# High frequency deep brain stimulation of the subthalamic nucleus versus continuous subcutaneous apomorphine infusion therapy: a review

Carron, Romain; Fraix, Valerie; Maineri, Carina; Seigneuret, Eric; Piallat, Brigitte; Krack, Paul; Pollak, Pierre; Benabid, Alim-Louis; Chabardes, Stephan

**How to cite**

CARRON, Romain et al. High frequency deep brain stimulation of the subthalamic nucleus versus continuous subcutaneous apomorphine infusion therapy: a review. In: Journal of neural transmission, 2011, vol. 118, n° 6, p. 915–924. doi: 10.1007/s00702-010-0556-7

This publication URL: https://archive-ouverte.unige.ch/unige:95923
Publication DOI: 10.1007/s00702-010-0556-7

J Neural Transm (2011) 118:915–924
DOI 10.1007/s00702-010-0556-7

MOVEMENT DISORDERS - CONY PRO/CON DEBATE

# High frequency deep brain stimulation of the subthalamic nucleus versus continuous subcutaneous apomorphine infusion therapy: a review

**R. Carron · V. Fraix · C. Maineri · E. Seigneuret · B. Piallat · P. Krack · P. Pollak · A. L. Benabid · Stéphan Chabardès**

Received: 2 May 2010 / Accepted: 6 December 2010 / Published online: 29 December 2010


**Abstract** In advanced Parkinson's disease, several therapeutical option including not only lesional surgery (VIM, GPi) and deep brain stimulation (STN, GPi, VIM) but also continuous subcutaneous apomorphine infusion therapy can be proposed to the patient. The choice depends on the hope of the patient, patient's general health condition and the experience and choice of the neurosurgical and neurologist team. Here we report our experience based on 400 STN-DBS cases and we discuss, on the basis of our experience and on the literature, the advantage and disadvantage of DBS strategy as compared with non-surgical option such as continuous subcutaneous apomorphine infusion therapy.

**Keywords** Subthalamic nucleus · Deep brain stimulation · Advanced Parkinson's disease · Apomorphine · Dopa therapy

R. Carron · C. Maineri · E. Seigneuret · S. Chabardès
Department of Neurosurgery, University Hospital, Grenoble, France

V. Fraix · P. Krack · P. Pollak
Department of Neurology, University Hospital, Grenoble, France

V. Fraix · B. Piallat · P. Krack · P. Pollak · S. Chabardès
Grenoble Institute of Neuroscience, INSERM U836, Grenoble, France

A. L. Benabid
CEA LETI Clinatec, Grenoble, France

R. Carron · B. Piallat · P. Krack · P. Pollak · S. Chabardès
Joseph Fourier University, Grenoble, France

S. Chabardès (✉)
Clinique de Neurochirurgie, CHU Michallon, 38043 Grenoble Cédex, France
e-mail: SChabardes@chu-grenoble.fr

## Introduction

The management of advanced Parkinson's disease (PD) is often complicated by the appearance of long-term side effects of levodopa therapy, including motor fluctuations and dyskinesias (Fraix et al. 2001; Lang and Lozano 1998). Approximately 90% of patients develop motor fluctuations and dyskinesias by 15 years of disease (Ahlskog and Muenter 2001) and with time, these complications prove to be extremely difficult to control with available oral medications. Apart from motor symptoms, patients may experience other fluctuating non-motor symptoms such as pain, dysautonomic and cognitive fluctuations that can sometimes be more disabling than motor fluctuations.

The best management of those advanced stages of PD is not clearly established and varies among teams. Several options can be discussed in patients with advanced PD and disabling motor fluctuations : high frequency deep brain stimulation (DBS) of subthalamic nucleus (STN-HFS) (Deuschl et al. 2006; Hariz et al. 2008; Limousin et al. 1998), globus pallidus (GPi) (Hariz et al. 2008; Moro et al. 2010) or Ventro-intermedial (Vim) motor thalamus (Benabid et al. 1993), lesions such as pallidotomy (Hariz and Bergenheim 2001; Lozano and Lang 2001; Esselink et al. 2009), thalamotomy (Burchiel 1995; Ohye et al. 2005; Tasker 1990) or subthalamotomy (Tseng et al. 2007) or continuous dopaminergic stimulation using either continuous subcutaneous apomorphine infusion therapy (CSAI) (Pietz et al. 1998; Poewe and Wenning 2000; Stibe et al. 1987, 1988) or duodenal levodopa continuous administration through a duodenogastrostomy (Antonini et al. 2007, 2008; Honig et al. 2009; Samanta and Hauser 2007).

In our institution, STN-HFS represents the best option providing long-term benefit with acceptable morbidity for the patient amenable to surgery (Krack et al. 2003;

Lagrange et al. 2002; Limousin et al. 1998). Indeed, STN-HFS has now become the mainstay of treatment of advanced Parkinson's disease. The clinical outcome proved satisfactory in both the short and long term with acceptable but non-null morbidity. The clinical improvement mainly stems from a dramatic reduction of daily levels of levodopa medication.

As any functional neurosurgical procedure, the best outcome is closely related to the appropriate selection of patients and the accurate lead placement. It is based on a standardised surgical procedure integrating multimodal data (Benabid et al. 2009, described below) coming from different imaging modalities, electrophysiological recordings and peroperative assessment of clinical effects.

In this paper, we will focus on the advantages and shortcomings of STN-HFS as compared with continuous dopaminergic stimulation. With this purpose, we will successively discuss the selection criteria, describe the surgical procedure and provide the clinical results and main complications. Eventually, we will give our dialectic view about the advantages of STN-HFS over the therapeutic alternatives and provide future perspective of DBS in PD to alleviate some unimproved symptoms.

## Selection of patients

### Indications

Patients affected by clinically diagnosed idiopathic PD and who have developed disabling motor fluctuations such as severe dyskinesias or 'off' periods or who suffer from severe rest tremor despite optimal medical treatment are ideal candidates. They are likely to be significantly improved as long as the symptoms keep a good or excellent response to levodopa therapy (Limousin et al. 1995, 1998).

Those who show improvement with the optimum adjustment of anti-PD drugs or a suprathreshold levodopa dose [first morning levodopa equivalent dose (LED) + 25% LED to ensure the best motor improvement] are highly likely to show a similar improvement after optimum placement of the leads within the STN (Charles et al. 2002).

Higher baseline scores on section III (motor) of the unified PD rating scale (UPDRS) and higher baseline levodopa responsiveness are independent predictors of greater change in motor score after surgery (Charles et al. 2002).

In our institution, our multidisciplinary team performs a careful screening of eligible PD patients. To summarise, in order to be eligible for STN-HFS, patients have to fulfil the following criteria:

- clinical diagnosis of *idiopathic* PD,
- good dopa-sensitivity and
- disabling motor fluctuations such as severe dyskinesia or and frequent "off" periods,
- absence of contraindications.

### Contraindications

#### *Atypical Parkinsonism, dementia, psychiatric conditions*

Contraindications are important to consider in order to avoid putting at risk the patients who might not benefit from surgery. Dementia and cognitive deficits are not improved by STN-HFS and might even worsen following the procedure. Atypical Parkinsonism (multiple systemic atrophy, progressive supranuclear palsy, Lewy body disease) must be ruled out before considering DBS. Psychiatric conditions, including severe depression has to be treated first and must be regarded as contraindications.

#### *General contraindications to surgery*

All general surgical contraindications apply to DBS, particularly if a bleeding diathesis is present or an anticoagulant therapy (warfarin) is mandatory for any coexisting cardiovascular conditions. Additional contraindications are related to the generation of electrical artefacts that might interfere with sensing devices, such as cardiac pacemakers and implantable cardioverter-defibrillator (Benabid et al. 2009). However, a few cases of patients having both a cardiac pacemaker and an implantable pulse generator (IPG) for DBS were reported by Medtronic®.

Severe comorbidities such as heart failure, uncontrolled progressive systemic or neoplastic conditions are also contraindications. Pregnancy and refusal to give a written informed consent preclude registration for DBS.

## Surgical procedure (Fig. 1)

Several factors can account for the results of DBS in a given patient. Proper selection of patients and the quality of the surgical procedure enabling to achieve optimal positioning of the lead are pivotal to the outcome. In addition, fine tuning and adjustments of both stimulation settings and concomitant pharmacological medication by a skilled neurologist is also of paramount importance (Krack et al. 2002; Pollak 2007).

The clinical results obtained in over 400 STN patients directly derive from this specific approach and might not be directly transferable to other surgical techniques and teams. However, meta-analyses of published data demonstrate improvements of the same order of magnitude (Kleiner-Fisman et al. 2006).

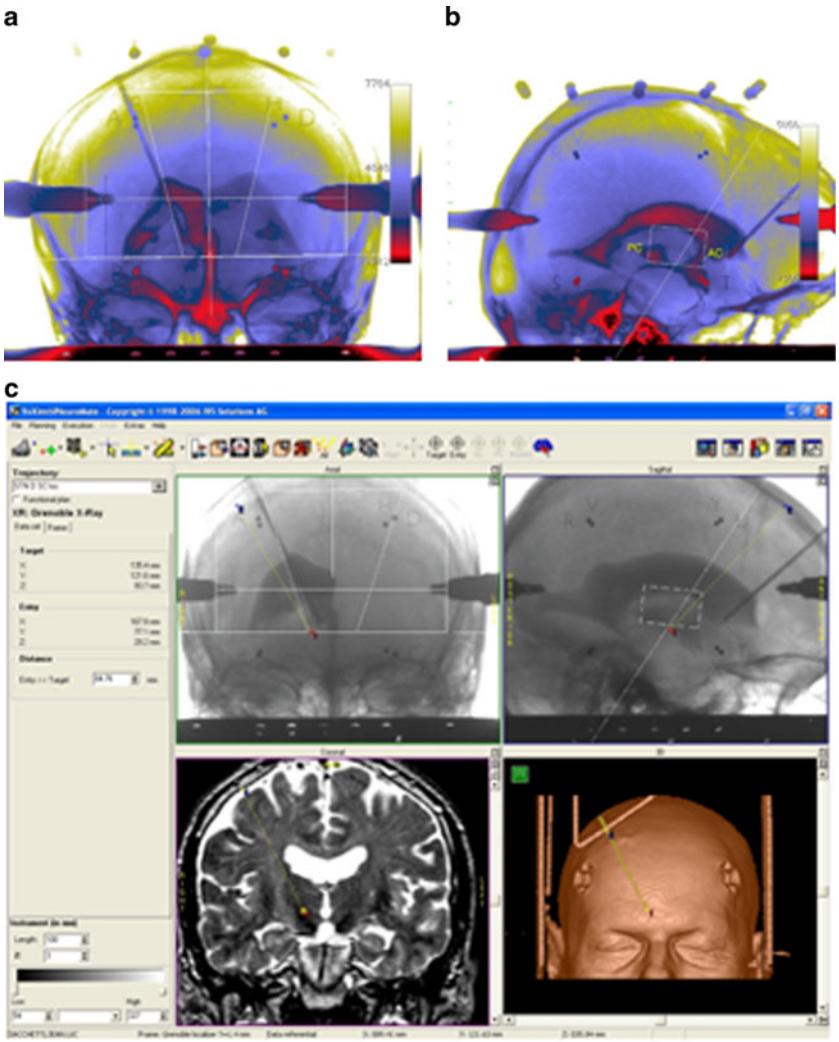


**Fig. 1** Construction of the target on the lateral and AP ventriculogram. **a** Lateral view. **b** A–P view. **c** Surgical planning targeting STN bilaterally with Voxim® software. *Upper part* entry point and target depicted on AP and lateral view of ventriculogram. *Lower part* trajectory depicted on stereotactic MRI (T2-weighted coronal section)

## Definition of the location of the target

In order to determine the best location of the target, ventriculography (Benabid et al. 2009) was performed by our team. The teleradiographic pictures acquired after injection of contrast medium into the right frontal horn of the lateral ventricle provide internal landmarks such as the boundaries of the third ventricle, the anterior and posterior commissures (AC–PC line) to which various atlases and coordinates of the targets can be related.

The possibility to perform X-rays in the same stereotactic position at any time during the procedure allows us to know the exact location of the microelectrodes.

Stereotactic MRI allows direct visualisation of the STN. It appears on T2-weighted sequences as an area of low signal surrounded by white matter tracts (*zona incerta* above and fields of Forel bundles below) that separate the STN from the *substantia nigra pars reticulata* (SNr). The procedure is planned from the MRI scans, which are eventually compared with and fused with the ventriculography. The stereotactic target is constructed by use of graphic tools that are included in the flat detector imaging software (Pixview, Bioscan, Switzerland) (Fig. 1a, b). The target used by our team actually represents the stereotactic location of the best active contact for the first 300 STN patients in Grenoble.

The planning stage allows the surgeons to check the match (or to detect any discrepancy) between the target and the MRI scan of the STN (Fig. 1c). The surgeon then chooses an entry point that corresponds to a vascular "window" (i.e. an area devoid of vascular structure) from the cortical surface to the depth, thus avoiding any damage during the insertion of the microelectrodes.

## Intraoperative recordings and peroperative microstimulation

Electrophysiological recordings are performed by use of five microelectrodes making millimetric tracks to the target. Data have been previously described for the targeting

of STN (Hutchison et al. 1998) and recently for new areas such as PPN (Piallat et al. 2009).

Experienced electrophysiologists are able to identify the electrophysiological signature of the main nuclear structures such as STN or SNr.

Extracellular recordings within STN usually show a typical firing pattern at 30–40 Hz made up of asymmetrical spikes in amplitude with bursting patterns. Furthermore, proprioceptive responses to passive movements of the controlateral body are characteristic features of the motor subdivision of STN (Fig. 2a).

By contrast, neuronal activity in the *substantia nigra pars reticulata* (SNr) comprises symmetrical spikes of large amplitude and regular activity at higher frequency, and is generally unresponsive to proprioceptive stimuli (Fig. 2b).

The insertion of the microelectrodes in our institution is almost always performed under local anaesthesia in order to take advantage of the cooperation of the patient. It provides 'on-line' essential information about the beneficial effects and any side effects that would be induced by the stimulation peroperatively.

In the operating theatre, the assessment of the clinical response to DBS by a skilled neurologist—degree of rigidity according to a semi-quantitative scale—is also pivotal to the decision of which trajectory out of the five must be chosen for the final positioning of the chronic lead. We think that this step is crucial to the success of surgery, especially for STN-DBS. Speech is not tested in routine during surgery and axial symptoms such as freezing of gate and postural instability are difficult to test consistently because of the position of the patients fixed to the frame. Furthermore, some patients might be exhausted by a lengthy exploration and also disturbed by the withdrawal of dopaminergic medication. However, in our experience, if the testing takes place early on, the patient can be cooperative and proper assessment is workable in the great majority of cases.

Efficiency and side effects are thus tested peroperatively to determine the location of the microelectrode that gives the best result in terms of beneficial effects (i.e. minimal side-effects and largest security margin between thresholds for improvement and side-effects) and in terms of electrophysiological data.

The side effects depend on the spread of current on the surroundings structures when the electrode is either outside the STN or close to its boundaries. Surrounding structures, among others, comprise the pyramidal tract, the lemniscus medialis, sympathetic pathways and the third cranial nerve fibres.

The microelectrode is then replaced by a chronic lead (Model 3389 Medtronic®, Inc., Minneapolis, MN, USA). The lead is then firmly anchored to the skull with the help of dental cement (methylmetacrylate) and suture. Control X-rays are performed throughout the procedure by means of flat detectors and at the end to check the final positioning of the leads (Fig. 3a, b).

The implantable pulse generator (Kinetra® or Soletra® Medtronic® Inc., Minneapolis, MN, USA) is inserted under general anaesthesia into a subcutaneous pouch in the subclavicular area. This step is usually done several days later in order to obtain a postoperative stereotactic MRI beforehand.

It is noteworthy to mention that a postoperative MRI was performed in all patients without any untoward effect (Fraix et al. 2010) (Fig. 4a, b).

## Results

### Clinical benefits

A great number of clinical studies or meta-analysis demonstrated the clinical improvement following of STN-HFS in advanced Parkinson's disease (Deuschl et al. 2006; Hamani et al. 2005; Hariz et al. 2008; Herzog et al. 2003; Kleiner-Fisman et al. 2006; Krack et al. 2003; Moro et al. 2010; Pahwa et al. 2003; Rodriguez-Oroz et al. 2005). Despite differences in the methodology of the surgical procedure and in the assessment of the level of improvement, numerous studies have reported improvements ranging from 30 to 60% or higher.

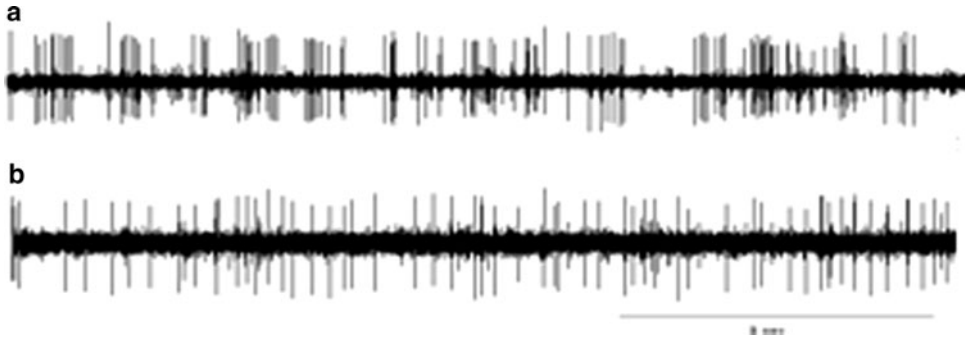


**Fig. 2** Extracellular micro recordings performed during the procedure. **a** Electrophysiological recordings of STN neurons. **b** Electrophysiological recordings of SNr neurons

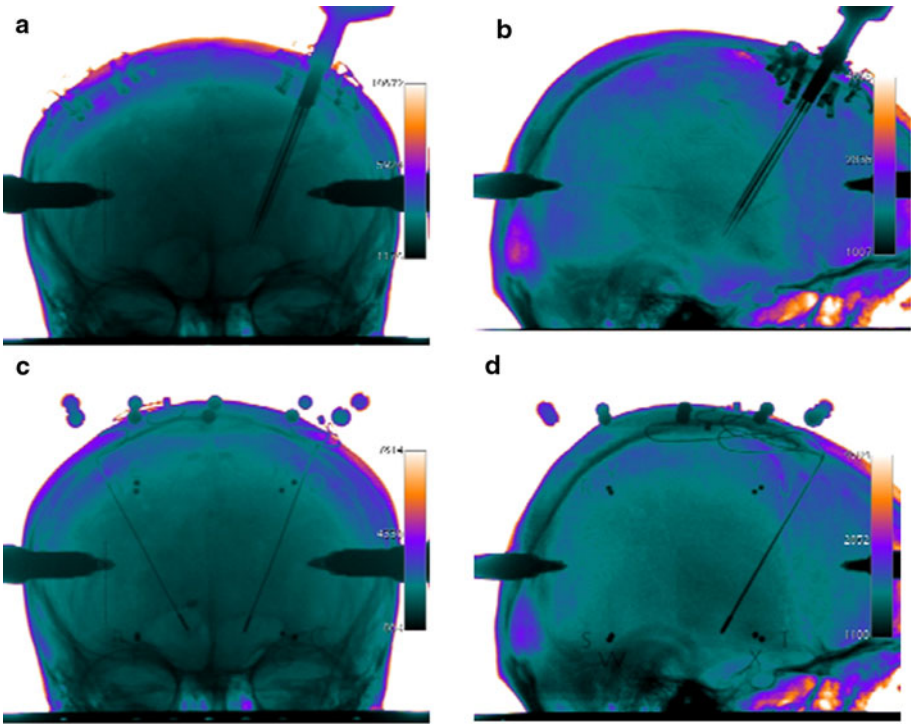


**Fig. 3** Control X-rays. **a** and **b** X-rays depicting the five microelectrodes (*left side*) during the electrophysiological exploration. **c** and **d** Final positioning of the Medtronic® 3389 leads

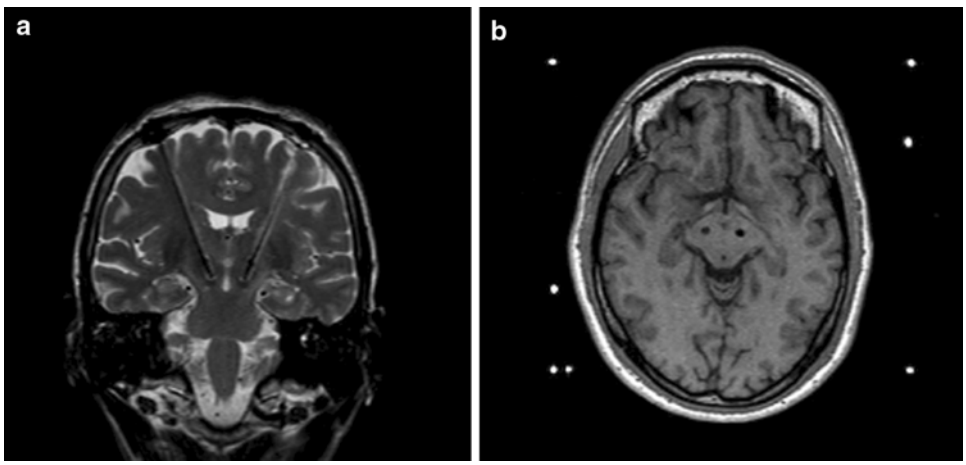


**Fig. 4** Postoperative MRI showing the final positioning of the leads. **a** Postoperative MRI coronal T2-weighted picture. **b** Postoperative MRI axial T1 showing the tip of the electrode as an area of low signal within the subthalamic nucleus

The main scale used to analyse the intensity of symptoms in PD is the Unified Parkinson's Disease Rating Scale (UPDRS).

The mean UPDRS III (motor section) score improved globally by 41% in the off-medication state and by 23% in the on medication state; the UPDRS II (activities of daily living) score also improved markedly (Kleiner-Fisman et al. 2006).

The STN-HFS improvement in UPDRS III scores, versus baseline values, is reasonably stable over time, decreasing from a 66% improvement at 1 year to 54% at 5 years after surgery. Additional studies with follow-up periods of 2–4 years have reported similar improvement over time (43–57%, respectively) (Ostergaard et al. 2002; Herzog et al. 2003; Kleiner-Fisman et al. 2006; Vingerhoets et al. 2002; Visser-Vandewalle et al. 2005).

All symptoms are not equally alleviated. The improvement at 5 years in hypertonia and tremor is evaluated at 70–75% and 50% in akinesia (Krack et al. 2003). Off-period dystonia is usually significantly decreased.

Mean postoperative reduction of dopaminergic drugs reaches 50–56% (Deuschl et al. 2006; Kleiner-Fisman et al. 2006).

Levodopa-induced dyskinesias and disability, and their duration are usually decreased by 69, 58, and 71%, respectively (Krack et al. 2003) which has a major impact on quality of life (Deuschl et al. 2006; Fraix et al. 2001).

One major advantage of STN-HFS is the stable and permanent improvement indicated by the 47–71% increase of the time during which patients have a medication-related reduction of motor symptoms (Deuschl et al. 2006; Fraix et al. 2001; Goodman et al. 2006; Kleiner-Fisman et al. 2006; Krack et al. 2003; Pahwa et al. 2003; Rodriguez-Oroz et al. 2005).

Speech is generally less improved with STN-HFS than other Parkinsonian signs (Krack et al. 2003; Limousin et al. 1998; Rodriguez-Oroz et al. 2005). Hypophonia might improve, but dysarthria might be aggravated due to current diffusion to corticobulbar fibres. Therefore, the patient's satisfaction, particularly with regard to hypophonia and ability to communicate with their family, can decline after surgery. Freezing of gait is also significantly less durably ameliorated by STN-HFS (Lozano and Snyder 2008) but tends to respond to lower frequency of stimulation (Moreau et al. 2008) or low-frequency stimulation of other targets (Ferraye et al. 2010; Stefani et al. 2007).

### Quality of life

Quality of life is improved under the combination of STN-HFS plus optimal medication versus optimum drug therapy alone as demonstrated in one large randomised controlled multicentre study (Deuschl et al. 2006) (Improvements in PDQ-39 subscales for mobility, ADL, emotional well-being and bodily discomfort).

Previous monocentric study had shown improvements in several aspects of quality of life on PD quality of life questionnaire (motor, systemic, emotional and social) (Diamond and Jankovic 2005; Lagrange et al. 2002).

### Economical issues

STN-HFS may also be advantageous in terms of public health and economy. In one study, apart from the good clinical outcomes, the economic burden was significantly decreased. The 6-month cost of PD diminished by sixfold before and after surgery, mainly because of a dramatic drop in the cost of medication but probably also because of the lower number of hospital admissions required for medication adjustments (Fraix et al. 2006; Meissner et al. 2001).

### Complications

Complications of STN-HFS may be classified into transient or permanent or into complications related to the surgical procedure, to the hardware and to the stimulation itself.

It is difficult to give an accurate report of the complications because the data reported vary substantially. Several studies have focused on DBS complications (Benabid et al. 2009; Hariz 2002; Joint et al. 2002; Seijo et al. 2007).

#### Haemorrhages

In a study of 526 DBS patients (Benabid et al. 2009), haemorrhages occurred in 8.4% (range 0.2–12.5%) of all procedures. However, 3.4% were asymptomatic, symptoms were transient in 4.4% and only 0.6% had permanent deficits (Binder et al. 2005). The overall risk of serious complications leading to a permanent deficit limiting the activity of daily life is 2–4% (Hariz 2002).

Death directly attributable to the surgical procedure is extremely rare in the setting of a DBS procedure, but may occur (Schoenen et al. 2005).

Among 570 cases in our cohort, among which 400 were operated on in the STN, two cases (0.35%) of intracerebral haemorrhage led to general complications and eventually to the death several months after the surgery. In one of the two patients, a spontaneous intracerebral haemorrhage occurred during DBS procedure but before insertion of the electrode. The diagnosis of amyloid angiopathy was highly likely but was not demonstrated pathologically.

Acute postoperative confusional state may occur in up to 10% of cases, possibly related to several factors (intracranial contusion, minimal bleeding along the tracts of the microelectrodes, duration of surgery or withdrawal from dopaminergic drugs). It usually subsides within a few days.

#### Hardware-related complications

Reported hardware-related complications, especially infection rates vary widely between the series from <1% to more than 15% (Hariz 2002; Joint et al. 2002; Lyons et al. 2004; Sillay et al. 2008). Skin infections adjacent to the inserted material are mostly superficial and occur in 1.1 and 15% of published cases. They happen most frequently at the site of the pulse generator. In case of infection, the stimulator and related hardware should be removed. Conservative management is potentially hazardous and may lead to spreading of the infection within the intracranial compartment and to the appearance of a brain abscess at the tip of the lead.

Other complications are common such as lead breakage, extension wire failure, premature battery consumption or malfunction of the pulse generator (Alesch 2005) and lead to discontinuation of treatment in 6.1% of patients in one series (Rodriguez-Oroz et al. 2005). However, these complications can generally be managed without subsequent morbidity.

#### Stimulation-induced side effect

Stimulation adverse effects are usually transient, reversible and can be minimised or eliminated by adjusting the settings to find the good compromise between untoward side effects and suboptimal clinical benefit.

Most patients with DBS (STN or GPi) gain weight (Macia et al. 2004; Strowd et al. 2010). The amount of weight gain is variable (Mean 2.3–3 kg or 4.2%; maximum 5 kg). In our cohort, the maximum weight gain was 31 kg and the mean 13 kg.

### Alteration of higher functions

Report about suicides after STN surgery (0.7% of 921 patients have made suicide attempts; 0.1% succeeded) have raised justifiable concerns (Burkhard et al. 2004; Houeto et al. 2002; Limousin et al. 1998). Depression, which is part of PD, and suicidal ideation are multifactorial. It cannot be specifically and exclusively related to STN-HFS, even if an interference with the limbic subdivision of the subthalamic nucleus may play a role in the appearance of such behavioural patterns (Krack et al. 2001; Mallet et al. 2008).

Postoperative apathy might occur (Czernecki et al. 2005; Funkiewiez et al. 2004), especially in patients addicted to levodopa (Krack et al. 1998), and is usually related to withdrawal of dopaminergic drugs to which it responds well (Thobois et al. 2010). However, the underlying mechanisms are poorly understood. A better knowledge of the physiology of apathy and related consequences will probably help prevent depression. The most frequently observed long-term neuropsychological change is decline in word fluency during the first post-operative months (Moro et al. 2010; Parsons et al. 2006).

No short-term cognitive deterioration was observed in selected young and non-demented patients (Ardouin et al. 1999; Dujardin et al. 2001; Pillon et al. 2000; Voon et al. 2005). After STN-HFS, patient tend to lose their normal ability to take time when confronted with decision conflict and tend to make impulsive decisions (Frank et al. 2007).

Despite the risks of complications related to STN-HFS, most of them are not severe and the clinical improvement in motor functions outweighs the risks for many severely incapacitated patients.

## Discussion

In the setting of advanced PD with severe motor fluctuations, the indications for both STN-HFS and continuous subcutaneous apomorphine infusion (CSAI) are globally equivalent and each therapeutic may be chosen indifferently.

Currently, there is no established consensus about the first line treatment. The question is still under debate. Local habits and the availability of the different therapeutic options including the degree of surgical expertise for DBS play an important role in the option chosen by the medical team. Patient's choice is pivotal to the decision since the whole procedure requires his full cooperation.

As long as no unrealistic expectancies or untrue fears are associated with DBS in the patient's mind, his choice must be taken into account and in our institution, deep brain stimulation will usually be proposed as a first option provided there are no general surgical contraindications. We will try to provide some reasons why we think STN-HFS should be regarded as the first option.

### Quality of life, beneficial effects and side-effects

Since the first application of STN-HFS in 1993, several thousand patients worldwide have been treated by DBS. Many papers have reported clinical results and provided accumulated evidence on the clinical outcome of STN-HFS, although large series and prospective multicentre clinical trials are rare.

Several studies reported a significant improvement in quality of life for PD patients following STN-HFS (Deuschl et al. 2006). Once operated on and once the surgical wound properly closed and provided the optimal combination between stimulation settings and medication is found, the patient becomes independent. The system is completely internalised and does not need any invasive manipulation until the battery is too low and the IPG has to be changed. The duration of battery strongly depends on the stimulation settings (intensity of stimulation, pulse width, frequency) and may vary substantially, usually 4–7 years. The change of IPG can be performed under local or general anaesthesia. New technological devices with reloadable battery will obviate these constraints.

With apomorphine pump, the patient needs daily refilling of the pump. The frequent manipulations of the pump may imply a strong dependency on the caregivers. Moreover, the pump itself is often regarded as quite cumbersome by the patients.

The major advantage of HFS is the stable and permanent beneficial effect on motor and non motor symptoms. As the stimulation ideally mimics the best 'on' medication motor state, there are virtually no fluctuations and no dyskinesias (except in case of overstimulation with stimulation-induced dyskinesias that respond well to decreasing the intensity of stimulation). The amount of time per day in which the patient is in 'on' state is dramatically increased (Fraix et al. 2006). The increase in the 'on' motor state duration contributes to the improvement in quality of life.

It is true that disabling peak-dose levodopa-induced dyskinesias can be successfully reduced and even abolished by continuous subcutaneous apomorphine infusion. However, some untoward effects may complicate its use. The most common side effect of apomorphine injection is nausea. It occurs in 15% of patients and responds usually

well to domperidone. Others side-effects include hypotension, confusion, delusion, psychosis, visual hallucinations, sedation and sleep attacks (Pietz et al. 1998).

Induration and subcutaneous nodules may appear at infusion sites. There are usually asymptomatic but they can reduce apomorphine absorption. Infection or skin necrosis is rare but requires discontinuation of treatment. A rare but serious side effect is the appearance of Coombs positif auto-immune haemolytic anaemia.

Neuropsychological side-effects are often ascribed to DBS. However, it has to be kept in mind that dopaminergic therapy may also be associated with serious side effects, particularly confusion and behavioural changes related to dopaminergic dysregulation such as impulse control disorders, punding and compulsive medication use (Voon et al. 2007, 2009).

It has been established that non-motor fluctuations (NMF) (Witjas et al. 2002) occur frequently in advanced PD and may be very disabling as well. There are usually classified into three types: dysautonomic, cognitive/psychiatric and sensory/pain. It has been shown that STN-HFS significantly reduces NMF (Witjas et al. 2007) mainly on sensory, dysautonomic and cognitive fluctuations but has a minor effect on psychic fluctuations that respond more inconsistently.

### Outcome of patients who were on continuous subcutaneous apomorphine injection with pump before STN-HFS

Among patients treated with STN-HFS, patients on CSAI before surgery usually stop it postoperatively or reduce significantly its use (Alegret et al. 2004; Meissner et al. 2001; Varma et al. 2003). Indeed, all 24 patients from our institution, who were on CSAI before surgery, had stopped it 1 year after surgery. In the long term, only two patients out of 400 (0.5%) required additional CSAI because of insufficiency of surgery.

Some symptoms such as freezing of gait are not durably improved by STN-HFS. The low-frequency stimulation of the mesencephalic locomotor region in the area of pedunculopontine nucleus has shown preliminary promising results with significant improvement of gait. These results need to be confirmed in the long term and in a greater number of patients, but open up new horizons for DBS in Parkinsonian patients.

To conclude, it is essential to point out that because of the lack of controlled study comparing STN-HFS with medical alternative (continuous subcutaneous apomorphine injection or duodopa), the choice of therapeutic strategies in cases of advanced PD must be made by an experienced, multidisciplinary team. We do believe that this is the way to offer the patients the best therapeutic option which takes into account at once the hope of the patient, the severity of the disease and the surgical and medical expertise of the team.

In a skilled team, STN-HFS can offer the patient a great motor improvement and a better quality of life with acceptable side-effects.

## Conclusion

The best treatment for advanced stages of PD is still a matter of debate as there are no evidence-based large controlled randomised trials showing superiority of any of available methods. However, it has been shown that STN-HFS results in dramatic improvement in the majority of patients and has so far been unchallenged by therapeutic alternatives or innovative strategies. In addition, some unimproved symptoms such as freezing of gait might be alleviated by the stimulation of new targets in the area of mesencephalic locomotor region (PPN, cuneiform nucleus). Basic research and new technology may provide insights into the mechanisms of action of DBS and into a better knowledge in delivering the current in a more specific and orientated way which will hopefully result in improvement of the clinical condition for PD patients.

## References

Ahlskog JE, Muenter MD (2001) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 16:448–458

Alegret M, Valldeoriola F, Marti M, Pilleri M, Junque C, Rumia J et al (2004) Comparative cognitive effects of bilateral subthalamic stimulation and subcutaneous continuous infusion of apomorphine in Parkinson's disease. Mov Disord 19:1463–1469

Alesch F (2005) Sudden failure of dual channel pulse generators. Mov Disord 20:64–66 discussion 66

Antonini A, Isaias IU, Canesi M, Zibetti M, Mancini F, Manfredi L et al (2007) Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome. Mov Disord 22:1145–1149

Antonini A, Mancini F, Canesi M, Zangaglia R, Isaias IU, Manfredi L et al (2008) Duodenal levodopa infusion improves quality of life in advanced Parkinson's disease. Neurodegener Dis 5:244–246

Ardouin C, Pillon B, Peiffer E, Bejjani P, Limousin P, Damier P et al (1999) Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 46:217–223

Benabid AL, Pollak P, Seigneuret E, Hoffmann D, Gay E, Perret J (1993) Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl (Wien) 58:39–44

Benabid AL, Chabardes S, Mitrofanis J, Pollak P (2009) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 8:67–81

Binder DK, Rau GM, Starr PA (2005) Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation

for movement disorders. Neurosurgery 56:722–732 discussion 722–732
Burchiel KJ (1995) Thalamotomy for movement disorders. Neurosurg Clin N Am 6:55–71
Burkhard PR, Vingerhoets FJ, Berney A, Bogousslavsky J, Villemure JG, Ghika J (2004) Suicide after successful deep brain stimulation for movement disorders. Neurology 63:2170–2172
Charles PD, Van Blercom N, Krack P, Lee SL, Xie J, Besson G et al (2002) Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 59:932–934
Czernecki V, Pillon B, Houeto JL, Welter ML, Mesnage V, Agid Y et al (2005) Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? J Neurol Neurosurg Psychiatry 76:775–779
Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K et al (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 355:896–908
Diamond A, Jankovic J (2005) The effect of deep brain stimulation on quality of life in movement disorders. J Neurol Neurosurg Psychiatry 76:1188–1193
Dujardin K, Defebvre L, Krystkowiak P, Blond S, Destee A (2001) Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. J Neurol 248:603–611
Esselink RA, de Bie RM, de Haan RJ, Lenders MW, Nijssen PC, van Laar T et al (2009) Long-term superiority of subthalamic nucleus stimulation over pallidotomy in Parkinson disease. Neurology 73:151–153
Ferraye MU, Debu B, Fraix V, Goetz L, Ardouin C, Yelnik J et al (2010) Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 133:205–214
Fraix V, Pollak P, Van Blercom N, Xie J, Krack P, Koudsie A et al (2001) Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease. 2000. Neurology 57:S60–S62
Fraix V, Houeto JL, Lagrange C, Le Pen C, Krystkowiak P, Guehl D et al (2006) Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry 77:443–449
Fraix V, Chabardes S, Krainik A, Seigneuret E, Grand S, Le Bas JF, Krack P, Benabid AL, Pollak P (2010) Effects of magnetic resonance imaging in patients with implanted deep brain stimulation systems. J Neurosurg 113(6):1242–1245
Frank MJ, Samanta J, Moustafa AA, Sherman SJ (2007) Hold your horses: impulsivity, deep brain stimulation, and medication in Parkinsonism. Science 318:1309–1312
Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H et al (2004) Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 75:834–839
Goodman RR, Kim B, McClelland S 3rd, Senatus PB, Winfield LM, Pullman SL et al (2006) Operative techniques and morbidity with subthalamic nucleus deep brain stimulation in 100 consecutive patients with advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 77:12–17
Hamani C, Richter E, Schwalb JM, Lozano AM (2005) Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature. Neurosurgery 56:1313–1321 discussion 1321–1324
Hariz MI (2002) Complications of deep brain stimulation surgery. Mov Disord 17(Suppl 3):S162–S166
Hariz MI, Bergenheim AT (2001) A 10-year follow-up review of patients who underwent Leksell's posteroventral pallidotomy for Parkinson disease. J Neurosurg 94:552–558
Hariz MI, Rehncrona S, Quinn NP, Speelman JD, Wensing C (2008) Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years. Mov Disord 23:416–421
Herzog J, Volkmann J, Krack P, Kopper F, Potter M, Lorenz D et al (2003) Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. Mov Disord 18:1332–1337
Honig H, Antonini A, Martinez-Martin P, Forgacs I, Faye GC, Fox T et al (2009) Intrajejunal levodopa infusion in Parkinson's disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. Mov Disord 24:1468–1474
Houeto JL, Mesnage V, Mallet L, Pillon B, Gargiulo M, du Moncel ST et al (2002) Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 72:701–707
Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE et al (1998) Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 44:622–628
Joint C, Nandi D, Parkin S, Gregory R, Aziz T (2002) Hardware-related problems of deep brain stimulation. Mov Disord 17(Suppl 3):S175–S180
Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R et al (2006) Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord 21(Suppl 14):S290–S304
Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A et al (1998) Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 121(Pt 3):451–457
Krack P, Kumar R, Ardouin C, Dowsey PL, McVicker JM, Benabid AL et al (2001) Mirthful laughter induced by subthalamic nucleus stimulation. Mov Disord 16:867–875
Krack P, Fraix V, Mendes A, Benabid AL, Pollak P (2002) Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 17(Suppl 3):S188–S197
Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C et al (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349:1925–1934
Lagrange E, Krack P, Moro E, Ardouin C, Van Blercom N, Chabardes S et al (2002) Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. Neurology 59:1976–1978
Lang AE, Lozano AM (1998) Parkinson's disease. Second of two parts. N Engl J Med 339:1130–1143
Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E et al (1995) Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 345:91–95
Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D et al (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 339:1105–1111
Lozano AM, Lang AE (2001) Pallidotomy for Parkinson's disease. Adv Neurol 86:413–420
Lozano AM, Snyder BJ (2008) Deep brain stimulation for parkinsonian gait disorders. J Neurol 255(Suppl 4):30–31
Lyons KE, Wilkinson SB, Overman J, Pahwa R (2004) Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. Neurology 63:612–616
Macia F, Perlemoine C, Coman I, Guehl D, Burbaud P, Cuny E et al (2004) Parkinson's disease patients with bilateral subthalamic deep brain stimulation gain weight. Mov Disord 19:206–212
Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D et al (2008) Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 359:2121–2134
Meissner W, Trottenberg T, Klaffke S, Paul G, Kuhn AA, Arnold G et al (2001) Apomorphine therapy versus deep rain stimulation.

Clinical and economic aspects in patients with advanced Parkinson disease. Nervenarzt 72:924–927
Moreau C, Defebvre L, Destee A, Bleuse S, Clement F, Blatt JL et al (2008) STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. Neurology 71:80–84
Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, Kulisevsky J, Obeso JA, Albanese A, Hariz MI, Quinn NP, Speelman JD, Benabid AL, Fraix V, Mendes A, Welter ML, Houeto JL, Cornu P, Dormont D, Tornqvist AL, Ekberg R, Schnitzler A, Timmermann L, Wojtecki L, Gironell A, Rodriguez-Oroz MC, Guridi J, Bentivoglio AR, Contarino MF, Romito L, Scerrati M, Janssens M, Lang AE (2010) Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord 25(5):578–586
Ohye C, Shibazaki T, Sato S (2005) Gamma knife thalamotomy for movement disorders: evaluation of the thalamic lesion and clinical results. J Neurosurg 102(Suppl):234–240
Ostergaard K, Sunde N, Dupont E (2002) Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. Mov Disord 17:693–700
Pahwa R, Wilkinson SB, Overman J, Lyons KE (2003) Bilateral subthalamic stimulation in patients with Parkinson disease: long-term follow up. J Neurosurg 99:71–77
Parsons TD, Rogers SA, Braaten AJ, Woods SP, Troster AI (2006) Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol 5:578–588
Piallat B, Chabardes S, Torres N, Fraix V, Goetz L, Seigneuret E et al (2009) Gait is associated with an increase in tonic firing of the sub-cuneiform nucleus neurons. Neuroscience 158:1201–1205
Pietz K, Hagell P, Odin P (1998) Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. J Neurol Neurosurg Psychiatry 65:709–716
Pillon B, Ardouin C, Damier P, Krack P, Houeto JL, Klinger H et al (2000) Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. Neurology 55:411–418
Poewe W, Wenning GK (2000) Apomorphine: an underutilized therapy for Parkinson's disease. Mov Disord 15:789–794
Pollak P (2007) Deep brain stimulation for movement disorders. In: Jankovic J (ed) Parkinson's disease and movements disorders. Lippincott Williams & Wilkins, Philadelphia, pp 653–691
Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S et al (2005) Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 128:2240–2249
Samanta J, Hauser RA (2007) Duodenal levodopa infusion for the treatment of Parkinson's disease. Expert Opin Pharmacother 8:657–664
Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M et al (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128:940–947
Seijo FJ, Alvarez-Vega MA, Gutierrez JC, Fdez-Glez F, Lozano B (2007) Complications in subthalamic nucleus stimulation surgery for treatment of Parkinson's disease. Review of 272 procedures. Acta Neurochir (Wien) 149:867–875 discussion 876
Sillay KA, Larson PS, Starr PA (2008) Deep brain stimulator hardware-related infections: incidence and management in a large series. Neurosurgery 62:360–366 discussion 366–367
Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D et al (2007) Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 130:1596–1607
Stibe C, Lees A, Stern G (1987) Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on-off fluctuations. Lancet 1:871
Stibe CM, Lees AJ, Kempster PA, Stern GM (1988) Subcutaneous apomorphine in parkinsonian on-off oscillations. Lancet 1:403–406
Strowd RE, Cartwright MS, Passmore LV, Ellis TL, Tatter SB, Siddiqui MS (2010) Weight change following deep brain stimulation for movement disorders. J Neurol 257(8):1293–1297
Tasker RR (1990) Thalamotomy. Neurosurg Clin N Am 1:841–864
Thobois S, Ardouin C, Lhommee E, Klinger H, Lagrange C, Xie J et al (2010) Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. Brain 133:1111–1127
Tseng HM, Su PC, Liu HM, Liou HH, Yen RF (2007) Bilateral subthalamotomy for advanced Parkinson disease. Surg Neurol 68(Suppl 1):S43–S50 discussion S50–S51
Varma TR, Fox SH, Eldridge PR, Littlechild P, Byrne P, Forster A et al (2003) Deep brain stimulation of the subthalamic nucleus: effectiveness in advanced Parkinson's disease patients previously reliant on apomorphine. J Neurol Neurosurg Psychiatry 74:170–174
Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J (2002) Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology 58:396–401
Visser-Vandewalle V, van der Linden C, Temel Y, Celik H, Ackermans L, Spincemaille G et al (2005) Long-term effects of bilateral subthalamic nucleus stimulation in advanced Parkinson disease: a four year follow-up study. Parkinsonism Relat Disord 11:157–165
Voon V, Moro E, Saint-Cyr JA, Lozano AM, Lang AE (2005) Psychiatric symptoms following surgery for Parkinson's disease with an emphasis on subthalamic stimulation. Adv Neurol 96:130–147
Voon V, Potenza MN, Thomsen T (2007) Medication-related impulse control and repetitive behaviors in Parkinson's disease. Curr Opin Neurol 20:484–492
Voon V, Fernagut PO, Wickens J, Baunez C, Rodriguez M, Pavon N et al (2009) Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. Lancet Neurol 8:1140–1149
Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J et al (2002) Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology 59:408–413
Witjas T, Kaphan E, Regis J, Jouve E, Cherif AA, Peragut JC et al (2007) Effects of chronic subthalamic stimulation on nonmotor fluctuations in Parkinson's disease. Mov Disord 22:1729–1734