Neurotherapeutics (2014) 11:47–59
DOI 10.1007/s13311-013-0235-0

REVIEW

Surgical Treatment of Parkinson's Disease: Patients, Targets, Devices, and Approaches

Aparna Wagle Shukla · Michael Scott Okun

Published online: 7 November 2013

Abstract Surgical treatment for Parkinson's disease (PD) has evolved from ablative procedures, within a variety of brain regions, to implantation of electrodes into specific targets of the basal ganglia. Electrode implantation surgery, referred to as deep brain stimulation (DBS), is preferred to ablative procedures by many experts owing to its reversibility, programmability, and the ability to be safely performed bilaterally. Several randomized clinical studies have demonstrated the effectiveness of DBS surgery for control of PD symptoms. Many brain targets, including the subthalamic nucleus and the globus pallidus internus, have emerged as potentially effective, with each target being closely associated with important pros and cons. Selection of appropriate PD candidates through a methodical interdisciplinary screening is considered a prerequisite for a successful surgical outcome. Despite recent growth in DBS knowledge, there is currently no consensus on the ideal surgical technique, the best surgical approach, and the most appropriate surgical target. DBS is now targeted towards treating specific PD-related symptoms in a given individual, and not simply addressing the disease with one pre-defined approach. In this review we will discuss the historical aspects of surgical treatments, the selection of an appropriate DBS candidate, the current surgical techniques, and recently introduced DBS-related technologies. We will address important pre- and postoperative issues related to DBS. We will also discuss the lessons learned from the randomized clinical studies for DBS and the shifting paradigm to tailor to a more patient-centered and symptom-specific approach.

A. Wagle Shukla (✉) · M. S. Okun
Center for Movement Disorders and Neurorestoration, Department of Neurology, University of Florida, 3450 Hull Road, Gainesville, FL 32607, USA
e-mail: aparna.shukla@neurology.ufl.edu

Keywords Parkinson's disease · Deep brain stimulation · subthalamic nucleus DBS · Globus pallidus DBS

Introduction

Over the last century, the surgical treatment of Parkinson's disease (PD) has evolved from an ablation with careful placement of lesions within a variety of brain structures into stimulation of very specific brain targets within the basal ganglia subregions. Brain targets are typically selected to tailor to an individual's specific symptoms [1, 2]. Early in the twentieth century, the basal ganglia received enormous attention as a potential target for surgical intervention. The chance observation of E. Jefferson Browder, a neurosurgeon by profession, that caudate nucleus extirpation improved Parkinsonian symptoms resulted in Dr. Russell Meyer advocating the targeting of the basal ganglia for treatment of tremor in the late 1930s [3]. Subsequently, several other neurosurgeons began to experiment with lesions in the basal ganglia as a potential therapeutic modality. Among these early neurosurgeons, Irving Cooper [4] published a critical observation in a single patient who had experienced disappearance of tremor and rigidity following accidental ligation of the anterior choroidal artery. The resulting striatal lesion was hypothesized to underpin the positive benefits.

Parallel to these surgically-based empiric observations, pioneering advances in technology were accomplished. Spiegel and Wycis introduced critical stereotactic techniques into movement disorders surgery [5]. These techniques gradually became refined, and ultimately led to the possibility of targeting specific subcortical structures with millimeter-based precision. Surgeons subsequently shifted their focus to performing thalamotomy and pallidotomy surgeries; however, in the late 1960s, with the introduction of levodopa therapy for treatment of PD, utilization of surgical therapies began to

wane. Though dopaminergic therapies initially showed tremendous, and in some cases significantly positive, improvements in tremors, rigidity, and bradykinesia [6] limitations and side effects of these medications soon emerged. Motor fluctuations and dyskinesias were closely associated with the use of these therapies, particularly at higher dosages [7]. These observations led to the realization that there was a window of optimal therapeutic benefit for the pharmacological approaches. The side effects of levodopa therapy led to a renewed interest in surgical therapies, and to a resurgence of thalamotomy [8], pallidotomy [9], and subthalamotomy surgeries [10]. In 1987, Benabid et al. [11] observed that high-frequency electrical stimulation delivered to the ventral intermediate (VIM) nucleus of the thalamus improved tremors in PD. Prior to this work, many neurosurgeons had performed only test stimulations of the basal ganglia regions in the setting of an ablative surgery [1]. Benabid et al. [11] innovated the idea of chronically applying electrical current to the brain in order to treat movement disorders. The use of electricity in this way opened the door for a new therapy, popularly known as deep brain stimulation (DBS).

In DBS surgery, leads are implanted into specific targets or specific regions within the brain. The general concept has been that brain circuitries have central nodal areas where many pathways converge, and that when these nodes are stimulated with electricity, it will result in alteration of a complex neural network. This change in the neural network is thought to lead to improvement of symptoms. According to the basal ganglia circuitry that has been proposed to explain pathophysiology of PD, the direct pathway through the globus pallidus (GPi) and the indirect pathway through the subthalamic nucleus (STN) serve as important nodal junctions for addressing the motor symptoms of PD.

DBS has rapidly evolved, and has recently been adopted for several indications. More than 100,000 DBS devices have been implanted worldwide [12]. Clinicians and patients have cited the reversibility, programmability, and the ability to safely perform bilateral procedures as key reasons to switch from the use of ablative surgeries. DBS was approved by the US Food and Drug Administration for the treatment of PD in 2002, and later received approvals for essential tremor, dystonia, and obsessive compulsive disorders.

Though DBS has proven to be a powerful therapy for treatment of motor symptoms in PD, there are significant adverse effects associated with this surgery, particularly in speech, mood, and cognitive domains. Currently, many groups are working to refine technologies and approaches to maximize benefits and minimize risks. This review will summarize the current state of the field, and will also present the relevant challenges that may occur in patients, targets, devices, and approaches.

Patient Selection and Best Candidate for DBS

DBS treatment is most effective when candidates are carefully and properly screened and selected. It is estimated that more than 30 % of DBS failures are associated with surgical candidacy issues [13]. There are several critical factors that require consideration when deciding on DBS candidacy. Age, disease duration, levodopa responsiveness, and the presence of other comorbid conditions are important considerations [14]. Welter et al. [15] observed that motor improvements—as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living section (section II) and also in the motor section or (section III)—were significantly more robust when operating on patients younger than 56 years of age, and with a disease duration of approximately 16 years or less. Similarly, in another study, patients were stratified according to their age into 2 groups: 1 group contained patients younger than 65 years of age and the other patients older than 65 years of age. Although there were no differences in motor improvements in either group, the elderly group demonstrated fewer improvements in quality of life [16]. In contrast, Kleiner-Fisman et al. [17] did not uncover any specific advantage when factors such as age at disease onset, age at surgery, or disease duration were considered in prediction of outcomes.

Currently, there is no specific age limit for consideration of DBS surgery. Most experts agree that younger age has a more favorable risk–benefit profile for any type of surgery, whether PD is present or not. Caution is needed when patients are over the age of 70 years and, particularly, if they have comorbidities. Some expert groups have advocated a unilateral approach for older or more frail patients who are more likely to have comorbid medical conditions and are more likely to develop complications such as stroke or hemorrhage [18].

Many studies have examined the role of preoperative levodopa responsiveness as an important predictor of outcome. Preoperative levodopa responsiveness is determined by calculating the reduction in UPDRS motor score (part III) when an effective dose or suprathreshold dose of levodopa is administered in a practically defined *off* state [15]. Most groups who have found this factor predictive for positive surgical outcome have a minimum threshold of 30 % or more improvement in the on–off testing [19–21], though some specific symptoms may be amenable to surgery even with less than 30 % improvement (e.g., tremor, dyskinesia) [22]. DBS has not been observed to have a satisfactory response when axial signs are present and DBS is, in general, not expected to improve gait, postural

instability, or freezing, particularly those with a poor response to levodopa [15, 23, 24].

Neuropsychological and neuropsychiatric factors also constitute important considerations for DBS outcomes. These factors relate both to the preoperative issues, which require attention prior to DBS surgery, and the postoperative issues that frequently emerge and may have substantive influence on the surgical outcomes. Postoperative hypomania has been reported in 4–15 % [25–27] and postoperative depression in 1.5–25 % of STN DBS patients [25, 26, 28]. Suicide attempts and/or suicides following STN DBS have been reported, though it has been unclear if these reports are all related to the effects of stimulation [29, 30]. In an international multicenter retrospective survey, Voon et al. [31] studied the records of more than 5000 patients with STN DBS, and found there was an increased risk of attempted and completed suicide rates in STN DBS patients in the first postoperative year, as compared with the lowest and the highest expected age-, gender-, and country-adjusted World Health Organization suicide rates (standardized mortality ratio). In this study, postoperative depression emerged as the single most important factor for a completed suicide, whereas factors identified to be important for attempted suicide included a previous history of impulse control disorder, a previous history of suicide attempt, and a younger age of onset [31]. Although prior use of antidepressant medications did not influence the prevalence of suicidal behavior, they observed a larger reduction in dopaminergic medications as an important factor that may influence suicide [31]. Recently, Weintraub et al. [32] examined the results of a large randomized Veterans Affairs (VA) study and found that suicidal ideation and behavior were similar in the DBS and best medication management cohorts when compared at 6 months postoperatively. In this study, the suicide-related question on the mood item of the UPDRS part I scale was examined and compared between the DBS and the medical group. The groups were matched for Beck Depression Inventory (BDI) scores at the time of inclusion, but the individual scores on this scale were not compared, Further the authors analyzed the DBS cohorts that underwent STN and GPi DBS, and found similar frequencies of suicidal ideations and behaviors. The authors postulated that a smaller reduction of dopaminergic medications seen postoperatively may have prevented the development of suicidal behaviors [32]. These studies collectively suggest that significant medical and psychiatric comorbidities, including the presence of pre- and postoperative depression, larger decreases in dopaminergic medications, and other general risk factors, may be associated with an increased risk for suicidal behavior after DBS surgery.

In examining DBS-related neuropsychological consequences, there is a general consensus that the presence of frank dementia and, in particular, severe executive dysfunction disqualifies most patients for a potential DBS surgery. Similar to psychiatric problems, neuropsychological issues have been observed to emerge post-DBS and the most consistent and robust issue is decline in word fluency [27, 33–35]. In a prospective randomized study that compared the effects of unilateral STN and GPi stimulation, both targets were observed to have similar negative effects on combined letter and semantic word fluency, though letter fluency was found to worsen more in the STN group [36]. Many follow-up studies have suggested that word fluency may be affected by both STN or GPi DBS, but the effect has been observed to be more of a surgical (insertional effect), than a stimulation induced one. In the recent randomized St. Jude constant current study [37] 25 % of patients had DBS implants, but were not activated for 3 months. The inactive patients were found to have verbal fluency issues in a similar proportion to those randomized to active DBS. This study revealed that verbal fluency issues were more of a surgical issue than a stimulation induced one. It is unknown how much of this decline stems from from changes in the ventromedial region of STN or anteromedial region of GPi, or, alternatively, from trajectories through caudate or other regions.

Finally, age-related comorbidity, previous medical therapies, and past surgical treatments and factors specific to an individual, including employability, interpersonal relationships, and postoperative expectations of functionality are other important considerations that may potentially affect surgical outcomes [14]. There are sparse data available on these issues.

Interdisciplinary and Multidisciplinary Teams for Selection Process

The careful selection of potential DBS candidates relies on the collective efforts of multiple experienced and trained specialties. An ideal pre-surgical screening involves a multi-, preferably interdisciplinary team. Multidisciplinary implies that a group of experts belonging to neurosurgery, psychiatry, neuropsychology, and rehabilitation disciplines evaluate a patient and communicate to reach an agreement on care. Interdisciplinary care occurs when the experts meet together and discuss the risks, benefits, and care strategies for each DBS candidate. Many DBS teams include a movement disorders neurologist, a neuropsychologist, and a neurosurgeon. These team members typically meet each other weekly or monthly to discuss all potential DBS candidates [12]. DBS centers have increasingly used psychiatry opinions, especially in the light of high rates of comorbid psychiatric issues that may occur both pre- and postoperatively. Rehabilitation disciplines, including physical therapists, occupational therapists, and speech therapists are utilized on a case-by-case basis, but are very useful and are standard in some centers. Members of this team meet in person, though each member performs an individual evaluation. Discussions at team meetings include such topics as past history, comorbidities, medical imaging studies, and, if available, a

video examination. Most centers perform a formal levodopa challenge with a supratheshold dose of levodopa during the pre-surgical screening evaluation in order to document an improvement of 30 % or more in the UPDRS scores at individual patients' peak improvement, though not all candidates may meet this threshold [22]. The final discussions are centered on each individual's risk–benefit profile and their desired expectations. Interdisciplinary teams frequently vet whether the patients' expectations are reasonable, achievable, and realistic, given their profile [18, 38, 39]. Following the interdisciplinary meeting, a decision on the suggested treatment approach is communicated to the patients and their families. As DBS is elective, individual patients and families—after receiving approval to proceed with DBS—will actually make the final decision as to whether to proceed with surgical therapy. In the event that a potential DBS candidate fails to qualify, plans are usually formalized to attempt to address the issue(s). Most studies have suggested that 10–20 % of PD patients are deemed reasonable candidates for DBS surgery, though this number may increase, especially in light of a recent large randomized study supporting the use of DBS earlier in the disease course [40].

Florida Surgical Questionnaire-PD and Rand Methods for Screening of Candidates

PD patients who are referred for multidisciplinary and interdisciplinary evaluations are typically sent by general neurologists or, alternatively, by primary care physicians. There are notions in the field as to the criteria for selection of the "best" surgery candidates; however, there are no firm guidelines. One published tool aimed at primary care doctors known as the Florida Surgical Questionnaire-PD was designed to address if patient referral to multi- and interdisciplinary teams was performed appropriately. The questionnaire has 5 sections. Scoring is based on meeting the criteria for the diagnosis of "probable" idiopathic PD, potential contraindications to the surgery, medication trials, and general patient characteristics. The final scores are totaled from all sections of the questionnaire. One important advantage of this triage tool is that primary doctors can complete it in just a few minutes. Additionally, a formal UPDRS medication on–off evaluation is not required. The tool was used on a group of PD patients who had under gone interdisciplinary evaluation at a single DBS center in order to determine the validity of this screening questionnaire. The study found a significant correlation between the FLASQ-PD scores recorded and the ultimate decision of the DBS interdisciplinary team [41]. In another study, Moro et al. [42] used the RAND method to evaluate surgical candidacy. In their study, the authors examined 972 patient profiles, and observed that the appropriateness for surgical referral was correct in 33 % of the patients. The factors that had the strongest impact on the surgical decision were the severity of tremors, dyskinesias, off symptoms, duration of disease, presence of levodopa-resistant axial symptoms, age≥70 years, and cognitive performance.

Surgical Techniques: Targeting, Microelectrode Recording, Stereotactic Frames, and Magnetic Resonance Imaging Guidance

Since the advent of DBS, numerous stereotactic surgical techniques have been introduced, and there remains no clear consensus as to the best approach for DBS surgery. Surgeons at individual DBS centers typically select their preferred technique(s) based on training, experience, available hardware, available scanners, and the capabilities of staff and facilities [43]. Many stereotactic frames are utilized, including commercially-available systems such as the Leksell, Cosman-Roberts-Wells (CRW), Riechert-Mundinger frame, and others. Surgical frames are applied to an individual patient's skull on the day of surgery [44]. These frames facilitate an accurate brain targeting method, but they can be uncomfortable for the patient. Once the frames are fixed to the skull, it is important to determine the brain target. Previously, many centers had employed an atlas-based coordinate system to select the target, and this was referred to as indirect targeting. This practice of indirect targeting has now fallen out of favor, with most expert centers utilizing advanced imaging techniques to directly target an area, and, ultimately, to choose a safe trajectory.

Neuroimaging of brain targets is accomplished with computed tomography (CT), magnetic resonance imaging (MRI), ventriculography, or a combination of procedures [45–47]. Ventriculography though facilitating direct visualization of the third ventricle, anterior and posterior commissures, the midline, and the floor of the lateral ventricle is, however, an invasive procedure with some associated risk, and therefore most centers have discontinued its use. In comparison, CT—and particularly MRI—have provided a better resolution of intracerebral structures. Many commercially-available image-guided systems offer merging and image fusion capabilities that facilitate integration of multiple imaging datasets [48]. Most centers obtain a MRI of the brain the day prior to DBS, and obtain a CT scan on the day of the surgery following fixation of the head ring. This CT–MRI fusion technique limits the time a patient is required to remain in an uncomfortable head frame. Image fusion techniques are, however, not without flaws in determining the final brain target location. Once the brain target is determined with the help of neuroimaging, many DBS centers commonly utilize physiological localization with microelectrode recording (MER) for further refinement of the target. Some centers use MER to verify a target region (single pass); however, many use a multiple pass mapping technique to attempt to refine the position of the final DBS lead. MER recordings are reported

to be highly beneficial, especially when utilized by trained experts [49]. DBS centers not employing MER techniques argue that MER poses an added risk of bleeding, especially if pre-morbid hypertension is present [50]. According to the DBS Study Group [51], there may be a relationship between the number of microelectrode tracks and the risk of hemorrhage. In this particular study, patients with hemorrhage had a mean of 4.1±2.0 passes compared with 2.9±1.8 passes in those without hemorrhage ($p \leq 0.05$). Hariz [52] performed a meta-analysis and reported that non-MER techniques were 5 times less likely to result in hemorrhagic complications [52]. Unfortunately, most of the evidence on MER has derived from retrospective studies and expert opinions, and therefore there is no clear consensus. In expert hands, MER can enhance the chances of an optimal lead location.

DBS techniques that avoid the use of MER continue to evolve. Frameless DBS and MRI-guided DBS are recently introduced techniques, with early studies showing promising results. Traditionally, stereotactic frames are used in conjunction with imaging to localize the DBS targets, to help guide the MER, and to implant the electrodes. The use of this frame can become a source of discomfort during lengthy operations [53]. In modern frameless surgery, as in one such system referred to as the Nextframe system, fiducial markers are placed in an outpatient procedure by a neurosurgeon prior to the DBS operation. The success of this system hinges on accurate fiducial point identification, system accuracy, and platform stability. The term "fiducial" refers to markers placed as a frame of reference that can later be used for targeting. The efficacy of frameless DBS surgery has been found to be similar to frame based DBS when applied by experienced neurosurgeons [54, 55], though there are still only a few studies on this issue. The use of frameless technology also requires extra procedures for pre- and postimplantation, and removal of fiducial markers from the skull.

MRI-guided DBS is another technique that does not require the use of MER guidance and has been validated in several small clinical studies [56, 57]. In one study of 79 PD patients who had bilateral STN electrodes, significant improvements were noted at 1 year in motor scores, as well as in quality of life outcomes; however, there was not a comparator or a control group. The accuracy of electrode placement was confirmed with postoperative MRI, which revealed the mean error of displacement to be approximately 1.3 mm [57]. Though these findings are encouraging, the progress of MRI-based techniques is currently hampered by limitations in adjustment of the lead placement in real time; in testing of the DBS lead in the intraoperative setting, the procedure requires anesthesia and sometimes it may be difficult to accurately visualize STN. Additionally, imaging alone should not be used to confirm accurate placement of a DBS lead, and patients undergoing MRI based procedures should have detailed testing in the clinic to confirm accurate placement of the lead.

Postoperative Programming

DBS programming is typically performed once the electrodes are implanted and the battery placed in the chest (or, in some cases, the abdomen). The usual postoperative time after the initial implantation surgery ranges from immediate to 30 days, depending on the center. Battery (neurostimulator) placement is performed under general anesthesia and requires 45 mins. DBS programming can be initiated immediately after the the neurostimulator has been placed. Programming is typically performed by a trained healthcare professional who traditionally is a neurologist, or can also be a neurosurgeon, nurse, nurse practitioner, or a physician assistant. These professionals must be well versed with the technical aspects of DBS, as well as the PD-related issues, which include behavioral and pharmacological management.

Prior to any device programming, it is helpful to verify the DBS lead location by postoperative imaging. During the initial programming, systematic testing of each of the 4 electrode contacts for each brain hemisphere is performed in order to determine the potentially optimal stimulation settings. The thresholds to elicit adverse and beneficial effects are recorded, and can be used in all future DBS programming sessions. The standard stimulation parameters employed in varying combinations include pulse width, frequency, voltage, and electrode configuration. Programming sessions can potentially result in thousands of different settings that often vary across individuals. Initially, lower current densities are employed, which are gradually escalated until an optimal setting is identified. An optimal setting is defined as one that reveals maximal benefits and minimal (or no) side effects. At the initial programming, monopolar stimulation is usually employed, but if adverse effects are encountered, the patient is switched to bipolar stimulation. The best possible combination of voltage, pulse width, and frequency that can be elucidated with programming is chosen, but can be highly variable among patients and can differ between each brain side. In some cases, multiple cathodes are needed to achieve optimal control of symptoms. Rigidity and tremor are typically observed to respond faster than other PD symptoms [58, 59]. Optimization of DBS parameters, medication adjustments, and behavioral management are often achieved over, approximately, a 6-month period, with most groups evaluating patients once every month, on average, during this time interval. Once the stimulation settings are chosen, management is shifted to focus on medication changes. Physicians and patients are educated and made aware of the general treatment expectation, which is that after the first 6 months of therapy and once stimulation settings are optimized, a change in DBS settings is usually not the answer to most problems encountered in PD. If a DBS lead is found to have low thresholds for side effects, or benefits are not sustained, a work-up for a failed DBS is then be pursued. In

many cases, if the lead is discovered to be suboptimally placed, a revision surgery is planned [13].

Evidence for DBS in PD from Randomized Studies

Since the 1990s, DBS has been touted as an efficacious treatment for motor fluctuations in PD, and, until recently, there was a lack of evidence based on randomized clinical trials. In a meta-analysis examining the efficacy of STN DBS in PD, 37 studies published between 1993 and 2004 were identified. However, these studies were not randomized and did not have controls [17]. Over the last decade, several important randomized controlled studies have been conducted (Tables 1 and 2).

These studies have contributed to an improved understanding on the appropriate surgical candidate, the appropriate surgical target, the debate on unilateral versus a bilateral surgical approach, the impact on quality of life, and the adverse event profiles. The large VA cooperative multicenter program (CSP) study [60], the NEJM Quality of Life Study by Deuschl et al. [61], and the UK PD Surge Trial [62], have all provided strong evidence to support DBS as a therapy with a superior outcome when compared with best medical management for treatment of motor fluctuations in appropriately screened patients. Across these studies it has been observed that with DBS therapy there are significant increases in the quality "on time", decreases in the "off time", and the dyskinesias are, in general, less severe after surgical intervention.

For many years, most studies in the literature used STN as their preferred target for treatment of PD symptoms. Consequently, GPi did not get fully explored as an alternative consideration. In the recent literature, numerous studies comparing the efficacy of STN DBS to GPi DBS have been published. These studies have revealed equivalent results with STN and GPi DBS. The VA CSP cooperative study was one of the first studies to randomly assign 299 patients to undergo either pallidal stimulation (152 patients) or subthalamic stimulation (147 patients). The primary outcome of the study at 24 months was a significant change in motor function as assessed blindly with the motor section of the UPDRS scale. These results demonstrated an equivalence in improvement of motor function regardless of the selected target. Although improvements seen with GPi DBS were encouraging, some investigators raised concerns whether benefits from GPi could potentially diminish over time [63, 64]. The VA study has now published its 36 months follow-up results: STN and GPi DBS demonstrated equivalent benefits, challenging the previous notion [65]. Some experts continue to debate that the overall medication reduction seen with STN DBS strongly favors the use of this target [61, 66]. Recently another large study from Netherlands—the NSTAPS study—showed similar equivalent improvements with STN and GPi DBS. In contrast to earlier studies, the primary outcome in this study did not focus on motor scores or quality of life measures. These investigators chose a disability scale (Academic Medical Center Linear Disability Scale) and examined an outcome score that was a composite of cognition, mood, and behavioral effects. The final results at 1 year did not reveal any target-specific differences [67].

Until recently, all the efficacy studies in DBS involved the use of voltage-controlled devices. These devices are incapable of adjusting the current against heterogenous tissue impedences. This is an issue that potentially affects symptom control, and also affects the battery life. A novel stimulation device that delivers a constant current was recently investigated as part of the St. Jude trial, and this device was observed to be

Table 1 Demographics and clinical outcomes with subthalamic nucleus (STN) deep brain stimulation surgery

Study	Sample size (% male)	Mean follow-up in mo (±SD)	Mean age at surgery in y (±SD)	Mean duration on medications before surgery in y (±SD)	% Change in postoperative UPDRS II score: MED OFF–STIM ON *vs* MED OFF score	% Change in postoperative UPDRS III score: MED OFF–STIM ON *vs* MED OFF score	LED (% decrease)	% Change in dyskinesia	% Change in Quality of Life (PDQ summary index)
Deuschl et al. [61]	156 (64)	6	60.5±7.4	13.0±5.8	39.0	40.0	50.0	40.0	22.7
Weaver et al.[66]*	61 (81)	6	62.6±8.3	12.4±5.8	–	29.0	23.0	36.0	17.5
Follett et al. [74]	147 (79)	24	61.9±8.7	11.1±5.0	15.7	33.0	31.5	44.0	10.6
Weaver et al. [65]	70 (80)	36	60.7±8.9	11.3±4.7	6.2	30.5	35.6	55.4	8.3
Williams et al. [62]	174 (68)	12	59.0	11.5	26.0	35.7	–	50.0	13.3
Deuschl et al. [40]	124 (76)	24	52.9±6.6	7.3±3.1	41.3	49.3	65.1	71.4	26.4
Okun et al. [37]	136 (62)	12	60.6±8.3	12.1±4.9		37.5	34.3	50.0	17.0
Odekerken et al. [67]	63 (70)	12	60.9±7.6	9.5±5.6	32.9	45.7	43.5	20.8	19.4
Anderson et al. [75]	12 (76)	12	61.0±9.0	10.3±2.0	25.9	48.0	38.0	43.5	–

UPDRS = Unified Parkinson's Disease Rating Scale; MED OFF–STIM ON = medication off - stimulation on; MED OFF = medication off; LED = Levodopa Equivalent Dose; PDQ = Parkinson's Disease Quality of Life

*Results indicate combined STN and globus pallidus stimulation group

Table 2 Demographics and clinical outcomes with globus pallidus (GPi) deep brain stimulation surgery

Study	Sample size (% male)	Mean follow-up in mo (±SD)	Mean age at surgery in y (±SD)	Mean duration on medica tions beforesurgery in y (±SD)	% Change in postoperative UPDRS II score: MED OFF–STIM ON *vs* MED OFF score	% Change in postoperative UPDRS III score: MED OFF–STIM ON *vs* MED OFF score	LED (% decrease)	% Change in dyskinesia	% Change in Quality of Life (PDQ summary index)
Weaver et al.[66]*	60 (80)	6	62.6±8.3	12.4±.8.0	–	29.0	23.0	36.0	17.5
Follett et al. [74]	152 (88)	24	61.8±8.7	11.5±5.4	21.0	39.3	17.8	38.6	11.9
Weaver et al. [65]	89 (86.5)	36	60.4±8.3	11.4±4.9	8.5	34.0	17.7	51.6	6.3
Odekerken et al. [67]	65 (68)	12	59.1±7.8	9.0±3.9	22.3	26.0	15.6	56.6	12.2
Anderson et al. [75]	11 (75)	12	54.0±12.0	15.6±5.0	17.0	39.0	3.0	37.5	–

UPDRS = Unified Parkinson's Disease Rating Scale; MED OFF – STIM ON = medication off - stimulation on; MED OFF = medication off; LED = Levodopa Equivalent Dose; PDQ = Parkinson's Disease Quality of Life

*Results indicate combined subthalamic nucleus and GPi stimulation group

successful in treating PD in 136 patients undergoing bilateral STN DBS surgery [37]. The UPDRS motor scores at a follow-up of 1 year in the off-medication and on-stimulation condition improved by 39 %, and the on time improved by 4 h when compared with baseline. These findings were consistent with other previously published results [37, 40, 61, 67] . The study, however, did not provide long-term outcomes, and did not compare outcomes to a group of patients using voltage-driven devices. It is likely that because of superior technical specifications, constant current devices will be used in all future trials, and this will render such comparisons moot.

Approach to DBS and Timing of Surgery

Many DBS centers advocate simultaneous implantation of bilateral electrodes. Advantages to this approach include patient convenience, and a lower cost of surgery [68]. However, many DBS candidates predominantly have unilateral or asymmetric symptoms, and the addition of a second contralateral procedure potentially adds risk without much additive benefit. Additionally, extended intraoperative time possibly contributes to complications, particularly in elderly patients (> 70 years old) and in those with multiple comorbidities [68].

There is also growing evidence to support the notion that unilateral DBS can be highly efficacious in select patients [69, 70]. The National Institutes of Health's COMPARE DBS study was the first randomized study of unilateral STN and unilateral GPi DBS. A secondary analysis of this cohort revealed an ipsilateral motor improvement with benefits sustained even after 3.5 years The study found that 48 % of patients remained satisfied with unilateral surgery at 3.5 years and the odds of remaining unilateral was significantly higher in those patients implanted with a GPi DBS. The reasons for proceeding to bilateral DBS included the presence of a higher preoperative UPDRS-III motor score, and a more symmetrical PD symptom pattern [71]. Additionally, the quality of life analysis revealed greater benefits for unilateral GPi DBS compared with unilateral STN DBS. These findings indicate that this factor may be important in target selection when the practitioner is considering a unilateral procedure [72]. Some centers initially perform a unilateral DBS and consider a staged second side only after optimization with the first is achieved. Prior to the addition of a second side procedure, they offer a discussion of the risks, benefits, and expectations that may be potentially addressed by a contralateral DBS [71].

Another debate for the field is the timing of DBS surgery. In current clinical practice, the average disease duration for patients undergoing DBS is usually about 10 or more years of disease, and rarely is DBS offered prior to 5 years. There has been a growing enthusiasm for introducing DBS surgery early in the course of PD. The most important rationale for early intervention is that it may enhance the quality of life, particularly in the context of activities of daily living and social status, and it may also potentially provide occupational gains [40]. In a randomized study conducted with a 24-month follow-up, 251 patients with PD and early motor complications who had a mean duration of disease of 7.5 years were either provided neurostimulation plus medical therapy or medical therapy alone. What set this study apart from its predecessors was that the patients experienced, on average, motor fluctuations for less than 2 years, despite optimal PD drug treatment, as verified by an independent panel. The primary outcome was the Parkinson's Disease Quality of Life (PDQ-39) summary index, and the study revealed robust benefits in favor of the DBS group, which had an average age in the 50s [73]. The study also found fewer surgically related adverse effects, perhaps owing to the age of the patients. It is not currently known whether similar benefits would be manifested in older PD patients with early motor fluctuations [40] and if these benefits seen in the short term will be sustained. These concerns may be alleviated with inclusion of broader categories of patients and longer-term follow-up.

Adverse Events and Failures Related to DBS

The randomized studies on DBS [36, 60, 61, 74] have drawn attention to a wide variety of adverse effects that could possibly emerge following DBS therapy (Table 3 summarizes these effects).

Most studies have categorized the adverse events into surgical or nonsurgical, and also into those related to hardware issues or to electrical stimulation. Adverse events have been further categorized as either serious or nonserious, with infection at the surgical site noted as one of the most common adverse events. DBS studies have reported serious adverse events as 3 times more likely in the DBS group than those randomized to best medical practice [61, 66]. Furthermore when comparing the effects of STN to GPi stimulation [36, 67, 74], although there were no major differences in the surgical or hardware-related complications, the effects on mood, cognition, and gait were found to be widely variable [36, 67]. For example, Anderson et al. [75] found the cognition and behavior to be worse with STN stimulation, although the motor outcomes were noted to be equivalent between STN and GPI DBS. The National Institutes of Health's COMPARE study observed the STN group to have a slightly higher frequency of reduced letter fluency, anger, anxiety, confusion, irritability, aggressiveness, obsessive–compulsive disorder, and manic symptoms [36].

Some of the issues, such as the reduced verbal fluency, have been suggested as a lesion effect from lead insertion, as demonstrated recently by the St. Jude constant current STN DBS study. This study had an immediate activation group and a delayed activation group that was not turned on for 90 days after implantation. The primary outcome of the study was the change in ON time with medication. There were significant improvements in both groups; however, the activated group was superior to the implantation-only group. Interestingly, in this study, the decline in verbal fluency was present in both groups, indicating a lesion or implantation effect. The St. Jude STN DBS study observed that dysarthria, fatigue, paresthesias, and edema occurred as part of STN stimulation, whereas gait problems, disequilibrium, dyskinesia, and falls were seen regardless of whether the device was activated [37].

With regard to the frequency of adverse events, most of the studies have reported similar findings. The VA CSP cooperative study recorded similar frequencies and types of serious adverse events in the bilateral GPi and bilateral STN groups with the exception of a greater worsening of depression scores and more falls with STN DBS [74]. Interestingly, when patients were followed for 36 months, depression scores were noted to be similar in the 2 groups, but the cognitive scores were worse for the STN group [65]. The UK PD Surge Trial only examined the effects of STN DBS, and the authors reported similar adverse event rates [62] to the VA CSP. However the NEJM Quality of Life Study reported only 13 significant adverse events with STN stimulation [61], and this discrepancy in frequency compared to other studies was likely attributed to how adverse events were defined and recorded.

DBS patients are also sometimes presented to experienced DBS centers owing to suboptimal results (prior surgery performed elsewhere). These patients are labeled as "DBS failures", and many of these patients, with appropriate interventions, will have improved outcomes. In one study that examined a series of 41 patients presenting with complaints of suboptimal results, many factors were identified that contributed to the poor response. These factors included inadequate preoperative screening, suboptimally-placed DBS leads, poor access to programming, battery failure, and damaged hardware. Reprogramming, adjustment of medications, and—in select cases—repositioning of suboptimally-placed DBS leads resulted in 51 % of patients reporting meaningful improvement [13]. Subsequently, many other centers published similar experiences. In one series of 100 DBS electrodes inserted in 55 patients for movement disorders, mostly for PD (50 patients), there were 2 electrode malpositions, 2 electrode fractures, 1 electrode migration, and 1 pulse-generator infection [76]. A similar frequency of electrode breakage and lead migration was observed in another study of 106 patients who underwent DBS surgery for various pathologies [77].

The adverse event profile findings that have been mainly derived from the randomized DBS studies have aided in shaping current clinical practice. Clinicians and patients are now more aware of these issues, and can better counsel patients pre- and postoperatively. Additionally, clinicians have become more adept in delivering changes to stimulation and medication that may both result in improved outcomes.

Brain Targets for DBS in PD: A Constant Evolution

Historically, in the ablative therapy era, the targets for surgery included the motor cortex, the VIM nucleus of the thalamus (thalamotomy) and the GPi (pallidotomy). When DBS emerged, STN quickly became the popular target for most surgeons. This decision was primarily based on the successful results of STN lesioning in parkinsonian primates [78] and the realization that dopaminergic medications could be reduced following STN DBS [79]. Only in more recent trials has GPi re-emerged as an effective choice for treatment of both levodopa-responsive symptoms and for motor fluctuations, as well as dyskinesias [36, 74].

The clinical studies conducted over the last decade have facilitated the development of multiple brain targets for DBS therapy and have shed light on a number of target-specific and potentially important clinical differences. For example, the

Table 3 Adverse effect profiles of subthalamic nucleus (STN) and globus pallidus (GPi) deep brain stimulation surgery (number in parenthesis indicates number of events)

STN surgery		
Study	Adverse events	
	Surgical- and device-related	Stimulation-induced neuropsychiatric, speech, gait, and balance
Deuschl et al. [61]	Death (3), confusion (7), cable discomfort (2), suicide (1)	Depression (4), psychosis (4), dysarthria (8)
Weaver et al. [66]	Confusional state (15), headache (20)	Dysarthria (11), falls (16)
Follett et al. [74]	Infection (12), confusional state (5), mental status change (1), cerebral hemorrhage (2)	Gait disturbance (45), balance (54), fall (63), depression (54), speech (51), suicidal depression(1),
Williams et al. [62]	Hemorrhage (4),infection (16), mental status change (13)	Falls (3), suicide (1), hallucinations (3)
Deuschl et al. [40]	Dislocation of device (4), impaired wound healing (4), intracerebral abscess (2)	Depression (6), impulse control disorder (1), worsening of mobility (4), suicide (2)
Okun et al. [37]	Infection (< 1), paresthesia (1), confusion (1)	Psychiatric disturbance (1), gait disorder (1), dysarthria (3), balance (2),
Odekerken et al. [67]	Delirium (15), infection (2), cerebral hemorrhage (3)	Emotional lability (53), dysarthria (25), balance(30)
Anderson et al. [75]	Delirium (3)	Anxiety (2), hallucination (1), cognitive (2)
Okun et al. [36]	Death (2), paresthesia (2), buzzing sound (2), pain (3), infection (1), confusion (10)	Obsessive–compulsive disorder (5), mania (5), depression (20), speech (8)
GPi surgery		
Weaver et al. [66]	Confusional state (15), headache (20)	Gait disturbance (49), balance (47), fall (58), depression (40), suicidal depression (2), speech (43)
Follett et al. [74]	Infection (12), confusional state (2), mental status change (4), cerebral hemorrhage (4)	Emotional lability (72), dysarthria (29), balance (35)
Odekerken et al. [67]	Delirium (22), infection (3)	Visual field defect (1)
Anderson et al. [75]	stroke (1), lead fracture (1), infraclavicular hematoma (3)	Obsessive–compulsive disorder (2), manic (1), depression (7), speech (12)
Okun et al. [36]	Confusion (6), infection (3), paresthesia (3), Air embolus (1), hemorrhage (1)	Gait disturbance (49), balance (47), fall (58), depression (40), suicidal depression (2), speech (43)

VIM of the thalamus has been targeted in some cases of tremor-dominant PD, but Hariz [52] and others [80–82] have observed that VIM DBS, although resulting in tremor improvements, has few effects on other PD symptoms. The VIM DBS in these studies mainly affected the distal upper extremity tremors. Many surgeons have moved away from this target, and, in difficult tremor cases associated with PD, prefer to stimulate in the posterior subthalamic region or the zona incerta and the prelemniscal radiations [83]. Anatomically, the zona incerta region lies dorsal and posterior to the STN, and is located at the junction of basal ganglia thalamocortical and cerebellar thalamocortical circuits. These circuits have been strongly implicated in the pathophysiology of tremors; therefore, stimulating this general region has provided some advantages [83]. Zona incerta stimulation appears to be more effective for control of proximal, as well as distal, tremors, particularly in non-PD patients, but this finding will require replication [84], and there is concern about stimulation-induced ataxia. Plaha et al. [85] compared the UPDRS scores, including the tremor scores, for patients undergoing caudal zona incerta DBS with a cohort of STN DBS patients. This group reported better benefits with zona incerta stimulation. The UPDRS scores improved by 76 % (zona incerta) compared with 55 % (STN), and the tremor scores improved by 93 % (zona incerta) compared with 61 % (STN) reduction. However, this study was small and suffered from many methodological limitations. Future randomized studies will help to better define how severe PD tremor responds to zona incerta stimulation, and whether this response is sustained. There are cases where PD tremor is accompanied by an essential tremors ET-like postural-action component that is very severe. In these cases, STN and GPi DBS may be less effective against the tremor than traditional VIM DBS.

The intra-laminar thalamic complex, which is composed of centromedian and parafascicular nucleus, has recently gained interest as a putative target for stimulation. The rationale for choosing this target is its central location within the basal ganglia circuitry, and the heavy input projections to the striatum. Stimulation in this region potentially modulates the pacemaker neurons for tremors and disrupts the abnormal thalamocortical activity. Furthermore, this target may have a very low potential for adverse effects on mood and cognition. Although all these

potential advantages seem encouraging, very few studies have been conducted on actual PD patients [86, 87].

Advanced PD is characterized by worsening of gait and balance, and this constitutes a major source of functional disability for many PD patients. As PD progresses freezing of gait noted during "on" may become unresponsive to levodopa therapy, and, in these cases, the use of STN and GPi DBS have both been largely disappointing. The pedunculopontine nucleus (PPN) was initially embraced by the field with significant enthusiasm as an appropriate target for control of gait, freezing, balance, and falls. The preliminary studies, which were all open-label evaluations, revealed some positive benefits [83, 88], though, subsequently, some issues of interpretation have emerged. Further analysis of these PPN studies has uncovered methodological concerns, including defining the patient population (on/off freezers, gait, balance, other issues), defining the outcome measures appropriate for these trials, and also issues in defining the actual region stimulated [89]. Khan et al. [90] found that the positive effects on PD symptoms were seen only if and when bilateral PPN stimulation was combined either with caudal zona incerta stimulation or, alternately, PPN stimulation in combination with STN stimulation. According to one study, low-frequency stimulation of STN and PPN resulted in significant improvements in freezing of gait [91]. The effects of STN on gait and freezing has also been found to differ by the side of stimulation. In one study, it was found that reduction in voltage on the less affected side resulted in a more symmetric gait pattern and a more normalized gait coordination [92].

Many investigators have attempted to tease out the independent effects of unilateral and bilateral PPN stimulation. Moro et al. [93] observed that with continuous unilateral PPN stimulation for 1 year there was a significant reduction in falls on the UPDRS II activities of daily living questionnaire. However, when the patients underwent examination with the UPDRS III motor scale, there were no significant improvements in gait and balance. There were also few improvements in bradykinesia, rigidity, and tremors, as recorded in a diary maintained by patients. Subsequently, Ferraye et al. [94] used bilateral PPN DBS and reported that the duration of freezing of gait at 1 year improved when the stimulator was turned on; however, results for gait and balance measures were disappointing. In a recent study of 5 patients, who had severe freezing of gait, postural instability and frequent falls that persisted despite being on dopaminergic medications, bilateral PPN stimulation was performed. These patients were administered a specific Gait and Falls Questionnaire, which improved significantly at 24 months; however, the gait and posture scores on the UPDRS III scale revealed no improvements [95]. The authors of this study suggested that the gait and posture items on the UPDRS III scale are likely insensitive to treatment effects and may not be appropriate for outcome assessment with PPN stimulation. They also suggested that stimulation of the caudal pedunculopontine region, which has predominantly cholinergic neurons and undergoes degeneration in PD, may be a better target for control of gait and freezing [95].

Thus, several studies have been performed that support the role of PPN as a target for control of gait and freezing, some with and some without STN DBS leads [83, 85, 93–96]. These early studies have been criticized for small sample sizes, short duration of follow-ups, and the validity of outcome measures used. Concerns have been raised over the possibility of inadvertent stimulation of the peripeduncular nucleus instead of the actual PPN [97, 98]. Nevertheless, despite these concerns, PPN continues to remain a potential target for treatment of PD. Future large-scale studies will provide a better insight into its clinical effectiveness.

Occasionally, if clinical improvements are not satisfactory—even in candidates who have been carefully selected—simultaneous stimulation of multiple targets is utilized in an attempt to enhance the clinical outcomes [87]. This type of aggressive approach will require more investigation in future studies.

In summary, there is a growing list of multiple brain targets for DBS therapy, and although the evidence is still limited and large-scale studies will be required, several targets may be encouraging, especially for specific symptoms not well addressed by STN or GPi DBS.

Lessons Learned from Clinical DBS Studies

The evidence gleaned from randomized DBS studies has facilitated an improved decision-making capacity for DBS practitioners. Many brain targets have emerged as effective for control of motor symptoms in PD [99]. The notion that STN is the single best target for treatment of PD has been weakened by the publication of multiple comparison studies using GPi and randomized designs [36, 67, 74]. The motor improvements recorded with both STN and GPi DBS have now been demonstrated to be sustained and of similar magnitude, even at long-term follow-up (e.g., 36 months) [65]. Clinical studies have also shed light on the key differences between GPi and STN DBS, though it may be too early to draw firm conclusions. GPi DBS seems to be preferred by many practitioners for severe dyskinesias and in cases where mood and cognition are a concern. Many practitioners believe that STN DBS is preferred for control of resting tremors and rigidity, and it results in a more robust reduction in dopaminergic medications (100). STN, being a smaller target, tends to require less electrical stimulation and may therefore require slightly fewer frequent battery changes. When examining the effects of DBS on quality of life, there are significant improvements that have been demonstrated in both targets. Although the effects of unilateral GPi DBS

compared with unilateral STN DBS may possibly be greater, the effects of bilateral GPi DBS have been observed to be equivalent to bilateral STN DBS [67, 74].

Many brain targets besides STN or GPi are under investigation, and each target has symptom specific differences. The new targets have been studied in only very small cohorts and these will require careful review and documentation of benefits and side effects, as well as a comparison to classical brain target regions. There has been a noticeable paradigm shift to tailor therapy to target the symptoms of patients (e.g., choosing the right brain target) and not just the disease in general. STN is no longer assumed to be the best DBS target for any given patient. The choice of one brain target over another is now based on the symptom profile, patient expectations, and the risk–benefit discussions of the DBS interdisciplinary team.

The newest study results on early DBS in patients with motor fluctuations and fewer than 2 years of disease duration are encouraging, and these will have to be weighed by practitioners, particularly in patients below the age of 60 years [40]. However, it remains unresolved if early DBS will be appropriate for older patients with PD, and if the benefits will remain sustained at long-term follow-up.

Conclusion

In summary, there is no single approach, no single brain target, and no single DBS technique that perfectly fits every patient seeking surgical treatment for PD. Based on the clinical studies, there has been a paradigm shift to tailor therapy to address an individual's needs. A tailored approach allows consideration of the complex and numerous variables that contribute to a positive or negative overall DBS outcome, and also addresses individual patient expectations. As the evidence-base continues to evolve, we anticipate further clarity on many of the issues that have surfaced over the last decade. This clarity will foster development of an optimal therapeutic approach for treatment of PD.

References

1. Kluger BM, Klepitskaya O, Okun MS. Surgical treatment of movement disorders. Neurol Clin 2009;27:633–677.
2. Kopell BH, Rezai AR, Chang JW, Vitek JL. Anatomy and physiology of the basal ganglia: implications for deep brain stimulation for Parkinson's disease. Mov Disord 2006;21(Suppl. 14):S238-S246.
3. Gabriel EM, Nashold BS,Jr. Evolution of neuroablative surgery for involuntary movement disorders: an historical review. Neurosurgery 1998;42:575–590.
4. Cooper IS. Surgical alleviation of Parkinsonism; effects of occlusion of the anterior choroidal artery. J Am Geriatr Soc 1954;2:691–718.
5. Spiegel EA, Wycis HT, Marks M, Lee AJ. Stereotaxic apparatus for operations on the human brain. Science 1947;106:349–350.
6. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967;276:374–379.
7. Obeso JA, Olanow CW, Nutt JG. Levodopa motor complications in Parkinson's disease. Trends Neurosci 2000;23(10 Suppl.):S2-S7.
8. Tasker RR, Siqueira J, Hawrylyshyn P, Organ LW. What happened to VIM thalamotomy for Parkinson's disease? Appl Neurophysiol 1983;46:68–83.
9. Laitinen LV, Bergenheim AT, Hariz MI. Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms. Stereotact Funct Neurosurg 1992;58:14–21.
10. Gill SS, Heywood P. Bilateral dorsolateral subthalamotomy for advanced Parkinson's disease. Lancet 1997;350:1224.
11. 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;50:344–346.
12. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol 2011;68:165.
13. Okun MS, Tagliati M, Pourfar M, et al. Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. Arch Neurol 2005;62:1250–1255.
14. Lang AE, Houeto JL, Krack P, et al. Deep brain stimulation: preoperative issues. Mov Disord 2006;21(Suppl. 14):S171-S196.
15. Welter ML, Houeto JL, Tezenas du Montcel S, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 2002;125:575–583.
16. Derost PP, Ouchchane L, Morand D, et al. Is DBS-STN appropriate to treat severe Parkinson disease in an elderly population? Neurology 2007;68:1345–1355.
17. Kleiner-Fisman G, Fisman DN, Sime E, Saint-Cyr JA, Lozano AM, Lang AE. Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. J Neurosurg 2003;99:489–495.
18. Okun MS, Foote KD. Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. Expert Rev Neurother 2010;10:1847–1857.
19. Charles PD, Van Blercom N, Krack P, et al. Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002;59:932–934.
20. Krack P, Pollak P, Limousin P, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 1998;121:451–457.
21. Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J. Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology 2002;58:396–401.
22. Morishita T, Rahman M, Foote KD, et al. DBS candidates that fall short on a levodopa challenge test: alternative and important indications. Neurologist 2011;17:263–268.
23. Landi A, Parolin M, Piolti R, et al. Deep brain stimulation for the treatment of Parkinson's disease: the experience of the Neurosurgical Department in Monza. Neurol Sci 2003;24(Suppl. 1):S43-S44.
24. Iansek R, Rosenfeld JV, Huxham FE. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Med J Aust 2002;177:142–146.
25. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–1934.
26. Herzog J, Volkmann J, Krack P, Kopper F, Potter M, Lorenz D, et al. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. Mov Disord 2003;18:1332–1337.
27. Daniele A, Albanese A, Contarino MF, et al. Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:175–182.

28. Rodriguez-Oroz MC, Gorospe A, Guridi J, et al. Bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neurology 2000;55(12 Suppl. 6):S45-S51.
29. Burkhard PR, Vingerhoets FJ, Berney A, Bogousslavsky J, Villemure JG, Ghika J. Suicide after successful deep brain stimulation for movement disorders. Neurology 2004;63:2170–2172.
30. Soulas T, Gurruchaga JM, Palfi S, Cesaro P, Nguyen JP, Fenelon G. Attempted and completed suicides after subthalamic nucleus stimulation for Parkinson's disease. J Neurol Neurosurg Psychiatry 2008;79:952–954.
31. Voon V, Krack P, Lang AE, Lozano AM, Dujardin K, Schupbach M, et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. Brain 2008;131:2720–2728.
32. Weintraub D, Duda JE, Carlson K, et al. Suicide ideation and behaviours after STN and GPi DBS surgery for Parkinson's disease: results from a randomised, controlled trial. J Neurol Neurosurg Psychiatry 2013;84:1113–1138.
33. Pillon B, Ardouin C, Damier P, et al. Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. Neurology 2000;55:411–8.
34. Alegret M, Junque C, Valldeoriola F, et al. Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. Arch Neurol 2001;58:1223–1227.
35. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:834–839.
36. Okun MS, Fernandez HH, Wu SS, 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;65:586–595.
37. Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol 2012;11:140–149.
38. Okun MS, Fernandez HH, Rodriguez RL, Foote KD. Identifying candidates for deep brain stimulation in Parkinson's disease: the role of the primary care physician. Geriatrics 2007;62:18–24.
39. Okun MS, Foote KD. A mnemonic for Parkinson disease patients considering DBS: a tool to improve perceived outcome of surgery. Neurologist 2004;10:290.
40. Deuschl G, Schupbach M, Knudsen K, et al. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLYSTIM-study. Parkinsonism Relat Disord 2013;19:56–61.
41. Okun MS, Fernandez HH, Pedraza O, et al. Development and initial validation of a screening tool for Parkinson disease surgical candidates. Neurology 2004;63:161–163.
42. Moro E, Allert N, Eleopra R, et al. A decision tool to support appropriate referral for deep brain stimulation in Parkinson's disease. J Neurol 2009;256:83–88.
43. Machado A, Rezai AR, Kopell BH, Gross RE, Sharan AD, Benabid AL. Deep brain stimulation for Parkinson's disease: surgical technique and perioperative management. Mov Disord 2006;21(Suppl. 14):S247-S258.
44. Maciunas RJ, Galloway RL, Jr, Latimer JW. The application accuracy of stereotactic frames. Neurosurgery 1994;35:682–694.
45. Benabid AL, Koudsie A, Benazzouz A, et al. Subthalamic stimulation for Parkinson's disease. Arch Med Res 2000;31:282–289.
46. Cuny E, Guehl D, Burbaud P, Gross C, Dousset V, Rougier A. Lack of agreement between direct magnetic resonance imaging and statistical determination of a subthalamic target: the role of electrophysiological guidance. J Neurosurg 2002;97:591–597.
47. Schuurman PR, de Bie RM, Majoie CB, Speelman JD, Bosch DA. A prospective comparison between three-dimensional magnetic resonance imaging and ventriculography for target-coordinate determination in frame-based functional stereotactic neurosurgery. J Neurosurg 1999;91:911–914.
48. Duffner F, Schiffbauer H, Breit S, Friese S, Freudenstein D. Relevance of image fusion for target point determination in functional neurosurgery. Acta Neurochir (Wien) 2002;144:445–451.
49. Rezai AR, Kopell BH, Gross RE, Vitek JL, Sharan AD, Limousin P, et al. Deep brain stimulation for Parkinson's disease: surgical issues. Mov Disord 2006;21(Suppl. 14):S197-S218.
50. Binder DK, Rau GM, Starr PA. Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. Neurosurgery 2005;56:722–732.
51. 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;345:956–963.
52. Hariz MI. Safety and risk of microelectrode recording in surgery for movement disorders. Stereotact Funct Neurosurg 2002;78:146–157.
53. Bjartmarz H, Rehncrona S. Comparison of accuracy and precision between frame-based and frameless stereotactic navigation for deep brain stimulation electrode implantation. Stereotact Funct Neurosurg 2007;85:235–242.
54. Holloway KL, Gaede SE, Starr PA, Rosenow JM, Ramakrishnan V, Henderson JM. Frameless stereotaxy using bone fiducial markers for deep brain stimulation. J Neurosurg 2005;103:404–413.
55. Tai CH, Wu RM, Lin CH, Pan MK, Chen YF, Liu HM, et al. Deep brain stimulation therapy for Parkinson's disease using frameless stereotaxy: comparison with frame-based surgery. Eur J Neurol 2010;17:1377–1385.
56. Patel NK, Plaha P, Gill SS. Magnetic resonance imaging-directed method for functional neurosurgery using implantable guide tubes. Neurosurgery 2007;61(5 Suppl. 2):358–365.
57. Foltynie T, Zrinzo L, Martinez-Torres I, et al. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. J Neurol Neurosurg Psychiatry 2011;82:358–363.
58. Kumar R. Methods for programming and patient management with deep brain stimulation of the globus pallidus for the treatment of advanced Parkinson's disease and dystonia. Mov Disord 2002;17(Suppl. 3):S198-S207.
59. Volkmann J, Moro E, Pahwa R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. Mov Disord 2006;21(Suppl. 14):S284-S289.
60. Follett K, Weaver F, Stern M, et al. Multisite randomized trial of deep brain stimulation. Arch Neurol 2005;62:1643–1644.
61. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896–908.
62. Williams A, Gill S, Varma T, 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;9:581–591.
63. Ghika J, Villemure JG, Fankhauser H, Favre J, Assal G, Ghika-Schmid F. Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow-up review. J Neurosurg 1998;89:713–718.
64. Volkmann J, Allert N, Voges J, Sturm V, Schnitzler A, Freund HJ. Long-term results of bilateral pallidal stimulation in Parkinson's disease. Ann Neurol 2004;55:871–875.
65. Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. Neurology 2012;79:55–65.
66. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 2009;301:63–73.

67. Odekerken VJ, van Laar T, Staal MJ, 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.
68. Okun MS, Foote KD. Subthalamic nucleus vs globus pallidus interna deep brain stimulation, the rematch: will pallidal deep brain stimulation make a triumphant return? Arch Neurol 2005;62:533–536.
69. Alberts JL, Hass CJ, Vitek JL, Okun MS. Are two leads always better than one: an emerging case for unilateral subthalamic deep brain stimulation in Parkinson's disease. Exp Neurol 2008;214:1–5.
70. Walker HC, Watts RL, Guthrie S, Wang D, Guthrie BL. Bilateral effects of unilateral subthalamic deep brain stimulation on Parkinson's disease at 1 year. Neurosurgery 2009;65:302–309.
71. Taba HA, Wu SS, Foote KD, Hass CJ, Fernandez HH, Malaty IA, et al. A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. J Neurosurg 2010;113:1224–1229.
72. Zahodne LB, Okun MS, Foote KD, et al. Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. J Neurol 2009;256:1321–1329.
73. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610–622.
74. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med 2010;362:2077–2091.
75. Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. Arch Neurol 2005;62:554–560.
76. Chan DT, Zhu XL, Yeung JH, et al. Complications of deep brain stimulation: a collective review. Asian J Surg 2009;32:258–263.
77. Boviatsis EJ, Stavrinou LC, Themistocleous M, Kouyialis AT, Sakas DE. Surgical and hardware complications of deep brain stimulation. A seven-year experience and review of the literature. Acta Neurochir (Wien) 2010;152:2053–2062.
78. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990;249:1436–1438.
79. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8:67–81.
80. Kumar R, Lozano AM, Sime E, Lang AE. Long-term follow-up of thalamic deep brain stimulation for essential and parkinsonian tremor. Neurology 2003;61:1601–1604.
81. Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 1999;66:289–296.
82. Lyons KE, Koller WC, Wilkinson SB, Pahwa R. Long term safety and efficacy of unilateral deep brain stimulation of the thalamus for parkinsonian tremor. J Neurol Neurosurg Psychiatry 2001;71:682–684.
83. Plaha P, Khan S, Gill SS. Bilateral stimulation of the caudal zona incerta nucleus for tremor control. J Neurol Neurosurg Psychiatry 2008;79:504–513.
84. Xie T, Bernard J, Warnke P. Post subthalamic area deep brain stimulation for tremors: a mini-review. Transl Neurodegener 2012;1:20.
85. Plaha P, Ben-Shlomo Y, Patel NK, Gill SS. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. Brain 2006;129:1732–1747.
86. Goff LK, Jouve L, Melon C, Salin P. Rationale for targeting the thalamic centre-median parafascicular complex in the surgical treatment of Parkinson's disease. Parkinsonism Relat Disord 2009;15(Suppl. 3):S167-S170.
87. Stefani A, Peppe A, Pierantozzi M, et al. Multi-target strategy for Parkinsonian patients: the role of deep brain stimulation in the centromedian-parafascicularis complex. Brain Res Bull 2009;78:113–118.
88. Mazzone P, Lozano A, Stanzione P, et al. Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. Neuroreport 2005;16:1877–1881.
89. Stefani A, Lozano AM, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130:1596–1607.
90. Khan S, Javed S, Mooney L, et al. Clinical outcomes from bilateral versus unilateral stimulation of the pedunculopontine nucleus with and without concomitant caudal zona incerta region stimulation in Parkinson's disease. Br J Neurosurg 2012;26:722–725.
91. Moreau C, Defebvre L, Devos D, et al. STN versus PPN-DBS for alleviating freezing of gait: toward a frequency modulation approach? Mov Disord 2009;24:2164–2166.
92. Fasano A, Herzog J, Seifert E, et al. Modulation of gait coordination by subthalamic stimulation improves freezing of gait. Mov Disord 2011;26:844–851.
93. Moro E, Hamani C, Poon YY, et al. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. Brain 2010;133:215–224.
94. Ferraye MU, Debu B, Fraix V, et al. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 2010;133:205–214.
95. Thevathasan W, Coyne TJ, Hyam JA, et al. Pedunculopontine nucleus stimulation improves gait freezing in Parkinson disease. Neurosurgery 2011;69:1248–1253.
96. Khan S, Mooney L, Plaha P, et al. Outcomes from stimulation of the caudal zona incerta and pedunculopontine nucleus in patients with Parkinson's disease. Br J Neurosurg 2011;25:273–280.
97. Mazzone P, Insola A, Lozano A, et al. Peripeduncular and pedunculopontine nuclei: a dispute on a clinically relevant target. Neuroreport 2007;18:1407–1408.
98. Yelnik J. PPN or PPD, what is the target for deep brain stimulation in Parkinson's disease? Brain 2007;130:e79.
99. Tagliati M. Turning tables: should GPi become the preferred DBS target for Parkinson disease? Neurology 2012;79:19–20.