subthalamic region are the most effective [36,37]. Regarding globus pallidus stimulation, contacts located in the dorsal GPi and in the GPi/GPe (globus pallidus pars externa) border are most often used [4].

Current limitations and TWH proposal

The initial programming of DBS devices can be a difficult and time-consuming process, requiring a highly trained and experienced individual to achieve desirable results [6]. Although other programming strategies based on local field potentials [38], neuroimaging [39,40], or computational models [41] have been proposed, there are no alternatives to classic manual programming to

Table 1
Studies evaluating the management of speech impairment, stimulation-induced dyskinesia and gait impairment after STN DBS.

Study	Type of study	N. of pts	Sex (F)	Age (SD)	DBS duration (months)	Intervention	Follow-up	Parameters	Outcome	Notes
Speech impairment										
Törnqvist, 2005 [8]	Observational	10	2F	65.1 (4.7)	15.5 (5)	Three conditions: (1) Increase/decrease in amplitude (2) Change in frequency (70,130,185 Hz) (3) Different contacts as cathode	Immediate	Different parameters for each patient	Increase in amplitude worsened intelligibility No significant differences with change in frequency (although higher frequency were associated to worse performances) or contact localization	
Tripoliti, 2008 [9]	Observational	14	NA	60 (6.5)	13.6 (8.6)	Six conditions: (1) STIM OFF (2) STIM ON with routine parameters (3) STIM ON with 2 V on the contact closest to STN center (4) STIMON with 4 V on the contact closest to the STN center (5) STIMON with 2 V on the contact furthest to the STN center (6) STIM ON with 4 V on the contact furthest to the STN center	Immediate	Pulse width (60 μs) and frequency (130 Hz) constant	Higher voltage had a negative impact on speech intelligibility, irrespective of the contact used (closest versus furthest contact) Voltage and contact had no effect on acoustic measures	Marked deterioration in speech intelligibility was associated with anteromedial positioning of the electrodes
Hammer, 2010 [10]	Observational	18	3F	59.5 (13)	11.5 (9.5)	STIM OFF/ON	Immediate	Different parameters for each patient	Negative correlation between stimulation frequency and aerodynamic measures of respirator and laryngeal control	Same cohort analyzed also in Hammer, 2011 [11]
Moreau, 2011 [12]	Observational	11	NA	69*	60 (36–96)*	Low frequency stimulation (60 Hz) with TEED constant was compared to both high frequency stimulation (130 Hz) and STIM OFF	Immediate	Different parameters for each patient	Low frequency stimulation improved both speech intelligibility (UPDRSIII speech item) and acoustic parameters	
Sidiropoulos, 2013 [13]	Observational	45	10F	59.5 (7.8)	NA	Low frequency stimulation with TEED constant (39 patients with 80 Hz and 6 patients with 60 Hz) was compared to high frequency stimulation (130–185 Hz)	111.5 (1–1513) days*	Different parameters for each patient	No improvement according to UPDRSIII item; 18/40 self-reported improvement in speech	
Stimulation-induced dyskinesia										
Alterman, 2004 [14]	Case report	1	F	63	12 (re-implant)	Reposition of the electrode allowing a more dorsal stimulation	3 months	R STN1–, 2–, 3 + 3.6 V/ 120 μs/185 Hz L STN2–, 3–, C+ 3.6 V/ 120 μs/185 Hz	Improvement (no scale provided)	
Katayama, 2006 [15]	Observational	45	NA	NA	Soon after surgery	Bipolar stimulation 2– 3+ or 0– 1– 3+	2 weeks 6/8 months	Amplitude 1.5–3.0 V	Control of peak-dyskinesia in 24 out of 45 patients according to a 5-point dyskinesia severity scale	
Herzog, 2007 [16]	Case series	3	1F	56 (6)	25 (32.5)	Double monopolar or monopolar stimulation involving contact 3 as a cathode with stimulation of the subthalamic fiber tract	Different for each patient	Case 1: L STN 1-3-C+ 3.0 V/60 μs/130 Hz Case 2: L STN 3-C+ 3.0 V/ 60 μs/130 Hz Case 3: R STN 1-3-C+ 1.75 V/60 μs/180 Hz L STN 1-3-C+2.0 V/60 μs/ 180 Hz	Improvement in the dyskinesia according to the Marconi Clinical Dyskinesia rating scale	One patient presented stimulation-induced dyskinesias only after repositioning of the electrode; not clear the relationship between dyskinesia/dystonia and levodopa

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Table 1 (*continued*)

Study	Type of study	N. of pts	Sex (F)	Age (SD)	DBS duration (months)	Intervention	Follow-up	Parameters	Outcome	Notes
Merola, 2013 [17]	Observational study	10	6F	59.4 (4.8)	24.4 (15.6)	Low frequency stimulation (80 Hz) with TEED constant	Immediate 1 month 12 months	8 unipolar bilaterally 1 bipolar unilaterally 1 bipolar bilaterally	Immediate: 6/10 improved 1 month: 9/10 improved 12 months: 5/5 improved (other 5 patients did not tolerate 80 Hz stimulation) Evaluation performed with the Rush Dyskinesia Rating scale administered by means a blinded video assessment	6/10 presented dyskinesia and 4/10 dystonia; 7/10 presented dyskinesia or dystonia related to levodopa intake; not clearly stated if specific strategies were tried before (dorsal contact, interleaving)
Miocinovic, 2014 [18]	Case report	1	M	58	NA	Interleaving stimulation involving contact 2 as dorsal contact	23 months	R STN CH1:C+1-2.0 V/90 μs/125 Hz CH2: C+21.5 V/90 μs/125 Hz	Dyskinesia improved (no scale)	
Minafra, 2014 [19]	Case report	1	F	44	8	Rescue GPi DBS	24 months	NA	Dyskinesia disappeared	STN DBS was turned off
Gait impairment										
Chastan, 2009 [20]	Observational	7	2F	61 (7)	43.6 (20.1)	Five conditions: (1) STIM ON (with chronic parameters of stimulation)/MED OFF (2) STIM ON (as above)/MED ON (3) STIM ON (with SNr stimulation)/MED OFF (4) STIM OFF/MED OFF (5) STIM OFF/MED ON	Immediate	Different parameters for each patient	According to UPDRSIII bilateral SNr stimulation improved only axial parkinsonian motor symptoms whereas bilateral STN stimulation improved global, distal and, to a lesser degree, axial symptoms Bilateral SNr stimulation also improved some gait analysis parameters	
Fasano, 2011 [21]	Observational	13	3F	63.5 (8.4)	42.1 (38.2)	Four conditions: (1) STIM ON with chronic parameters of stimulation (2) STIM OFF (3) STIM ON with worst side reduction (4) STIM ON with best side reduction	Immediate	Different parameters for each patient	Best side reduction reduced FOG frequency and duration of episodes as compared to chronic parameters of stimulation	
Moreau, 2008 [22]	Observational	13	NA	70 (66–72)*	60 (48–60)*	Four conditions: (1) STIM OFF (2) STIM ON with 130 Hz with the usual voltage (3) STIM ON with 130 Hz with higher voltage (4) STIM ON with 60 Hz with the usual voltage (5) STIM ON with 60 Hz with higher voltage	Immediate	Different parameters for each patient	STIM ON with 60 Hz (both with the usual and the higher voltage) determined improvement in freezing episodes and parameters of the stand–walk–sit test compared with STIM ON with 130 Hz conditions	Benefit still satisfactory for 11 patients after 8 months, 2 switched back to 130 Hz due to worsening of movements
Ricchi, 2012 [23]	Observational	11	3F	62.9 (4.3)	4.5 (1.4)	Low frequency stimulation (80 Hz)	Immediate 1 month 5 months 15 months	Different parameters for each patient	Improvement in the stand–walk–sit test in the immediate follow-up (11 patients), but not in the long term follow-up (8 patients)	Amplitude of stimulation adjusted to keep TEED constant; three patients did not complete the study because they did not tolerate low frequency stimulation due to worsening of tremor and gait

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Table 1 (*continued*)

Study	Type of study	N. of pts	Sex (F)	Age (SD)	DBS duration (months)	Intervention	Follow-up	Parameters	Outcome	Notes
Phibbs, 2014 [24]	Randomized, double blinded cross over	20	4F	62	36	Low frequency stimulation (60 Hz) versus high frequency stimulation (130 Hz)	1 hour	Different parameters for each patient	Worsening of UPDRSIII tremor scores in patients with 60 Hz No difference in gait parameters (GaitRide) and stand–walk–sit test	No voltage adjustment according to TEED
Sidiropoulos, 2013 [13]	Observational	45	10F	59.5 (7.8)	NA	Low frequency stimulation with TEED constant (39 patients with 80 Hz and 6 patients with 60 Hz) was compared to high frequency stimulation (130–185 Hz)	111.5 (1–1513) days	Different parameters for each patient	No improvement according to UPDRSIII axial and gait subscores	
Weiss, 2013 [25]	Randomized, double blinded cross over	12	3F	65 (9.2)	31.3 (24.4)	Standard STN versus STN plus SNr stimulation	Immediate 3-weeks	Interleaving stimulation with concomitant activation of STN plus SNr	Significant improvement of the freezing of gait assessment both in the immediate and 3-weeks follow-up with concomitant stimulation of STN plus SNr	
Xie, 2012 [26]	Observational	2	1F	64 (4.2)	2 weeks	Low frequency stimulation (60 Hz) compared with high frequency (130 Hz)	Immediate	Case 1: L STN C+2-2.2 V/60 μs R STN C+ 2- 2.0 V/60 μs Case 2: L STN C+2-3.2 V/60 μs R STN C+ 2- 2.3 V/60 μs	Improvement in FOG and UPDRSIII	Only immediate follow-up provided; no voltage adjustment according to TEED

Studies related to STN DBS management and considered for the algorithms are divided into subsections of speech impairment, stimulation-induced dyskinesia and gait impairment. Data are in mean (standard deviation), unless otherwise specified.

* Median (range).

DBS, deep brain stimulation; FOG, freezing of gait; F, female; GPi, globus pallidus pars interna; L, left; MED OFF, off medication; MED ON, on medication; N, number; NA, not applicable; R, right; SD, standard deviation; SNr, substantianigra pars reticulate; STIM OFF, off stimulation; STIM ON, on stimulation; STN, subthalamic nuclei; TEED, total energy delivered; UPDRSIII, unified Parkinson's disease rating scale part III.

Table 2
TWH steps and considerations for initial programming visit.

1.	Initial programming is performed in clinic at least 3 weeks after surgery when the insertional effect is likely over. Patients should be MED OFF.
2.	Check electrodes placement post-operatively using approved MRI protocols to (a) envisage the source of potential side effects; (b) evaluate the symmetry of electrode placement; (c) and, thus, support the selection of the best contact for the less affected hemibody after having determined the best contact for the most affected hemibody. Post-operative MRI is not performed in many centers due to either economic or safety concerns [42]. An alternative approach is the fusion of post-operative computed tomography and pre-operative MRI.
3.	Determine the target sign according to patient's clinical features. Bradykinesia or tremor may be used as an alternative to rigidity when the latter is not present (e.g., on the least affected hemibody). Evaluating the effect of stimulation on gait is also recommended at the end of the programming session, given the delayed effects on axial motor functions [43].
4.	Use CCS for blind assessments to compare contacts with similar results in order to control for the different impedance around each contact level [44].
5.	Start chronic stimulation with 1.0–1.5 V, then patient is asked to take his morning dose of antiparkinsonian medication and evaluated STIM ON/MED ON staying under observation for about 2 hours to detect the occurrence of delayed side effects, i.e., stimulation-induced dyskinesias and mania (note that stimulation-induced dyskinesias may take hours to develop). To this respect, it is particularly important to teach both the patient and caregiver on how to turn the stimulation off with the patient's remote. A reduction of antiparkinsonian medications is not advisable at this stage [1,45].
6.	Another important reason to assess the patient STIM ON/MED ON is the unwanted block of levodopa positive effects, theoretically seen with too ventral stimulation (with either STN or GPi) [4], which is anyway associated with an improvement of baseline rigidity.
7.	Following the first programming visit, patients go home and come back for 4–6 weekly appointments to adjust both stimulation parameters (e.g., stimulation voltage is slowly increased weekly by 0.5–1.0 V on both sides) and medications (to be weaned off slowly to lessen the risk of post-operative depression induced by dopaminergic drug withdrawal [45]).
8.	Clinicians may set a given range of a parameter (typically voltage) and patients are instructed on how to slowly tune the stimulation at home with the help of the patient's remote control.
9.	In patients with GPi DBS: (i) medications are usually unchanged since the chance to induce stimulation-induced dyskinesias is very rare and usually seen with stimulation close to GPe whereas middle/ventral stimulation is very effective in reducing levodopa-induced dyskinesias [4]; (ii) further stimulation adjustments can be performed after a medication challenge to explore the effectiveness in treating levodopa-induced dyskinesias.
10.	Traditionally, when both modes are available (Medtronic, Minneapolis, MN, USA) the management of the patients is performed with VCS. There are no published studies comparing CCS and VCS in PD [46]. Furthermore, it is still unclear the effect of CCS on battery life, although a trial on primary dystonia showed that it tended to drain more energy compared to VCS [47]. It might be useful to switch from VCS to CCS when dealing with stimulation-induced side effects possibly induced by fluctuations in impedances [personal observation].

CCS, current-constant stimulation; DBS, deep brain stimulation; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; MED OFF, off medication; MED ON, on medication; MRI, magnetic resonance imaging; PD, Parkinson's disease; STIM ON, on stimulation; STN, subthalamic nucleus; TWH, Toronto Western Hospital; VCS, voltage-constant stimulation.

date. In addition, a lack of data is available for GPi DBS programming. Over the years, we have implemented our standard algorithm with additional steps and considerations as listed in Table 2 and depicted in Fig. 1. During programming is strongly recommended to train the patient and caregiver on to use remote control and always set the previous settings in a different group when changing stimulation parameters. This allows the patient to switch back to previous settings if problems arise with new ones.

Management of speech impairment

Available data and recommendations

Although loudness may improve after STN DBS, a 1-year prospective study demonstrated that intelligibility decreased significantly by 14% compared to a control group [48]. As a matter of fact, speech impairment is a frequent adverse event during both the initial programming and long-term follow-up of STN DBS [49–51]. The outcome of speech after DBS depends on both clinical (severity and response to medication at baseline) and surgical (site and parameters of stimulation) factors [52,53]. Up to 4 different voice impairment patterns have been described after STN DBS: strained, spastic, stuttering and hypophonic type [54]. Strained and spastic patterns are associated with current spread into the internal capsule [39,54–56], yet factors associated with the stuttering and hypophonic types are less clear [54].

Tripoliti et al. demonstrated that higher voltages have a negative impact on speech intelligibility especially with antero-medial placements regardless of the contact used [9]. In keeping with previous data [8,57,58], this supports the notion that stimulation-induced speech disorders are due to the current spreading into the pallidofugal and cerebello-thalamic fibers [54,59]. In addition, studies surveyed the differential impact of left- and right-sided STN stimulation on different aspects of speech performance and found that left-sided stimulation in right-handed patients had a negative effect on prosody, articulation and overall intelligibility [60–63]. Regardless of pre-surgical impairment, an active electrode medial to the left STN affects speech particularly in patients with a longer history of PD [64].

In contrast, speech disturbances rarely occur during the programming of GPi DBS [28]; however, albeit less commonly, delayed speech worsening has been reported during 5–6 year follow-ups [65].

Current limitations and TWH proposal

Patients with post-operative speech impairment should be trialed with strategies that reduce the current spread (e.g., voltage reduction, bipolar or interleaving stimulation, with the latter being second choice as it drains more battery). Although it has been suggested that left STN plays a major role in generating speech impairment [60–63], it is advisable to turn each side off alternatively to understand if the issue is related to one side stimulation or to the combination of both sides. In that way, it is possible to infer which is the side needing the stimulation adjustment (i.e., only one side versus both) (Fig. 2). Such approaches are particularly useful for strained or spastic patterns while in patients with speech impairment resistant to these strategies, low frequency stimulation is a valid option. In accordance with previous results [10,11], acute switching from high (≥100 Hz) to low frequency (<100 Hz) stimulation improved both speech intelligibility and acoustic parameters, especially for patients with hypophonia [12]; however, this option often prevents clinician from reducing antiparkinsonian medications as patients report intolerable worsening of appendicular motor symptoms (e.g., tremor) and a lack of long-term benefits [13]. Furthermore, Medtronic IPG does not allow the clinician to reduce the frequency only in one electrode. Thus, we suggest low frequency stimulation as last option to manage speech impairment especially during initial programming.

Further, the effect of DBS on stuttering is unclear as contradictory findings have been described [66,67]. In our experience at TWH, a worsening of stuttering is much more common, especially in

Figure 1. Basic algorithm for initial programming. Abbreviations: *: after reaching the threshold for side effects we suggest to increase and diminish the amplitude with 0.1 V increments to be as accurate as possible in defining the side effect threshold/therapeutic window; **: medications are usually left unchanged in GPi DBS; DBS: deep brain stimulation; GPi: globus pallidus pars interna; MED ON: on medication; MRI: magnetic resonance imaging; STIM ON: on stimulation; STN: subthalamic nuclei.

patients with a history of transient developmental stuttering during childhood. We found that low frequency stimulation can be successfully applied in those cases with either STN or GPi DBS [68]. Finally, supportive measures such as the Lee Silverman Voice Treatment should be initiated in patients with persistent unsatisfactory speech performances after stimulation adjustments [63].

Our proposed algorithm for the management of speech impairment is depicted in Fig. 2 and is mainly designed for Medtronic IPGs. The recently available Boston Scientific (Marlborough, MA, USA) Vercise is an IPG capable of providing Multiple Independent Current Control stimulation with a dedicated power source for each of the outputs (up to 16) on the lead at up to two independent frequencies. In addition, this IPG allows the use of pulse widths lower than 60 μs, a feature that may reduce the incidence of side-effects, including speech impairment [69].

Management of stimulation-induced dyskinesia

Available data and recommendations

GPi DBS exerts a direct antidyskinetic effect and very rarely induces dyskinesia, with very dorsal sites of stimulation [4,28]. In contrast, patients undergoing STN DBS achieve an improvement of dyskinesias due to the reduction of dopaminergic drugs. Nevertheless, STN DBS may induce stimulation-induced dyskinesias, which include choreiform, ballistic or dystonic movements resembling levodopa-induced dyskinesia, occurring during the initial postoperative programming period and considered a favorable outcome [70]. Although the contact eliciting dyskinesia is generally the most effective in relieving parkinsonian symptoms [71,72], sometimes the occurrence of stimulation-induced dyskinesias has a negative effect on overall DBS outcome. The available recommendations of DBS programming suggest a slow increase of stimulation amplitude to prevent the occurrence of stimulation-induced dyskinesias [2,3,28] with an accompaniment of a greater reduction in medication, but risking the emergence of apathy [45]. Indeed, the first step should always include a proper management of antiparkinsonian medications after DBS as medications can worsen stimulation-induced dyskinesias. In addition, the presence of peak-dyskinesias (paralleling the highest levodopa plasma levels) or biphasic dyskinesias (appearing at the onset and offset of the levodopa effect) suggests a close relationship with levodopa and prompt the clinician to reduce the amount of the single levodopa intake during the programming.

Current limitations and TWH proposal

Patients may be very sensitive and develop stimulation-induced dyskinesias with very low parameters and a slow increment of stimulation amplitude. In such cases smaller increments of stimulation (by 0.1 V or 0.05 V) and a longer interval between assessments may further reduce the chance of developing stimulation-induced dyskinesias. In addition, teaching the patient to use the remote control may also be an approach to prevent stimulation-induced dyskinesias. Nonetheless, in some patients, the therapeutic window still remains very narrow and only a suboptimal control of motor symptoms without stimulation-induced dyskinesias is achievable. In such cases, other strategies such as activate dorsal contacts in the Zona incerta above the STN have been reported to have an antidyskinetic effect [14–16]. The beneficial effect of Zona incerta stimulation has been speculated to be caused by an effect on pallidofugal fibers that convey GPi outflow to the motor thalamus,

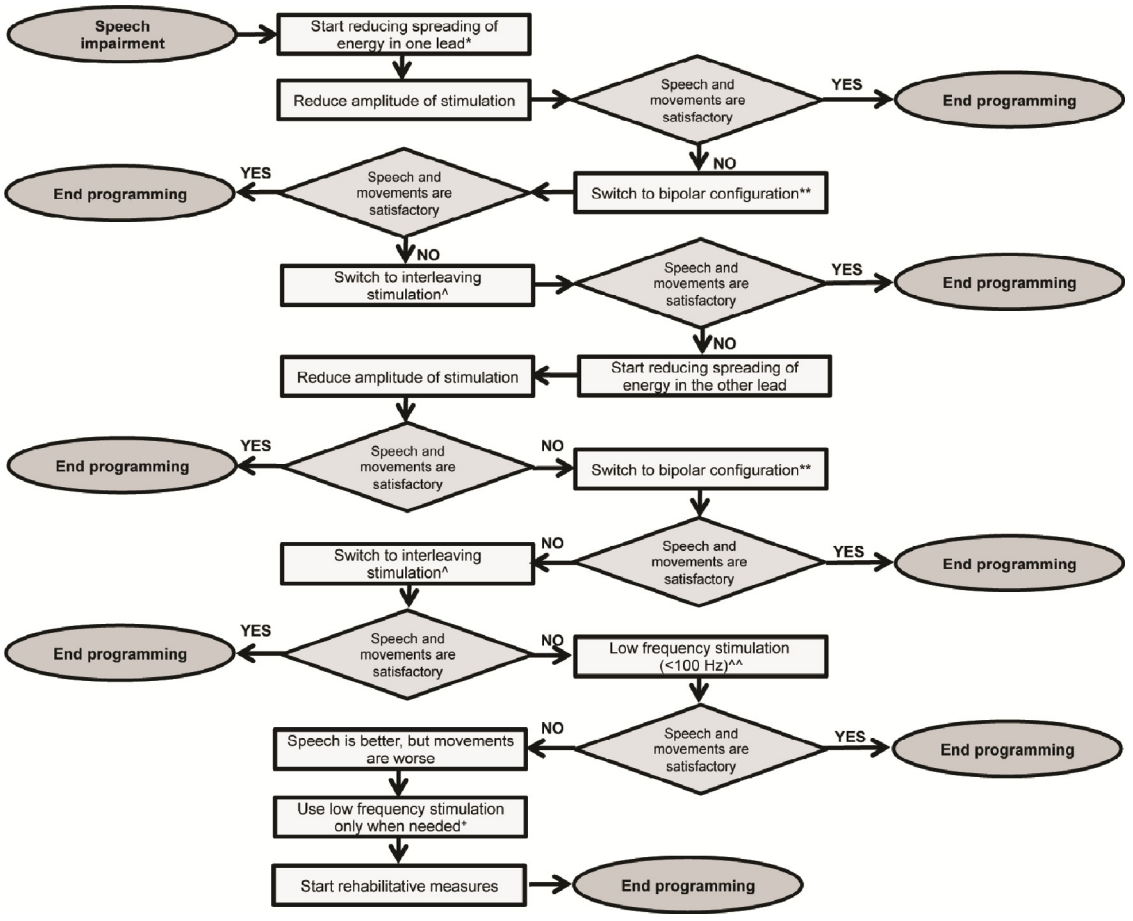

Figure 2. Basic algorithm for management of speech impairment. This algorithm is mainly based on Medtronic IPGs. With Multiple Independent Current Control stimulation provided by Boston Scientific Vercise IPG, different approaches are possible, including programming dedicated power sources for each of the outputs (up to 8/hemisphere) at up to two independent frequencies. Abbreviations: *: start turning each side off alternatively to understand if the issue is related to one side stimulation or to the combination of both sides. In that way, it is possible to infer which is the side needing the stimulation adjustment (i.e., only one side versus both). Evidence suggests that left STN plays a major role in generating speech impairment in right-handed patients [60–63]; **: also consider a tripolar type of stimulation (called "guarded cathode"), which implies the use of a ring-shaped electrical field generated by the cathode (generally the most effective contact) when it is surrounded by two anodes; ^: available with Medtronic IPGs; ^^: with total energy delivered constant; +: teaching the patient how to use the patient's remote.

providing an overall clinical effect resembling a combined stimulation of ventral GPi and STN DBS [16].

Different settings involving the dorsal contact have been described (e.g., monopolar, bipolar or double monopolar) [14–16]. However, with double monopolar configuration new side effects may emerge as both contacts deliver the same amount of energy [14,16]. This issue may be avoided with the new IPGs which are able to differentiate and tailor the amount of energy delivered at each contact. 'Interleaving stimulation' (Activa IPG, Medtronic) is one of them and allows for two contacts to vary in amplitude and/or pulse width but with the same frequency [18]. Clinicians should keep in mind that 'interleaving stimulation' is a battery-draining configuration. Another option is provided by Vercise IPG (Boston Scientific), which allows using different stimulation amplitudes for up to 16 independent outputs (eight contacts/electrode) at up to two independent frequencies [69]. Recent preliminary data show that low frequency stimulation keeping the total energy delivered (TEED) constant may reduce stimulation-induced dyskinesias [17,73]. Finally, rescue surgery with GPi DBS has been described as an option for patients developing stimulation-induced dyskinesias resistant to medication and stimulation adjustments following STN DBS [19]; however definite evidence to recommend this procedure is still lacking.

A proposed algorithm for the management of stimulation-induced dyskinesias in STN DBS is depicted in Fig. 3.

Management of gait impairment

Available data and recommendations

Axial symptoms, such as gait, festination and freezing of gait (FOG), may respond variably to DBS [74]. Overall, when axial symptoms are responsive to dopaminergic medications, they are likely to improve with STN DBS [75]. Various studies reported gait improvement with either STN or GPi DBS [28,76–83]. A study that monitored ambulation before and 6 months after STN DBS showed an improvement in gait performance with a reduction of FOG [84]. Evidence for GPi DBS is more limited [85]. Long-term observations for STN DBS (11 years) [86] and GPi DBS (6 years) [65] have consistently shown that axial motor features decline over time consistent with the natural history of PD [51]. One meta-regression study has shown that gait and axial impairment decline after both STN and GPi DBS as opposed to the improvement in cardinal signs which is sustained over time, suggesting a differential effect of DBS on the distal and axial neural control circuits [87]. Indeed, GPi DBS is

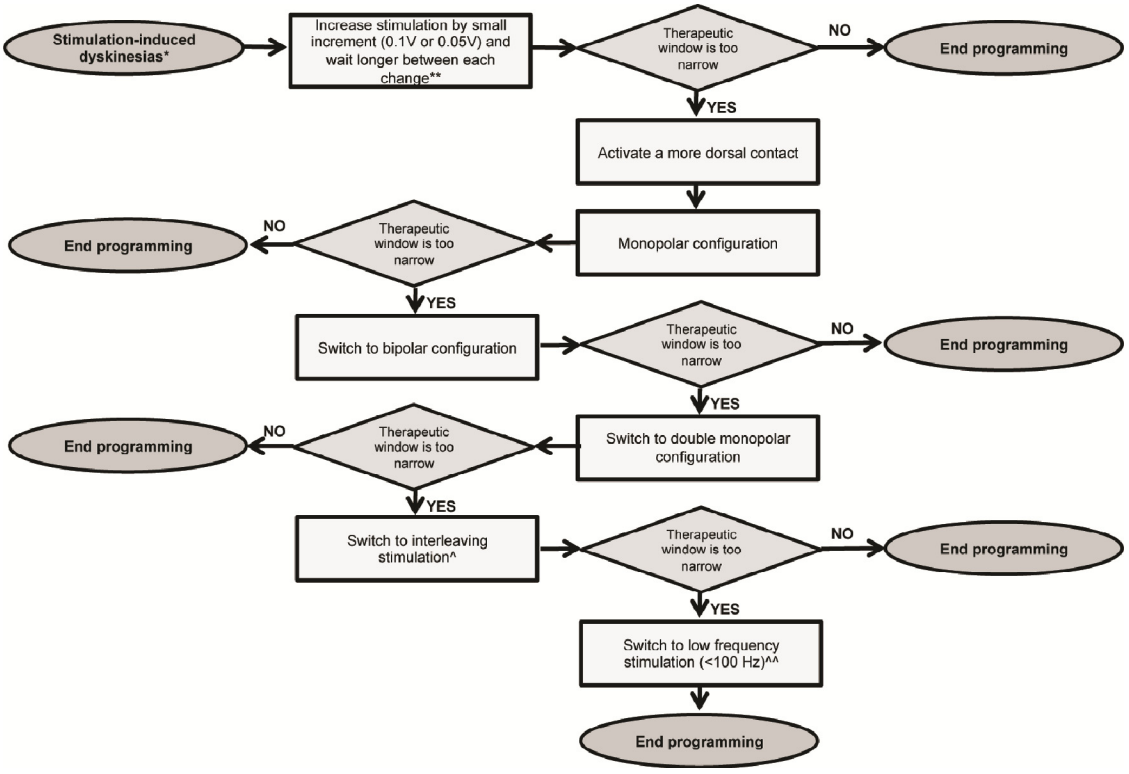

Figure 3. Basic algorithm for management of stimulation-induced dyskinesia in STN DBS. Abbreviations: *: reduce medications at the same time to avoid peak-dose levodopa-induced dyskinesia and/or the worsening of stimulation-induced dyskinesia; **: training the patient on to use remote control may be a valid strategy; ^: option limited to Medtronic pulse generators, for Boston Scientific pulse generators see the text; ^^: with total energy delivered constant; DBS: deep brain stimulation; GPi: globus pallidus pars interna; STN: subthalamic nuclei.

associated with a better preservation of gait function as compared with STN DBS, supporting the indication for GPi as a target for those patients with severe gait impairment [87,88]. As for other gait issues, FOG is likely to respond to STN DBS when only present in MED OFF condition and characterized by a good response to levodopa. On the other hand, when FOG persists during MED ON condition (and medication under-dosage has been ruled out) STN DBS is not useful and can also worsen it; in such cases GPi DBS may be a better target [87,88]. More complicated is the issue of the FOG induced by medications ("ON state FOG") [89] because ideally STN DBS allows the reduction of dopaminergic drugs, thus improving FOG (personal observation).

Although the available evidence is not conclusive, the onset or worsening of gait impairment following DBS is likely determined by a complex interaction between the progression of the disease, effect of surgery or stimulation, reduction in postoperative medication dosage, aging processes, and co-morbidity [7]. The timing (immediate or delayed) between DBS surgery and deterioration of axial motor symptoms suggests different underlying pathophysiological mechanisms. Immediate worsening of gait impairment soon after surgery compels the clinician to check for structural brain lesions or the correct position of the electrodes through neuroimaging. However, the DBS itself may also be conducive to immediate postoperative worsening of gait through spreading of the electric field to other structures and interfering with limb coordination [1,22], especially when electrodes are misplaced [90]. In keeping with these notions, although the evidence is scarce and suggested only by case reports, patients with FOG immediately after activation of newly implanted STN electrodes have been found to improve after switching to low frequency stimulation, with or without adjustments on voltage [22,26]. Finally, a detrimental effect of the surgery on gait function should be considered [91], especially for elderly patients [91,92].

Current limitations and TWH proposal

In a sample of 50 patients with an unsatisfactory clinical response after STN DBS, the chief complaint was related to axial symptoms (including speech) in 74% of the cases and suboptimal stimulation accounted for 52% of cases [93]. Therefore, patients with axial worsening should be evaluated after an extra-dose of levodopa or after increasing the DBS stimulation voltage, to rule out underdosage of either medication or stimulation. Increasing the stimulation voltage (e.g., by 0.5 V bilaterally) may substantiate the impact of stimulation on axial motor performance: selective worsening strengthens a direct role of stimulation and drives further adjustments of therapy (e.g., low frequency stimulation). The modulation of motor symmetry with STN DBS can worsen or improve FOG [21]. It has been demonstrated that a reduction in stimulation amplitude in the hemisphere contralateral to the best hemibody results in increased stride length, reduction of gait variability, and a reduction in freezing episodes compared with the conventionally applied STN DBS stimulation mode [21].

Low frequency stimulation of STN has been adopted with transient [22,23] or no [13,24] effect at all; however, to compare among stimulating conditions, clinicians should keep constant the total electrical energy delivered in 1 s ($TEED_{1\,sec}$) after having changed one of the stimulating parameters, according to the formula: $TEED_{1\,sec} = [(volts)^2 \times pulse\ width \times frequency]/impedance$ [73].

An attractive approach to improve axial symptoms through the modulation of the brainstem locomotor circuits is to stimulate the substantia nigra pars reticulata (SNr) by activating the most ventral

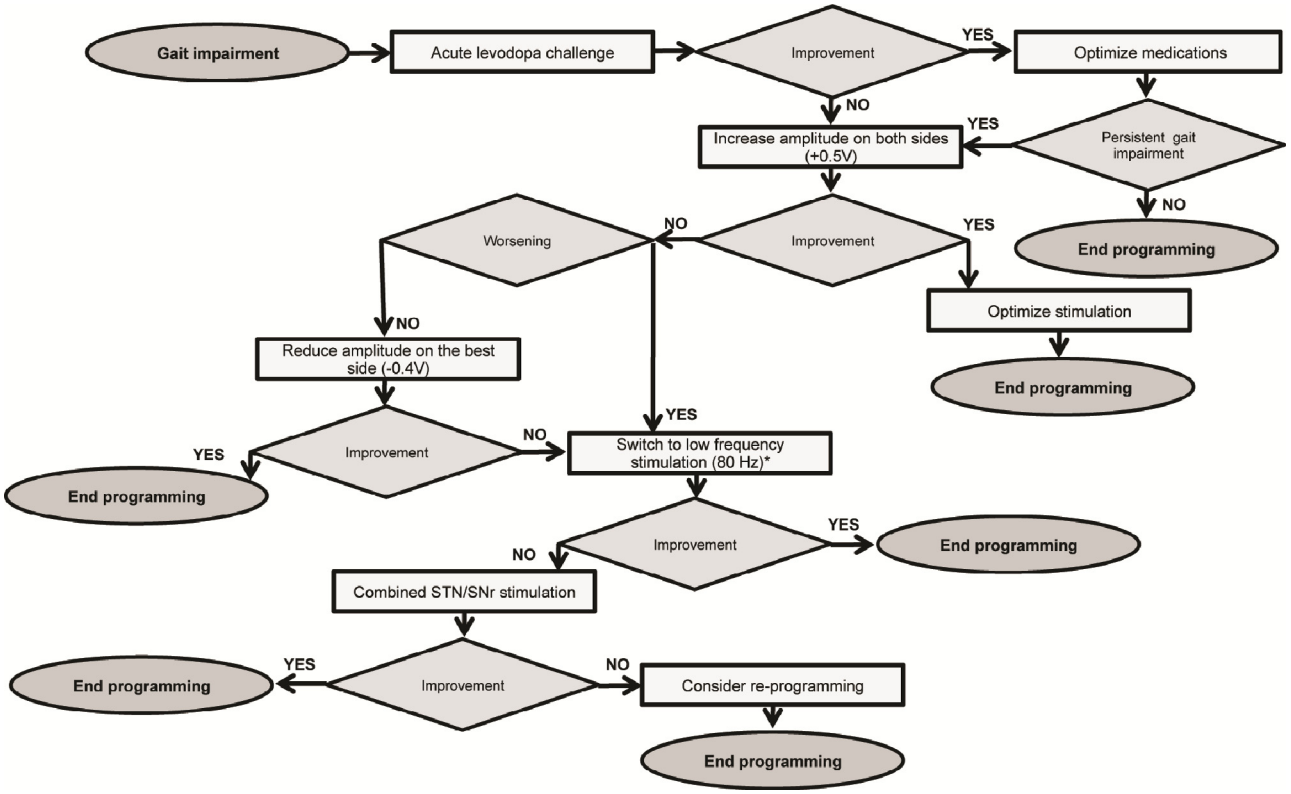

Figure 4. Basic algorithm for management of gait impairment (festination, FOG) in STN DBS. Abbreviations: *: with total energy delivered constant; DBS: deep brain stimulation; FOG: freezing of gait; SNr: substantianigra pars reticulata; STN: subthalamic nuclei.

contact of the lead (while the dorsal active contact is in the STN) [20,25,94]. Advanced programming with 'interleaving stimulation' allows independent stimulation of contacts with different amplitudes and pulse widths at a common frequency [25,94] and therefore enables the co-stimulation of segregate functional motor loops at the level of the STN and SNr [25,94]. Significant improvement in FOG in short-term follow-up has been demonstrated with combined STN and SNr as compared to standard STN stimulation in a randomized, double-blind, cross-over trial [25]. When all the strategies fail, a reassessment of the stimulation parameters should always be considered in patients with postoperative gait worsening, as shown in a large series operated at TWH (although electrode location was not taken into account for the analysis) [6].

There is scanty evidence regarding the effect of stimulation adjustments in PD patients with GPi DBS and gait impairment as most studies focus on STN stimulation. We recently reported the improvement of axial symptoms in two patients with GPi DBS after switching to low frequency stimulation (either 60 or 80 Hz) [68]. Thus, low frequency stimulation may lessen a detrimental effect of stimulation in GPi DBS, as described for STN DBS [7]. Alternatively, low frequency stimulation may be more efficient at disrupting pathological output or modulating brainstem locomotor regions. Further studies are needed to better understand the clinical relevance of such stimulation paradigm in patients with GPi DBS [68].

Gait may be also affected by appendicular issues, typically stimulation-induced dyskinesias involving lower limbs. For the management of such cases refer to the specific section of the paper (see above).

A proposed algorithm for the management of gait impairment in STN DBS is shown in Fig. 4.

Management of postural instability

Available data and recommendations

Postural instability is the least likely to respond to DBS [7]. Several studies show the worsening of postural instability after STN DBS [7,28,88] and, again, very limited data are available for GPi DBS [95,96]. A randomized, double-blind study showed that both STN and GPi DBS improved balance scores at 6-month follow-up after surgery, and scores further improved with medication [97]. However, when turning the stimulation off, the GPi group showed improved performance and better ratings of balance confidence compared to the STN group, suggesting a possible detrimental effect on balance only after STN surgery [97]. Indeed, different types of evidence from randomized, double-blind, controlled trials [97,98] or reviews [7,99] strongly suggest that GPi may be preferable over STN in PD patients with stability problems.

Levodopa and DBS improve some measures of balance but worsen others. Thus, medical and surgical therapies may affect measures in opposing directions, violating the clinical rule that levodopa predicts the response to DBS. The differences in the effects of levodopa and of DBS in STN and GPi suggest that balance is mediated by several distinct circuits and is only partly under the control of dopaminergic motor circuits [97,99].

Current limitations and TWH proposal

As for the gait impairment, the time of onset of post-operative postural instability worsening suggests different pathophysiological mechanisms and therefore therapeutic approaches: immediate

worsening is often underlined by either structural lesions or misplaced electrodes while delayed onset is likely multifactorial [7].

There are scanty data regarding the management of postural stability. To avoid under-treatment, patients should be evaluated after an extra dose of levodopa and/or increased stimulation voltage [7]. Indeed, some aspects of balance can be restored by levodopa, whereas others might be worsened. In patients with postural instability, a levodopa challenge could be particularly helpful to better understand what aspects may benefit from increasing in medications [100].

In a meta-analysis including 38 studies from 34 centers in 13 countries, the authors concluded that the benefits of STN DBS for axial symptoms show a decline in the long-term follow-up, although they failed to include data on the progression of axial symptoms in non-DBS patients [101]. Although firm conclusions about the causality link between STN DBS and axial issues cannot be drawn, patients with 'long-term DBS syndrome' present with a new phenotype comprising relatively well-controlled bradykinesia, rigidity and tremor, but with increasing axial motor problems [7,51]. In this view it may be worthwhile to have a trial with some of the parameters used to improve gait impairment as low frequency stimulation or simultaneous stimulation of STN and the SNr (Fig. 4) [20,23,25]. Accordingly, a recent study suggested that minimizing the spread of current to the non-motor territories of the STN would free up cognitive resources that could be allocated to maintaining a steady posture and therefore improve postural stability [102]. Indeed, future development of computational modeling approaches may improve the outcome in patients with postural instability [102]. However, to date there is insufficient data to propose a formal algorithm with stimulation adjustments to improve postural instability in PD patients with DBS. Hence, the management of postural instability after DBS remains an unsolved issue [7]. Turning the STN stimulation off for prolonged time may markedly improve postural instability (personal observation). Re-programming may be considered, although when applied in patients with STN DBS, it failed to specifically improve Unified Parkinson's Disease Rating Scale postural stability scores [6].

Other approaches to treat axial disturbances

Exploring stimulation in different targets, such as the pedunculopontine nucleus or spinal cord, or examining the effects of other neurotransmitter systems, such as the cholinergic system, can further elucidate our knowledge of balance dysfunction in PD [7,99]. To date, the management of axial symptoms (and postural instability in particular) with medications and/or DBS remains frustrating [7]. Physiotherapy is a therapeutic approach among the novel strategies to manage postural instability in PD. Although evidence-based guidelines have been developed for physical therapy [103], the optimal intervention type and regimen as well as the overall role of physical therapy in axial disability in patients receiving DBS remain uncertain [7]. Indeed, dopaminergic drugs are very often unsuccessful and drugs modulating different neurotransmitters are then considered (i.e., methylphenidate, amantadine, donepezil [104–106]).

Conclusion and future perspectives

In the last few years, the field of DBS has been witnessing a surge in technological innovation [69]. Emerging techniques for the optimization of stimulation include multiple-source CCS, directional electrodes, multi contact and multi target electrodes (e.g., STN and SNr), more MRI compatible electrodes and adaptive closed-loop systems [69]. Multiple-source CCS enables separate contacts to be programmed independently with different stimulation parameters shaping the electric field to reduce side effects and increase selectivity for therapeutic regions [69]. New electrodes with a higher density of contacts allow the current to be shaped and steered in specific directions to prevent omnidirectional stimulation [69]. Measured chronaxies and model data suggest that pulse durations <60 μs applied with a novel neurostimulation system (Vercise®; Boston Scientific, Valencia, CA) may lead to a focusing of the neurostimulation effect on smaller diameter axons close to the electrode while avoiding stimulation of distant pyramidal tract fibers [107]. Further, the application of closed-loop sensing systems that analyze neuronal activity from the electrode and change the stimulation in an adaptive fashion is a novel therapeutic strategy in the pipeline [69]. With the ever-increasing number of contacts and electrode combinations, manual programming will be actively assisted by tools that provide a visual representation of tissue activation (Boston Scientific Guide DBS™) and a prediction of the stimulating field with the patient's brain MRI (Medtronic Optivise™) [69]. Thus, our algorithms are expected to evolve soon to take into account all the abovementioned innovations. Yet, currently, there are no actual alternatives to the classic manual programming procedure, which remains a difficult and time-consuming process for highly trained and experienced clinicians [6]. Based on available literature and our experience at TWH, we propose standardized protocols with algorithms to overcome current limits and gaps in common clinical issues during DBS programming of PD patients. Our future directions include implementing our algorithms and quality evaluation in comparison to previous practice. We acknowledge that a potential limitation of such review is the one single-center approach. Although the algorithms were built taking into account published evidence from many DBS centers (Table 1), application and validation of our protocols by independent DBS teams is warranted. Furthermore, the feasibility of implementing our algorithms in new DBS centers will be an exciting avenue to explore.

Contributorship

1. Research project: (A) Conception: MP, AF; (B) Organization: MP, AF; (C) Execution: MP.
2. Manuscript Preparation: (A) Writing of the first draft: MP; (B) Review and Critique: AML, NK, RPM, AF.

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