JIM Review

doi: 10.1111/joim.13541

Deep brain stimulation for Parkinson's disease

Marwan Hariz[1,2] & Patric Blomstedt[1]

From the [1]Department of Clinical Neuroscience, University Hospital of Umeå, Umeå, Sweden; [2]UCL-Queen Square Institute of Neurology, London, UK

Abstract. Hariz M, Blomstedt P. Deep brain stimulation for Parkinson's disease. *J Intern Med.* 2022;**292**:764–778.

Parkinson's disease (PD) is a progressive neurodegenerative illness with both motor and nonmotor symptoms. Deep brain stimulation (DBS) is an established safe neurosurgical symptomatic therapy for eligible patients with advanced disease in whom medical treatment fails to provide adequate symptom control and good quality of life, or in whom dopaminergic medications induce severe side effects such as dyskinesias. DBS can be tailored to the patient's symptoms and targeted to various nodes along the basal ganglia–thalamus circuitry, which mediates the various symptoms of the illness; DBS in the thalamus is most efficient for tremors, and DBS in the pallidum most efficient for rigidity and dyskinesias, whereas DBS in the subthalamic nucleus (STN) can treat both tremors, akinesia, rigidity and dyskinesias, and allows for decrease in doses of medications even in patients with advanced stages of the disease, which makes it the preferred target for DBS. However, DBS in the STN assumes that the patient is not too old, with no cognitive decline or relevant depression, and does not exhibit severe and medically resistant axial symptoms such as balance and gait disturbances, and falls. Dysarthria is the most common side effect of DBS, regardless of the brain target. DBS has a long-lasting effect on appendicular symptoms, but with progression of disease, nondopaminergic axial features become less responsive to DBS. DBS for PD is highly specialised; to enable adequate selection and follow-up of patients, DBS requires dedicated multidisciplinary teams of movement disorder neurologists, functional neurosurgeons, specialised DBS nurses and neuropsychologists.

Keywords: deep brain stimulation, globus pallidus, pallidotomy, Parkinson's disease, subthalamic nucleus, thalamotomy

Abbreviations: ADL, activities of daily living; BG, basal ganglia; DBS, deep brain stimulation; FDA, Food and Drug Administration; GPi, globus pallidus internus; MRI, magnetic resonance imaging; NBM, nucleus basalis of Meynert; PD, Parkinson's disease; PPN, pedunculopontine nucleus; PSA, posterior subthalamic area; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is a progressive illness due to loss of dopaminergic neurons in the substantia nigra compacta (Fig. 1), and degeneration of its projections to the corpus striatum (nucleus caudatus and putamen) [1, 2]. The main motor symptoms of PD are tremors, rigidity, akinesia (both bradykinesia, i.e., slowness of movement, and hypokinesia, i.e., small amplitude of movement) and postural instability. These motor features can vary between patients, and also within the same patient during the course of the illness. Phenotypically, at any point in time, a PD patient can be classified as tremor dominant, rigid akinetic (often accompanied by postural instability and gait disorders) or so-called intermediary [3, 4]. Nonmotor symptoms of PD include constipation, depression, pain, sleep disorders, loss of sense of smell and, eventually, cognitive decline and autonomic dysfunction. There is no cure for PD. The hallmark of symptomatic treatment is levodopa, which is converted to dopamine in the brain. As needed, one can add other drugs such as dopamine agonists acting on dopamine receptors in the striatum, inhibitors of monoamine oxidase B and/or inhibitors of the catechol-o-methyl-transferase that prevent peripheral degradation of levodopa.

Alternative proofreader: Patric Blomstedt, Department of Clinical Neuroscience, University Hospital of Umeå, 901 85 Umeå, Sweden. Email: patric.blomstedt@umu.se

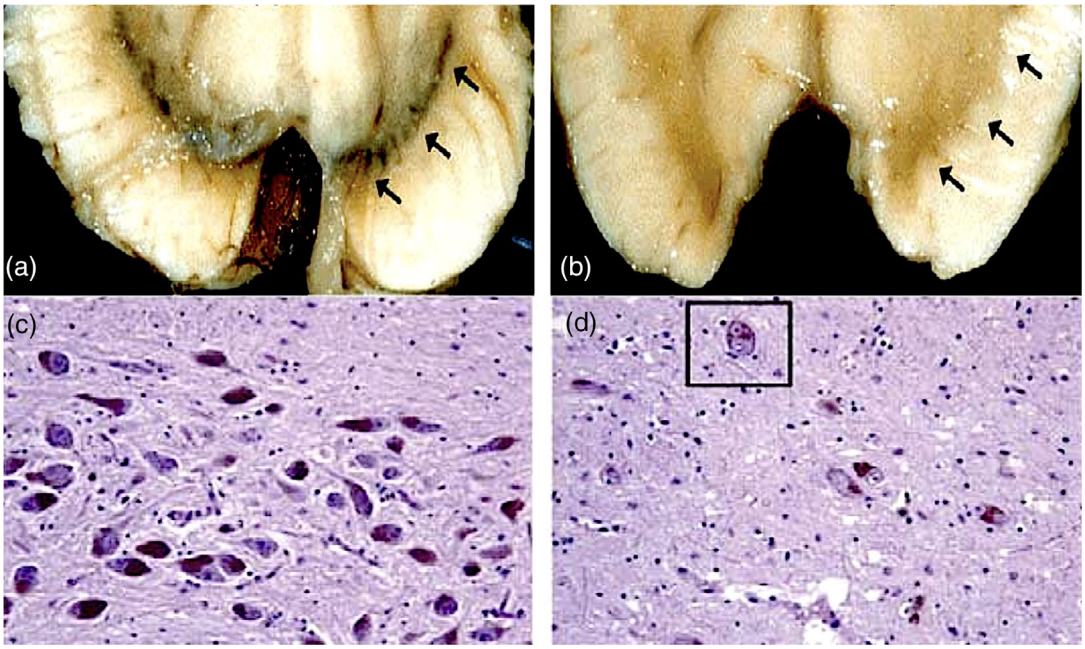

Fig. 1 *Appearance of substantia nigra compacta (SNc) in a person without and a person with Parkinson's disease (PD). (a) Macroscopic view of healthy pigmented SNc (arrows). (b) Loss of neurons leads to loss of pigmentation of the SNc (arrows). (c) Histology of SNc in a person without PD shows a dense network of melanin-pigmented dopaminergic neurons. (d) Loss of dopaminergic neurons in a person with PD; the cell in the black square shows a cytoplasmic protein aggregate called Lewy body (figure adapted from the dissertation 'Genetic analysis of dopaminergic neuron survival' by Liviu Aron, PhD, with kind permission from the author).*

As the disease progresses, the duration of the good effect of medication will decrease, necessitating a further increase in doses of dopaminergic medications, which leads to the appearance of motor fluctuations between 'off state' (decreased mobility) and 'on state', which is mobility often accompanied by disabling involuntary movements (dopa-induced dyskinesias). This 'on/off' stage of the disease is labeled a state of 'advanced PD' and will require 'advanced' more or less invasive treatments, even called 'device-aided' treatments [5]. These device-aided treatments fall into two categories—medical and neurosurgical. The medical treatment includes continuous delivery through a pump of either the potent dopamine agonist apomorphine subcutaneously, or a levodopa gel delivered through ventriculostomy into the duodenum (Duodopa). The neurosurgical treatment involves either making a stereotactic lesion in subcortical structures (the thalamus or the globus pallidus) or the more modern and widespread 'neuromodulation', which is the delivery by an implantable 'neuropacemaker' of high-frequency electric current through electrodes permanently implanted into distinct nodes of the basal ganglia's (BG) motor circuitries. This technique, called deep brain stimulation (DBS), is the most common today. The present work will briefly review the history of neurosurgery for PD, especially that of DBS, as well as explain the rationale for DBS in PD, and will then expand on the indications, contraindications, results and future prospects of modern DBS in the treatment of PD.

Neurosurgery for PD: The lesional era

Before the advent of levodopa in the late 1960s, PD was considered a surgical disease. At that time the almost sole available medical treatment for PD was anticholinergic medication for tremors. The stereotactic technique—allowing safe and precise introduction of a probe into deep brain structures—was developed in the late 1940s, and soon applied to treat patients with PD by making small thermolesions in distinct areas of the brain [6]. It was already known that the brain circuitry implicated in mediating some of the cardinal symptoms of the disease such as tremors and rigidity involved what

was then labeled the 'extrapyramidal system'—that is, the medial globus pallidus and its projections to the ventrolateral motor thalamus, as well as the cerebellothalamic pathway that also terminated in the ventrolateral thalamus. Neurosurgeons relied on detailed human brain atlases and X-ray ventriculography to enable calculation of deep brain target coordinates, and used the stereotactic technique to pinpoint the medial globus pallidus and/or the ventrolateral thalamus as well as various nodes in the pathways between them to perform thalamotomy or pallidotomy lesions in order to interrupt the pathological neuronal activity in these circuitries, and thus alleviate symptoms of PD [6–9]. Most operations were directed towards alleviating mainly the tremor, which was the most apparent and most socially stigmatizing symptom for patients, even if akinesia, not the tremor, was considered to be the most disabling symptom. Hence thalamotomy, which had the most dramatic and consistent effect on tremors, became the most popular surgical method until the advent of levodopa in the late 1960s, after which almost all surgery for PD ceased.

In 1985, Lauri Laitinen, a neurosurgeon in Umeå, Sweden, heralded the renaissance of surgery for PD [6, 9–12]. He reinvigorated posteroventral pallidotomy, which was a forgotten old procedure of Lars Leksell, published in 1960 by neurologists Svennilson et al. [12, 13], who had shown that this procedure could also improve other symptoms of PD than tremors, and could result in less disability in patients' activities of daily living (ADL). Svennilson–Leksell's posteroventral pallidotomy was performed in the 1950s—that is, before the advent of levodopa, whereas the revived pallidotomy of Laitinen took place more than 15 years after the introduction of levodopa, at a time when it became evident that many patients suffered from on–off fluctuations and levodopa-induced dyskinesias. It appeared that posteroventral pallidotomy had an excellent effect on fluctuations and dopa-induced dyskinesias, aside from its good effect on tremors, rigidity and akinesia. The clinical results of modern-era pallidotomy were evaluated objectively by using the newly developed standardised and holistic rating scale called the Unified Parkinson's Disease Rating Scale [14], which quantifies changes in motor performance, ADL and mood, before surgery and at various follow-up intervals, as well as provides outcomes according to the Hoehn and Yahr scale for staging the disease [15], and the Schwab and England disability scale [16]. Posteroventral pallidotomy thus became the main surgical treatment for post-levodopa-era advanced PD during the 1990s [6] and was eventually officially endorsed as efficient and safe by the International Parkinson and Movement Disorders Society [17, 18].

Both performing pallidotomy and making thalamotomy lesions could be done safely only unilaterally on one brain hemisphere because performing bilateral lesions increased the risks of dysarthria, dysphonia and disturbances of balance [19]. It was the advent of DBS that paved the way for performing bilateral surgery safely and for enabling the 'discovery' of new brain targets that provided more efficient control of symptoms of PD.

Deep brain stimulation

The initial tentative use of electrostimulation of deep brain structures in the 1950s and 1960s was for the treatment of chronic pain and psychiatric illnesses, whereby the brain target would be stimulated chronically through implanted electrodes instead of being destroyed by heating [20, 21]. Similarly, during the early era of stereotactic lesional surgery in PD, there have been some attempts at using DBS instead of making lesions [22]. However, the technology at that time was crude and the hardware too complicated and cumbersome to use. It was the introduction of implantable cardiac pacemakers that prompted the development of implantable 'brain pacemakers' [23], facilitating thus the application of the method of chronic stimulation of subcortical brain areas, hence the name 'deep' brain stimulation as opposed to superficial cortical brain stimulation. In fact, the label 'DBS' had been trademarked by Medtronic, Inc. (Minneapolis, MN, USA), for the first commercially marketed devices introduced in the mid-1970s [23] and used mainly to treat chronic pain by electric stimulation through electrodes implanted in central pain pathways such as the lemniscus bundle in the brainstem and the sensory nuclei of the thalamus.

It was exactly 35 years ago, in 1987, in Grenoble, France, that the modern era of DBS for movement disorders saw the light at the hands of neurosurgeon Alim Louis Benabid and neurologist Pierre Pollak [24]. During a regular thalamotomy procedure to treat tremors, the surgeon applied high-frequency (100–130 Hz) stimulation to the ventral intermediate (VIM) nucleus of the thalamus, and

the tremor stopped abruptly each time the current was applied, without affecting negatively the strength or dexterity of the hand. Instead of heating the area and doing the thalamotomy, the surgeon implanted a permanent electrode and connected it to a neuropacemaker that would deliver continuous electrical stimulation at 130 Hz, blocking thus the tremor as long as the current was on [24]. It appeared that the effect of high-frequency DBS mimicked that of a lesion but without actually lesioning the brain. Additionally, aside from being nondestructive, DBS was also reversible and adaptable, and most importantly, it was possible to perform DBS safely on both sides of the brain. Thus, a new therapy was born. Thalamic DBS gained worldwide acceptance, including Food and Drug Administration (FDA) and Conformité Européenne approval, and replaced gradually thalamotomy in the treatment of both Parkinsonian tremor as well as essential tremor [25]. At the same time, unilateral posteroventral pallidotomy continued to be used to treat other symptoms of advance PD such as akinesia, on–off fluctuation and levodopa-induced dyskinesias.

Since the effect of DBS on tremors mimicked the effect of thalamotomy, could the same be valid for DBS in the pallidum instead of pallidotomy in patients with advanced PD? Siegfried and Lippitz in 1994 in Zurich were the first to perform high-frequency DBS in the posteroventral globus pallidus internus (GPi) instead of pallidotomy [26], showing that DBS resulted in an equivalent improvement of akinesia, on–off fluctuations and dyskinesias. Similar to DBS in thalamus for tremors, DBS in the GPi could also be performed safely bilaterally in patients with advanced PD.

In 1990, Neuroscientist Hagai Bergman, working at Johns Hopkins in Baltimore, USA, published a paper in Science showing that lesioning the subthalamic nucleus (STN) in a nonhuman primate model of PD had a striking effect on akinesia and tremors [27]. This was confirmed the following year in a similar experiment by Aziz et al. in Manchester, UK [28]. In 1993, Benazzouz in Bordeaux showed that high-frequency DBS of the STN in a similar animal model of PD had a striking effect on the Parkinsonian symptoms of the animal [29]. Hence, the stage was set for trying DBS of the STN in patients with advanced PD. Here again, it was the Grenoble group who performed the first human trial of STN DBS, first unilaterally in one patient in 1993 [30], then bilaterally in three advanced PD patients, the results of which were published in the Lancet in 1995 [31]. It was shown that DBS in the STN was efficient not only on akinesia, rigidity and motor fluctuations but also on tremors. According to the famous movement disorders neurologist, the late UK professor David Marsden, DBS of the STN was 'the most important discovery since levodopa'. It was subsequently shown in a larger cohort of patients published in 1998 [32] that this procedure allowed in most patients a radical decrease of the doses of anti-Parkinsonian medications, which was something unique compared to any other surgery for advanced PD.

Following the publication in September 2001 in the New England Journal of Medicine of a worldwide multicentre trial of DBS in STN or in GPi [33], FDA approved these procedures for surgical treatment of patients with advanced PD, and they eventually received endorsement as efficient and safe by the International Parkinson and Movement Disorders Society [18]. DBS of the STN and the GPi became, since then, and still are, the most popular and world-spread methods for surgical treatment of PD [34].

BG-thalamo-cortical circuitry in PD

The BG consist of the corpus striatum (that is, the caudate nucleus and the putamen), the GPi and globus pallidus externus, the STN, the pedunculopontine nucleus (PPN) and the substantia nigra, and are involved in motor, associative-cognitive and limbic functions through segregated parallel circuits to and from the cortex [35, 36]. In relation to execution of movements, the BG 'are responsible for the automatic execution of learned motor plans' [37], and the GPi is the main output structure towards the thalamus and further to the cerebral cortex and brain stem nuclei. Thus, one of the roles of the BG is to modulate and streamline execution of movements. This occurs through a balance between Gaba-ergic inhibitory and glutamatergic excitatory pathways. In PD, this balance is disturbed. The lack of dopamine in the striatum leads to increased inhibitory activity of the striatum on the globus pallidus externus, which in turn decreases its inhibition on the STN, allowing the latter to increase its glutamatergic excitation on the GPi whose inhibitory activity on the thalamus is increased. At the same time, the striatum's direct inhibitory projection to the GPi is decreased allowing a further increased inhibitory activity of the GPi on the thalamus. The net effect is that both the

STN and the GPi become overactive, contributing thus to an inhibition of the thalamo-cortical projections and thus contributing to the rigidity and akinesia of PD [38, 39]. By 'silencing' the pathological increased neuronal activity of the GPi or the STN through lesioning or through high-frequency DBS of these nuclei, akinesia, rigidity and tremors are decreased, which leads to the re-establishment of a more or less normal movement pattern. This is the rationale behind the use of high-frequency DBS of either the GPi or the STN in the surgical treatment of patients with advanced PD (Fig. 2).

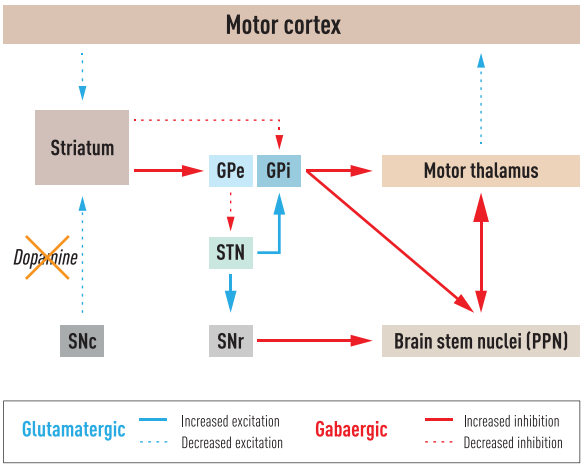

Fig. 2 *Simplified basal ganglia-thalamo-cortical circuitry in Parkinson's disease (PD) and rationale for deep brain stimulation (DBS) in various targets: in PD there is an imbalance between gabaergic inhibitory pathways and glutamatergic excitatory pathways. Death of dopaminergic cells in the substantia nigra compacta (SNc) leads to depletion of dopamine in the corpus striatum (caudate and putamen). This leads to changes in the output of the striatum towards the globus pallidus along two pathways; in the indirect pathways, the striatum increases its gabaergic inhibition of the globus pallidus externus (GPe), which leads to a decreased inhibition of the GPe on the subthalamic nucleus (STN). The STN then becomes overactive and exerts an increased glutamatergic excitation on the globus pallidus internus (GPi) and on the substantia nigra reticulata (SNr), both of which become overactive. At the same time, there is a decrease in the striatum's inhibitory activity on the GPi through the direct pathway, leading to further increase of the inhibitory activity of the GPi. The highly overactive GPi then exerts an increased inhibition on the motor thalamus, the activity of which is decreased on the cortex. There is also increased inhibition on brain stem nuclei including the locomotor centre in the pedunculopontine nucleus (PPN). The net effect is the akinesia, rigidity and tremors of PD. Hence, the rationale for targeting the GPi or the STN by high-frequency DBS is to decrease their pathological overactivity, which would thus contribute to restoring normal movement patterns in patients with PD.*

DBS hardware, surgical procedure and mechanism of action of DBS

Modern-era DBS hardware consists of the following: an electrode, 1.3 mm in diameter, with 4–8 contacts of 1.5 mm each at its tip, separated by 0.5 or 1.5 mm. These electrodes are introduced stereotactically to the desired brain target identified on three-dimensional magnetic resonance imaging (MRI). The surgery is traditionally performed with the patient awake, but can now, thanks to modern imaging, be performed with the patient asleep without compromising the clinical outcome [40–43]. The electrodes are fixed at the burrhole of the skull and connected with cables that run under the skin to a pocket fashioned usually below the collarbone where the cables are connected to an implantable neuropacemaker. The accurate location of the brain electrodes is verified by intra- or postoperative imaging on either an MRI or a computed tomography machine. An overview of how the surgery is performed is provided in this video: https://youtu.be/sZu2PYdocJQ. The electrostimulation is applied by the neurologist, the neurosurgeon or a dedicated DBS nurse some days after surgery, through an external computer remotely connected with the neuropacemaker, by screening the various contacts of the lead, looking for an effect on the symptoms and eventual side effects. Typical programming of the stimulation uses a current of 130 Hz, 60 ms pulse width and the amplitude is varied between 1 and 4 milliampere according to the clinical response. One can use monopolar or bipolar stimulation and the various electrode contacts can be activated separately or together, as clinically indicated (Fig. 3). The latest brands of DBS hardware use electrodes with directional contacts that can 'direct' the current perpendicular to the axis of the lead to focus the stimulation more precisely on the relevant brain target instead of having an omnidirectional electric field. The neuropacemaker consists of either primary cells and will need to be replaced when its battery is empty (typically after 3–5 years of continuous stimulation) or can be rechargeable and will then last 15–25 years.

The exact mechanism of high-frequency DBS is not fully understood. In most targets used in the treatment of PD (STN, GPi, VIM), high-frequency DBS mimics an ablation, as explained above. It

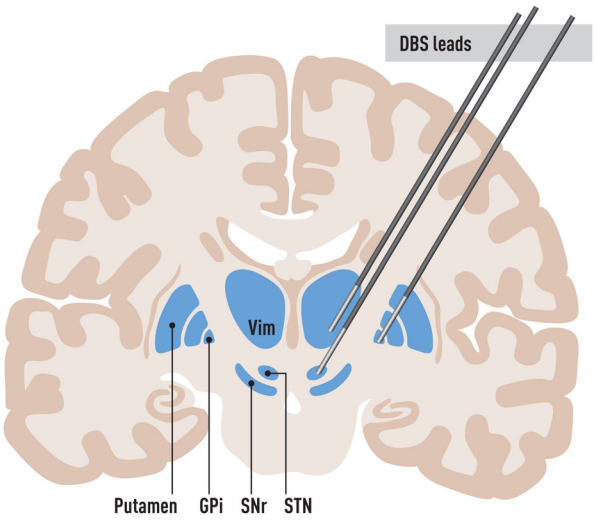

Fig. 3 *Anatomical template of basal ganglia and thalamus with three quadripolar leads in situ, one in the VIM, one in the STN and one in the GPi. Abbreviations: DBS, deep brain stimulation; GPi, globus pallidus internus; SNr, substantia nigra reticulata; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus.*

is thought that a high-frequency stimulation will create a noise jamming the pathological neuronal firing pattern of the cells in the stimulated structure. However, axons are also affected by the stimulation in both orthodromic and antidromic directions. Hence, DBS may act by several nonexclusive mechanisms on the disruption of pathological oscillatory neuronal activity in BG–thalamus circuitry at various nodes in the network [44]. Be it as it may, the net clinical effect of high-frequency DBS is pretty much similar to that of a lesion, albeit a reversible one, which means that the symptoms are suppressed as long as the stimulation is on, and the symptoms return when the stimulation is turned off.

Current practices of DBS for PD

DBS for PD requires a dedicated multidisciplinary team including a functional neurosurgeon, movement disorders neurologist, neuropsychologist and a specialist DBS nurse. This is necessary to enable a proper selection of patients suitable for DBS and an adequate life-long follow-up of operated patients. The neurosurgical procedure of implanting deep-seated electrodes in the brain is today a very safe routine procedure with virtually no mortality and a very low surgical morbidity in experienced multidisciplinary centres [44–47]. The main surgical complication, although rare, is a risk for infection of the extracranial implanted hardware and occasionally mistargeting electrodes in case proper intraoperative or postoperative imaging verification of targeting accuracy is not performed [48, 49]. Although DBS has expanded to the realm of other movement disorders than PD such as essential tremor and dystonia, and is being investigated for the treatment of some other neurological and neuropsychiatric illnesses, PD has remained by far the main indication for DBS [34]. A recently published review of the literature revealed that almost half of the publications on DBS of the last 35 years concerned DBS for PD, and the most published brain regions targeted by DBS have been the STN, followed by the GPi then the VIM nucleus of the thalamus [34]. In the following, the indications, contraindications, clinical results and potential side effects of DBS will be detailed for each of the most common DBS procedures performed in PD patients (Tables 1 and 2).

VIM DBS for tremors

Tremor (both Parkinsonian as well as essential) was the first application in the modern era of DBS [24]. Although dopaminergic treatment provides a good relief from akinesia and rigidity, the tremor responds less well. Thus, in PD patients whose other symptoms of PD are well controlled by medication and who do not exhibit dopa-induced dyskinesias, and in whom the only disturbing symptom is tremor, VIM DBS provides a solid and long-lasting control of their tremors [25, 50]. There is no age limit for this procedure, provided the patient is in an otherwise good condition and the brain does not show extensive atrophy on MRI. VIM DBS can, if needed, be performed bilaterally, although in elderly patients it would be wise to stage the two procedures at an interval of at least 6 months. Stimulation of the VIM is turned 'on' typically during the waking hour and should be stopped when the patient goes to sleep at night. Possible side effects of stimulation in the VIM, especially if bilateral, include dysarthria and affection of balance, but this can sometimes be managed by alteration of the stimulation's electric parameters. In some patients, with time, tolerance or habituation to stimulation develops, whereby control of tremors requires higher amplitudes of stimulation [51]. Rarely, ataxia may develop, which will require stopping the stimulation for some time ('stimulation vacation') to get rid of the ataxia [52]. The risk for both tolerance and ataxia is greater in patients

Table 1. *Indications for, and possible side effects of, bilateral DBS in various brain targets*

DBS target	Indication	Potential side effects	Comments
VIM	Tremors	Dysarthria Balance disturbance Rarely: tolerance	Risk of side effects increases with age
GPi	Advanced PD[a] Dyskinesias	Dysarthria	Well tolerated by elderly patients Less mood issues; patient can keep or increase medication doses Excellent effect on dyskinesias
STN	Advanced PD[a]	Dysarthria Mood swings Behavioural changes	Allows/requires some decrease of doses of medications; requires more expertise in the management of patients; Risk for apathy and depression if too much decrease of medications

Abbreviations: DBS, deep brain stimulation; GPi, globus pallidus internus; PD, Parkinson's disease; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus.
[a]Advanced PD refers to patients with on/off fluctuations, dyskinesias, and so on.

Table 2. *Impact of DBS on various motor symptoms of PD according to the brain target*

	Tremors	Rigidity	Akinesia	Gait/axial	Dyskinesias
VIM DBS	+++	++	(+)	–	(+)
GPi DBS	++	+++	++	+	+++
STN DBS	++	+++	+++	++[a]	++[b]

Abbreviations: DBS, deep brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus.
Note: +++, excellent; ++, good; +, fair; (+), doubtful; –, no effect or worsening.
[a]Assumes that axial and gait symptoms are still responsive to dopaminergic medication.
[b]Assumes decrease in doses of dopaminergic medications.

who do not turn off the DBS at night. In current practice, since most patients referred for surgery are in a more advanced stage of the disease, and suffer also from symptoms other than tremors, VIM DBS is not performed as often as DBS in the GPi or in the STN.

GPi DBS for advanced PD and dopa-induced dyskinesias

DBS in the posteroventral GPi has virtually replaced pallidotomy. This surgery addresses all major motor symptoms of PD including akinesia, rigidity and dyskinesias. Although performed bilaterally in patients with more advanced disease, bilateral-GPi DBS is better tolerated than bilateral VIM DBS or bilateral STN DBS (see further below). There is no age limit for GPi DBS and the risk of negative affection of balance and dysarthria is less than that following VIM DBS. The impact profile of GPi DBS is mainly of dopa-induced dyskinesias, including painful dystonia, followed by rigidity, then akinesia and tremors, with the least effect on gait disturbances, such as freezing of gait [11, 47, 53, 54]. Given its excellent effect on dyskinesias, GPi DBS allows the patient to continue taking the same doses of dopaminergic medications or even increase them if needed, without the risk for dopa-induced dyskinesias. Despite its positive effects on symptoms and its lenience for patients with advanced PD, GPi DBS has been in most countries overshadowed by DBS in the STN.

STN DBS for PD

There has been no surgical procedure for PD as much publicised and as much hailed as STN DBS. A PubMed survey (16 May 2022) of 'deep brain stimulation' and 'Parkinson's disease' yielded 7677 papers. When adding 'subthalamic nucleus' to the above search words, the PubMed lists 4758 papers. The main reasons for the popularity of this procedure are as follow: STN DBS is the most efficient surgical treatment for the cardinal symptoms of PD; it is the only surgery allowing patients

with advanced PD to radically decrease daily doses of dopaminergic medications, and sometimes even stop them altogether; STN DBS has undergone the strictest scrutiny with several multicentre randomised blinded studies and meta-analyses of outcomes [55–60], and it has the longest documented follow-up [61–65]. At the same time, STN DBS demands the strictest criteria when selecting PD patients for this procedure, compared to DBS in other brain targets, and it requires a meticulous postoperative management of patients by expert movement disorders neurologists.

Since the beginning of the era of STN DBS in the mid-1990s, there have been continuous attempts to fine tune its indications and to provide clinical criteria for the eligibility for this procedure in order to maximise the benefit for patients, and decrease unwanted side effects of stimulation [47, 53]. The first criterium for eligibility to STN DBS was found to be the response to levodopa [66, 67]: in patients with good symptomatic response to levodopa, STN DBS resulted in good motor outcome. Since then, all PD patients referred for DBS undergo a so-called L-dopa challenge by which motor symptoms are quantified first with the patient without medication then after administration of a substantial dose of levodopa. The more the improvement of symptoms after this L-dopa challenge the more the patient will benefit from STN DBS. The second criterium was age [47, 68]: it was found that the older the patient was at the time of surgery the less improvement from STN DBS, and the more side effects from stimulation, even though there still was indeed a relevant benefit from surgery [69, 70]. In some centres, a cutoff age for this procedure was decided at an age of 69–70 years. The third criterium for good outcome was a good cognition because it has been reported that cognitive decline could be exacerbated following STN DBS [71, 72]; hence all patients referred for DBS undergo a neuropsychologic test to evaluate cognitive skills including memory and executive function. Finally, the last criteria is related to the mood of the patient, which should be formally evaluated in order to avoid performing STN DBS in patients with relevant or untreated depression. Thus, an expert consensus for ensuring the best results following STN DBS in patients with advanced PD has established the following selection criteria: excellent levodopa response, younger age, no or very mild cognitive impairment, and absence of, or well controlled, psychiatric disease [47, 53]. Strict contra-indications for STN DBS involve levodopa unresponsiveness of cardinal symptoms of PD, especially rigidity and akinesia (which would question the diagnosis of idiopathic PD in the first place); severe axial symptoms that are not ameliorated by levodopa; so-called nondopaminergic symptoms, such as poor balance, falls, advanced freezing of gait, or severe dysarthria; relevant cognitive decline; and severe depression.

Since STN DBS has proven to be quite safe and efficient, provided strict inclusion criteria, and especially in younger patients, some leading neurologists proposed that maybe it should be offered to patients earlier in the course of their progressive disease. This would enable the younger patients to pursue their normal life, avoid early retirement, decrease the burden on family, avoid marital conflicts and contribute to maintain their opportunities in life. Hence, a randomised trial called the 'EARLYSTIM' trial comparing best medical management strategies to STN DBS has been conducted in patients with early on/off motor complications who received STN DBS after a mean of 7 years after diagnosis (instead of the usual 11 years or more) [58]. It was shown that at 2 years follow-up, patients who had received STN DBS did significantly better than those with the best medical treatment alone, both concerning measures of quality of life as well as motor symptoms. Other aspects of the disease that show amelioration after STN DBS are some of the nonmotor symptoms of PD, including sleep difficulties, pain and anxiety [73–75].

STN DBS versus GPi DBS

While there is a general consensus among movement disorders clinicians that stimulation of the thalamic VIM is an effective surgical treatment for PD patients whose main and sometimes only symptom is tremor, opinions diverge on which is better, STN DBS or GPi DBS, in patients with advanced PD suffering from motor fluctuations and dyskinesias. There have been several trials comparing the outcome of these two procedures [76–80]. Some trials showed superiority of STN DBS over GPi DBS in terms of motor improvement [76, 77], while others showed no difference [78, 79].

Interestingly, even the two most recent major publications [59, 60] providing detailed metaanalysis of the available literature on STN DBS versus GPi DBS provided two different results: the North-American paper from 2018 analysing 13

randomised trials of STN DBS versus GPi DBS concluded that up to 36 months after surgery, the motor benefit was similar between the two brain targets; however, medications were significantly reduced only following STN DBS while depression scores were better with GPi DBS [60]. The European paper from 2021 analysed relevant papers over a 19 years period, including only studies with more than 10 patients that provided formal detailed outcome up to 1 year after surgery. There were 39 eligible studies of STN DBS (2035 patients) and five eligible studies of GPi DBS (292 patients). It was shown that motor scores improved by 50.5% with STN DBS and 29.8% with GPi DBS. It was also confirmed that a good pre-operative levodopa response was a prerequisite for a good response to STN DBS [59]. Besides, especially for patients with STN DBS, it is of utmost importance that they are cared for by highly experienced movement disorders neurologists in order to titrate judiciously both medication doses and stimulation amplitude in the months and years after surgery to maintain improvement as well as to minimise the occurrence of a hypodopaminergic syndrome (apathy, depression, suicide) or a hyperdopaminergic syndrome (dyskinesias, impulsivity, hypersexuality, mania) [81–88].

Side effects of DBS

DBS in any brain target is not without risk of inducing side effects. These are partly different for different brain targets, and are due to diffusion of the electric current beyond the area aimed at, especially in cases where the electrodes are not perfectly placed. Table 1 provides a summary of effects and potential side effects according to the brain target. Also, most stimulation-induced side effects can be partly reversible and managed by alteration of the stimulation strength, including its amplitude, pulse width, frequency and/or polarity. A common potential side effect to bilateral DBS to any brain target, albeit to different degrees, is stimulation-induced dysarthria. In VIM thalamic DBS, especially when bilateral, there is a risk for dysarthria and disturbance of balance, mainly due to diffusion of the current to the adjacent motor internal capsule. In GPi DBS, dysarthria may also worsen but less than with bilateral VIM DBS. In the STN, asides from the risk for dysarthria [89–91], there is potential risk for eyelid opening dyspraxia (that can be treated with botulium toxin injections) [92], as well as risk for behavioural disturbances if the electrode is too ventral–anterior–medial because that area of the STN is connected to limbic cortical structures. Additionally, if doses of dopaminergic medications, especially dopamine agonists are not decreased after surgery, STN DBS will potentiate their effect, leading to increased impulsivity and mania [82–86]. On the other hand, if dopa medication is decreased too much because STN DBS per se can provide a very good motor improvement for the patient, patients will suffer from apathy and even depression, leading, rarely, to suicide [87, 88]. All this explains why this most potent surgical procedure, that is, STN DBS, needs expert management by a movement disorders neurologist who is specialised in the management of PD [47, 53]. This also explains why GPi DBS, although not as efficient on motor symptoms as STN DBS, is considered more lenient for older patients and preferred by some clinicians even for younger patients, because it is less laborious, less time demanding and easier to manage than STN DBS and, in GPi DBS, doses of medications do not need to be adjusted. However, if patients with advanced PD suffer from relevant dopaminergic medication-induced impulse control disorders, then it may be wise to avoid GPi DBS and offer STN DBS, because it is only the latter that would allow a decrease in doses of dopaminergic medication, contributing thus to treat the medication-induced impulse-control disorder [84, 93]. Tables 1 and 2 provide a summary of indications, potential side effects and symptomatic impact profile of the three established brain targets for DBS procedures, based on the present authors' own 30-year-long experience of DBS for PD, and based on the literature.

Limits of, and issues in, DBS for PD

Even if DBS, especially STN DBS, is the best that has happened for patients with PD since the introduction of levodopa [11], one has to remember that all that glitters is not gold [94]. To start with, similar to levodopa treatment, DBS is not a cure of the disease, and the progression of the illness will continue no matter, but at variable and individual speed [95]. DBS is, as previously explained, a symptomatic treatment of some of the main symptoms of the disease. In some patients, as the disease progresses, nondopaminergic symptoms appear that no longer respond to dopa and therefore no longer respond to DBS. These nondopaminergic symptoms affect mainly axial features such as speech, gait difficulties including gait freezing, postural instability and cognitive decline, and remain a challenge for both medical

and surgical treatments. However, as with any treatment for PD, a new phenotype of the illness may appear after years of STN DBS [96]: while the effect on appendicular symptoms such as hand tremors, rigidity and dyskinesias is still good, and measures of quality of life are still better than before surgery, the axial symptoms deteriorate and the patient may have difficulty walking, and may suffer from falls, dysarthria and cognitive decline.

Another issue with DBS is that knowing who will continue to benefit from it and who will not can be difficult to ascertain, especially in some genetic types of PD [97]. Patients with mutation in the Parkin gene or the *leucine-rich repeat kinase 2* (*LRRK2*) have excellent dopa responsiveness and their good outcome from DBS is long lasting [98–100]. On the other end of the spectrum, patients with glucocerebrosidase mutation are generally older, and present mostly with the akinetic–rigid phenotype and may develop cognitive decline sooner, so that in them both the good dopa effect and the results from DBS are not long lasting [101, 102]. Therefore, when counselling PD patients and their family before DBS surgery, it may be of interest to know whether there is a genetic predisposition for the disease because even if most idiopathic PD is sporadic, a genetic screening of some patients with atypical presentation or whose onset of disease occurs at younger age (before 40 years) may be recommended.

DBS for PD is a life-long treatment: 'once DBS, always DBS' [103]. This means, again, that patients with DBS must be under the care of clinicians familiar with both the disease and DBS. Especially in patients with STN DBS, a sudden arrest of stimulation due, for example, to a technical issue or battery depletion of the neuropacemaker may lead to a severe rebound of PD symptoms, necessitating emergency care, including emergency surgery to replace the neuropacemaker [104]. A status of therapy-resistant malignant Parkinsonian crisis has been described in patients who could not afford to pay for a replacement of the neuropacemaker [105], and in patients in whom the implanted hardware had to be removed because of infection, leading sometimes to a fatal outcome [106, 107].

Other issues with DBS are of a more general nature: it has been shown that globally, DBS is much more prevalent in male PD patients than in females [108], beyond the male/female prevalence of the disease. This may have to do with referral patterns and societal issues [109]. Also, DBS being a therapy that needs frequent replacements of the neuropacemaker, means that in countries without a general and free healthcare system, DBS is limited only to patients who can afford it [105].

Other investigated brain targets for DBS in PD

There are ongoing attempts to investigate DBS in other brain targets, either to provide more efficient therapy to some symptoms, or to address some motor symptoms otherwise resistant to DBS in conventional brain targets, or aiming to alleviate nonmotor symptoms of PD such as dementia [110]. The posterior subthalamic area (PSA) is an area below the thalamus that is crowded with sensory and motor tracts. One such tract is the dentato–rubro–thalamic tract involved in mediating the symptom of tremor. Studies of DBS targeting this area of the PSA [111, 112], including a randomised trial [113], have shown an excellent effect on both Parkinsonian and essential tremor, and possibly lesser side effects than DBS in the VIM.

The PPN, part the brain stem locomotor area, and the substantia nigra reticulata, part of the output structures of the BG (Fig. 2), have been investigated as targets for DBS to treat therapy-resistant gait and balance disturbances. So far, these studies have included too few patients, their follow-up has been too short, and the results have been conflictual [110, 114, 115].

The nucleus basalis of Meynert (NBM) is the main source of cholinergic innervation of the cortex and undergoes atrophy in patients with PD dementia. It was assumed that low-frequency DBS to stimulate that nucleus (not high frequency to inhibit it!) may be beneficial to slow down the cognitive decline. A previous single-case report of DBS in the NBM ameliorated apraxia in a PD patient with cognitive decline [116]. Subsequently, a randomised controlled study comparing 6 weeks of DBS on versus 6 weeks DBS off was conducted in six PD patients with cognitive decline and showed no difference in the cognitive outcome [117].

Future prospects of DBS in PD

After three decades of DBS, this procedure remains the most used and most efficient surgical treatment for some cardinal symptoms of PD. Investigations of the new brain targets mentioned above,

and maybe of other brain areas, will continue aiming to further improving outcome [110]. This will be facilitated by improved imaging of the brain, including functional MRI [118] and connectivity imaging [119, 120]. Additionally, from DBS having been initially the exclusivity of one company, there are now at least three major DBS companies, resulting in several technical DBS innovations that are already being implemented or investigated [121–123], such as MRI-compatible DBS hardware; neuropacemakers with rechargeable batteries and extended life up to 25 years; neuropacemakers with sensing technology allowing to record the depth electroencephalogram, especially beta activity, and adapt the stimulation accordingly, so called closed loop stimulation, with the potential to decrease side effects and battery drain; directional DBS electrodes allowing the electric current to be focused precisely on the region of interest, again to decrease side effects such as dysarthria and improve outcome; remote web-based follow-up programming and troubleshooting of the stimulation to help patients who live far away from the DBS centre; and new modes of stimulation based on judicious use of more flexible electric parameters (such as pulse width, pulse shape, frequency, amplitude, etc.).

Regardless of all the features mentioned above, DBS for PD remains an efficient symptomatic treatment, although the magnitude of improvement tends to decline over time [124], and DBS may contribute to delay some of the late-stage disability milestones [95]. With the expanding technical innovations and increasing sophistication of DBS, this therapy will put even more constraints on clinicians to keep themselves à jour, requiring thus their enhanced specialization in the multifaceted modern treatments of PD and the increased potentials offered by DBS technology to further improve patients' outcome.

Conclusions

There is still no cure for PD but there are effective symptomatic treatments. Similar to levodopa being and remaining the mainstay and most efficient medical treatment for PD ever since the late 1960s, DBS for the motor fluctuations and dyskinesias of advanced stages of that disease is, and will remain, the mainstay of its neurosurgical treatment since the 1990s. Especially DBS of the STN and DBS of the pallidum have proven to be the most efficient treatments for the myriad motor symptoms of advanced stages of the disease, including the side effects of medications. However, unlike levodopa, whch can be administered to any PD patient, DBS, in order to be efficient and stable, requires stricter patient selection to avoid submitting to the surgery patients who have developed nondopaminergic symptoms, including cognitive decline, or patients who have unrealistic expectations. Therefore, patients referred for DBS treatment need to undergo a comprehensive evaluation prior to surgery by a multidisciplinary team of at least a specialised movement disorders neurologist and a functional neurosurgeon.

Conflict of interest

Marwan Hariz has received honoraria from Boston Scientific for lecturing at meetings. Patric Blomstedt is a consultant for Medtronic, Abbott and Boston Scientific, and a shareholder in Mithridaticum.

References

1 Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet.* 2009;**373**:2055–66.
2 Lindvall O. Clinical translation of stem cell transplantation in Parkinson's disease (review). *J Intern Med.* 2016;**279**:30–40.
3 Katz M, Luciano MS, Carlson K, Luo P, Marks WJ Jr, Larson PS, et al. Differential effects of deep brain stimulation target on motor subtypes in Parkinson's disease. *Ann Neuro.* 2015;**77**:710–9.
4 Fan S, Liu D, Shi L, Meng F, Fang H, Liu H, et al. Differential effects of subthalamic nucleus and globus pallidus internus deep brain stimulation on motor subtypes in Parkinson's disease. *World Neurosurg.* 2022. https://doi.org/10.1016/j.wneu.2022.04.084
5 Dietrichs E, Odin P. Algorithms for the treatment of motor problems in Parkinson's disease. *Acta Neurol Scand.* 2017;**136**:378–85.
6 Cif L, Hariz M. Seventy years with the globus pallidus: pallidal surgery for movement disorders between 1947 and 2017. *Mov Disord.* 2017;**32**:972–82.
7 Laitinen LV, Hariz MI. Movement disorders. In: Youmans JR, editor. *Neurological surgery.* 4th ed. Philadelphia: Saunders; 1996. p. 3575–609.
8 Gildenberg PL. Surgical therapy of movement disorders. In: Wilkins RH, Rengachary SS, editors. *Neurosurgery.* New York: McGraw-Hill; 1985. p. 2507–16.
9 Gildenberg PL. Evolution of basal ganglia surgery for movement disorders. *Stereotact Funct Neurosurg.* 2006;**84**:131–5.
10 Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg.* 1992;**76**:53–61.
11 Pollak P, Krack P. Deep-brain stimulation for movement disorders. In: Jankovic J, Tolosa E, editors. *Parkinson's disease and movement disorders.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 653–691.

12 Krauss JK, Fernandes FW. Svennilson's publication on pallidotomy for Parkinsonism in 1960: a most influential paper in the field. *Mov Disord Clin Pract.* 2021;**9**:173–7.
13 Svennilson E, Torvik A, Lowe R, Leksell L. Treatment of Parkinsonism by stereotactic thermolesions in the pallidal region. A clinical evaluation of 81 cases. *Acta Psychiatr Scand.* 1960;**35**:358–77.
14 Fahn S, Elton RL, UPDRS Development Committee. Unified Parkinsons Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. *Recent developments in Parkinsons disease*. Florham Park: Macmillan Healthcare Information; 1987. p. 153–63.
15 Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;**17**:427–42.
16 Schwab RS, England AC Jr. Projection technique for evaluating surgery in Parkinsons disease. In: Gillingham FJ, Donaldson IML, editors. *Third symposium on Parkinsons disease*. Edinburgh and London: E&S Livingstone Ltd; 1969. p. 152–7.
17 Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Movement disorder society evidence-based medicine committee. *Mov Disord.* 2018;**33**:1248–66.
18 Fox SH, Katzenschlager R, Lim SY, Ravina B, Seppi K, Coelho M, et al. The movement disorder society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease. *Mov Disord.* 2011;**26**(Suppl 3):S2–41.
19 De Bie RM, Schuurman PR, Esselink RA, Bosch DA, Speelman JD. Bilateral pallidotomy in Parkinson's disease: a retrospective study. *Mov Disord.* 2002;**17**: 533–8.
20 Hariz MI, Blomstedt P, Zrinzo L. Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg Focus.* 2010;**2**(2):E1.
21 Heath RG. Modulation of emotion with a brain pacemaker. Treatment for intractable psychiatric illness. *J Nerv Ment Dis.* 1977;**165**:300–17.
22 Blomstedt P, Hariz MI. Deep brain stimulation for movement disorders before DBS for movement disorders. *Parkinsonism Relat Disord.* 2010;**16**:42–33.
23 Coffey RJ. Deep brain stimulation devices: a brief technical history and review. *Artif Organs.* 2009;**33**:208–20.
24 Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol.* 1987;**50**:344–46.
25 Rehncrona S, Johnels B, Widner H, Törnqvist AL, Hariz M, Sydow O. Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord.* 2003;**18**:163–70.
26 Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all Parkinsonian symptoms. *Neurosurgery.* 1994;**35**:1126–29.
27 Bergman H, Wichmann T, DeLong MR. Reversal of experimental Parkinsonism by lesions of the subthalamic nucleus. *Science.* 1990;**249**:1436–38.
28 Aziz TZ, Peggs D, Sambrook MA, Crossman AR. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinsonism in the primate. *Mov Disord.* 1991;**6**:288–92.
29 Benazzouz A, Gross C, Féger J, Boraud T, Bioulac B. Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *Eur J Neurosc.* 1993;**5**:382–9.
30 Pollak P, Benabid AL, Gross C, Gao DM, Laurent A, Benazzouz A, et al. Effects of the stimulation of the subthalamic nucleus in Parkinson disease. *Rev Neurol.* 1993;**149**:175–6.
31 Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, et al. Effect of Parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet.* 1995;**345**:91–5.
32 Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med.* 1998;**339**:1105–11.
33 The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med.* 2001;**345**:956–63.
34 Harmsen IE, Wolff Fernandes F, Krauss JK, Lozano AM. Where are we with deep brain stimulation? A review of scientific publications and ongoing research. *Stereotact Funct Neurosurg.* 2022;**100**:184–97.
35 Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci.* 1986;**9**:357–81.
36 Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, et al. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. *Mov Disord.* 2008;**23**(3):S548–59.
37 Marsden CD. The mysterious motor function of the basal ganglia: the Robert Wartenberg lecture. *Neurology.* 1982;**32**:514–39.
38 Lang AE, Lozano AM. Parkinson's disease. First of two parts. *N Engl J Med.* 1998;**339**:1044–53.
39 Lang AE, Lozano AM. Parkinson's disease. Second of two parts. *N Engl J Med.* 1998;**339**:1130–43.
40 Mirzadeh Z, Chapple K, Lambert M, Evidente VG, Mahant P, Ospina MC, et al. Parkinson's disease outcomes after intraoperative CT guided "asleep" deep brain stimulation in the globus pallidus internus. *J Neurosurg.* 2016;**124**:902–7.
41 Ho AL, Ali R, Connolly ID, Henderson JM, Dhall R, Stein SC, et al. Awake versus asleep deep brain stimulation for Parkinson's disease: a critical comparison and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2018;**89**:687–91.
42 Engelhardt J, Caire F, Damon-Perrière N, Guehl D, Branchard O, Auzou N, et al. A phase 2 randomized trial of asleep versus awake subthalamic nucleus deep brain stimulation for Parkinson's disease. *Stereotact Funct Neurosurg.* 2021;**99**:230–40.
43 Holewijn RA, Verbaan D, van den Munckhof PM, Bot M, Geurtsen GJ, Dijk JM, et al. General anesthesia vs local anesthesia in microelectrode recording-guided deep-brain stimulation for Parkinson disease: the GALAXY randomized clinical trial. *JAMA Neurol.* 2021;**78**:1212–19.
44 Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. *J Neurophysiol.* 2016;**115**:19–38.
45 Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: a large

case series and systematic literature review. *J Neurosurg.* 2012;**116**:84–94.
46 Pepper J, Meliak L, Akram H, Hyam J, Milabo C, Candelario J, et al. Changing of the guard: reducing infection when replacing neural pacemakers. *J Neurosurg.* 2017;**126**:1165–72.
47 Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol.* 2011;**68**:165–71.
48 Rolston JD, Englot DJ, Starr PA, Larson PS. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: analysis of multiple databases. *Parkinsonism Relat Disord.* 2016;**33**:72–7.
49 Ellis TM, Foote KD, Fernandez HH, Sudhyadhom A, Rodriguez RL, Zeilman P, et al. Reoperation for suboptimal outcomes after deep brain stimulation surgery. *Neurosurgery.* 2008;**63**:754–60.
50 Hariz MI, Krack P, Alesch F, Augustinsson LE, Bosch A, Ekberg R, et al. Multicentre European study of thalamic stimulation for Parkinsonian tremor: a 6 year follow-up. *J Neurol Neurosurg Psychiatry.* 2008;**79**:694–9.
51 Hariz MI, Shamsgovara P, Johansson F, Hariz G, Fodstad H. Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor. *Stereotact Funct Neurosurg.* 1999;**72**:208–18.
52 Garcia Ruiz P, Muñiz de Igneson J, Lopez Ferro O, Martin C, Magariños Ascone C. Deep brain stimulation holidays in essential tremor. *J Neurol.* 2001;**248**:725–6.
53 Foltynie T, Hariz MI. Surgical management of Parkinson's disease. *Expert Rev Neurother.* 2010;**10**:903–14.
54 Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain.* 2005;**128**:2240–49.
55 Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med.* 2006;**355**:896–908.
56 Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol.* 2010;**9**:581–91.
57 Schüpbach WM, Maltête D, Houeto JL, du Montcel ST, Mallet L, Welter ML, et al. Neurosurgery at an earlier stage of Parkinson disease: a randomized, controlled trial. *Neurology.* 2007;**68**:267–71.
58 Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med.* 2013;**368**:610–22.
59 Lachenmayer ML, Mürset M, Antih N, Debove I, Muellner J, Bompart M, et al. Subthalamic and pallidal deep brain stimulation for Parkinson's disease-meta-analysis of outcomes. *NPJ Parkinsons Dis.* 2021;**7**:77.
60 Mansouri A, Taslimi S, Badhiwala JH, Witiw CD, Nassiri F, Odekerken VJJ, et al. Deep brain stimulation for Parkinson's disease: meta-analysis of results of randomized trials at varying lengths of follow-up. *J Neurosurg.* 2018;**128**:1199–1213.
61 Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med.* 2003;**349**:192–34.
62 Rizzone MG, Fasano A, Daniele A, Zibetti M, Merola A, Rizzi L, et al. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? *Parkinsonism Relat Disord.* 2014;**20**:37681.
63 Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol.* 2011;**68**:1550–6.
64 Bove F, Mulas D, Cavallieri F, Castrioto A, Chabardès S, Meoni S, et al. Long-term outcomes (15 Years) after subthalamic nucleus deep brain stimulation in patients with Parkinson disease. *Neurology.* 2021. https://doi.org/10.1212/WNL.0000000000012246
65 Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord.* 2011;**26**:2327–34.
66 Charles PD, Van Blercom N, Krack P, Lee SL, Xie J, Besson G, et al. Predictors of effective bilateral subthalamic nucleus stimulation for PD. *Neurology.* 2002;**59**:932–34.
67 Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. *Brain.* 2002;**125**:575–83.
68 Saint-Cyr JA, Trépanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain.* 2000;**123**:2091–108.
69 de Noordhout AM, Mouchamps M, Remacle JM, Delstanche S, Bonhomme V, Gonce M. Subthalamic deep brain stimulation versus best medical treatment: a 12-year follow-up. *Acta Neurol Belg.* 2022;**122**:197–202.
70 Shalash A, Alexoudi A, Knudsen K, Volkmann J, Mehdorn M, Deuschl G. The impact of age and disease duration on the long term outcome of neurostimulation of the subthalamic nucleus. *Parkinsonism Relat Disord.* 2014;**20**:47–52.
71 Hariz MI, Johansson F, Shamsgovara P, Johansson E, Hariz GM, Fagerlund M. Bilateral subthalamic nucleus stimulation in a Parkinsonian patient with preoperative deficits in speech and cognition: persistent improvement in mobility but increased dependency: a case study. *Mov Disord.* 2000;**15**:136–9.
72 Bucur M, Papagno C. Deep brain stimulation in Parkinson disease: a meta-analysis of the long-term neuropsychological outcomes. *Neuropsychol Rev.* 2022. https://doi.org/10.1007/s11065-022-09540-9
73 Georgiev D, Mencinger M, Rajnar R, Mušič P, Benedičič M, Flisar D, et al. Long-term effect of bilateral STN-DBS on non-motor symptoms in Parkinson's disease: a four-year observational, prospective study. *Parkinsonism Relat Disord.* 2021;**89**:13–16.
74 Jafari N, Pahwa R, Nazzaro JM, Arnold PM, Lyons KE. MDS-UPDRS to assess non-motor symptoms after STN DBS for Parkinson's disease. *Int J Neurosci.* 2016;**126**:25–9.
75 Dafsari HS, Dos Santos Ghilardi MG, Visser-Vandewalle V, Rizos A, Ashkan K, Silverdale M, et al. Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson's disease. *Brain Stimul.* 2020;**13**:1697–705.

76 Odekerken VJ, van Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijssen PC, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol.* 2013;**12**:37–44.

77 Odekerken VJ, Boel JA, Schmand BA, de Haan RJ, Figee M, van den Munckhof P, et al. GPi vs STN deep brain stimulation for Parkinson disease: three-year follow-up. *Neurology.* 2016;**86**:755–61.

78 Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol.* 2005;**62**:554–60.

79 Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med.* 2010;**362**:2077–91.

80 Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol.* 2009;**65**:586–95.

81 Lhommée E, Wojtecki L, Czernecki V, Witt K, Maier F, Tonder L, et al. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. *Lancet Neurol.* 2018;**17**:223–31.

82 Sierra M, Carnicella S, Strafella AP, Bichon A, Lhommée E, Castrioto A, et al. Apathy and impulse control disorders: yin & yang of dopamine dependent behaviors. *J Parkinsons Dis.* 2015;**5**:625–36.

83 Ardouin C, Chéreau I, Llorca PM, Lhommée E, Durif F, Pollak P, et al. Assessment of hyper- and hypodopaminergic behaviors in Parkinson's disease. *Rev Neurol.* 2009;**165**:845–56.

84 Amstutz D, Paschen S, Lachenmayer ML, Maradan-Gachet ME, Deuschl G, Krack P, et al. Management of impulse control disorders with subthalamic nucleus deep brain stimulation in Parkinson's disease. *CNS Neurol Disord Drug Targets.* 2020;**19**:611–7.

85 Kulisevsky J, Berthier ML, Gironell A, Pascual-Sedano B, Molet J, Parés P. Mania following deep brain stimulation for Parkinson's disease. *Neurology.* 2002;**59**:1421–4.

86 Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. *Parkinsonism Relat Disord.* 2006;**12**(5):265–72.

87 Voon V, Krack P, Lang AE, Lozano AM, Dujardin K, Schüpbach M, et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. *Brain.* 2008;**131**:2720–8.

88 Zoon TJC, van Rooijen G, Balm GMFC, Bergfeld IO, Daams JG, Krack P, et al. Apathy induced by subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Mov Disord.* 2021;**36**:317–26.

89 Tripoliti E, Limousin P, Foltynie T, Candelario J, Aviles-Olmos I, Hariz MI, et al. Predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease. *Mov Disord.* 2014;**29**:532–8.

90 Wertheimer J, Gottuso AY, Nuno M, Walton C, Duboille A, Tuchman M, et al. The impact of STN deep brain stimulation on speech in individuals with Parkinson's disease: the patient's perspective. *Parkinsonism Relat Disord.* 2014;**20**:1065–70.

91 Chiu SY, Tsuboi T, Hegland KW, Herndon NE, Shukla AW, Patterson A, et al. Dysarthria and speech intelligibility following Parkinson's disease globus pallidus internus deep brain stimulation. *J Parkinsons Dis.* 2020;**10**:1493–502.

92 Krishnan S, Shetty K, Puthanveedu DK, Kesavapisharady K, Thulaseedharan JV, Sarma G, et al. Apraxia of lid opening in subthalamic nucleus deep brain stimulation for Parkinson's disease—frequency, risk factors and response to treatment. *Mov Disord Clin Pract.* 2021;**8**:587–93.

93 Weiss D, Volkmann J, Fasano A, Kühn A, Krack P, Deuschl G. Changing gears—DBS For dopaminergic desensitization in Parkinson's disease?. *Ann Neurol.* 2021;**90**(5):699–710.

94 Linazasoro G. Subthalamic deep brain stimulation for advanced Parkinson's disease: all that glitters is not gold. *J Neurol Neurosurg Psychiatry.* 2003;**74**:827.

95 Mahlknecht P, Foltynie T, Limousin P, Poewe W. How does deep brain stimulation change the course of Parkinson's disease? *Mov Disord.* 2022. https://doi.org/10.1002/mds.29052

96 Bejjani BP, Nohra G. The new phenotype of Parkinson's disease: the postsubthalamic stimulation era. *Neurology.* 2008;**7**(suppl 1):A179.

97 Angeli A, Mencacci NE, Duran R, Aviles-Olmos I, Kefalopoulou Z, Candelario J, et al. Genotype and phenotype in Parkinson's disease: lessons in heterogeneity from deep brain stimulation. *Mov Disord.* 2013;**28**:1370–5.

98 Lohmann E, Welter ML, Fraix V, Krack P, Lesage S, Laine S, et al. Are Parkin patients particularly suited for deep-brain stimulation? *Mov Disord.* 2008;**23**:740–3.

99 Sayad M, Zouambia M, Chaouch M, Ferrat F, Nebbal M, Bendini M, et al. Greater improvement in LRRK2 G2019S patients undergoing subthalamic nucleus deep brain stimulation compared to non-mutation carriers. *BMC Neurosci.* 2016;**17**:6.

100 Johansen KK, Jørgensen JV, White LR, Farrer MJ, Aasly JO. Parkinson-related genetics in patients treated with deep brain stimulation. *Acta Neurol Scand.* 2011;**123**:201–6.

101 Lythe V, Athauda D, Foley J, Mencacci NE, Jahanshahi M, Cipolotti L, et al. GBA-associated Parkinson's disease: progression in a deep brain stimulation cohort. *J Parkinsons Dis.* 2017;**7**:635–44.

102 Pal G, Mangone G, Hill EJ, Ouyang B, Liu Y, Lythe V, et al. Parkinson disease and subthalamic nucleus deep brain stimulation: cognitive effects in GBA mutation carriers. *Ann Neurol.* 2022;**91**:424–35.

103 Hariz M. Once STN DBS, always STN DBS?—Clinical, ethical, and financial reflections on deep brain stimulation for Parkinson's disease. *Mov Disord Clin Pract.* 2016;**3**:285–87.

104 Hariz MI, Johansson F. Hardware failure in Parkinsonian patients with chronic subthalamic nucleus stimulation is a medical emergency. *Mov Disord.* 2001;**16**:166–8.

105 Rajan R, Krishnan S, Kesavapisharady KK, Kishore A. Malignant subthalamic nucleus-deep brain stimulation withdrawal syndrome in Parkinson's disease. *Mov Disord Clin Pract.* 2016;**3**:288–91.

106 Reuter S, Deuschl G, Falk D, Mehdorn M, Witt K. Uncoupling of dopaminergic and subthalamic stimulation: life-threatening DBS withdrawal syndrome. *Mov Disord.* 2015;**30**:1407–13.

107 Neuneier J, Barbe MT, Dohmen C, Maarouf M, Wirths J, Fink GR, et al. Malignant deep brain stimulation-withdrawal syndrome in a patient with Parkinson's disease. *Mov Disord.* 2013;**28**:1640–1.
108 Hariz GM, Nakajima T, Limousin P, Foltynie T, Zrinzo L, Jahanshahi M, et al. Gender distribution of patients with Parkinson's disease treated with subthalamic deep brain stimulation; a review of the 2000–2009 literature. *Parkinsonism Relat Disord.* 2011;**17**:146–9.
109 Hamberg K, Hariz GM. The decision-making process leading to deep brain stimulation in men and women with Parkinson's disease—an interview study. *BMC Neuro.* 2014;**14**:89.
110 Baumgartner AJ, Thompson JA, Kern DS, Ojemann SG. Novel targets in deep brain stimulation for movement disorders. *Neurosurg Rev.* 2022. https://doi.org/10.1007/s10143-022-01770-y
111 Coenen VA, Sajonz B, Prokop T, Reisert M, Piroth T, Urbach H, et al. The dentato-rubro-thalamic tract as the potential common deep brain stimulation target for tremor of various origin: an observational case series. *Acta Neurochir (Wien).* 2020;**162**:1053–66.
112 Hamel W, Herzog J, Kopper F, Pinsker M, Weinert D, Müller D, et al. Deep brain stimulation in the subthalamic area is more effective than nucleus ventralis intermedius stimulation for bilateral intention tremor. *Acta Neurochir (Wien).* 2007;**149**:749–58.
113 Blomstedt P, Stenmark Persson R, Hariz GM, Linder J, Fredricks A, Häggström B, et al. Deep brain stimulation in the caudal zona incerta versus best medical treatment in patients with Parkinson's disease: a randomised blinded evaluation. *J Neurol Neurosurg Psychiatry.* 2018;**89**:710–6.
114 Weiss D, Walach M, Meisner C, Fritz M, Scholten M, Breit S, et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. *Brain.* 2013;**136**:2098–108.
115 Bourilhon J, Mullie Y, Olivier C, Cherif S, Belaid H, Grabli D, et al. Stimulation of the pedunculopontine and cuneiform nuclei for freezing of gait and falls in Parkinson disease: cross-over single-blinded study and long-term follow-up. *Parkinsonism Relat Disord.* 2022;**96**:13–7.
116 Barnikol TT, Pawelczyk NB, Barnikol UB, Kuhn J, Lenartz D, Sturm V, et al. Changes in apraxia after deep brain stimulation of the nucleus basalis Meynert in a patient with Parkinson dementia syndrome. *Mov Disord.* 2010;**25**:1519–20.
117 Gratwicke J, Zrinzo L, Kahan J, Peters A, Beigi M, Akram H, et al. Bilateral deep brain stimulation of the nucleus basalis of Meynert for Parkinson disease dementia: a randomized clinical trial. *JAMA Neurol.* 2018;**75**:169–78.
118 Loh A, Gwun D, Chow CT, Boutet A, Tasserie J, Germann J, et al. Probing responses to deep brain stimulation with functional magnetic resonance imaging. *Brain Stimul.* 2022;**15**:683–94.
119 Ferreira F, Akram H, Ashburner J, Zrinzo L, Zhang H, Lambert C. Ventralis intermedius nucleus anatomical variability assessment by MRI structural connectivity. *Neuroimage.* 2021;**238**:118231.
120 Wu C, Matias C, Foltynie T, Limousin P, Zrinzo L, Akram H. Dynamic network connectivity reveals markers of response to deep brain stimulation in Parkinson's disease. *Front Hum Neurosci.* 2021;**15**:729677.
121 Krauss JK, Lipsman N, Aziz T, Boutet A, Brown P, Chang JW, et al. Technology of deep brain stimulation: current status and future directions. *Nat Rev Neurol.* 2021;**17**:75–87.
122 Deeb W, Giordano JJ, Rossi PJ, Mogilner AY, Gunduz A, Judy JW, et al. Proceedings of the Fourth Annual Deep Brain Stimulation Think Tank: a review of emerging issues and technologies. *Front Integr Neurosci.* 2016;**10**:38.
123 Vedam-Mai V, Deisseroth K, Giordano J, Lazaro-Munoz G, Chiong W, Suthana N, et al. Proceedings of the Eighth Annual Deep Brain Stimulation Think Tank: advances in optogenetics, ethical issues affecting DBS research, neuromodulatory approaches for depression, adaptive neurostimulation, and emerging DBS technologies. *Front Hum Neurosci.* 2021;**15**:644593.
124 Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol.* 2019;**15**:234–42.

Correspondence: Marwan Hariz, Department of Clinical Neuroscience, University Hospital of Umeå, 901 85 Umeå, Sweden.
Email: marwan.hariz@umu.se

