

Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation



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Deep brain stimulation (DBS) is an established procedure for the symptomatic treatment of Parkinson's disease. Several deep brain nuclei have been stimulated, producing a wide range of effects on the motor and non-motor symptoms of Parkinson's disease. Long-term, high-quality evidence is available for stimulation of the subthalamic nucleus and globus pallidus internus, both of which uniformly improve motor features, and for stimulation of the thalamic ventralis intermedialis, which improves tremor. Short-term data are available for stimulation of other deep brain targets, such as the pedunculopontine nucleus and the centremedian/parafascicular thalamic complex. Some non-motor symptoms improve after DBS, partly because of motor benefit or reduction of drug treatment, and partly as a direct effect of stimulation. More evidence on the effects of DBS on non-motor symptoms is needed and specifically designed studies are warranted.

Introduction

Parkinson's disease is a progressive neurodegenerative disorder that affects several regions of the central and peripheral nervous system.¹ The symptoms of Parkinson's disease encompass the classic parkinsonian triad (tremor, bradykinesia, and rigidity) associated with dopaminergic denervation, other motor signs associated with non-dopaminergic transmission (postural instability and impairment of gait, speech, and posture), and non-motor symptoms (NMS).

Surgical treatments for Parkinson's disease were developed before the introduction of levodopa² and re-emerged as a means to overcome difficulties in the medical management of motor complications in patients with advanced Parkinson's disease. After pioneering experiments on various CNS targets, stereotactic ablations focused on the pallidothalamic pathway, including the globus pallidus, its outflow pathways, and the thalamus (table 1). Lesions in the globus pallidus internus (GPi) consistently improved dyskinesias and parkinsonian motor symptoms.³² However, there was a risk of inducing permanent neurological deficits with pallidotomy (especially when bilateral). Lesions of the subthalamic region also improved parkinsonian symptoms, but caused hemiballism in some patients.³³

Deep brain stimulation (DBS) was historically used to check the area to be lesioned in a given functional target³⁴ and later became an adjustable and reversible alternative procedure to stereotactic ablation,⁵ which was an important advancement in the treatment of tremor. Subsequently, GPi DBS was successfully introduced for the management of bradykinesia and rigidity.³⁵ After the discovery of the key part played by hyperactivity of the subthalamic nucleus (STN) in the pathophysiology of Parkinson's disease,³⁶ STN lesions were shown to improve experimental parkinsonism,³⁷ and the first experiences in patients with Parkinson's disease²⁷ highlighted that STN DBS could become the surgical treatment of choice for Parkinson's disease. However, experimental lesions of the pedunculopontine nucleus (PPN) induced akinesia³⁸ and PPN DBS has not provided consistent motor benefits

in patients with Parkinson's disease.³⁹ The main anatomical structures that are targeted by DBS are shown in figure 1. In this Review, we aim to address the available evidence on the effect of DBS on motor aspects of Parkinson's disease and particularly on NMS of the disorder, and to highlight the emerging role of new stimulation targets.

Motor features

Motor control is the main treatment goal for patients with Parkinson's disease. The motor effects of DBS are usually assessed by comparing the effects of stimulation with or without added drug treatment,⁴⁰ as measured on the unified Parkinson's disease rating scale (UPDRS) motor score. After STN DBS, patients' motor condition slowly deteriorates⁴¹ and often becomes unacceptable. Observations for up to 1 h have shown incomplete motor decay in patients who have had STN stimulation for 10 years.⁴² No study has specifically assessed the reappearance of motor signs after switching off GPi DBS; findings from patients assessed while not receiving drug treatment and with the stimulator turned off showed a gradual return of Parkinson's disease signs, similar to that seen after STN DBS.^{40,43,44} By contrast, hyperkinetic features recur more quickly after withdrawal of thalamic or GPi stimulation, which enables assessment of the reappearance of tremor⁴⁵ or dyskinesias induced by dopamine replacement therapy (DRT).⁴⁶

The effects of STN and GPi implants on the motor features of Parkinson's disease have been extensively assessed in class 4 studies, and a few randomised controlled trials have provided a higher class of evidence (appendix). The most robust data are for short-term (1–2 years) follow-up after surgery. STN DBS induces many of the antiparkinsonian effects of DRT, and preoperative response to levodopa contributes to prediction of the outcome after STN DBS.⁴⁷ Fewer studies, which had short follow-up, are available for DBS of the GPi and other nuclei. Long-term UPDRS-based data are available for STN DBS (10 years);⁴² medium-term data are available for GPi DBS (5–6 years)⁴⁴ and thalamic ventralis

Lancet Neurol 2012; 11: 429–42

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See Online for appendix

	Historical indications for ablation	Indications for deep brain stimulation
Thalamus		
Ventralis intermedialis nucleus	Tremor in Parkinson's disease and other movement disorders (thalamotomy) ^{3,4}	Essential tremor and tremor in Parkinson's disease ^{5*} Symptomatic tremors ⁶ Orthostatic tremor ⁷ Dystonia ⁸
Nuclei ventro-oralis anterior and posterior	Dystonia ⁹	Dystonia ¹⁰
Centre median nucleus/parafascicular complex	Tourette's syndrome ¹¹ Other movement disorders ¹²	Parkinson's disease ¹³ Tourette's syndrome ^{14*}
Globus pallidus	Parkinson's disease and other movement disorders (pallidotomy) ^{15,16}	Parkinson's disease (GPi) ^{17*} Dystonia (GPi) ^{18*} Huntington's disease (GPi) ¹⁹ Tourette's syndrome (GPi) ²⁰
Ansa lenticularis	Parkinson's disease (ansotomy) ²¹	None
Forel's fields	Parkinson's disease and other movement disorders (campotomy) ²²	Parkinson's disease (caudal zona incerta) ²³ Parkinson's disease (prelemniscal radiation) ²⁴ Tremor ²⁵
Subthalamic nucleus	Parkinson's disease (subthalamotomy) [†] ²⁶	Parkinson's disease ^{27*} Dystonia ²⁸ Essential tremor ²⁹
Pedunculopontine nucleus	None	Parkinson's disease ^{30,31}

GPi=globus pallidus internus. *Consolidated indication. †The term subthalamotomy, originally developed to describe stereotactic ablations of the subthalamic region, is now used to describe stereotactic lesions confined to the subthalamic nucleus.

Table 1: Identification of targets for stereotactic ablation and present indications for deep brain stimulation in movement disorders

intermedius nucleus (Vim) DBS (5 years);⁴⁸ and short-term data are available for PPN DBS (2 years).⁴⁹ Over the past 5 years, a significant improvement in parkinsonian motor features has been reported in selected patients after unilateral DBS of either the STN or GPi.^{50–52}

Several medium-term^{53–59} and some long-term studies^{42,60} have confirmed that STN DBS improves motor fluctuations, dyskinesias, and the cardinal motor manifestations of Parkinson's disease, with less consistent effects on bradykinesia in the on-treatment condition. Moreover, after STN implant, the levodopa-equivalent dose (LED) is readily reduced on average by 55·9%,⁶¹ and a trade-off between LED and the total energy delivered by DBS can be also measured 5 years,⁵⁶ 8 years,⁶⁰ or 10 years after surgery.⁴² By contrast, the medium-term effects of GPi DBS are less consistent, with some studies reporting stable^{43,44} or reduced beneficial effects⁶² up to 5 years after surgery.

Bradykinesia and rigidity

In a meta-analysis of 38 short-term studies from 34 neurosurgical centres in 13 countries,⁶³ STN DBS improved rigidity and bradykinesia by 63% and 52%, respectively, after 12 months. With the addition of DRT, these improvements increased to 73% and 69% respectively.⁶³ GPi DBS reduced rigidity and bradykinesia 1–2 years after implantation,^{40,64,65} to the same extent as that reported after STN DBS.⁶⁶ Whether bradykinesia and

rigidity are also improved by stimulation of other targets is unclear. The subthalamic region contains pallidal outflow pathways that can be influenced by stimulation in concert with the STN.⁶⁷ Stimulation of its posterior part (including the zona incerta [Zi] and the prelemniscal radiation) improved contralateral rigidity by 92·7% and contralateral akinesia by 65·7%.²⁴ By contrast, thalamic stimulation does not improve rigidity and bradykinesia,⁴⁵ and the effects of PPN stimulation are still disputed.

Evidence suggests that the initial benefit of STN DBS on akinesia decreases over time (appendix) and that the symptomatic effects of stimulation and drug treatment do not necessarily add up in the long term.^{53–55} 8 years after STN DBS, improvement of rigidity was retained with or without additional drug treatment, whereas bradykinesia was improved only partially by stimulation alone (25·1% compared with baseline) and worsened by 21·6% when patients received stimulation and drug treatment (compared with the drug treatment alone at baseline).⁶⁰ This finding, which was confirmed at 10 years,⁴² is probably due to the progression of Parkinson's disease and the appearance of drug-resistant and stimulation-resistant symptoms. Similarly, a reduction of beneficial effects after GPi DBS has been reported at 5 years.⁶² The dramatic reduction in LED noted after STN DBS has not been reported for GPi DBS (appendix). Because of the size of the GPi, stimulation must deliver more energy to the GPi than the STN, leading to shorter battery life.⁶⁴ STN DBS improves bradykinesia more than GPi stimulation:⁶⁸ 70–80% compared with 30–40% according to retrospective comparison's.⁶⁹ Findings from other studies suggest that the efficacy of GPi stimulation on akinesia is lost in the early post-implant phase⁶² or later.⁷⁰ Some patients who had GPi DBS successfully underwent subsequent STN DBS.^{62,70} The GPi is large and contains discrete segregated output pathways; individual variability of subnuclear location of the stimulating electrode accounts at least in part for a lower efficacy compared with STN DBS. Stimulation in the anteromedial-ventral GPi is associated with a greater improvement in rigidity than stimulation in the central-dorsal GPi, whereas those located in the central-dorsal GPi are more effective on bradykinesia than stimulation in the anteromedial-ventral GPi.⁴⁶ Conversely, stimulation of a smaller target than the GPi, such as the STN, might be associated with a greater predictability of effective outcome, but can result in a higher incidence of adverse effects.^{44,52,66}

Tremor

Parkinsonian tremor is thought to result from oscillating networks within basal ganglia circuits, and various nuclei within and outside the basal ganglia are potential targets for managing tremor. According to a traditional symptom-based approach, lesions or DBS of the thalamic Vim relieve tremor.⁵ Common DBS-related adverse events are paraesthesia and, in patients with bilateral implants, dysarthria and balance difficulties.⁵ Although STN or GPi

stimulations also improve Parkinson's disease tremor, thalamic DBS remains a valuable surgical option for treatment of disabling tremor—eg, in patients with advanced age when other targets are not practicable.^{71,72} Stimulation of the caudal Zi produced a 93% improvement in tremor compared with 86% improvement after stimulation of the dorsal border of STN and 61% after stimulation of the STN itself.⁷³ Unilateral Zi stimulation is also effective for treatment of contralateral Parkinson's disease tremor.²⁴ The centremedian/parafascicular (CM/Pf) thalamic complex has also been proposed as a successful target for control of tremor.^{13,74} Long-term efficacy in tremor management has been reported for STN,^{53,60} GPi⁶² (appendix), and thalamic DBS, as noted in a multicentre study with a 5-year follow-up that enrolled patients with either unilateral or bilateral Vim implants.⁴⁸

Gait and balance

Gait and postural difficulties usually occur in the late stages of Parkinson's disease, on average 10–15 years after onset, and represent a substantial problem in the management of Parkinson's disease symptoms that might be particularly resistant to both DRT and DBS. A meta-analysis showed that, during the first year after implantation, STN DBS improved postural instability gait difficulty (PIGD) complex, roughly equalling the preoperative effects of drug treatment.⁷⁵ The addition of drug treatment provides further improvement in the short term.⁷⁶ Findings from several studies have shown that off-period freezing is improved by STN DBS whereas freezing resistant to DRT is not,^{53,77} although this can rarely be improved.⁷⁸ Gait analysis study findings consistently showed that STN DBS and levodopa independently have a similar positive effect on spatiotemporal gait parameters early after implantation.⁷⁹ However, individual patients might show poor or no gait improvement after STN implantation, even in the short term.⁷⁵

Inaccurate positioning of the stimulating electrode within the STN can cause stimulation-induced freezing.⁸⁰ Furthermore, spread of current to the substantia nigra, Zi, or other adjacent regions can cause stimulation-related akinesia, as confirmed by the negative effect on gait induced by a voltage increase.⁸¹ Reduction of the frequency of stimulation can improve gait and freezing,⁸¹ although the benefit might not be sustained over time.⁸² In the long term, axial motor features decline despite STN stimulation.^{53,54,56} 5 years after STN implantation, gait problems that respond poorly to STN DBS arise in 15–40% of patients.^{55,58} In a patient cohort with excellent preoperative gait improvement with DRT, continuous STN stimulation for 8 years improved gait by 41% compared with the preoperative condition.⁶⁰ The long-term efficacy of GPi DBS is less well documented (appendix). Findings from some studies suggest that GPi is less efficacious than STN DBS on axial features,⁶⁸ but a recent meta-regression analysis revealed that PIGD

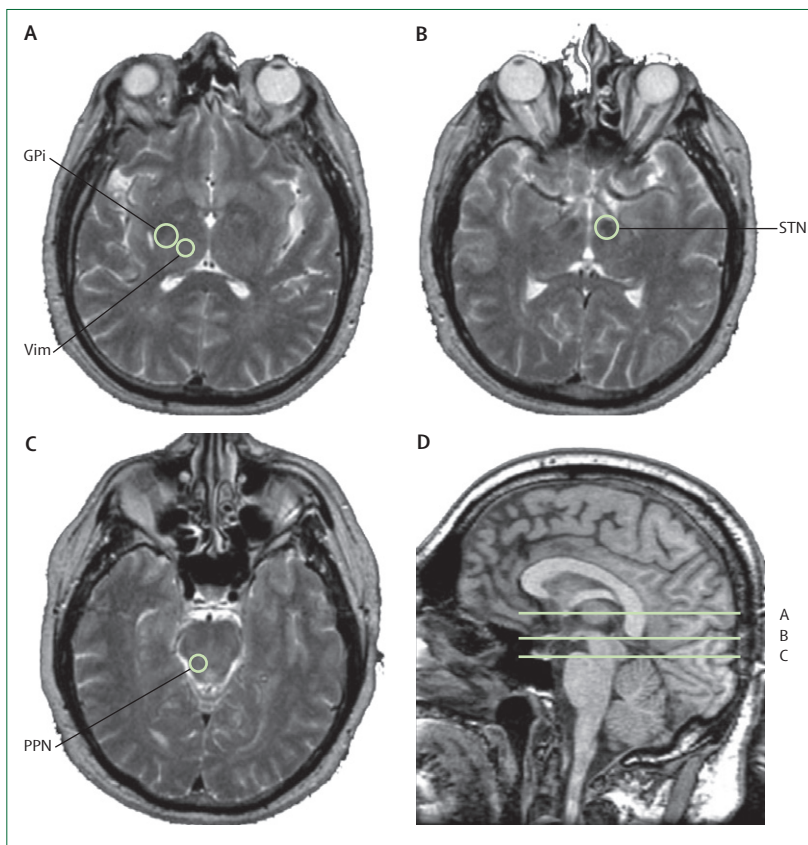


Figure 1: Main anatomical structures targeted by deep brain stimulation, as they appear on T2-weighted brain MRI

Axial sections correspond to the level of anterior commissure (A), superior colliculus (B), and inferior colliculus (C). Locations of sections are shown in D. The target nuclei are shown by the green circles. The STN is observed as a small lens-shaped hypointense nucleus ventral to the red nucleus; the GPi appears as a hypointense region located laterally to the anterior limb of internal capsule. Vim cannot be observed with brain MRI and has been traditionally identified during surgery on a conscious patient by recording its physiological signature (so-called tremor cells). Conventional MRI sequences are unsuitable for clear visualisation of the PPN and there are no hallmarks that allow a clear identification of its boundaries. Other nuclei not displayed are the centremedian/parafascicular complex (medial to Vim in A), Forel's fields and the zona incerta (surrounding the STN in B). GPi=globus pallidus internus. PPN=pedunculopontine nucleus. STN=subthalamic nucleus. Vim=ventralis intermedius nucleus.

initially improved after DBS of either the STN or GPi and gradually declined to presurgery values 2 years after implantation in the STN but not the GPi.⁸³

Up to 35% of patients have a clinically meaningful worsening of postural stability between 5 and 8 years after implantation.⁶⁰ In a 10-year follow-up study⁴² there was no difference between baseline and last visit in UPDRS postural stability scores in the practically defined off-condition, although the on-condition score greatly worsened compared with baseline.

PPN DBS has been proposed for patients with Parkinson's disease who have severe axial signs that are unresponsive to drug treatment. Initial reports described an improvement of gait with stimulation at low frequencies (10–25 Hz) and a worsening at higher frequencies (>80 Hz).^{30,31,84} A synergistic effect was reported in patients with bilateral simultaneous STN and PPN implants, with PPN stimulation more effective on axial signs and STN

stimulation more effective on limb features.^{31,84} Findings from studies suggest a small effect of PPN stimulation on some motor signs, particularly gait and balance, despite large interindividual variability (appendix).^{39,85,86}

Speech

The effect of STN DBS on hypokinetic dysarthria is limited⁸⁷ (appendix). STN DBS has produced clinically significant improvements in speech intelligibility,⁸⁸ phonation, or articulation.^{89,90} However, these positive effects might weaken over time⁸⁹ or not be clinically meaningful.^{90,91} A consistent retrospective finding is that speech worsens after STN implantation, with 56% of patients with worsening speech at 1 year after implantation,⁹² 70% at 3 years,⁵⁵ 57% at 5 years,⁵⁸ and 90% at 8 years.⁶⁰ In a prospective controlled study, loudness increased 1 year after STN DBS but speech intelligibility deteriorated by a mean of 14.2% (compared with 3.6% in the control group; $p < 0.05$).⁹³ Speech rate and rhythm are affected in patients with Parkinson's disease and stuttering can recur or be aggravated after STN DBS.^{94,95}

Delayed speech worsening 5–6 years after implantation and stimulation-induced dysarthria were reported in patients with GPi implants, albeit less commonly than after STN DBS.⁴⁴ Vim stimulation does not improve hypokinetic dysarthria.⁷¹

Motor fluctuations and dyskinesias

Clinical trials and meta-analyses^{61,63} have assessed the beneficial effects of STN DBS in reducing motor fluctuations (appendix), with stable benefits that last for several years after surgery.⁶⁰ STN DBS does not have an appreciable antidyskinetic effect and can even induce dyskinesias (which prevent increase of stimulation during programming).²⁷ Notwithstanding, dyskinesia reduction has been consistently reported after STN implantation, owing to the reduction of postoperative DRT by an average 60%,^{56,61} as confirmed by the finding that acute levodopa administration can still provoke dyskinesias after STN implantations.⁹⁶ Additionally, a further decrease of on-period dyskinesias can be induced by an overall stabilisation of basal ganglia networks and striatal synaptic function after STN DBS.⁵⁹ Finally, at least in some patients and depending on the electrode trajectory, surrounding stimulation diffusing outside the STN can also influence the surrounding subthalamic region, particularly the ansa lenticularis and the lenticular fasciculus, mimicking the antidyskinetic effect of GPi stimulation (figure 2).

After GPi DBS there is negligible long-term reduction in DRT, as confirmed by two large multicentre STN-GPi comparative studies^{40,66} that reported a reduction in drug doses only in the STN group. However, GPi DBS has a direct and acute antidyskinetic effect, especially when stimulation is delivered through the ventral regions:⁴⁶ apomorphine-induced dyskinesias are almost abolished by GPi DBS, in a similar way whereas they remain unchanged after STN stimulation.⁹⁷ In addition to the

direct effect of stimulation, GPi DBS might produce long-term plastic changes that further contribute to dyskinesia reduction.⁹⁸ Finally, GPi DBS might also induce dyskinesias when stimulation is delivered through the dorsal contacts.⁴⁶

Preliminary data suggest that stimulation of the caudal Zi might affect dyskinesia scores and drug reduction to STN DBS.²³ No effect on motor fluctuations and dyskinesias has been noted after stimulation of the PPN or thalamic nuclei.

Non-motor symptoms

NMS of Parkinson's disease encompass various clinical manifestations, including cognitive dysfunction, behavioural changes, hyposmia, dysautonomia, and sleep dysfunction.⁹⁹ These features are often more disabling and resistant to treatment than motor symptoms and are key determinants of quality of life. Behavioural disorders might be substantial in patients treated by STN DBS,^{100–102} whereas the few data available for implants in other targets (ie, Vim, GPi, or PPN) suggest low non-motor morbidity.^{52,103–106} Table 2 summarises the interactions between stimulation at different targets and NMS.

Cognition

Studies of the effects of STN DBS on cognition have consistently reported a postoperative decline on phonological and semantic verbal fluency tasks,^{107,108} which was detectable a few months after surgery and gradually increased in the long term (up to 8 years).^{60,109} Besides a postoperative decline on a phonological verbal fluency task, long-term cognitive follow-up revealed a slight but significant decline in tasks of episodic memory, executive function, and abstract reasoning.⁶⁰ Recent studies in patients with Parkinson's disease who were treated with STN DBS compared with those given drug treatment showed that 1 year¹¹⁰ and 3 years after implantation¹¹¹ the STN groups had a greater decline only on a phonological verbal fluency task. The decline that has been detected shortly after STN DBS surgery might be caused by surgical microlesions affecting the cortical-basal ganglia circuits that are involved in word retrieval processes.¹¹² Alternatively, STN stimulation might cause decreased activity of inferior frontal and temporal cortical areas in the left cerebral hemisphere, resulting in decreased verbal fluency.¹¹³ Finally, because withdrawal of dopaminergic drugs can affect performance of patients with Parkinson's disease on verbal fluency tasks,¹¹⁴ a postoperative reduction in DRT might also play a part in the decline in verbal fluency after STN DBS. Overall, STN DBS is safe from a cognitive standpoint when strict inclusion criteria are used,¹¹⁵ although some studies have reported cognitive decline even when patients are subject to strict inclusion criteria.¹¹⁶

Bilateral GPi DBS has low cognitive morbidity, with some studies reporting a mild decline in semantic

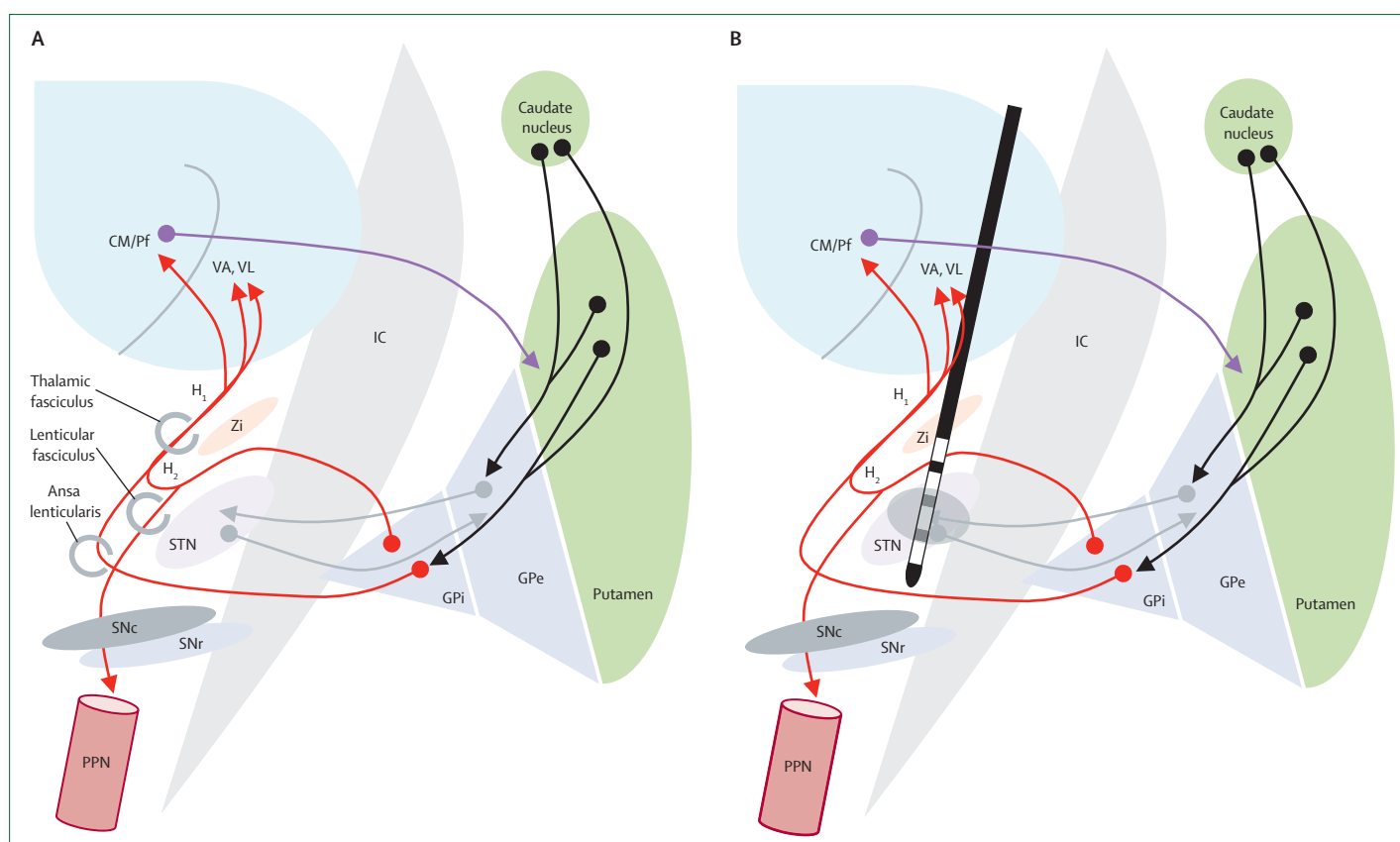


Figure 2: Organisation of the efferent projection from the basal ganglia

Simplified anatomical structures and pathways (A) and the theoretical position of DBS electrode placement in the STN (B) are shown. A discrete number of subcortical nuclei, all involved in the wide basal ganglia circuitry, have been targeted in patients with Parkinson's disease who have had stereotactic surgery. The STN is a glutamatergic nucleus located ventral to the thalamus. The globus pallidus is a large GABAergic nucleus composed of two functionally segregated subparts: the GPe, which receives inputs from the neostriatum (caudate nucleus and putamen) and the STN and in turn projects to STN and GPi (not shown); and the GPi, which is the main output structure of the basal ganglia (the other being the SNr) and projects to the nuclei of the motor thalamus (VA and VL), the CM/Pf complex, and the PPN. There are at least two different functional regions within the GPi, due to the segregation of pallidofugal fibres that ventrally form the ansa lenticularis (conveying projections from the outer portion of the GPi) and dorsally give rise to the lenticular fasciculus that conveys projections from the inner portion of the GPi. The subthalamic region is a white matter area abutting the STN and encompassing the Zi, Forel's fields, and the prelemniscal radiation. The ansa lenticularis and the fasciculus lenticularis surround the STN before reaching Forel's H₁ field, where they merge into the thalamic fasciculus. This crosses Forel's H₁ field before distributing to the thalamus. Stimulation of STN can also influence the different fibre tracks surrounding the nucleus (B: the grey shadow represents the rough size of the electrical field under unipolar stimulation of the second contact). The thalamic Vim is an ill-defined anatomical structure located posterior to the VL and anterior to the VP (which is involved in sensory processing). Its main function is to relay afferents from the cerebellar nuclei. CM/Pf=centromedian/parafascicular thalamic complex. GPi=globus pallidus internus. GPe=globus pallidus externus. IC=internal capsule. PPN=pedunculopontine nucleus. SNc=substantia nigra pars compacta. SNr=substantia nigra pars reticulata. STN=subthalamic nucleus. VA=ventral anterior thalamic nucleus. Vim=ventral intermediate nucleus. VL=ventral lateral thalamic nucleus. VP=ventral posterior thalamic nucleus. Zi=zona incerta. H₁=Forel's H₁ field. H₂=Forel's H₂ field.

verbal fluency,⁶² and no significant effect on cognitive functioning occurred 6 months after surgery in patients with advanced Parkinson's disease.¹⁰⁴ GPi DBS has lower cognitive morbidity than STN DBS, as shown by a greater decline on tasks of phonological verbal fluency,⁵² overall cognition,⁴⁴ and visuomotor processing speed in patients treated with STN DBS.⁶⁶ A meta-analysis of reports on STN and GPi DBS over 10 years concluded that cognitive and behavioural adverse events were more common in the STN group than the GPi group.¹¹⁷

Cognitive effects of PPN DBS have been assessed in a few unmasked studies on a small number of patients from one centre. Bilateral PPN implants reduced reaction time in tests assessing executive function and working memory, and improved performance on delayed recall and verbal fluency.^{105,106} Such an improvement might be mediated by

activation of ascending cholinergic neurons to the CM/Pf thalamic complex, leading to widespread activation mediated by the intralaminar thalamic nuclei. PET studies have reported an increase in fluorodeoxyglucose consumption in prefrontal areas, suggesting a modulation of thalamic metabolism after PPN DBS.¹¹⁸ Vim DBS is thought to have a low cognitive morbidity, although this has not been extensively investigated.¹⁰³

Impulse control disorders

Up to 13·6% of patients with Parkinson's disease develop impulse control disorders (ICDs).¹¹⁹ DRT might play an important pathogenic part in ICDs by overstimulating mesolimbic dopaminergic circuits that are involved in motivation and response to reward.¹²⁰ STN DBS variably influences pre-existing ICD features. In most studies,

	Subthalamic nucleus	Globus pallidus internus	Pedunculopontine nucleus
Cognition			
Memory	0/+*	0	0
Executive functions	-*†	0	+†
Mood disorders			
Apathy	-*†	0	0
Depression	-*†	0/-†	0
Anxiety	-/+*†‡	0/+†	0
Behaviour and other psychiatric issues			
Impulse control disorders	0/+*	0	0
Delusions and hallucinations	0/+*	0	0
Dopamine dysregulation syndrome	-/+*†	0/+†	0
Punding	-/+*†	0/+†	0
Autonomic dysfunction			
Sweating	+‡	0/+‡	0
Urinary function	+†‡	0/+‡	0
Bowel function	0/+*‡	0/+‡	0
Cardiovascular dysautonomia	0/+*‡	0	0
Sleep			
Quality	+*†‡	+‡	+†
Architecture	0	0	+†
Rapid eye movement sleep behaviour disorder	0/+*	0	0/+†
Restless leg syndrome	-*	0	0
Daytime sleepiness	+*	0	+†
Pain	+†‡	0/+‡	0

0=no effect. +=improvement. -=worsening. 0/-=no effect or worsening. 0/+*=no effect or improvement. *Secondary to drug reduction. †Due to direct effect of stimulation. ‡Secondary to motor improvement.

Table 2: Synopsis of the effects of deep brain stimulation at different targets on Parkinson's disease non-motor symptoms

ICDs markedly improved or disappeared after STN DBS in patients with Parkinson's disease.^{121–123} This effect might be due to the reduction of DRT after implantation, resulting in decreased stimulation of mesolimbic dopaminergic circuits,¹²² or to the direct inhibition of the ascending dopaminergic and serotonergic pathways that are involved in reward.¹²¹

A few studies have reported onset of ICDs (pathological gambling, hypersexuality, and compulsive eating)^{123,124} in patients with Parkinson's disease after STN DBS despite a postsurgical reduction of DRT.¹²⁵ A cross-sectional study that compared patients with Parkinson's disease treated with STN DBS to patients treated with drugs alone reported a higher incidence of impulsivity in the DBS group.¹²⁶ However, no preoperative data were available from this study. STN DBS might disrupt the activity of limbic circuits within the STN or the neighbouring fibre tracts, resulting in increased impulsivity.¹²⁷ Additionally, STN DBS might alter the coupling between the prefrontal cortex and basal ganglia during decision-making processes, resulting in impulsive behaviour during high-conflict situations.^{100,128} Finally, STN DBS might mimic the action of DRT, thus facilitating the onset of ICDs, particularly in patients taking high doses of DRT. ICDs have been associated with

oscillatory theta-alpha activity in the ventral STN, which suggests that the limbic ventral STN might be involved in the development of ICDs.¹²⁹

The effects of GPi DBS on ICDs are still poorly known: in two men with Parkinson's disease, preoperative hypersexuality did not improve after surgery.¹²³ In patients with Parkinson's disease treated with STN DBS, pre-existing ICDs improved postoperatively, with a significant reduction in DRT.

Dopamine dysregulation syndrome and punding

Patients with dopamine dysregulation syndrome (DDS) develop an addictive pattern of DRT use. In a series of 21 patients with Parkinson's disease who underwent bilateral STN DBS, symptoms improved or resolved in 29% of the patients with preoperative DDS; in two patients symptoms of DDS appeared only after surgery (in one case after an 8-year latency).¹²³ Resolution of symptoms has been associated with motor improvement and LED reduction after STN DBS.^{121,123}

Punding is a stereotyped behaviour that is triggered by DRT; it is characterised by intense fascination with complex, excessive, non-goal-oriented, repetitive activities, and is linked to dyskinesia severity, DDS, and occurrence of other ICDs.^{130,131} Punding can worsen or even arise after STN DBS surgery, despite DRT reduction.^{123,132,133}

Apathy

Several studies have reported a worsening of apathy in patients with Parkinson's disease after STN DBS.^{109,134} In a prospective study of patients with STN implants, apathy occurred after a mean of 4.7 months in 54% of patients and was reversible in half of them at 1 year.¹³⁴ Apathy might be associated with insufficient DRT after DBS, resulting in a postoperative deactivation of dopaminergic receptors within the mesocortical and mesolimbic pathways.¹³⁴ Accordingly, in patients with Parkinson's disease who developed apathy after complete withdrawal of DRT after successful STN DBS, a 6-week trial of ropinirole induced reversal of apathy.¹³⁵ In another study, apathy was assessed in patients with Parkinson's disease who received unilateral GPi or STN implants and in a control group of drug-treated patients.¹³⁶ Apathy was unchanged in the drug-treated group, whereas it progressively increased during the first 6 months after implantation in both DBS groups, with no relation to postsurgical drug changes.

Mood disorders and anxiety

Postoperative mood disorders (depression or mania) can occur after STN implantation, either as acute and transient or chronic and persistent disorders.^{102,125,137,138} In patients with bilateral chronic STN stimulation, depressive features improved,¹⁰⁸ remained unchanged,^{60,117} or even worsened compared with the preoperative condition.¹³⁸ Postoperative improvement of depression might result from a

psychological response to the alleviation of disabling motor symptoms¹³⁹ or from the effects of STN stimulation on neural circuits involved in mood.¹²⁵ Suicidal tendencies have been reported in some patients with Parkinson's disease after STN DBS.^{101,102} A retrospective study aimed at identifying the suicide rate after STN DBS in a large sample of patients with Parkinson's disease reported a 0.9% rate of attempted suicide and a 0.45% rate of successful suicides.¹⁰² Suicide rates were higher during the first postoperative year than at any other time. Various factors (postoperative depression, being single, previous history of ICDs, or compulsive drug use) were associated with attempted suicide risk; social and cultural variables might also play a part.¹⁴⁰ Various mechanisms might be involved in the pathophysiology of postoperative depression after STN DBS, such as tapering DRT too fast or an indirect inhibition of the activity of ascending serotonergic neurons,¹⁴¹ possibly exerted by projections from the basal ganglia to the dorsal raphe nucleus.

Manic symptoms occur in about 4% of patients with Parkinson's disease with bilateral STN implants,¹³⁸ sometimes in the immediate postoperative period.^{109,125} By contrast, 7 months after surgery, no overt mood variations were noted in patients with unilateral GPi or STN DBS.⁵² Manic symptoms can last for hours or a few days and might be closely linked to STN stimulation.^{125,142} Stimulation of the most ventral contacts within the STN can generate mood abnormalities, which are seldom suppressed by switching off.¹⁴³ More rarely, stimulation of the substantia nigra pars reticulata¹⁴² or of axons arising from the medial (limbic) portion of the STN and entering the medial forebrain bundle can give rise to DBS-induced reversible acute hypomania.¹⁴⁴ In patients with stimulation-induced manic symptoms, PET shows increased regional cerebral blood flow during the manic state, mainly in the right cerebral hemisphere in the anterior cingulate and medial prefrontal cortex.¹⁴² Readjusting the stimulation settings¹⁴³ or switching to another stimulation target¹⁴⁵ can resolve manic symptoms in some patients.

GPi and thalamic implants can also occasionally affect mood. Recurrent manic and hypomanic episodes, each lasting several days, were reported in one patient treated with bilateral GPi DBS.¹⁴⁶ Manic symptoms have not been reported after thalamic implants, but improvement of mood was reported in 23% of patients after CM/Pf DBS.⁷⁴ and in a small sample of patients with Parkinson's disease with unilateral Vim DBS.¹⁰³

Various studies reported a postoperative improvement of anxiety in patients with Parkinson's disease after STN DBS,^{108,147} others have reported no change¹¹⁶ or even the appearance or worsening of pre-existing anxiety.⁴³ In a short-term comparison trial (STN DBS vs DRT), anxiety was reduced in the DBS group.¹⁴⁸ In the long term, no significant changes in anxiety levels compared with baseline have been reported.⁶⁰ Postoperative worsening of anxiety might result from a dopamine withdrawal syndrome.¹³⁴ Variations in postoperative management of

DRT and individual variations of mesolimbic dopaminergic denervation might explain the variability in mood, anxiety, and motivation after STN DBS.¹³⁴ Improvement of motor symptoms also contributes to a reduction in anxiety after STN DBS.¹⁰⁹

Psychosis

In a series of patients with Parkinson's disease treated with STN DBS, short-lasting transient hallucinations and delusions were noted shortly after surgery.¹²⁵ Whether patients with a history of hallucinations are appropriate candidates for STN DBS is still debated. Pre-existing severe drug-induced hallucinations or delusions disappeared postoperatively in eight of ten patients with bilateral STN DBS after a reduction of DRT.¹⁴⁹ In the remaining two patients, hallucinations and delusions worsened immediately after surgery, despite complete DRT withdrawal, and disappeared after a few months of treatment with antipsychotic drugs. Another study investigated the effects of STN DBS on pre-existing hallucinations in 18 patients with advanced Parkinson's disease and noted a significant postoperative improvement of hallucination severity 6 months after DBS compared with baseline.¹⁵⁰ These findings suggest that a history of hallucinations does not formally contraindicate STN DBS in patients with advanced Parkinson's disease.

There have been few studies on the occurrence of hallucinations and delusions in patients treated by GPi DBS. Preliminary evidence suggests that the incidence of visual hallucinations might be lower after GPi DBS than STN DBS.¹⁵¹ In a 6-year follow-up multicentre study of 38 patients with Parkinson's disease treated by Vim DBS, the occurrence of cognitive and psychiatric adverse events was low, with one case of hallucinations reported among all centres.⁷¹

Autonomic dysfunction

Although orthostatic dizziness, bladder dysfunction (urge, incontinence, and frequency), hyperhidrosis, and erectile dysfunction are common NMS of Parkinson's disease, only a few class 4 studies have addressed these features. After STN DBS, an improvement of dysautonomia after reduction of DRT (as suggested for bowel function)¹⁵² or an improvement in motor functioning (as for excessive sweating secondary to dyskinesias) might occur.¹⁵² Accordingly, the sympathetic skin response does not change after STN implantation, although dyshidrosis is improved by 66.7% compared with before surgery.¹⁵³ Furthermore, a direct effect of stimulation on autonomic regions might explain the improvement of urinary symptoms after STN DBS,^{152,154} by an increase of bladder capacity and reflex volume¹⁵⁵ and improved integration of afferent bladder signals by the basal ganglia, with subsequent modulation of activity of the lateral frontal and anterior cingulate cortex.^{154,156}

STN DBS seems to have little effect on cardiovascular dysautonomia.¹⁵⁷ One study noted that STN stimulation

increases peripheral vasoconstriction and baroreflex sensitivity and stabilises blood pressure, thereby improving postural hypotension.¹⁵⁸

Sleep

Bilateral STN DBS improves objective measures of sleep on polysomnography, decreases nocturnal and early morning dystonia, and increases sleep efficiency in the on-stimulation condition.¹⁵⁹ Around-the-clock stimulation improves nocturnal mobility, continuous sleep time, and sleep efficiency compared with before surgery.^{160,161} The duration of slow wave sleep and rapid eye movement (REM) sleep is increased after STN DBS, but the relative percentage of sleep stages does not vary; there is no association with motor improvement.¹⁶¹ A subjective benefit of STN DBS on sleep quality has also been reported.^{160,162} In a 2-year follow-up study, the total sleep time increased after bilateral STN DBS; these changes were associated with an improvement in bradykinesia.¹⁶³ The reported improvement in nocturia after STN DBS was consistent with the noted increase in bladder capacity. Other factors can influence sleep quality, such as DRT reduction and the ensuing improvement in daytime somnolence. No improvement in REM sleep behaviour disorder or periodic limb movements of sleep was detected after STN DBS.¹⁶⁰ Some studies have reported benefit in restless legs syndrome,¹⁶² whereas findings from others suggested that restless legs syndrome might occur postoperatively, possibly due to reduction in DRT.¹⁶⁴

A few studies have addressed the effects of GPi DBS on sleep quality in patients with Parkinson's disease and reported subjective improvement of daytime sleepiness even though these patients did not reduce DRT.¹⁶⁵ However, Vim DBS does not influence sleep architecture or sleep spindles.¹⁶⁶

Experimental studies have shown that the PPN is involved in sleep functions. Polysomnographic studies reported a significant increase in the absolute or relative duration of REM sleep after PPN DBS.^{105,167,168} The observation that REM behaviour disorder is improved after PPN DBS⁴⁹ has not been confirmed.¹⁶⁸ Daytime polysomnography during different stimulating conditions revealed that low-frequency stimulation (10–25 Hz) promotes alertness, whereas high-frequency pulses induce light sleep (stages N1 and N2).¹⁶⁹

Pain and sensory symptoms

Sensory symptoms (pain and paraesthesia) might represent unwanted side-effects of stimulation at different targets (Vim, STN, or PPN) if the current from the stimulating electrode reaches the medial lemniscus or the internal capsule. By contrast, little is known about the variations of Parkinson's disease-related sensory symptoms after DBS. STN DBS can improve pain,^{170,171} particularly during off periods. Objective pain sensitivity was unchanged in patients who reported

pain improvement with STN DBS or drug treatment, suggesting that these treatment options do not directly influence central pain processing.¹⁷²

Emerging issues

With a rapidly growing body of evidence on DBS for Parkinson's disease, new clinical issues have emerged. These have not yet been systematised in clinical practice, but are relevant for making appropriate clinical decisions.

Target choice

The traditional anatomoclinical approach of stereotactic surgery (ie, one symptom equals one target) has its quintessential hallmark in tremor surgery, since appropriate Vim targeting has been consistently shown to provide immediate and long-lasting relief of contralateral tremor.⁷¹ However, the choice of the most suitable DBS target for each patient with Parkinson's disease cannot be made solely on the basis of symptoms, because each target influences the activity of multiple brain structures within the basal ganglia network (figure 3).

There are no guidelines for the choice of DBS target in Parkinson's disease. Randomised studies have provided evidence that there are no differences in short-term motor outcome after unilateral or bilateral implants in the STN or GPi^{52,66} (appendix), although non-motor outcome favours the GPi. However, long-term open-label results favour STN stimulation, because of the decay in motor efficacy reported in the few available GPi studies.^{62,70} Target choice might also depend on technical reasons. Easier targeting in the larger GPi and easier medical management (with no need to adjust DRT) favour GPi implants, whereas the possibility to also influence the subthalamic region (which contains pallidofugal fibres) and lower energy consumption favour the STN. The patient's age might support the choice of one nucleus over the other: the STN should be chosen in younger patients who have prominent akinesia and tremor, who might otherwise have to have rapid DRT increases and could be exposed to the potential side-effects of antiparkinsonian drugs. Accordingly, monogenic early-onset Parkinson's disease has been successfully treated with STN DBS.^{173–175}

PPN was initially selected as a target in patients with Parkinson's disease who had severe axial symptoms resistant to DRT.^{84,85} This target has also been stimulated in combination with others to achieve an additive symptomatic effect: bilateral four-electrode implants have been used in the STN and PPN⁸⁴ or in the caudal Zi and PPN.¹⁷⁶ However, the indications for PPN targeting are controversial and outcomes are highly variable. After initial enthusiasm, there has been a decline in optimism^{106,177} and at present there is no suggestion to propose PPN DBS as a primary option.

Unilateral stereotactic surgery has been traditionally done in patients with unilateral tremor by targeting the Vim contralateral to the tremulous body side.¹⁷⁸ Implants

in the STN or GPi are usually done bilaterally, although unilateral DBS has been proposed recently either as a definitive procedure^{50–52} or as part of a staged approach. Logistic regression analysis of the COMPARE (cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus internus deep brain stimulation) trial revealed that the odds of proceeding to bilateral DBS were 5.2 times higher in patients with unilateral STN implants than in those with unilateral GPi DBS,¹⁷⁹ suggesting that STN DBS ends up being bilateral in most cases.

Quality of life and psychosocial functioning

STN and GPi stimulation represent two consolidated treatment options with known indications and adequate follow-up of functional variables,⁶⁶ although high quality data have been mostly collected in patients with STN DBS. A recent meta-analysis reported a seven-point average functional improvement after STN DBS compared with DRT alone, as measured by a 39-item Parkinson's disease questionnaire.¹⁸⁰ Additionally, disabling motor complications that are not successfully managed by drug treatment are better managed after bilateral STN or GPi DBS compared with DRT alone.^{180–182}

Quality of life and psychosocial functioning are important measures for therapeutic intervention in Parkinson's disease. Although there is no formal age limit for DBS, age is inversely associated with improvement of motor function^{182,183} and positively associated with perioperative complications.¹⁸² To only use efficacious surgical interventions, such as DBS, as a last resort once patients have experienced psychosocial decline is not of great help for the patients. In such situations, restoration of mobility through DBS does not necessarily restore quality of life.¹⁸⁴ At present, the mean delay before neurosurgery is 14 years after diagnosis,⁶¹ but is expected to be reduced as evidence on earlier surgery is gathered.

Timing for surgery

Age and disease duration at time of surgery are important factors to take into account when selecting patients for DBS. Younger patients might have fewer cognitive complications,¹⁸⁵ less deterioration of axial signs over time,¹⁸⁶ and better improvement of rigidity,¹⁸⁷ and there is evidence that, despite the expected motor improvement, quality of life improves only in younger patients.¹⁸⁸ Patients with early-onset genetic Parkinson's disease benefit from STN DBS and have a much younger age at implant (49.6 years in a series of patients with *PARK2* mutations¹⁷³ compared with 61.2 years in a non-genetically caused Parkinson's disease cohort).⁴² A recent retrospective study concluded that undertaking surgery in patients with short disease duration might delay functional impairment¹⁸⁷ and an 18-month prospective pilot trial favoured early DBS (after average disease duration of 7 years) over medical therapy alone in quality of life measures.¹⁴⁷

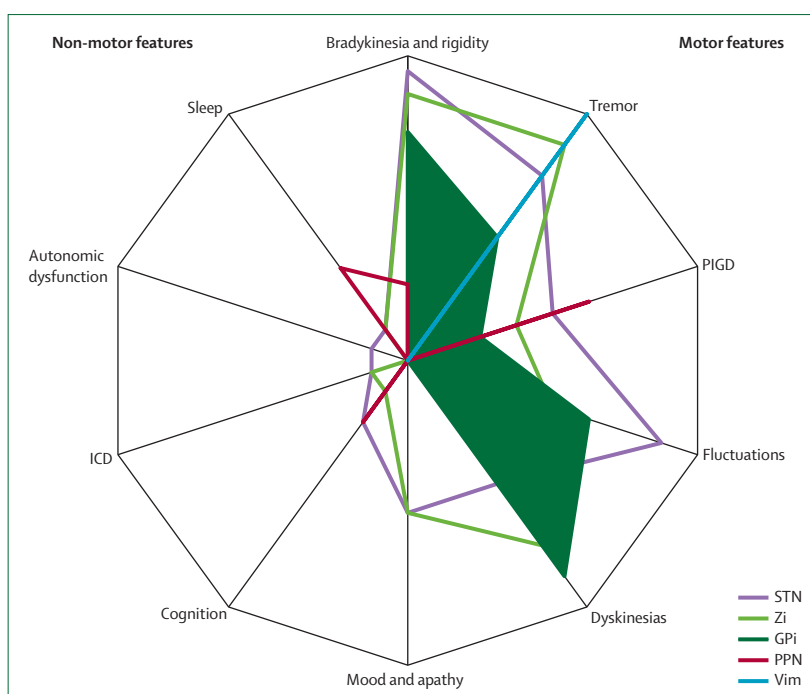


Figure 3: Synoptic diagram of the different motor and non-motor effects of deep brain stimulation at various targets

For each Parkinson's disease feature, a prominent effect of deep brain stimulation is shown by a long radial distance from the centre of the polygon. Non-motor features are shown on the left side of the graph and motor features are on the right side. Stimulation of some targets (eg, the STN, Zi, or GPi) influences various features, particularly bradykinesia and rigidity, tremor, PIGD, fluctuations, and dyskinesias. By contrast, Vim stimulation selectively affects tremor. STN implants also have a moderate effect on mood and apathy and a mild effect on cognition, whereas PPN implants influence PIGD, sleep, and cognition. STN=subthalamic nucleus. Zi=zona incerta. GPi=globus pallidus interna. PPN=pedunculopontine nucleus. Vim=ventralis intermedius nucleus. PIGD=postural instability gait difficulty. ICD=impulse control disorders.

At present, there is no consensus for timing of stereotactic surgery after disease onset; core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD) recommendations¹⁸⁹ suggest that disease duration should be at least 5 years before DBS is considered. Controlled trials are needed to ascertain whether undertaking surgery in earlier disease stages is advantageous or even ethical. Two such trials, a German–French multicentre study (EARLYSTIM [The Effect of Deep Brain Stimulation of the Subthalamic Nucleus on Quality of Life in Comparison to Best Medical Treatment in Patients With Complicated Parkinson's Disease and Preserved Psychosocial Competence], ClinicalTrials.gov NCT00354133) and a North American single centre trial (ClinicalTrials.gov NCT00282152) are underway.

Conclusions and outlook

DBS is an established procedure that can be applied to different brain targets to treat patients with Parkinson's disease. Vim DBS is an accepted treatment for Parkinson's disease-related tremor; its indications have been largely replaced by STN and GPi DBS, which also improve other Parkinson's disease symptoms. PPN DBS has to be regarded still as an experimental option, which potentially

Search strategy and selection criteria

We searched PubMed from January 2004, to January 2012 with the search terms "Parkinson disease"[MH] AND "deep brain stimulation"[MH] AND "English"[LA], which yielded 1179 papers. Data or additional articles were also recovered from other sources, such as recent reviews, reference lists of relevant publications, and a search of the authors' own reference database, which yielded an additional 123 papers (covering also the period 1947–2003). From the retrieved papers, we selected only meta-analyses and randomised controlled trials on ventralis intermedialis nucleus, subthalamic nucleus, or globus pallidus internus stimulation and all the available studies (including open-label trials) on less studied targets (eg, the centromedian/parafascicular complex, pedunculopontine nucleus, and zona incerta) or non-motor symptoms. We referred only to papers with broad-term outcomes on ventralis intermedialis nucleus (≥ 5 years), subthalamic nucleus (> 5 years), or globus pallidus internus (> 3 years) stimulation. In total, 377 papers were taken into account for this Review.

influences PIGD. Other nuclei, such as the caudal Zi and the CM/Pf nucleus, are under investigation. The available evidence on the stimulation of targets different from the STN and GPi are mostly from class 4 studies.

The rapidly growing body of evidence highlighted in this Review provides a synoptic picture of the effects of DBS on motor and non-motor features of Parkinson's disease. Integrating clinical evidence with preclinical research allows future treatment scenarios to be identified and issues that still need to be addressed to be focused on. First, bilateral DBS represents the standard procedure, whereas unilateral or staged implants can be considered in individual cases; furthermore, there is no evidence that implanting into multiple targets has a clinical advantage; rather, this method exposes patients with Parkinson's disease to the risk of highly invasive surgery. Furthermore, despite widespread use of DBS, the mechanisms through which it alleviates the symptoms of Parkinson's disease are not fully understood; further research is needed on this important topic. Moreover, the present data show that the amount of improvement after DBS implants depends on relevant individual variations: there is a cogent need to associate the precise electrode location with surgical outcome as well as to search for predictive factors of long-term outcome after DBS. Careful patient selection is a key variable for improvement of outcome after DBS.¹⁹⁰ Because more than 30% of DBS failures can be ascribed to an inappropriate indication for surgery,¹⁹¹ a refinement of patient selection criteria is needed. Finally, a few electrode models are used for nearly all DBS applications, despite substantial anatomical differences among targeted nuclei. Constant-current STN DBS has proven effective in a recent controlled trial,¹⁹² and future trials should compare constant-current with voltage-controlled stimulation. DBS technology will evolve through the implementation of multicontact electrodes and sensing capabilities, allowing modulation of DBS by monitoring motor and non-motor conditions.

Contributors

AF did the literature search, drew the figures, collected data, and wrote the first draft. AD did the data analysis and interpretation and reviewed the manuscript. AA designed the study outline, ideated the figures, and reviewed and finalised the manuscript.

Conflicts of interest

AF has received speaker's fees from Abbott, Medtronic, Chiesi Farmaceutici, and UCB. AD has received honoraria from Pfizer, Novartis, and Eli-Lilly. AA has received honoraria from Abbott, Eisai, Ipsen, and Merz.

Acknowledgments

This work was supported in part by a grant from the Italian Ministry of Health to AA.

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