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NEUROLOGICAL UPDATE

Deep brain stimulation for movement disorders: update on recent discoveries and outlook on future developments

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Abstract Modern deep brain stimulation (DBS) has become a routine therapy for patients with movement disorders such as Parkinson's disease, generalized or segmental dystonia and for multiple forms of tremor. Growing numbers of publications also report beneficial effects in other movement disorders such as Tourette's syndrome, various forms of chorea and DBS is even being studied for Parkinson's-related dementia. While exerting remarkable effects on many motor symptoms, DBS does not restore normal neurophysiology and therefore may also have undesirable side effects including speech and gait deterioration. Furthermore, its efficacy might be compromised in the long term, due to progression of the underlying disease. Various programming strategies have been studied to try and address these issues, e.g., the use of low-frequency rather than high-frequency stimulation or the targeting of alternative brain structures such as the pedunculopontine nucleus. In addition, further technical developments will soon provide clinicians with an expanded choice of hardware such as segmented electrodes allowing for a steering of the current to optimize beneficial effects and reduce side effects as well as the possibility of adaptive stimulation systems based on closed-loop concepts with or without accompanying advances in programming and imaging software. In the present article, we will provide an update on the most recent achievements and discoveries relevant to the application of DBS in the treatment of movement disorder patients and give an outlook on future clinical and technical developments.

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Introduction

The advent of modern deep brain stimulation (DBS) in the late 1980s has led to a major change in the therapeutic armamentarium for movement disorders. Major achievements have been accomplished using chronic stimulation of the thalamus for patients with tremor disorders, the subthalamic nucleus (STN) and the globus pallidus internus (GPi) for advanced Parkinson's disease (PD), and the GPi for patients with hyperkinetic movement disorders in particular dystonia [1–3]. While there is also great interest in the use of DBS in the treatment of other neurological conditions such as chronic pain [4, 5] and medically refractory psychiatric/behavioral conditions such as obsessive compulsive disorder [6–8] or depression [9, 10], these will not be discussed here. Instead this article aims to provide an update on the current uses of DBS in its therapeutic and experimental indications in movement disorder patients, including discussion of the optimal timing of its implementation, insights into some of the side effects that DBS may induce and how these may be overcome, and some of the recent advances in DBS technology and how these may help improve outcomes for patients.

DBS targets in movement disorders

DBS in Parkinson's disease

There is a subgroup of individuals with PD in whom it is impossible to obtain satisfactory symptom control using

conventional oral pharmacological approaches that should be considered for DBS surgery. This includes patients with disabling motor fluctuations and dyskinesias, patients limited by behavioral side effects induced by oral dopaminergic therapies, or those with persistent tremor despite optimization of dopaminergic replacement. Both subthalamic and pallidal DBS were first used more than two decades ago and have since become routine treatment options for such patients in many centers around the world. The efficacy and superiority of DBS over best medical treatment (BMT) in appropriate patient groups have been established in several carefully conducted randomized controlled trials [2, 11].

Follow-up studies in bilateral STN DBS-treated PD patients have consistently documented a sustained, significant benefit on motor features, coupled with reduced need for dopaminergic treatment in the medium term. Blinded observations at 10-year follow-up suggest that STN DBS continues to exert beneficial effects on bradykinesia, tremor and rigidity in the long term, whereas there may be a loss of benefit on gait and other axial motor symptoms [12]. Both STN and GPi DBS have been designated as efficacious symptomatic adjuncts to levodopa for the treatment of dyskinesia and/or motor fluctuations in advanced PD patients by the Movement Disorder Society Evidence-Based Medicine Review Update [13].

Which target? Subthalamic versus pallidal DBS in PD

There has been an ongoing debate whether the STN or the GPi represents a better target for stimulation [14]. Both targets have been shown to have useful effects on OFF symptoms of PD even when assessed under double-blind methods [15], although the conventional wisdom from the original non-randomized studies has led to a general acceptance that STN DBS has greater effects on OFF symptoms of PD, while GPi DBS has greater effects on dyskinesia reduction. In a 5-year follow-up of a non-randomized multicenter study of bilateral STN and GPi DBS, there was a sustained benefit from both subthalamic and pallidal stimulation on blinded OFF versus ON stimulation motor scores as well as on activities of daily living (ADL) and dyskinesia measures [16]. However, adverse events such as disturbance of speech, balance and gait, as well as depression and cognitive decline occurred more frequently in the STN group, suggesting that subthalamic stimulation can aggravate axial motor symptoms, as well as cognitive impairment and low mood.

There have been 4 trials directly comparing these two targets in a randomized, double-blinded fashion (Table 1) [17–20]. In summary, it appears that both targets consistently prove efficient in the reduction of UPDRS off medication scores, slightly favoring the STN particularly with regard to bradykinesia and rigidity, whereas a significant reduction of the levodopa equivalent dose can usually be achieved with STN stimulation only. A reduction of duration and severity of dyskinesias has also been shown with stimulation of both targets; however, more markedly with GPi stimulation. In patients undergoing STN DBS, dyskinesia reduction requires lowering of dopaminergic replacement made possible by the beneficial effects of STN DBS on OFF symptoms. Quality of life appears improved with stimulation at either target.

Overall, a careful patient selection seems to be of utmost importance when choosing the target of stimulation in PD. DBS therapy tailored to individual patients in combination with multi-disciplinary care will optimize overall long-term outcomes. Mild cognitive impairment, particularly executive dysfunction, may predict the development of further cognitive decline in PD patients undergoing STN DBS [21] and a thorough neuropsychological assessment should be part of the presurgical diagnostic workup. In general, our practice is to favor STN DBS in younger patients likely requiring many years of effective stimulation unless speech or cognitive impairment clearly contraindicates this approach, in which case GPi DBS may be a little more "lenient".

Pedunculopontine nucleus and substantia nigra pars reticulata stimulation

There has been persistent interest in pedunculopontine nucleus (PPN) DBS for improving gait and freezing of gait (FOG) in PD. The PPN is embedded in the lateral pontine and mesencephalic tegmental reticular zones and degeneration of cholinergic neurons in the PPN may be crucial in the pathophysiology of gait and balance deterioration in PD [22]. Many studies have assessed the effects of unilateral or bilateral low-frequency (10–60 Hz) stimulation within the PPN area and found improvements in gait and FOG in PD, although surgical and programming approaches as well as outcomes are highly variable [23–25]. Some studies even used additional targets of stimulation and reported synergistic effect when the PPN was stimulated in conjunction with the STN [26], the zona incerta [27], or the GPi [28].

Despite encouraging publications, there remain only a limited number of individuals who have had long-term follow-up following PPN DBS. Furthermore, negative effects on speech have been reported with PPN stimulation [29] and this nucleus also influences other non-motor domains such as sleep, attention, arousal, and cognition and as yet it is unclear how its stimulation effects such functions [23]. PPN DBS is thus still experimental and further studies with long follow-ups are needed to clarify appropriate patient selection, optimal target identification and

Table 1 Randomized, double-blind, controlled studies comparing subthalamic versus pallidal DBS for Parkinson's disease

References	*n*	Follow-up (months)	Remarks	Outcome measure(s) (I = primary; II = secondary)	Results
Anderson et al. [17]	23	12	Single-center extension study of Burchiel et al. [110]	I: Change in off medication UPDRS motor scores	Improvement of motor scores with both GPi and STN stimulation (39 vs. 48 %)
				II: Dyskinesia severity and activities of daily living (UPDRS)	Bradykinesia improvement more with STN stimulation ($p = 0.06$)
					Levodopa equivalent dose reduction by 38 % in STN and 3 % in GPi stimulation ($p = 0.08$)
					Dyskinesia reduction with both GPi and STN (89 vs 62 %)
Compare Okun et al. [18] Zahodne et al. [111]	45	7	Unilateral DBS No dyskinesia-related measures	I: Visual Analog Mood Scale and verbal fluency (semantic and letter)	No difference between STN and GPi DBS in mood-related and cognitive outcomes
				II: Change in off medication UPDRS motor scores, 7 months assessment in four randomized DBS conditions (optimal, ventral, dorsal, and off DBS)	Larger deterioration of letter verbal fluency in STN, especially when off DBS (surgical effect?)
					UPDRS motor scores improved with both GPi and STN stimulation (27 vs. 30 %)
					No Levodopa equivalent dose reduction in either group
					STN group had greater improvement in rigidity ($p = 0.01$)
					Subjects in both targets were less "happy", less "energetic" and more "confused" when stimulated ventrally
					Quality-of-life improvements in GPi greater than in STN group (38 vs. 14 %; $p = 0.003$)
Follet et al. [19]	299	24	There is an observer-blinded FU at 36 months (Weaver et al. [112]) 23 % of participants >70 years old	I: Change in off medication UPDRS motor scores	UPDRS motor scores improved with both GPi and STN stimulation (28 vs. 25 %)
				II: Self-reported function, quality of life, neurocognitive function, and adverse events	No difference in self-reported function
					Levodopa equivalent dose reduction by 32 % in STN and 18 % in GPi stimulation ($p = 0.02$)
					Reduction of time spent with dyskinesias with both GPi and STN (83 vs 65 %)
					Visuomotor processing decline in STN vs GPi stimulation ($p = 0.03$), but no difference in verbal fluency
					Level of depression worsened with STN and improved with GPi stimulation ($p = 0.02$)
					At 36 months: motor improvements similar between targets and stable over time; Health-related QoL improved at 6 months, but improvement diminished over time; Mattis Dementia Rating Scale scores declined faster for STN than GPi patients ($p = 0.01$)

Table 1 continued

References	*n*	Follow-up (months)	Remarks	Outcome measure(s) (I = primary; II = secondary)	Results
NSTAPS Odekerken et al. [20]	128	12		I: Functional health and composite score for cognitive, mood, and behavioral side effects II: Symptom scales (UPDRS off medication), activities of daily living scales, a quality-of-life questionnaire, adverse events, and drug use	Reduction of disability with no significant group differences Cognitive, mood, and behavioral side effects in 58 % with GPi and 56 % with STN stimulation UPDRS motor scores improved with both GPi and STN stimulation (26 vs. 46 %; $p = 0.03$) Levodopa equivalent dose reduction by 44 % in STN and 16 % in GPi stimulation ($p = 0.01$) Dyskinesia severity reduction with both GPi and STN (57 vs 21 %) No difference in adverse event rates

GPi globus pallidus internus, *QoL* quality of life, *STN* nucleus subthalamicus, *UPDRS* Unified Parkinson's Disease Rating Scale

programming before this procedure can be recommended in clinical practice. Overall, patients with L-dopa refractory gait freezing but preserved postural reflexes probably represent the individuals most likely to benefit.

More recently, there has been interest in stimulation of the substantia nigra pars reticulata (SNr), which is closely located ventrally and medially to the STN. One study found that among PD patients treated with STN DBS stimulation of the SNr at 130 Hz via the most distal contact of the quadripolar electrode resulted in an improvement of gait and posture [30]. Subsequently, another group of researchers used the interleaved mode (alternate pulses of stimulation delivered to 2 or more individual contacts via a single electrode) to stimulate both the STN and the SNr [31, 32]. In this randomized, double-blinded, crossover trial including 12 patients with PD, the primary outcome measure of "axial symptoms on the UPDRS" did not differ significantly between conventional STN DBS and combined STN/SNr stimulation [31]. However, FOG specifically was significantly improved with combined STN/SNr stimulation.

GPi and non-GPi targets for dystonia

Triggered by reports of successful treatment of PD motor symptoms including dyskinesias, chronic pallidal DBS was also applied to patients with cervical and generalized dystonia in the late 1990s [33, 34]. Its remarkable effects have since been confirmed and established further in large well-designed multicenter trials in segmental and generalized primary dystonia as well as myoclonus–dystonia and tardive dystonia [3, 35, 36]. The effectiveness of DBS appears to be greater in those with primary forms of dystonia, or tardive dystonia although modest beneficial effects can be seen in some patients with other secondary forms [37]. In patients with primary generalized and segmental dystonia, pallidal DBS exerts sustained beneficial effects in the long term and there is no evidence of tolerance effects to neurostimulation [38, 39], although in some patients, additional electrode placement may be performed because of restricted benefit following their original surgery [40].

The optimal stimulation target has also been the subject of interest in dystonia patients particularly since the observation that patients with pallidal DBS may develop stimulation-induced parkinsonism especially if the deeper pallidal contacts are used [41, 42]. There are a number of publications reporting on the merits of thalamic DBS, either in the thalamus ventralis intermedius (VIM) [43] or in the nucleus ventralis oralis anterior (Voa) combined with the subthalamic area [44] in patients with dystonic tremor, and this might be a reasonable alternative target in this particular group of patients. STN stimulation has also been

studied in dystonia patients with positive results [45–47] and further studies are needed to clarify the value of chronic subthalamic simulation in this hyperkinetic movement disorder.

VIM DBS for non-PD tremor

Medically intractable essential tremor (ET) [1, 48], dystonic tremor [44, 49], and orthostatic tremor [50] can all respond to DBS of the VIM. High-frequency stimulation is required. Tremor occurring in multiple sclerosis can also respond [51], although these patients often have coexisting disabling ataxia which may be less predictably responsive to the surgery. The extent of functional disability due to tremor, rather than coexisting ataxia should be clarified during preoperative assessment.

Data on long-term efficacy and safety are available for DBS in ET. In a blinded study of 13 ET patients treated with VIM DBS over more than 10 years, neurostimulation led to a tremor reduction of 37 % resulting in a functional improvement of 32 % [52]. However, speech and balance problems were commonly noted in patients with bilateral stimulation. Moreover, the effect of thalamic stimulation on tremor may diminish over time [53, 54] and overnight withdrawal from stimulation has been suggested to prevent tolerance effects. However, not all authors support the hypothesis that tolerance effects account for worsening of response to DBS over time and disease progression may additionally contribute to this phenomenon [55]. In view of the possible occurrence of speech or balance difficulties that can be seen with bilateral VIM DBS, unilateral or staged bilateral procedures may be preferred [1, 56, 57].

The caudal zona incerta (cZI), also known as the posterior subthalamic area, has been identified as a target for patients with tremor and cZI stimulation may even surpass tremor control achieved with stimulation of the VIM [58, 59]. These findings are consistent with results from diffusion tensor imaging data suggesting that the best tremor control is obtained with stimulation of the cerebello-thalamic afferents, which are embedded in the subthalamic area [60]. An electrode trajectory that straddles VIM and cZI enables both targets to be assessed using a single electrode and makes both stimulation options available.

Timing of DBS

“Early-Stim” and “Earliest-Stim”

The decision to perform DBS should always consider a balance between the potential benefits for an individual in comparison to their individualized risks. The theoretical risks of invasive neurosurgery are higher in individuals with more brain atrophy or with greater comorbidity, i.e., in general those individuals who are elderly, cognitively impaired or of longer disease duration. Nevertheless, invasive neurosurgery is never free of risk and presently, its use requires justification based on the preexistence of disabling problems likely to respond to DBS, or as part of properly conducted, ethically approved clinical trials.

Whether intervention with neurostimulation might provide greater improvement of quality of life and motor symptoms when performed at an earlier point in the course of PD has recently been assessed in the Early-Stim trial [61]. This study randomized 251 PD patients with a mean age of 52 years, a mean disease duration of 7.5 years and a recent onset (less than 3 years) of levodopa-related motor complications to either STN DBS plus BMT or BMT alone. Early DBS resulted in significant and clinically meaningful improvements of quality of life, motor disability, activities of daily living, and levodopa-induced motor complications after 2 years of follow-up. These advantages need to be considered in the context of serious adverse events related to surgical implantation or the neurostimulation device, which occurred in 17.7 % of patients. There were 2 suicides in the neurosurgical group and 1 in the BMT group. These results are in broad agreement with a previous smaller trial of similar design in patients who were on average 48 years old [62].

Following the Early-Stim trial, there has been a further trial exploring whether DBS might be considered even sooner, i.e., before the onset of motor complications [63]. STN DBS and BMT was compared to BMT alone in very early PD patients with a mean age of 60 years and a mean disease duration of 2 years, Hoehn and Yahr stage II off medication, and without motor fluctuations or dyskinesias. The authors found no differences in their primary outcomes—time to reach a 4-point worsening from baseline in the UPDRS-III off therapy nor in the change in levodopa equivalent daily dose from baseline to 24 months, nor in any of the multiple motor and quality of life-related secondary outcome measures among treatment groups.

The results from these trials have provoked much discussion. The inclusion criteria for the Early-Stim trial included individuals with existing disabling motor complications of PD (UPDRS part 4 mean score 5.6 at baseline) and this supports the trend to consider DBS surgery as soon as disability despite optimal medical management occurs. However, the latter study, aside from reaching negative results, raises various issues including that operating patients too early in their disease (1) poses unnecessary exposure to surgical risks for individual patients, which cannot be easily justified by the preexisting PD disability, (2) may lead to intervention on atypical cases and (3) might have negative health economic implications [64]. In fact, in this particular study, 2 of the 15

operated patients had serious adverse events (1 perioperative stroke and 1 lead infection with subsequent device removal) [63].

The recommendation for commencing DBS in patients meeting inclusion criteria for Early-Stim should not ignore additional individualized factors. A very important issue is the impact of patients' expectations, which has been demonstrated to substantially enhance acute DBS responses in a blinded protocol [65]. Furthermore, unrealistic patient expectations can lead to patient disappointment even following successful surgery, which may theoretically pose a suicide risk. Longer term outcome of the Early-Stim cohort is eagerly awaited and may help to clarify the benefits of DBS in PD patients with early motor complications.

In other patient groups, the merits of performing DBS earlier or later following symptom onset have not been so well studied. There is a body of evidence suggesting that the introduction of DBS early in the disease course of generalized and segmental (primary) dystonias may be beneficial in preventing the development of contractures or other secondary skeletal deformities (reviewed elsewhere [3, 37]). DBS is increasingly considered in children with severe medically intractable dystonia even at a very young age [3, 66]. Patients undergoing DBS for essential tremor (ET) can often have acceptable improvement in function following a unilateral VIM DBS procedure that can often be tolerated even in more elderly patients.

DBS programming

Chronic side effects of subthalamic DBS on speech and gait: use of low frequency

While STN stimulation has been associated with improvement of stride length and in gait velocity as well as increased amplitude of arm and leg swing movements [67, 68], over time many STN-stimulated patients complain about gait and balance deterioration and there may be an increased risk of falls and worsening of levodopa-resistant FOG [69, 70]. Speech may also be significantly worsened with STN DBS, directly correlated with amplitude and duration of stimulation, along with abnormal laryngeal muscle contraction [71–73]. Lower preoperative speech intelligibility, longer disease duration, and medially placed left hemisphere active electrode contact seem to be predictive factors for deterioration of speech 1 year after surgery [74].

To overcome the limiting side effects of stimulation on axial motor symptoms, various strategies have been tried. In one study, reduction of stimulation strength on the clinically less affected side resulted in an increased stride length and a reduction of freezing episodes compared with the conventionally applied STN DBS stimulation [75]. Therefore, reducing asymmetry by balancing the laterality of STN stimulation may be a feasible first approach when facing a patient with FOG in clinical practice.

Another approach may be the reduction of the stimulation frequency as suggested by multiple studies assessing the effects of low frequency on axial motor signs. Two studies found that using 60 Hz instead of 130 Hz subthalamic stimulation significantly reduced number of FOG episodes [76, 77]. Furthermore, improvements in dysarthria and aerodynamic speech parameters with 60 Hz compared to 130 Hz subthalamic stimulation have been reported [78]. Importantly, the use of low-frequency stimulation is also associated with a reduced aspiration tendency, as demonstrated by barium swallow studies, along with a reduction of perceived swallowing difficulty [76]. Low-frequency stimulation might even help to overcome STN DBS-induced verbal fluency impairment [79].

Although some studies have failed to show positive effects of low-frequency stimulation on axial symptoms [80], a reduction from 130 to 100–60 Hz is a practical programming option when FOG, speech deterioration or other axial motor symptoms dominate the clinical picture. If this is accompanied by loss of the control of the appendicular motor symptoms (particularly limb tremor), a simultaneous increase in stimulation amplitude may be necessary.

Experimental uses of DBS in movement disorders

The potential use of DBS has been assessed in a wide range of movement disorders other than PD, tremor or dystonia such as Tourette's syndrome, chorea and PD/Lewy body-related dementia (Table 2).

Tourette's syndrome

DBS has been shown to be potentially effective in the reduction of tic frequency and severity in patients with medication refractory Tourette's syndrome (TS) [81]. There have been randomized, double-blind trials of Centromedian/parafascicular (CM-Pfc) thalamic DBS [82–84] as well as DBS within the GPi [84, 85], with accompanying improvement in quality of life. Of these, one small trial compared bilateral stimulation of the CM-Pfc, the anteromedial GPi, both targets combined, and sham stimulation, and found that the anteromedial GPi was the most effective target for stimulation in all 3 Tourette's patients treated [84]. In the most recent and largest trial performed so far, bilateral GPi DBS was associated with 15 % tic improvement in a strict double-blind comparison with OFF stimulation and a 40 % reduction in the open-label

Table 2 Other movement disorders as potential indications for DBS

Indication	For review	Target(s)	Stimulation frequency and suggested mechanism of action	Publications/patients	Results/remarks	Planned/ongoing RCTs on cinicaltrials.gov
Tourette's syndrome	Schrock et al. [81]	Thalamus (CM-Pfc, Voa, Vop, Voi), GPi (posteroventral—motor, anteromedial—limbic), internal capsule/NAcc, and others	HFS; inhibitory effect on the pathological network between cortical (premotor and motor) and subcortical (striatum, GPi, thalamus) structures	More than 130 patients in several case reports/series and a few controlled studies	Variable results with improvements in tic severity up to 50 %. Concomitant psychiatric conditions such as OCD, depression, and anxiety may remain unchanged. Largely unknown effects on QoL Increased risk of infections and hardware malfunction compared to other indications	Double-blind trial with sham stimulation; no target specified; $n = 20$; NCT02253498 Double-blind crossover trial aiming at improving anterior pallidal DBS; $n = 10$; NCT02112253
Huntington's disease and Chorea-acanthocytosis	Edwards et al. [86]	GPi, Thalamus (Vop)	HFS; largely unknown mechanism of action	Approx. 20 patients with HD and 20 patients with Chorea-acanthocytosis in several case reports/series. No controlled studies	In the largest HD case series ($n = 8$) [89], GPi DBS leads to a mean improvement in chorea of 58 % at 12 and of 60 % at 36 months. Bradykinesia and dystonia tended to worsen over time In the largest Chorea-acanthocytosis case series ($n = 15$) [88], GPi DBS leads to a mean improvement in chorea of 54 % at 1–5 and of 44 % at >6 months. Parkinsonism did not improve	Double-blind trial with sham stimulation in HD; $n = 8$ (NCT02263430)
Lewy body dementias	Gratwicke et al. [113]	NBM	LFS; excitatory effects, hereby increasing the cholinergic output of the NBM	One case report in PDD ($n = 1$) [90] and also one phase I RCT in AD ($n = 6$) [91]	Case report in PDD: Improved cognitive functions (attention, concentration, alertness, drive, and spontaneity) RCT in AD: no significant difference in the double-blind crossover phase but in 4 out of the 6 patients stable or improved primary outcome parameters 12 months after surgery were observed	Double-blind crossover trial in LBD and PDD; NBM vs. sham stimulation; $n = 12$ (NCT02263937 and NCT01701544) Double-blind crossover trial in LBD; NBM vs. sham stimulation; $n = 6$ (NCT01340001)

CM-Pfc centromedian parafascicular thalamus, *DB* double blind, *GPi* globus pallidus internus, *NAcc* nucleus accumbens, *NBM* nucleus basalis of Meynert, *QoL* quality of life, *PDD* Parkinson's disease dementia, RCT randomized controlled trial, *STN* nucleus subthalamicus, VP thalamus ventral posterior thalamus, *VC/VS* ventral capsule/ventral striatum, *Voa* nucleus ventro-oralis anterior, *Voi* nucleus ventro-oralis internus, *Vop* nucleus ventro-oralis posterior

observation up to 36 months [85]. Recent recommendations for the use of DBS in Tourette's syndrome have been published [81].

Chorea

Patients with Huntington's disease or other forms of chorea such as Chorea-acanthocytosis can experience improvements in movement with bilateral GPi DBS as suggested by many case reports and some case series [86–89]. Beneficial effects occur both for axial and limb chorea. The major issue relates to patient selection in view of the frequency of accompanying cognitive or psychiatric comorbidity experienced by these patients. No randomized controlled trials have been published so far.

Lewy body dementias

Brief additional mention will be made on this subject given it is of major potential relevance to PD patients. Stimulation of the nucleus basalis of Meynert (NBM) has been used in PD dementia reported in a single case [90] and there is also a phase I trial of NBM stimulation in Alzheimer's dementia [91]. Despite the mostly advanced age of these patients, a recent analysis has shown that clinical and economic thresholds required for DBS to be cost-effective for dementia are relatively low [92].

Despite some encouraging results, the number of patients with these conditions treated with DBS is still low and there is considerable uncertainty regarding the optimal stimulation target and stimulation mode. Randomized controlled trials are underway (Table 2) and will help to clarify the value of DBS and its single targets in these diseases. However, for the time being, the use of DBS remains entirely experimental in these indications.

Advances in DBS technology

Electrodes

Classical monopolar, double monopolar or bipolar stimulation sometimes fails to provide sufficient beneficial effects or causes undesired side effects at stimulation amplitudes needed to sufficiently control symptoms. Therefore, more advanced stimulation techniques have been recently introduced. The *interleaving* stimulation mode (Medtronic Inc. Minneapolis) allows independent stimulation of two contacts of the quadripolar DBS electrode with different values for voltage and pulse width in an alternating fashion [93] which can to some extent allow the clinician to shape the field of electrical stimulation along the vertical axis. A newly developed DBS device called *Vercise* (Boston Scientific Corporation, Natick, Massachusetts, USA) is capable of delivering multiple source constant current allowing the allocation of completely different stimulation parameters independently to each of eight contacts of the electrodes [94] (Fig. 1). This gives the opportunity to further shape the current along the vertical axis of the electrode.

A further prospect is to shape or steer the current delivered according to all three axes and respective devices are currently being developed. There are two independent proof of concept studies using such devices—one using a 32 or 40 contact electrode (Fig. 2) steering in 4 different directions [95] and a further lead with rings of 3 electrodes each steering in 3 different directions [96]—(thus far assessed in an intraoperative setting only). Both electrode designs consistently showed a significant widening of the therapeutic window with stimulation in the best direction compared to the conventional spherical stimulation [95, 96]. Chronic implantation is now needed to establish the usefulness of directional steering in the long term.

Impulse generator

A further potential innovation is the introduction of a so-called "adaptive" or "closed-loop" stimulation. In movement disorders, particularly PD, symptoms may fluctuate driven by factors such as medication intake as well as

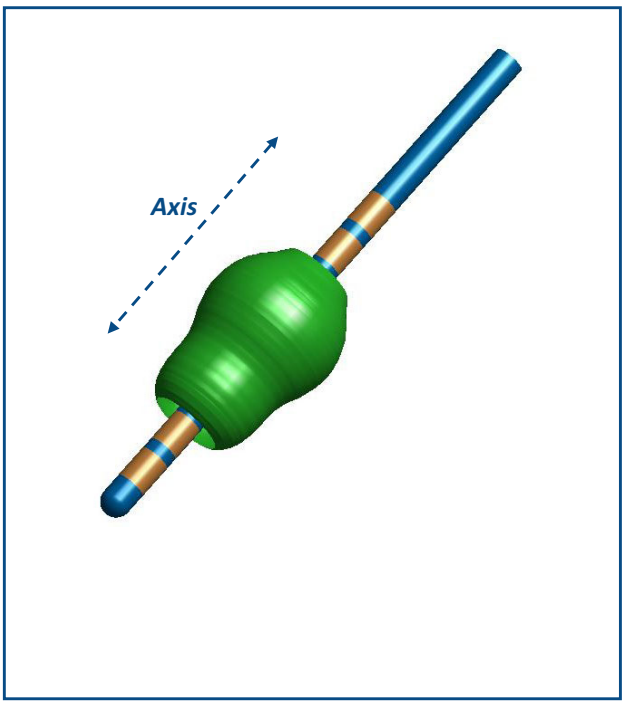

Fig. 1 Eight contact electrode allowing variable titration of current between contacts. (Reproduced with permission from Boston Scientific)

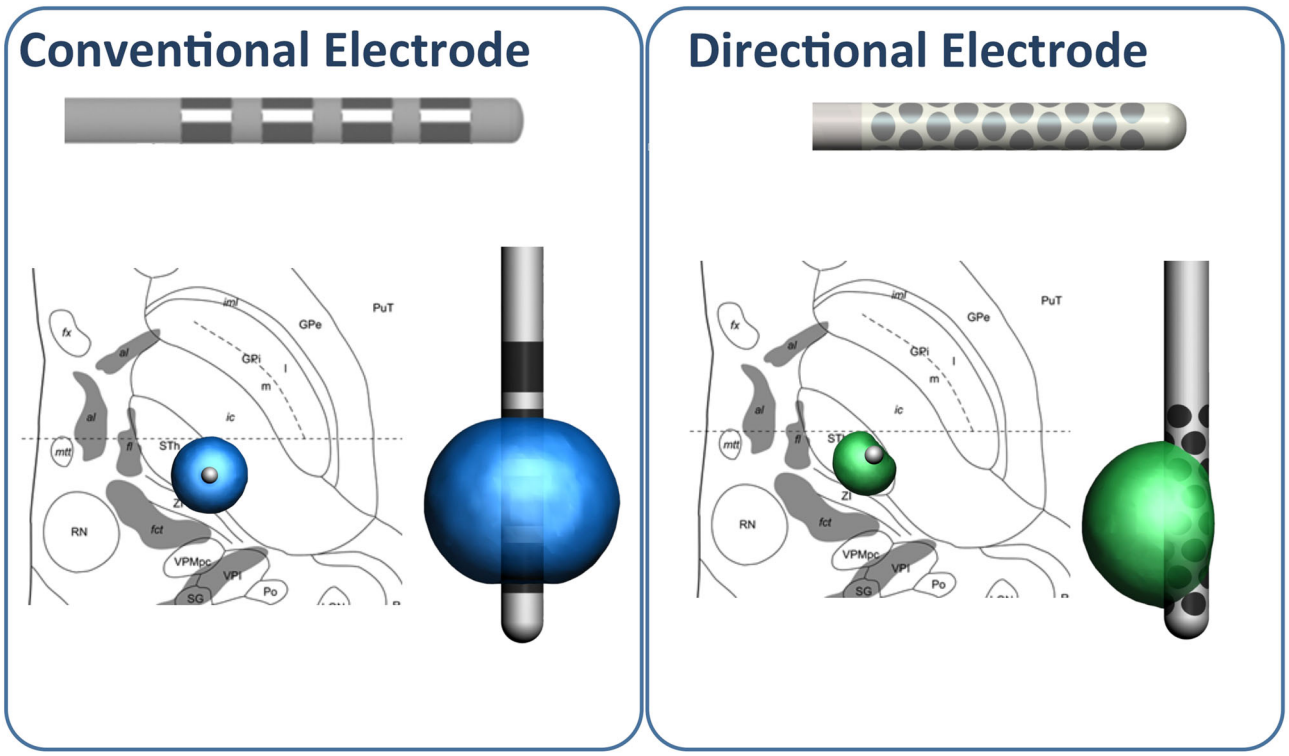

Fig. 2 Conventional quadripolar electrode **a** producing a spherical electric field that may spread outside the target area (STN) compared to the multipolar (32 contacts) lead, **b** creating a directional electric field allowing for restriction of the current to the target structure. *STN* subthalamic nucleus, *ZI* zona incerta, *CI* capsula interna (reproduced with permission from Medtronic)

physical activity, cognitive load or mood swings. Therefore, an intelligent DBS system capable of tracking these fluctuations using a neurophysiological biomarker and simultaneously delivering stimulation on demand may potentially be a major advance. A proof of concept study has been undertaken in PD using a brain–computer interface system that tracks the beta-frequency activity in the STN, as a marker of akinesia/rigidity of PD [97]. Beta activity-triggered therapeutic stimulation was found to be superior in alleviation of motor symptoms compared to conventional-continuous, intermittent-random and no stimulation, moreover reducing stimulation time and thus potentially prolonging battery life with chronic use.

A similar approach has been made in a study on ET using a peripheral electrophysiological marker namely tremor amplitude and phase [98]. Stimulation near the tremor frequency could both reduce or enhance tremor amplitude depending on when the stimulation impulse was delivered in the phase of the tremor cycle. At optimal phase alignment, tremor was suppressed by 27 %. Chronic delivery of adaptive DBS could thus play a major role in the neurosurgical treatment of PD, tremor and it has also been proposed for other indications such as Tourette's syndrome [99] and development of such devices is underway.

Imaging

Along with new developments in the DBS technology itself, advances in imaging techniques, mainly magnetic resonance imaging (MRI), and in related visualization software programs will hugely impact the field of invasive neurostimulation. New DBS systems are becoming increasingly compatible with 1.5T MR machines combined with special head coils [100] enabling both improvement in targeting and verification of electrode location with good clinical outcomes [101]. Furthermore, a change in product labeling has the potential to greatly reduce the difficulty in performing whole body MRI in patients with implanted DBS systems (provided specific sequences and protocols are carefully adhered to; http://www.medtronic-mrisafety.co.uk). This improvement in technology and safety [102] has also allowed evaluation of the mechanistic effects of STN DBS using functional MRI both at rest [103] and during movement [104].

The structural connectivity between basal ganglia and other nuclei can also be assessed with preoperative diffusion tensor imaging, which may help to define new DBS targets such as the subgenual cingulate cortex for treatment-resistant major depression [105] and might also help to refine definition of the target within individual structures

such as the STN [106]. Moreover, along with functional MRI, tractography allows the study of the effects of chronic stimulation on brain circuitries involved in the respective disease.

Specialized visualization software (e.g., Optivise; Neurotargeting, Nashville, USA) estimating the volume of tissue activated represents another useful and particularly practical tool to assist in programming by visualizing the activation map based on the stimulation parameters used in relation to the prespecified target map [107].

Future directions

While the introduction of DBS earlier in the course of PD remains the subject of debate and requires careful audit of longer term outcomes, it seems certain that the indications of DBS will continue expanding, not only in movement disorders but also in other neurological and psychiatric indications. To maximize beneficial effects and minimize side effects from DBS, new or alternative programming approaches that are currently being studied will be very helpful. Moreover, implanted electrodes will offer refined options including the possibility to steer current toward a certain direction along with multiple source IPGs that allow for highly customizable stimulation patterns. The programming clinician may therefore, be faced with so many options that new software tools will be needed to aid in the adjustment of settings.

The advent of closed-loop stimulation, allowing for a delivery of stimulation on demand, based on real-time recording of neurophysiological biomarkers for the patient's clinical state will be one way of optimally tailoring stimulation parameters to an individual's need. In the meantime, postoperative verification of DBS electrode placement [108] can allow the incorporation of imaging platforms to help guide DBS programming [107].

While DBS in itself may be one of the most exciting and intriguing recent achievements in the treatment of brain disorders, the surgical procedure inevitably required, might in itself facilitate trials of experimental biologic approaches that require co-administration of a gene, growth factor or cell therapy being directly delivered to the central nervous system [109]. Many of the patients meeting inclusion criteria for DBS trials would also be suitable for such biological trials. This strategy would provide the possibility of a "sham-biological" neurosurgical procedure with diminished ethical concerns as all included participants could benefit from DBS, as well as reducing the overall trial costs. This approach may in the first instance be of interest in PD (Clinicaltrials.gov: NCT02369003) but also may become of additional relevance to a range of other disorders of the brain.

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