Deep Brain Stimulation for Parkinson's Disease

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Abstract

Deep brain stimulation (DBS) is an established treatment for advanced Parkinson's disease (PD). The two most used targets for PD are the subthalamic nucleus and the internal globus pallidus. DBS is especially efficacious for the treatment of otherwise refractory tremor, medication-related motor response fluctuations, and dyskinesia. In general, the best motor response of DBS is as good as that of dopaminergic medication but more constant. The three cardinal pillars for successful DBS treatment comprise optimal patient selection, accurate DBS lead placement, and thorough postoperative care, which includes programming and medication adjustments.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease. Its core feature is bradykinesia, in combination with rest tremor, rigidity, or both (Kalia and Lang 2015). Most patients also have non-motor manifestations, such as sleep dysfunction, autonomic dysfunction (e.g., constipation, daytime urinary urgency, and orthostatic hypotension), hyposmia, cognitive decline, and psychiatric disorders, such as depression, anxiety, and psychosis (Schapira et al. 2017). Although motor symptoms are a prerequisite to diagnose PD, non-motor features may dominate the clinical picture. The disorder mostly begins in later life with an average disease onset of 60 years of age. The prevalence of PD is 425 per 100,000 in the population between 65 and 75 years of age and increases with older ages (Pringsheim et al. 2014).

Pathophysiology

The etiology of PD is still unknown. Characteristic neuropathological findings in PD are neuronal loss, depigmentation of the substantia nigra, and the presence of Lewy bodies (Fahn 2018). Although the function of the protein alpha-synuclein is not known, its pivotal role in the pathophysiology of PD seems irrefutable as

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alpha-synuclein aggregates are abundant in Lewy bodies, and genetic profiles that are related to impaired forming of alpha-synuclein or its degradation are risk factors for PD (Spillantini et al. 1997; Singleton 2003; Fahn 2018). The classic symptoms of PD are caused by dysfunction of the dopaminergic neurotransmission in the nigostriatal system due to degeneration of dopamine producing neurons. The substantia nigra and the striatum (caudate nucleus, putamen, and nucleus accumbens), together with the claustrum, globus pallidus, and subthalamic nucleus, form the basal ganglia. They were usually regarded as components of several largely segregated circuits serving motor, oculomotor, limbic, and cognitive functions (Afifi 1994). It is now apparent that the basal ganglia system is a complex and widely distributed neuronal network comprising a markedly branched axon collateral network system by which the output nuclei of the basal ganglia can be influenced in multiple ways (Graybiel 2008; Redgrave et al. 2010; Nelson and Kreitzer 2014) (see also Chap. 2 for Anatomy). In addition to impaired basal ganglia functioning, PD pathology gradually spreads throughout the brain, *grosso modo* from the brainstem through the temporal mesocortex and allocortex to the sensory association areas of the neocortex and premotor areas. This process has an important role in "non-dopaminergic" symptoms such as autonomic dysfunction, psychiatric disorders, and cognitive decline (Braak et al. 2003; Alves et al. 2005; Hawkes et al. 2009; Lieberman and Krishnamurthi 2013; Rietdijk et al. 2017).

Conservative Treatment

There is still no cure for PD. Symptomatic treatment predominantly consists of adding-on the dopamine deficiency with levodopa plus a peripheral decarboxylase inhibitor or—and often in combination with—a dopamine agonist. These medications can bring about an important improvement of bradykinesia and rigidity, but tremor may not always respond sufficiently.

After 4–6 years of disease progression, patients may experience variations in symptoms during the day (Calabresi et al. 2010; Aquino and Fox 2015). Initially, these fluctuations tend to occur in a clear temporal relationship to levodopa intake, and the impact of the variation in symptoms can be reduced with medication adjustments. With progressing disease however, other adverse effects may emerge, such as medication-related involuntary movements (i.e., dyskinesias) or psychiatric complications, such as hallucinations and paranoid delusions. The phenomenon of episodes with good levodopa effect—which may be accompanied by involuntary movements—alternating with episodes of re-emerging parkinsonism is called response fluctuations. The condition in which the antiparkinson effect of the medication is noticeable (i.e., the patient is mobile) is named "on-phase" and the situation during which the Parkinson symptoms have recurred (i.e., less or no beneficial effect of medication) is named "off-phase." The transition of on-phase to off-phase may take some time (e.g., 15 min or longer) and is termed "wearing-off" phase. With advancing disease, the response fluctuations may become abrupt oscillations in motor state and with a more complex medication schedule the temporal relationship with levodopa dosing may be lost.

There are several pharmacological options to address motor response fluctuations. The basic idea is to stabilize continuous dopaminergic stimulation. Most of these strategies have never been compared with each other in a randomized head-to-head trial, and consequently, there are insufficient data to guide the choices from the possible treatment options (Fox et al. 2018). The order of the strategies mentioned below is arbitrary and the list is not complete. One option is to adjust the number of times levodopa is taken during the day, for example, from three times per day to five times per day. Another option is to start or increase a dopamine agonist (e.g., ropinirol, pramipexol, or rotigotine), especially in long-acting formulations, and add to, or convert, some of the levodopa daily dose to a dopamine agonist in an equivalent dose (Fox et al. 2018). Dopamine agonists are more likely to cause side effects such as nausea, hallucinations, psychosis, impulse control disorders, and excessive daytime sleepi-

ness (Stowe et al. 2008). Other options are to add an inhibitor of an enzyme that catalyzes the breaking down of dopamine into inactive metabolites and by this means increase the duration of effect of each levodopa dose. This can be done with catechol-O-methyltransferase inhibitors (COMT inhibitors such as entacapone or opicapone) (Müller 2015) and monoamine-oxidase-B inhibitors (MAOB inhibitors such as selegiline or rasagiline) (Schapira 2011). If dyskinesias increase following the addition of a COMT or MAOB inhibitor, it may be required to lower the levodopa dose. For bothering dyskinesias, amantadine can be tried (Pereira da Silva-Júnior et al. 2005).

In addition to the more complex situation regarding motor symptoms evolving over time, patients gradually develop non-motor symptoms, and these may also have a large impact on disability and the feeling of well-being (Bhidayasiri and Wolters 2008). The time of onset and the range of non-motor symptoms are very heterogeneous.

Advanced Treatments

DBS has been proven to be an effective treatment for advanced PD since its introduction in the 1990s (Limousin et al. 1995). Several randomized controlled trials (RCTs) have confirmed that DBS is more effective than best medical treatment for symptom reduction and disease-related quality of life (Spottke et al. 2002; Deuschl et al. 2006; Schuepbach et al. 2013; Becerra et al. 2016). For DBS treatment of PD motor symptoms, the main targets are subthalamic nucleus (STN) and globus pallidus internus (GPi). In patients with PD, STN activity is characterized by an increased firing rate with bursting activity and augmented synchrony when parkinsonism is present (Albin et al. 1989; Hassani et al. 1996). In the STN, cells may exhibit signals that are related synchronously to the clinical tremor, and these cells are called tremor cells (Levy et al. 2000, 2002). Movements elicited by patients as well as high frequency stimulation of STN decrease not only tremor but also tremor-related cell activity. The activity pattern of about 50% of STN neurons changes in concordance with active or passive movements, and most of these movement-related neurons reside in the dorsolateral and dorsal part of the STN, which appears to be the most effective target for DBS within the STN (Williams et al. 2005; Coenen et al. 2008). Similarly, posterior and ventral GPi activities are also augmented when the patient displays parkinsonism (Williams et al. 2005)

Patients with disabling medication-related motor response fluctuations may also benefit from continuous intrajejunal levodopa infusion (CLI) and continuous subcutaneous apomorphine infusion (CAI) (Espay 2010; Worth 2013; Antonini et al. 2018). No randomized head-to-head comparison of the three treatments (i.e., DBS, CLI, and CAI) has been performed and individual studies have used several different outcome measures, experimental designs, and follow-up durations, which makes mutual comparisons difficult. Little is known about comparative adverse effect profiles of the therapies. Currently, the choice for one of the three treatments is based on a mix of the following: device characteristics (e.g., brain surgery versus wearing a pump), assumptions regarding efficacy for particular symptoms, adverse effect profiles, availability of the treatments, patient preference, and physician experience (Table 12.1) (Antonini et al. 2018). There exists considerable practice variation between and within countries (Antonini et al. 2018).

A small proportion of PD patients has the tremor-dominant form of the disease, meaning that their initial rest and/or postural tremor is very bothersome, and accompanied by only mild bradykinesia and rigidity (Rajput et al. 2009; Thenganatt and Jankovic 2014). For this group of patients, the perspectives regarding disease progression and impact on daily life are less grave, mainly because bradykinesia, gait, and postural instability have more impact on functioning in daily life, and these features are by definition less prominent in tremor-dominant PD (Thenganatt and Jankovic 2014). Tremor is less likely to improve with dopamine replacement therapy—though a considerable number of patients do respond, albeit with a higher dose (Sethi 2008).

Table 12.1 Treatment characteristics of three advanced therapies for medication-related motor response fluctuations in Parkinson's disease

	Deep brain stimulation (DBS)	Continuous subcutaneous apomorphine infusion	Continuous levodopa/carbidopa gel infusion (CLI)
	Administration of electrical pulses into a target area of the brain	Administration of medication through a subcutaneously placed needle	Administration of medication to the duodenum through a PEG tube
Mono- or combination therapy	DBS is combined with oral medication	Apomorphine is combined with oral medication	CLI can be used as monotherapy
Possible side effects and risks	Brain hemorrhage	Painful nodules under the skin on the injection sites	Obstruction of the tube
	Infections due to surgery	Nausea	Nausea
	Delirium	Perspiration	Inflammation around the PEG tube entry site
	Cognitive problems	Low blood pressure	Leakage around the opening in the abdominal wall
	Behavioral changes	Heart failure	Displacement of the tube
	Speech problems	Dopamine dysregulation syndrome and impulse control disorders	Constipation
	Technical problems or empty battery leading to re-operation		Orthostatic hypotension
	Balance and gait problems		
Possible disadvantages	Risks inherent to a neurosurgical procedure	The patient must carry the pump during the day	The patient must carry the pump during the day
	No possibility for test treatment	Every day, placing the subcutaneous needle and connecting the pump, clean the pump, care for the skin at the insertion site	Every day, connecting and disconnecting the pump, cleaning the tube, and care for the skin at the insertion site
	Some systems are not MRI-compatible	There is a considerable chance of getting painful nodules under the skin at the injection site	An operation is needed for the placement of the tube
	Can be problematic for passing of a metal detector	Possible problems/malfunctions of the pump	Possible problems/malfunctions of the pump
	Battery needs to be replaced every 5–9 years	Oftentimes another treatment is needed after a number of years	
Possible advantages	In comparison with continuous subcutaneous apomorphine infusion and CLI, there are no daily limitations, not to have carrying an external pump	No surgery is required	Many patients are eligible
		Many patients are eligible	Possibility of testing treatment
		Possibility of testing the treatment	

DBS deep brain stimulation, *CLI* continuous levodopa/carbidopa infusion, *PEG* percutaneous endoscopic gastrostomy, *MRI* magnetic resonance imaging

In these cases, additional medical treatments such as anticholinergics (though preferably not above the age of 60 years) and propranolol may be tried (Marjama-Lyons and Koller 2000). If the tremor is disabling despite medical treatment, surgery of the ventral intermediate nucleus (VIM) of the thalamus is an option besides GPi and STN DBS (Marjama-Lyons and Koller 2000; Reinacher et al. 2018). Considering that most patients with tremor-dominant PD will eventually also develop worsening bradykinesia, most DBS teams prefer STN DBS for these patients providing that this is not contraindicated (such as in the case of cognitive impairment).

Selection for Surgery

When considering DBS for PD, it is important that a multidisciplinary team properly screens the candidate. The team will assess the characteristics such as symptom severity, fluctuation of symptoms, presence of dyskinesias, and possible medication side effects (Rodriguez et al. 2007). In addition to determining whether the patient is a good candidate for DBS, the team also has to manage the possible unrealistically high expectations the patient or their family might have.

Preoperative Screening for DBS

To evaluate the indication for DBS, the extent of symptoms in "on-drug" phase and "off-drug" phase, the medication side effects, and cognitive and psychiatric symptoms are assessed. Most of the DBS teams assess the severity of symptoms with the patient in standardized off-drug and "on-drug phases" using the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) and a dyskinesias rating scale (Goetz et al. 2008). In general, off-drug phase symptom severity is assessed in early morning following an overnight withdrawal of dopaminergic medication, and the on-drug phase symptoms 1 h after the first medication in the morning. To ascertain that the patient actually reaches an on-phase, the patient may take levodopa in a rapid formulation, for example, dispersible levodopa/benzeraside 100/25 mg, after fasting in the morning and in a slightly higher dose than the usual first morning dose (e.g., 120–150% of the levodopa equivalent first morning dose). The off-drug and on-drug phase assessments are the cornerstone of the screening for PD DBS indications, because symptoms that respond well to levodopa are very likely to respond well to DBS (Rodriguez et al. 2007). There is considerable practice variation with respect to cut-off values for "off-on" improvement. Mostly the strived-for values range from 30 to 50% (Welter et al. 2002; Morishita et al. 2011; Schuepbach et al. 2013).

An MRI of the brain (to assess for example vasculature, brain atrophy, and unexpected structural lesions such as a meningioma), laboratory investigations, electrocardiogram, and evaluation by an anesthesiologist may be performed to assess the safety and feasibility of DBS surgery. Additionally, in many DBS centers formal neuropsychological screening is performed in the work-up before possible surgery, because cognitive impairment may be associated with additional cognitive worsening following DBS surgery (Rodriguez et al. 2007; Foley et al. 2018). Current psychiatric disorders such as depression or psychosis, as well as cognitive impairment, can complicate surgery as well as programming. Also, in the presence of these comorbidities, it can be difficult to determine which symptom is most limiting for the patient's functioning in daily life. Some psychiatric conditions could pose problems for awake surgery, such as active psychosis and posttraumatic stress disorder. In specific cases, evaluation by a psychiatrist prior to DBS is advisable.

It is important to evaluate the individual patient's and families' expectations regarding the benefits of DBS and possible side effects before deciding to perform surgery, since over 30% of the non-successful surgeries are due to incorrect patient selection (Okun et al. 2005). Expectations may sometimes be unrealistic, for example, in the patient who requests DBS but has not yet accepted the fact that he or she suffers from PD with the accompanying impairments and anticipates all will be normal following DBS.

It is also important to inform the patient and family beforehand about the procedures of surgery, the anticipated beneficial effects of DBS, symptoms that may not improve, potential side effects, the trajectory after surgery, including micro-lesioning effects associated with electrode placement, monopolar review (or "mapping session"), and the time for programming with gradual increase of stimulation parameters and necessary adjustments of the medication schedule (see also Chap. 8: Programming). When the optimal setting of stimulation parameters is reached, there is no need for adjustments on a regular basis, which may be confusing for patients because this contrasts with the situation before surgery when medication schedules were frequently adjusted.

A movement disorder DBS team usually consists of a neurologist specialized in movement disorders, a DBS neurosurgeon, a psychiatrist, neuropsychologist, and a nurse specialized in PD and DBS. We discuss indications and contraindications for DBS in PD below.

Medication-Related Motor Response Fluctuations

The most important indications for treatment with DBS of PD are disability and bothersome symptoms, such as dystonia and pain, due to medication-related motor response fluctuations, and disabling medication resistant tremor (Duker and Espay 2013). The indications and contraindications for DBS are summarized in Table 12.2. Because the potential maximal effect of DBS is more or less equal to the maximal effect of the dopaminergic medication, the level of disability after surgery is in general unlikely to be better than the level of disability during the best on-drug phase before surgery (Williams et al. 2010). This rule of thumb does not apply to medication-resistant tremors where functional neurosurgical interventions (such as DBS and lesioning) can be very efficacious. Tremor will be discussed in the next paragraph. Contrary to oral dopaminergic medical treatment, especially levodopa, DBS exerts its effect stable and continuously throughout the day and night, and fluctuations are reduced. In clinical practice this means that during the "off-phase" parkinsonian symptoms improve and in the "on-phase" patients may experience little to no improvement—although "on-phase" dyskinesia may be reduced with DBS (Williams et al. 2010).

Thus, in patients with a big difference in disability between off-drug and on-drug phases (i.e., a large levodopa response), DBS may have a large beneficial effect, while for patients with mild symptoms during off-drug phases (and without disability during off-drug phases), DBS may not bring much, which also accounts for patients who are severely disabled during their best on-drug phases. In addition, a small portion of patients fail to show a full therapeutic response to dopaminergic medication due to dopaminergic absorption problems but do improve when DBS is applied (Zaidel et al. 2010).

Table 12.2 Indications and contraindications for DBS treatment of Parkinson's disease

Indications
– Medication-related motor response fluctuations and disability due to bradykinesia, pain, dystonia, and/or dyskinesias
– Disabling tremor despite medical therapy
Contraindications
– Severe disability in on-drug phase (e.g., due to postural instability)
– Severe cognitive problems (e.g., a Mattis Dementia Rating Scale score below 120) (Matteau et al. 2011)
– Current psychosis or depression
– Contraindications for a neurosurgical procedure, like anticoagulant use that cannot be interrupted, severe hypertension, and dysphagia

Tremor

Tremor is an indication for DBS. This is also true for the subcategory of patients who suffer from disabling tremors despite maximum doses of medication, since the symptom may improve more with DBS than with dopaminergic medication (Morishita et al. 2011). This is because the effect of DBS on tremor is not correlated to the effect of dopaminergic (and other) medication on tremor (Zaidel et al. 2010).

Dyskinesia

Dyskinesia can directly be reduced by DBS (Krack et al. 1998; Wu et al. 2001). This is valid for both peak-dose and biphasic dyskinesia.

Behavioral Disorders

For years, PD-associated behavioral disorders such as anxiety, impulse control disorders, and addiction to dopaminergic medication have been considered by many to be a contraindication for DBS treatment. Importantly, disabling neuropsy-

chiatric symptoms may also fluctuate analogic to motor symptoms. Several publications reported on behavioral disorders that worsened or began following DBS (Lim et al. 2009); the mechanism being a direct stimulation effect (Sensi et al. 2004; Smeding et al. 2006) or a consequence of medication adjustments after DBS treatments (Smeding et al. 2006). Hyperdopaminergic phenomena, such as impulse control disorders, punding, and addiction to dopaminergic treatment, have been reported to improve, remain unchanged, or start following DBS but are not considered a contraindication per se (Lhommée et al. 2018).

What Will Not or Only Slightly Improve with DBS?

Patients whose main problem are symptoms that respond poorly to DBS, such as gait problems, autonomic dysfunction, or dysarthria, constitute a group of patients in which DBS should not be considered for these symptoms alone because the expected health-related functional improvement is small.

Appropriate Age for DBS

There is no absolute age limit for DBS surgery, but higher age is associated with more comorbidity and cognitive dysfunction, which increases the risks of DBS. PD patients with a higher age tend to have a less profound levodopa response (difference in motor function between off-drug and on-drug states) and therefore may have less benefit from DBS treatment (Weaver et al. 2009). Nevertheless, patients older than 70 years with a clear levodopa response and an indication for DBS treatment that are otherwise healthy may be good candidates for surgery.

Appropriate Timing of DBS Relative to Disease Progression

In the early days of DBS, patients were operated relatively late in their disease; i.e., at the time when all other treatment options had failed. Gradually, patients were operated on earlier. For this change in policy the EARLYSTIM trial has been pivotal. In this trial, patients could be recruited with at least a 4 years disease duration and motor response fluctuations, for which only one or two drugs had been tried. The mean disease duration in the trial is 7.5 years. After 2 years follow-up, patients on STN DBS had a significant better outcome on health related quality of life—measured with the PD Questionnaire (PDQ-39) (Jenkinson et al. 1995)—than patients with best medical treatment alone (Deuschl et al. 2013). Nowadays DBS is not considered to be a last resort treatment but can be used earlier for treatment of motor response fluctuations.

Target Selection

Multiple factors can influence the target selection for DBS in PD patients. The difference in effect between GPi and STN DBS found in different clinical trials will be discussed later in this chapter, but some considerations on DBS target selection in PD patients merit discussion here.

The Subthalamic Nucleus

DBS of the STN more or less imitates the effect of dopaminergic medication and has a beneficial effect on bradykinesia, tremor, rigidity, and pain (Limousin et al. 1998). If at least one of these symptoms causes disability, STN DBS may be considered. The STN is also a suitable target for drug-resistant tremor in PD, after all progression of the disease is anticipated and other symptoms, such as bradykinesia, may become the main determinant of disability in the future (Pfeiffer 2016).

STN DBS may increase dyskinesia and may even induce dyskinesia during "off-phases" (Zheng et al. 2010). In general, this is considered a positive phenomenon because it confirms that the active DBS contact is positioned in the motor part of the STN. Because the daily dopaminergic medication can be reduced with 30–50%

following STN DBS (Deuschl et al. 2006; Weaver et al. 2012; Odekerken et al. 2013), medication-related involuntary movements may gradually diminish or disappear. The reduction of dopaminergic medication after STN surgery may unmask hypodopaminergic symptoms such as apathy, depression, and anxiety. Previous to the broad awareness of the dopamine agonist withdrawal syndrome (DAWS) (Patel et al. 2017), dopamine agonists were reduced considerably and stopped in a short time after surgery by some teams, which may have elicited DAWS. Importantly however, the results of a recent RCT indicated that medication-induced disabling hyperdopaminergic states and neuropsychiatric fluctuations should be considered as reasons favoring STN DBS in patients who are candidates for STN surgery because of their motor symptoms (Lhommée et al. 2018). Postoperative behavioral problems do not seem to differ much between STN and GPi DBS (Weaver et al. 2012; Odekerken et al. 2013).

The Internal Globus Pallidus

As is the case with the STN, the GPi is also a suitable target for drug-resistant tremor in PD, because disease progression is to be expected and other symptoms may become the main determinant of disability in the future (Pfeiffer 2016). When stimulating the GPi, higher current amplitudes are needed compared to STN DBS, which can lead to faster battery depletion. Also, GPi DBS will allow for a less pronounced reduction of dopaminergic medication compared to STN DBS (Odekerken et al. 2013). In case of disabling dyskinesias, DBS of the GPI can directly reduce contralateral dyskinesia (Krack et al. 1998; Wu et al. 2001).

The Ventral Intermediate (VIM) Nucleus of the Thalamus

For tremor-dominant PD and in case STN DBS and GPI DBS are not an option, for example, in case the patient is elderly and has cognitive impairments, VIM surgery may be considered. VIM thalamotomy by means of radio frequency thermolesions or MRI-guided focused ultrasound surgery can only be used unilaterally because of the risk of side effects accompanying bilateral thalamotomies (Alomar et al. 2017). VIM DBS can be done bilaterally and contralateral to a thalamotomy (Lozano 2000; Schuurman et al. 2000).

Surgical Approach

DBS in PD mainly involves the STN and GPi, and in selected cases the VIM. The pedunculopontine nucleus (PPN) is a target in research setting only. Arguments for selecting a specific target are given in the previous section. Given that the correct placement of DBS leads is one of the most important predictors of good outcome, it is crucial that the DBS leads are on the right location (Welter et al. 2014). The implantation of the DBS leads involves a stereotactic procedure after which the implanted leads are subcutaneously "tunneled" to an internal pulse generator that in most patients is placed below the clavicle. The process of lead implantation and post-implantation verification has been extensively described in Chap. 4 (Technical aspects). In the following section, the detailed anatomy of the targets, the relation between intraoperative findings and clinical outcome, and the main controversies are discussed.

Subthalamic Nucleus Targeting

The subthalamic nucleus is a subcortical structure with anatomical dimensions of approximately 9 (length) $*$ 10 (width) $*$ 3 (height) mm (Patil et al. 2012). The STN is oriented diagonally in the coronal, sagittal, and axial plane, which makes the estimation of its dimensions dependent on the angle of view. Furthermore, the dimension between the STN on 1.5 Tesla MRI findings and postmortem cadavers differ (Mavridis et al. 2013). At field strengths of 3 Tesla, the literature provides mixed reports regarding the differences between the functional and anatomical delineation of the STN. Some

studies indicate great concordance (Patil et al. 2012), whereas others show differences (Verhagen et al. 2016). Given these discrepancies, neurophysiological microelectrode recordings (MER) can be of added value for the correct delineation of the STN, especially when only MR images with lower field strengths or CT images are available. This is of importance given that there is an iatrogenic risk, especially for intracranial hemorrhage, related to performing multiple track MER recordings (Binder et al. 2005)

Although the STN is nowadays most often visually ("directly") targeted, typical coordinates in stereotactic space with reference to the mid commissural point are: $x = 12$ mm, $y = 2$ mm posterior, and $z = 4$ mm inferior (Andrade-Souza et al. 2005; Rabie et al. 2016) Given the heterogeneity between patients, direct targeting based on MR images can be more accurate. However, despite the developments of MR sequences and the increasing MR field strengths, the STN itself is still difficult to visualize on MR. One way to circumvent this is to use the red nucleus (RN) as a proxy for direct targeting. The RN is a more visible hypo-intense structure on T2-weighted imaging and is located posteromedially from the STN. When using the RN as fiducial marker for the STN, comparable results relative to direct and indirect targeting of the STN are reported (Andrade-Souza et al. 2005).

Beyond the targeting of the STN is the targeting within the STN. Although there is no strict functional partition within the STN, the afferent and efferent fibers have a functional segregation in which a motor, associative, and limbic part can be discerned which are located in the dorsolateral, central, and ventromedial STN, respectively (Haynes and Haber 2013). Targeting the dorsolateral STN yields the best motor outcome, whereas electrodes in the other partitions, especially the limbic part of the STN, can lead to side effects (Welter et al. 2014). Besides the direct targeting of the dorsolateral part of STN based on MR images, MER recordings can be guiding (Gross et al. 2006). With MER, single neurons of the STN and surrounding tissue can be detected. A typical MER recording starts approximately 6 mm above the intended target after which the MER electrode is moved to, and beyond, the target in steps of 0.5–1 mm. This trajectory most often starts with thalamic recordings where little neural activity can be detected, after this, the zona incerta is reached, and single spikes occur. Subsequently, a marked increase in neural activity is detected, which represents the dorsal border of the STN. This activity continues throughout the STN and fades away when the lower border of the STN is reached (Gross et al. 2006). Below the STN, the substantia nigra (SN) pars reticulata is located, that can show similar neural activity; however, between the STN and SN, a significant drop in neural activity is most often observed.

The STN is surrounded by the internal capsule on the (antero)lateral side, the thalamus, and the zona incerta on its superior border and the fibers of the third cranial nerve on its medial side. The surrounding of these structures makes that minor lead displacements lead to disequilibrium between effects and side effects. One approach to circumvent this is by intraoperative testing of efficacy thresholds and side effect thresholds, so-called macrostimulation. Typical side effects that can occur are oculomotor dysfunction, dysarthria and tonic contractions due to positioning too medial or lateral, respectively. For this reason, intraoperative testing of both symptom suppression and side effects with different voltages at different stages of the DBS trajectory can be helpful. Typical intraoperative testing occurs in the off-drug state and involves the assessment of cardinal contralateral motor signs, oculomotor function, speech, and involuntary movements. However, despite extensive peri-operative testing, ultimate therapeutic and side effect profile are only predicted for a small fraction by intraoperative test stimulation (Blume et al. 2017). For this reason, intraoperative testing should especially be used to test for very low side effect thresholds and a crude estimation of effect. In general the temporal window for intraoperative testing is short, mainly due to patient fatigue. This makes it challenging to assess multiple electrode locations. Furthermore, it is important to realize that peri-operative stimulation washout effects are patient specific and are shorter with increased disease duration (Cooper et al. 2013).

Targeting of the Internal Part of the Globus Pallidus

The internal part of the globus pallidus (GPi) is part of the lentiform nucleus, which also consists of the external part of the globus pallidus (GPe) and the putamen. It should be noted that the lentiform nucleus is more an anatomical term than that it relates to a functional structure. The GPi is located medially from the GPe. As for the STN, direct and indirect approaches can be applied for the targeting of the GPi. Typical coordinates for the GPi are x = 20–22 mm, y = 2 mm posterior and z = 1–2 mm inferior, all relative to the midcommisural point (Schaltenbrand and Wahren 1977). Early experimental work has found that only modulation of the sensorimotor (posteroventral and lateral) part of the GPi leads to the reduction of contralateral parkinsonian symptoms (Taha et al. 1996).

Compared to the STN, the GPi is more visible on MRI, and T1-weighted sequences, instead of T2 weighted, are usually applied including more advanced T1-weighted sequences (Nowacki et al. 2015). However, as with the STN, MER recordings can deviate from imaging findings (Baker et al. 2010). The typical signal of an MER trajectory targeted at the GPi shows an absence of neural activity in the putamen, followed by sporadic spiking activity at the border of the putamen and GPe, bursting activity in the GPe, continuous spiking activity in the GPi, and again more sporadic spiking activity below the GPi (Vitek et al. 2009). The findings obtained from MER may guide, in combination with preoperative imaging, which part of the GPi should be explored for clinical testing with macro-stimulation.

The GPi is surrounded by the internal capsule (pallidocapsular border) and optic tract on its medial and ventral side. Given this anatomical delineation, the following aspects can be considered during intraoperative clinical testing: speech volume and articulation, tonic contractions of the face or contralateral extremities, and the occurrence of visual phenomena.

Targeting of the Ventro-Intermediate Nucleus of the Thalamus

Unlike the GPi or the STN, the VIM is generally not directly targeted. This has to do with its poor visibility on MRI, although newer MR sequences might resolve this issue (Vassal et al. 2012). The indirect targeting of the VIM is achieved by visualization of neighboring structures like the internal capsule or third ventricle and by using distances relative to thalamus height and the midcommisural point. In contrast to the difficulties with the visualization of the VIM, of all motor symptoms responsive to DBS, tremor can be assessed most easily intraoperatively. For this reason, clinical testing is important for VIM targeting. Next to this, MER recordings can be helpful. For the VIM, MER signals may modulate based on (passive) movements. MER criteria for the delineation of the VIM are defined by kinaesthetic fields corresponding to the hand, 2–4 mm anterior to the border of the ventrocaudal thalamic nucleus (Gross et al. 2006). The latter is neurophysiologically defined by the reaction to tactile stimuli.

The results of a recent double-blind study indicated that in (essential) tremor patients, DBS of the posterior subthalamic area (PSA), including the zona incerta (ZI), is equally effective, with less energy consumption, compared to VIM DBS (Barbe et al. 2018). The same holds for PD patients, in whom stimulation of the ZI led to significant tremor reduction, comparable to VIM stimulation (Blomstedt et al. 2018). Given the possibility of stimulating both the VIM and PSA with one DBS lead, intraoperative findings can pragmatically determine the best target for tremor suppression in the individual patient.

Controversies of the DBS Procedure

Although DBS has now been clinically applied for several decades, there are still controversies regarding the best surgical approach. Several of these issues have been touched upon in the previous sections. An important issue is whether DBS

procedures under general anesthesia lead to similar results as those performed under local anesthesia, in which intraoperative clinical testing can be performed. Due to the recent developments in MRI techniques, planning procedures have improved substantially, and a number of DBS teams have changed their procedures to perform surgery for DBS under full anesthesia. Although separate cohort studies report comparable outcomes for procedures performed under generalized and local anesthesia, no head-to-head comparison in a randomized-controlled setting has been published yet, but one is currently ongoing (Holewijn et al. 2017). Similarly, surgery with the use of MER in multiple tracts is more likely to cause hemorrhages than surgery without MER (Zrinzo et al. 2012). However, surgery with and without MER appear to be equally efficacious for the suppression of parkinsonian symptoms on a group level (Foltynie et al. 2011). To date, no direct comparison between implantations with and without MER has been performed. Because the incidence of hemorrhages is relatively low, a comparative study would need a large sample size. Other recent advances in surgical approach include the application of diffusion tensor imaging for tractography-based implantation of DBS leads (Akram et al. 2017) and frameless robot-assisted implantations (Ho et al. 2019).

Results of DBS

DBS has been proven to be an effective treatment for advanced PD since its introduction in the 1990s (Limousin et al. 1995).

STN DBS

STN DBS reduces bradykinesia, rigidity, pain, and tremor and may also have a positive impact on speech and gait if these symptoms improve after levodopa intake (Table 12.3) (Bronstein et al. 2011). Initially, DBS of the STN may induce dyskinesias. With test stimulation during awake surgery, dyskinesia may be seen, which then is a confirmation that the contact of the test electrode is in the motor part of STN (Houeto et al. 2003). Over time, dyskinesia may improve following the often-necessary reduction of dopaminergic medication after STN DBS. The threshold medication dose for the generation of dyskinesia and the threshold for DBS to generate dyskinesia may also become higher following the reduction of dopaminergic medication, especially following the reduction of the "pulsatile" administration of higher levodopa doses (Espay and Lang 2017).

Several RCTs have confirmed that for the treatment of medication-related motor response fluctuations in PD, DBS is more effective than best medical treatment for symptom reduction (measured with the Unified PD rating Scale; UPDRS (Fahn et al. 1987) and disease-related quality of life (measured with the PD Questionnaire; PDQ-39) (Spottke et al. 2002; Schuepbach et al. 2013; Becerra et al. 2016). In a large German, as well as in a large French-German trial (the 'EARLYSTIM' trial), this was shown for STN DBS compared to best medical treatment up to 2 years after surgery (Deuschl et al. 2006; Schuepbach et al. 2013). In the EARLYSTIM trial, patients were recruited if they had early motor complications (Schuepbach et al. 2013). The key inclusion criteria for this trial were a disease duration of 4 years or more, improvement of motor signs of 50% or more with dopaminergic medication, as assessed with the UPDRS motor examination part (part III), fluctuations or dyskinesia present for 3 years or less, and a score of more than 6 points for activities of daily living in the worst condition despite medical treatment on the UPDRS activities of daily living part (part II), or mild-to-moderate impairment in social and occupational functioning (Schuepbach et al. 2013). Thus, this study showed that DBS could be effective at improving quality of life earlier in the disease course (Schuepbach et al. 2013). Importantly, all clinical trials showed that DBS had a large clinical effect, but none of these trials had a double-blind assessment of the primary outcome (Deuschl et al. 2006; Schuepbach et al. 2013).

Table 12.3 Results of randomized controlled trials of deep brain stimulation for Parkinson's disease

Trial	Target	Number of patients	Follow-up (months)	Age at surgery (years)	Duration of preoperative medical PD therapy	Decrease UPDRS II (%)	Decrease UPDRS III (%)	Decrease LED (%)	Decrease dyskinesia (%)	Improvement of quality of life (%)
Anderson et al. (2005)	STN	12	12	61.0	15.6	25.9	48	38	43.5	N/A
	GPi	11	12	54.0	10.3	18	39	3	89	N/A
Deuschl et al. (2006)	STN	156	6	60.5	13.0	39	40	50	40	22.7
Esselink et al. (2004)	STN	20	6	61	12	46.3	48.5	33	56.3	23.2[a]
Follett et al. (2010)	STN	147	24	61.9	11.1	15.5	33	31.5	44	8.7
	GPi	152	24	61.8	11.5	17.3	39.3	17.9	72.7	11.6
Okun et al. (2012)	STN	136	12	60.6	12.1	N/A	37.5	34.3	50	17.0
Odekerken et al. (2016)	STN	63	12	60.9	9.5	32.9	45.7	43.5	20.8	19.4
	GPi	65	12	59.1	18	21.8	26	15.6	16.7	12.3
Schuepbach et al. (2013)	STN	124	24	52.9	7.3	41.3	49.3	65.1	71.4	26.4
Weaver et al. (2012)	STN	70	36	60.7	11.3	6.2	30.5	35.6	55.4	8.0
	GPi	89	36	60.4	11.4	8.6	34.1	17.8	73	5.6
Williams et al. (2010)	STN	174	12	59.0	11.5	26	35.7	N/A	50	13.3

PD PD, *STN* subthalamic nucleus, *GPi* globus pallidus pars interna, *UPDRS* unified PD rating scale, *LED* levodopa equivalent dose

[a]Measured with PDQL instead of PDQ39

GPi DBS

GPi DBS also improves bradykinesia, rigidity, pain, and tremor (Table 12.3). GPi DBS may block dyskinesias directly. In particular parts of the GPi, DBS may worsen parkinsonism (Bonifati et al. 2016). Potential reasons to favor the GPi as a DBS target could be its robust dyskinesia suppression and the relative ease of programming (Williams et al. 2014)

GPi DBS Versus STN DBS

Due to the successes of pallidotomy in the treatment of PD in the 80s and 90s of the last century, the GPi was initially broadly considered to be the most appropriate target for DBS. Later, the STN gained popularity as a target, sparking the discussion of which target was best for the treatment of PD (Williams et al. 2014). This led to a few head-to-head comparisons performed by different groups. In one clinical trial, parkinsonism in the off-drug phase was reduced less with GPi DBS than STN DBS (Odekerken et al. 2013). In the larger trial, GPi DBS and STN DBS were equally efficacious in reducing the severity of off-drug phase parkinsonism (Weaver et al. 2012). In both trials, daily dopaminergic medication was reduced after STN DBS and did not change after GPi DBS (Weaver et al. 2012; Odekerken et al. 2013).

The results of a small blinded randomized controlled trial, published in 2005, also suggested that STN and GPI DBS are equally effective for motor symptoms and dyskinesia (Anderson et al. 2005). However, STN DBS seemed to be associated with more problems in cognition, mood, and behavior (Anderson et al. 2005). In the Veterans Affairs Cooperative Studies Program (CSP)-468 study, the first 255 patients participated in the 6-month comparison in which patients were randomly assigned to receive medical therapy or to undergo DBS (randomized to either GPi DBS or STN DBS) (Follett et al. 2010). Of the 134 patients who were initially randomized to medical therapy, 117 subsequently proceeded to DBS, with random assignment to either GPi or STN DBS. Since an interim analysis had indicated that a sample of 255 patients was sufficient for the comparison between medical therapy and DBS, the remaining 61 patients were randomly assigned directly to undergo GPI or STN DBS (total 299 patients) (Follett et al. 2010). Twenty-four months after surgery, in a blinded setting for the DBS target, patients had a similar improvement in motor function after GPI DBS and STN DBS. In the smaller Netherlands SubThalamic and Pallidal Stimulation (NSTAPS) study, 65 patients were randomly assigned to GPi DBS and 63 to STN DBS (Odekerken et al. 2013). There was no statistically significant difference in the primary outcomes after 1 year, which was the change in disability (weighted for off-drug and on-drug phases) and the number of patients with cognitive, mood, and behavioral side effects. However, secondary outcome measures showed larger improvements in the STN group compared to the GPI group in standardized off-drug phase UPDRS part III scores and disability. In both studies, there was no difference in the number of adverse events between the GPi DBS and STN DBS groups (Follett et al. 2010; Odekerken et al. 2013). The use of dopaminergic medications decreased more with STN DBS than with GPI DBS, and stimulation amplitudes were significantly lower in the groups that had STN DBS compared to the groups undergoing GPI DBS. In the VA-trial and NSTAPS follow-up results were prolonged to up to 3 years after surgery; in general, the long-term outcomes are similar as the initial comparisons of the two targets in the two studies (Follett et al. 2010; Odekerken et al. 2013).

Side Effects

The effectiveness of DBS can be limited by bothersome side effects such as dysarthria, tonic muscular contraction, gait imbalance, conjugate eye deviation, and paresthesia (Pollo et al. 2014). These side effects can be caused by the spillover of stimulation current into adjacent structures (Cubo et al. 2014;

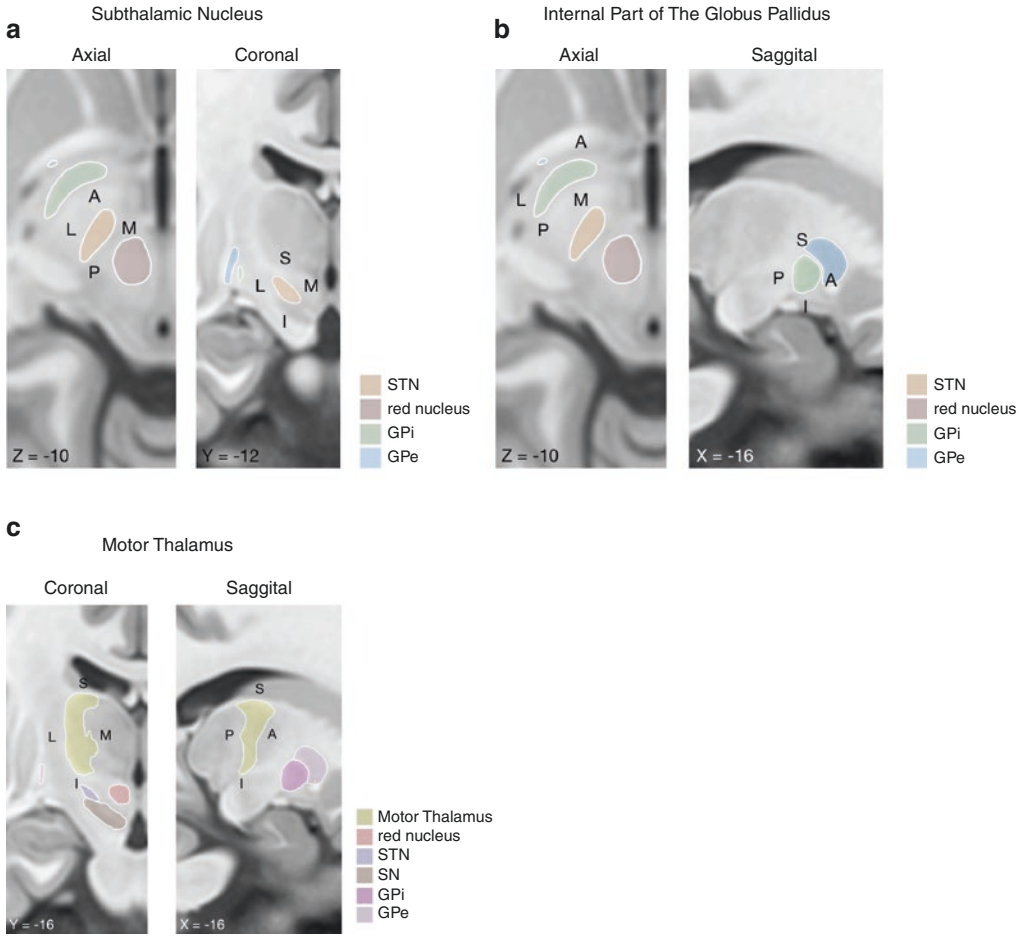

Fig. 12.1 (**a**) Axial and coronal MRI image at the level of the subthalamic nucleus (STN) and its surrounding structures. (**b**) Axial and sagittal MRI image at the level of the internal part of the globus pallidus (GPi) and its surrounding structures. (**c**) Coronal and sagittal MRI image at the level of the motor thalamus (including the ventrointermediate nucleus of the thalamus) and its surrounding structures. The letters surrounding the relevant structure refer to the direction, and specific side effects can be found in table. Images were generated using the Lead DBS toolbox (Horn and Kühn 2015), with additional 3D thalamic reconstructions (Ilinsky et al. 2018), *GPe* external part of the globus pallidus, *SN* substantia nigra. *X*, *Y*, and *Z* refer to the stereotactic coordinates in MNI space

Pollo et al. 2014) in and around the STN, GPi, and VIM. Please see Fig. 12.1 for possible side effects and their "anatomical" relationship with the targeted nucleus. Dysarthria and impaired postural reflexes may be a consequence of disease progression but may also be due to DBS. A possible pitfall is dysarthria and balance problems that are caused by the gradual increase of the DBS parameters, which is not recognized as such, and disease progression is considered to be the culprit. DBS of the STN and GPi may also cause cognitive, mood, and behavioral problems (Anderson et al. 2005; Okun et al. 2009; Castrioto et al. 2014). Cognitive, mood, and executive problems may be directly induced by DBS and is then related to stimulation of adjacent limbic and frontal circuits. The reduction of dopaminergic

medication, which is more likely to occur after STN DBS, may incite apathy and depressed mood (Lhommée et al. 2018). A sudden reduction of dopamine agonist use may provoke DAWS, which may take 2 years to resolve if not recognized as such (Patel et al. 2017). Although DBS may be accompanied by behavioral side effects, these symptoms may also be an additional indication to start DBS in case there is already a reason to perform DBS because of motor symptoms (Lhommée et al. 2018). After all, with STN DBS, mood and behavioral disorders improve on a group level compared to continuing best medical care only. In larger randomized controlled studies, there was no difference between STN DBS and GPI DBS with respect to cognitive, mood, and behavioral disorders after surgery (Weaver et al. 2012; Odekerken et al. 2013).

Micro-lesion Effect

Manipulating the test electrodes and the final electrodes in the brain during DBS surgery may cause small lesions in the brain and subsequent transient edema in these areas. Patients may experience temporary side effects due to these (micro-)lesions such as facial weakness, dysarthria, and behavioral changes (e.g., hypomania), but they may also experience a reduction of PD symptoms or worsening of dyskinesia (Maltête et al. 2008; Gago et al. 2009; Groiss et al. 2009). The pallet of symptoms associated with the edema are determined by the specific DBS target and surrounding structures. The clinical effect takes a day or two to peak and then gradually fades and may last up to about 4 weeks (Maltête et al. 2008). The amount of transient PD symptom reduction following STN and GPi DBS electrode placement is a predictor for the efficacy of the DBS treatment (Maltête et al. 2008). Patients have to be informed beforehand that when the initial benefits of the micro-lesion wear off, this does not mean "DBS will not work anymore." Incidentally, the edema may affect a large area resulting in more severe focal neurological symptoms, but this will also dissipate spontaneously (Maltête et al. 2008).

Programming

An extensive description of programming is provided in Chap. 8.

Monopolar Review

Detailed monitoring during DBS surgery and postoperative imaging may guide the selection of electrode contact to be used during chronic stimulation. Nevertheless, for final contact selection, monopolar test stimulation is also necessary (see also Chap. 8: Programming). First, the assessment of the impedance of each contact is done to test the integrity of the DBS hardware. During monopolar testing, the amount of current needed (i.e., the threshold) for symptom reduction (of bradykinesia, rigidity, and tremor) and the thresholds for side effects are determined for each contact. Practically, patients need to be in off-drug phase to be able to assess the effects on PD symptoms. For each contact and with standard parameters (e.g., 60 μs and 130 Hz), the current is increased with small steps (0.5 V or 0.5 mA) and with each subsequent step PD symptoms and possible side effects (such as dysarthria, parasthesias, and tonic contractions) are assessed. The contact with the best trade-off between a low threshold for PD symptom reduction and high threshold for side effects, i.e., the one with the largest therapeutic window, can then be chosen to start chronic stimulation. A thorough monopolar review is time consuming and may take up to 1.5 h. Because the severity of parkinsonism during the off-drug phase may be improved due to the micro-lesion effect, thus masking the true DBS effect, the monopolar review is more

informative if it is performed several weeks after surgery.

During monopolar review, it is important to realize that the time it takes for DBS to exert its effect on symptoms differs between patients and may differ for each symptom. For example, rigidity may disappear in seconds after the stimulation is switched on, while tremor may take minutes to hours and bradykinesia minutes to days (Temperli et al. 2003; Cooper et al. 2011, 2013). It may also take minutes to several days for dyskinesia to develop fully after switching on DBS. Analogously, it may take minutes to several days for symptoms to recur after switching of DBS, and this may also be different for various symptoms (Temperli et al. 2003; Cooper et al. 2011, 2013). These phenomena have to be taken into account when conducting the monopolar review.

Programming

If the optimal contacts for stimulation are determined, chronic stimulation can start at a low to medium voltage or current of, for example, 1.0 or 1.5 V or mA. Regular visits for programming and adjustments of PD medication are then scheduled every 4–6 weeks. In a few cases, a satisfactory setting with one contact as cathode and the pulse generator as anode cannot be reached, and more complex programs have to be explored, such as a bipolar setting or double monopolar setting. In Chap. 8, programming is discussed in more detail. In most patients a new equilibrium is reached after 4–6 months (Wagle Shukla et al. 2017). Typical settings for PD can be seen in Table 12.4. With STN DBS patients may need to reduce dopaminergic medication by 30–50% of the daily levodopa equivalent dose (Weaver et al. 2012; Odekerken et al. 2013). Generally, the daily dose does not change with GPi DBS. In most patients, the settings do not need to be adjusted on a regular basis after 6 months. It is a good practice to record the settings and impedance during each programming visit. The newer DBS systems have options to program several stimulation settings which are coded (e.g., program A, program B, program C). With the patient-programmer, the patient can choose and try the different programs to evaluate efficacy and side effects of each program. There is also the option to program a range in which the patient can decrease or increase stimulation amplitude, either voltage or current, depending on the system that is used.

Table 12.4 Typical deep brain stimulation settings[a]

	Amplitude	Frequency	Pulse width
STN			
Deuschl et al. (2006)	2.9 ± 06 V	139 ± 18 Hz	63 ± 7.7 μs
Esselink et al. (2004)	Median 2.3 V (range 1.4–3.5)	Median 145 Hz (range 100–130)	Median 60 μs (range 60–90)
Follett et al. (2010)	3.16 V	165 Hz	75.9 μs
Okun et al. (2012)	2.3 mA	151.1 Hz	74 μs
Odekerken et al. (2016)	2.6 ± 0.6 V	135.0 ± 20.8 Hz	63.9 ± 9.6 μs
Schuepbach et al. (2013)	2.8 ± 0.7 V	142 ± 27 Hz	66 ± 13 μs
GPI			
Follett et al. (2010)	3.95 V	168 Hz	95.7 μs
Odekerken et al. (2016)	2.9 ± 0.5 V	137.5 ± 20.0 Hz	73.0 ± 23.8 μs
VIM			
Parihar et al. (2015) (retrospective review of 18 medication-refractory tremor in PD patients)	3.3 ± 0.9 V	164 ± 27.2 Hz	98 ± 41.7 μs
Pahwa et al. (2006) (5-year follow-up study of 8 bilateral DBS PD patients, only 20% were stimulated monopolar)	4.4 V	166 Hz	138 μs

[a]Numbers are mean ± SD unless stated otherwise

DBS programming can sometimes become very complex due to a heterogeneous disease with several symptoms changing over time (including tremor, bradykinesia, dyskinesias, mood, anxiety), disease progression, complicated medication schedule, and DBS effects which may differ for the left and right electrode, and of which the effects may interact (e.g., no dysarthria with left or right electrode turned on separately, but dysarthria present if both electrodes are turned on). It may be very difficult for the patient and the doctor to see the forest for the trees. In these situations, it may be helpful to assess the symptoms with the MDS-UPDRS part III in four conditions after an overnight withdrawal of PD medication: off-drug with DBS "off," off-drug with DBS "on," on-drug with DBS "off," and on-drug with DBS "on."

Long-Term Follow-Up

The effect of STN and GPI DBS on bradykinesia, rigidity, and tremor is long lasting (Limousin and Foltynie 2019). Non-dopaminergic symptoms are unfortunately not treated with DBS and gradually progress. After several years, patients may suffer from cognitive impairment, hallucinations, dysarthria, impaired postural reflexes, freezing, and impairments of the autonomic nervous system, which are currently all difficult to treat. In this stage, patients may not look like the archetypical PD patients because of the discrepancy between the absence of dopamine responsive motor symptoms on one-hand and dysarthria with balance and gait problems on the other (Fasano et al. 2010; Yamamoto et al. 2017). With long-term DBS treatment, hardware problems may occur in up to 15% of patients followed for 10 years. These problems are diverse and include infection of hardware, decubitus over the leads, fractures of the leads, twiddler's syndrome (due to twisting of the pulse generator resulting in tightening of the leads), infections, and accidental cutting of a lead during surgery for a battery change (Blomstedt and Hariz 2005).

Conclusions

Deep brain stimulation is an established treatment for PD. It can be especially effective in ameliorating refractory tremor, wearing-off symptoms, and dyskinesia. The three cardinal pillars for successful DBS treatment comprise optimal patient selection, accurate DBS lead placement, and thorough postoperative care, including programming and medication adjustments. When these conditions are met, the motor response will be comparable to that of optimal preoperative dopaminergic medication, but with a more constant effect.

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