Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease

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High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN-HFS) is the preferred surgical treatment for advanced Parkinson's disease. In the 15 years since its introduction into clinical practice, many studies have reported on its benefits, drawbacks, and insufficiencies. Despite limited evidence-based data, STN-HFS has been shown to be surgically safe, and improvements in dopaminergic drug-sensitive symptoms and reductions in subsequent drug dose and dyskinesias are well documented. However, the procedure is associated with adverse effects, mainly neurocognitive, and with side-effects created by spread of stimulation to surrounding structures, depending on the precise location of electrodes. Quality of life improves substantially, inducing sudden global changes in patients' lives, often requiring societal readaptation. STN-HFS is a powerful method that is currently unchallenged in the management of Parkinson's disease, but its long-term effects must be thoroughly assessed. Further improvements, through basic research and methodological innovations, should make it applicable to earlier stages of the disease and increase its availability to patients in developing countries.

Introduction

In 1987, the discovery that high-frequency deep brain stimulation (DBS) was able to mimic, in a reversible and adjustable manner, the effects of ablation of functional targets has revived functional neurosurgery of movement disorders, thus allowing clinicians to target areas suggested by basic neuroscience, such as the subthalamic nucleus (STN; figure 1).[1–3] In the first patients with advanced Parkinson's disease (PD) to receive high-frequency stimulation of the STN (STN-HFS) in 1993,[4,5] tremor, rigidity, and bradykinesia improved significantly, thus allowing levodopa doses to be decreased by an average of 60%.[6] This reduction in turn alleviated levodopa-induced motor fluctuations and dyskinesias.[7] Since then, several thousands of patients all over the world have received STN-HFS implants and shown marked improvements, making this method the reference surgical procedure for advanced PD. Many reports of clinical experience with this procedure have been published, and have documented how the method has rapidly become an established therapy.

In this Review, we briefly describe the surgical techniques used and provide an overview of the prognostic factors and clinical improvements of patients with PD. We also discuss the limitations and morbidity associated with STN-HFS, and explore its clinical efficiency and areas that need to be improved, in addition to future progress and potential successors.

Surgical procedure

The surgical procedure itself varies between neurosurgery teams, depending on their equipment and usual practices. The aim of pre-operative imaging is to determine the best location for target stimulation (figure 2). Stereotactic ventriculography is still used by some teams, although many do not use it because of concern over complications or because they consider MRI localisation to be satisfactory. The problem of MRI distortion, which is the main reason why ventriculography

is still used, has not been satisfactorily addressed. The radiographic images taken after injection of contrast medium into the right frontal horn of the ventricle provide internal landmarks, represented by features of the third ventricle, to which various atlases and coordinates of the targets can be related.

Stereotactic MRI provides direct visualisation of the STN target, visible on T2-weighted sequences as a hyposignal surrounded by white matter (zona incerta above, and fields of Forel bundles below) that separates the STN from the substantia nigra pars reticulata. The procedure is planned from the MRI scans, which are eventually merged with the ventriculographic images. The stereotactic target is constructed by use of graphic tools that are included in the navigation software. The planning stage allows the surgeons to check the match between the target and the MRI scan of the STN, and to choose an entry point that will allow the team to avoid hitting the vessels of the cortical surface and the sulci, ventricle, caudate nucleus, etc.

Electrophysiological exploration is done by use of microelectrodes and multiple tracks, either subsequently or simultaneously. Some teams prefer not to make several tracks if the first track has provided satisfactory results, and some even explore the planned track directly with the chronic tetrapolar electrode. Typical firing patterns, particularly asymmetrical spikes at high frequency with bursting patterns, and proprioceptive responses to passive movements, are characteristic features of the STN. By contrast, neuronal activity in the substantia nigra pars reticulata comprises symmetrical spikes of large amplitude and regular activity, and is generally unresponsive to external stimuli.

Implantation is usually done under local anaesthesia. However, some teams use general anaesthesia[8] to decrease the stress and pain for the patient, although in doing so they lose the intraoperative observation of the clinical benefits of DBS. We believe that the assessment of the clinical response to DBS, by a skilled neurologist
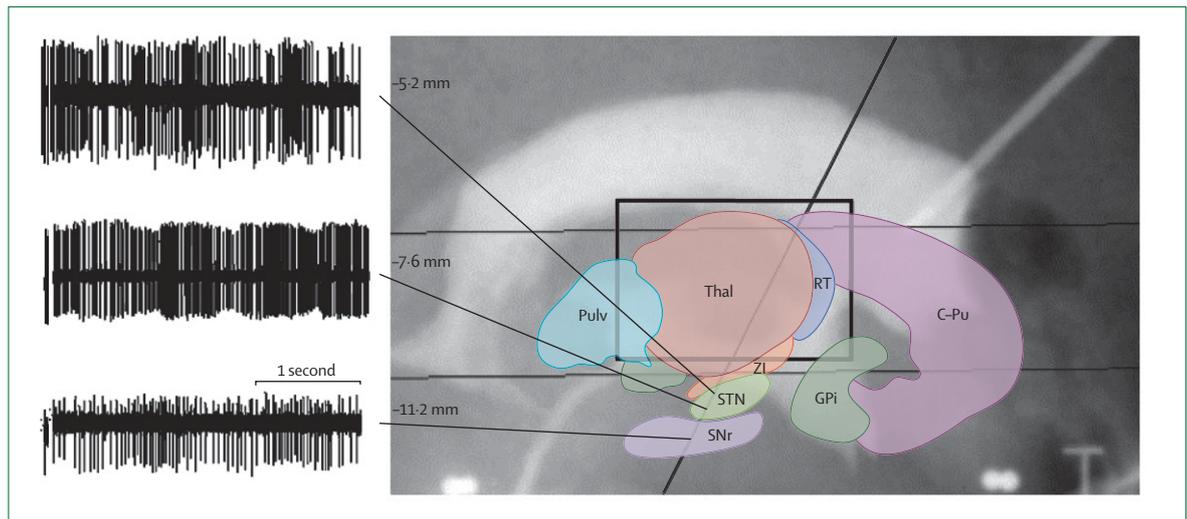
Figure 1: **Schematic anatomical location and characteristic firing patterns of the subthalamic nucleus**
MRI representation of the major structures are overlaid onto a ventriculogram. The trajectory can be determined from the anterior and posterior commissures and the top of the thalamus (black rectangle). The trajectory (black oblique line) encounters the thalamus, at the bottom of which the microelectrode recording is started. This subsequently shows a rich, irregular, burst of neural activity in the kinesthetic neurons in the subthalamic nucleus (STN; 5·2 mm and 7·6 mm below the commissural line), which is responsive to passive movements of the limbs (not shown), and high-amplitude, regular, and unresponsive neural activity in the substantia nigra pars reticulata (SNr; 11·2 mm below the commissural line). C-Pu=caudate and putamen (striatum). GPi=internal globus pallidus. Pulv=pulvinar. RT=reticularis thalami. Thal=thalamus. ZI=zona incerta.

in the operating theatre, is pivotal to the decision of where to place the electrode and is therefore crucial to the success of surgery. All symptoms, except gait, can be tested, but rigidity of the wrist seems to be the most convenient because it does not require the patient's active participation and can be scored in the operating theatre by use of a semi-quantitative scale. Speech and akinesia can sometimes be difficult to test consistently because the patient might be too tired by a lengthy exploration, but if testing is done early in the procedure, the patient could be cooperative enough to enable the testing of these functions. Tremor is an excellent symptom to use, but is often absent in the advanced akinetic-rigid stages of patients selected for surgery. The side-effects depend on which of the structures that surround the STN are reached by the spread of current when the electrode is either outside the STN or close to its boundaries.

When the best track (in terms of beneficial effects, fewest side-effects, largest security margin between thresholds for improvement and side-effects) has been identified, the corresponding microelectrode is removed and replaced by a chronic lead (DBS 3389, 1·5 mm contact length, 0·5 mm spacing, 1·27 mm diameter), which is fixed to the skull by various means (eg, plate and screw, plug, dental cement, or clips). The pulse generator is inserted under general anaesthesia into a subcutaneous pouch in the subclavicular area, either at the end of the surgery or several days later. This delay allows post-operative MRI to be done if local regulations, the MRI manufacturer's recommendations, or reluctance among the neuroradiologists does not allow an MRI to be done on an implanted stimulator.

Programming is a direct continuation of the surgical procedure and is as important as accurate electrode placement in ensuring successful treatment. The neurologists start programming either during the week after pulse-generator implantation or several weeks later. Only four settings, involving various combinations of the number of electrodes (one to four) and the polarity of the contacts and case of the stimulator, are used initially. The frequency is set at 130 Hz and the pulse length at 60 μs. Usually, the polarity is positive for the case of the stimulator and negative for the DBS contact. The four contacts on the electrode (numbered from zero for the distal contact to three for the proximal contact) are subsequently investigated. The voltage is progressively increased from zero while checking the efficiency of stimulation, initially on the rigidity of the wrist, which is a particularly sensitive sign that is easy to explore by passive manipulation. Similarly, the neurologist checks the induction threshold of side-effects such as paraesthesias (due to diffusion to the lemniscus medialis), dyskinesias, eye deviation (usually monocular and ipsilateral to stimulation, related to the involvement of the oculomotor nerve fibres), or muscular contraction (in the face or arm). The best setting (the highest threshold for side-effects and the lowest threshold for symptom improvement) is typically 2·0–3·5 V, 130 Hz, 60 μs, the metallic case of the stimulator is set as the positive pole, the negative pole being the chosen contact (or contacts) of the deep tetrapolar electrode. Conversely, if the electrode has been suboptimally placed, the neurologist can test different combinations, including bipolar settings, that might allow the side-effects induced by the involvement of adjacent
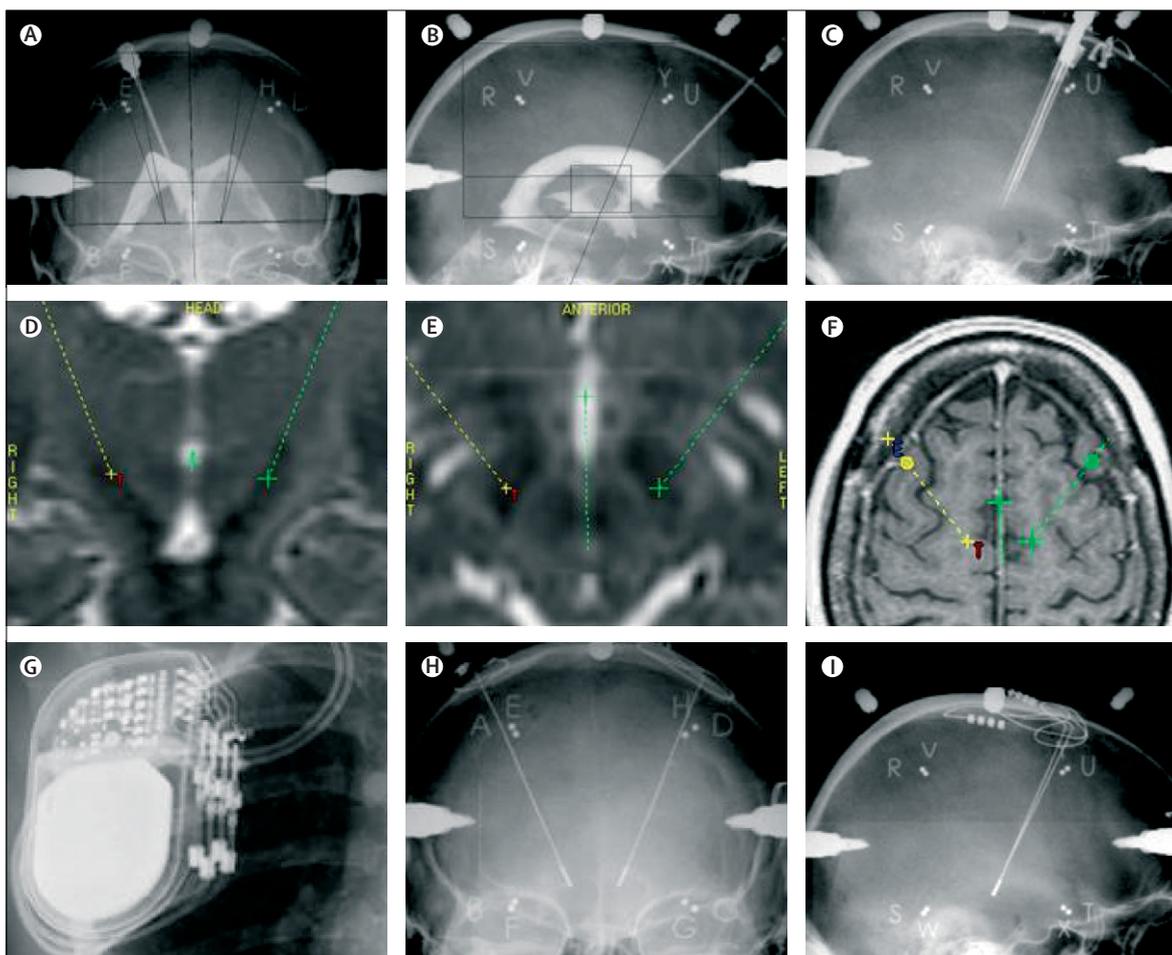
***Figure 2:* Surgical implantation of stimulation electrodes into the subthalamic nucleus in advanced Parkinson's disease**
(A,B) Pretargeting of the subthalamic nucleus (STN) by stereotactic contrast ventriculography, which allows visualisation of the ventricular landmarks: the anterior and posterior commissures of the third ventricle, top of the thalamus (at the floor of the lateral ventricle), and midline. (C) Intraoperative microrecording is done along the trajectory designed on the basis of multimodal pretargeting with stereotactic ventriculography and MRI, by use of a microdrive with five parallel microelectrodes spaced 2 mm apart, providing the ultimate functional signature of the STN target (see figure 1), and the final determination of the target. Coordinates, with respect to the posterior commissure, bicommissural plane, and midline, are as follows: 43·2±5·8% of bicommissural distance anterior to the posterior commissure, 15·6±8·7% of the thalamus height below the bicommissural plane, 11·6±1·8 mm lateral to the midline. Stereotactic MRI by use of T2-weighted, coronal (D) and axial (E) images, and (F) T1-weighted axial images, showing the hyposignal of the STN target and the underlying SNR structures (D,E) and the entry points at the cortical level to avoid vessels (F). (G) The implantable programmable generator is in the right subclavicular area. (H,I) Post-operative imaging of the permanent electrodes show that they are mainly symmetrical.

structures to be minimised, and thus reach an acceptable compromise without the need to replace the electrodes.

When the best settings for contacts and polarity have been selected, the voltage is progressively increased over a few days to avoid the induction of dyskinesias, which are very similar to levodopa-induced dyskinesias. These tend to settle down over time as their induction threshold increases. At the same time, drug doses, already reduced before the operation, are further decreased, and set at a compromise level that is low enough to avoid dyskinesias but high enough to prevent apathy and hypophonia.

Mechanism of action

The mechanism of action of high-frequency DBS is still not clear, even 21 years after its introduction. The mechanism is believed to be independent of the target, because DBS mimics the effects of ablation in all targets used to date, but its effects depend on stimulation rather than on the creation of a lesion. Several submechanisms are probably involved in producing functional inhibition: (1) a jamming of the neuronal message transmitted through the stimulated structure[9] and desynchronisation of abnormal oscillations;[10,11] (2) extinction or strong inhibition of neuronal firing, supported by direct observation of the decrease in discharge rate during stimulation;[12,13] (3) dual effects, combining excitation and induction of high-frequency bursts; and (4) inhibition of the production or release of certain neurotransmitters and hormones.[14]

The putative mechanisms of action suggest that neuroprotection might be a consequence of STN-HFS.

In patients with PD and in animal models, the neuronal activity of the glutamatergic STN is profoundly altered as shown by the association of a rhythmic bursting pattern with a general increase in firing rate.[1,3,6,10,11,13] The increased STN output of glutamate (an excitatory amino acid) on the dopaminergic neurons of the substantia nigra pars compacta might participate in their degeneration. STN-HFS, by decreasing glutamate output, could slow down the neurodegenerative process that affects the nigral dopaminergic system. To assess this hypothesis, several studies in laboratory animals have been done, by use of lesion or STN-HFS in rats and non-human primates.[15–19] Their results tend to support the neuroprotection hypothesis. However, one study in human patients, using PET scans, did not confirm these experimental data, although the disease might have progressed too far in these patients for STN-HFS to have had a beneficial effect.[20]

Patient selection

Indications

Patients who are thought to benefit from STN-HFS are those affected by clinically diagnosed idiopathic PD, in whom the cardinal symptoms of the disease—bradykinesia, rigidity, and tremor—are likely to be significantly improved.[5,6,21,22] Those who show improvement with the optimum adjustment of anti-PD drugs or suprathreshold levodopa dose (300 mg per dose) are highly likely to show a similar improvement after optimum placement of the electrodes into the STN.[23] 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.

Contraindications

Contraindications are important to consider in order to avoid putting at risk those patients who might not benefit from surgery. Dementia and cognitive deficits are not improved by STN-HFS and might even be increased by the multifactorial trauma of the procedure. Moreover, these symptoms might include elements indicative of an atypical parkinsonian syndrome or the start of additional system (ie, cholinergic) degeneration. At this stage, the patient might benefit from the motor improvements induced by STN-HFS, but only for a short period, because their quality of life will be greatly impaired by the progressing cognitive disorder. All general surgical contraindications apply to DBS, particularly if risks related to brain penetration are involved (ie, bleeding). Additional contraindications are related to the generation of electrical artefacts that might interfere with sensing devices, such as cardiac pacemakers and defibrillators.

Prognostic factors

In general, poor prognostic factors are difficult to establish. Age, as in all surgical therapies, is negatively related to general outcome, and varies substantially between patients. Age and the response to levodopa are predictive of motor outcome,[23] and although high-frequency stimulation of the STN reduces motor complications in all patients, postoperative quality of life improves only in patients aged younger than 65 years.[24]

Gait disturbance must be carefully assessed by the neurologists before surgery. Freezing, as part of the pattern of akinesia, usually responds to levodopa. When freezing of gait persists, and is not improved by drugs, it is usually not improved by STN stimulation.[25] However, gait might be improved by the low-frequency stimulation of a new target, the pedunculopontine nucleus.[26–28]

Speech can be improved by STN-HFS, but less so than other motor symptoms.[29] The improvement of hypophonia by STN-HFS is not as great as that achieved by drugs. Preoperative hypophonia might even progress to severe hypophonia when drug doses are significantly decreased after surgery, and low doses of levodopa must therefore be reintroduced to prevent this outcome.

Use of STN-HFS in atypical parkinsonism (multiple systemic atrophy, progressive supranuclear palsy) has not been the subject of clinical trials, but the overall experience seems to be negative. During the initial phases, improvement in motor symptoms might significantly help patients for a limited period, but this is not the case for other symptoms (cognitive decline and dementia, oculomotor disturbance, autonomic disorders, etc). Thus, the benefits are secondarily obliterated by cognitive decline.

Previous ablative surgery (thalamotomy, pallidotomy) is not a contraindication for DBS in general, or of DBS of the STN in particular, provided that the ablative procedure has not destroyed the target.[30,31] Previous unsuccessful DBS does not alter the target; thus, if during the patient's selection all criteria predict a beneficial effect, reimplantation is always possible and is usually successful.[32] The inefficient electrode might even be left in place, provided that it is at least 2 mm from the corrected target and that intraoperative imaging is done (ie, by fluoroscopy).

Clinical outcome

Since the first application of STN-HFS in 1993, several thousand patients worldwide have received implants. 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.

Improvement of symptoms

The main scale used to analyse the intensity of symptoms in PD is the UPDRS, which is based on the rating of a series of symptoms for both sides of the body. The UPDRS comprises four parts: section I assesses changes in mentation and cognition (including behaviour and mood); section II assesses changes in activities of daily

living; section III assesses motor symptoms; and section IV assesses therapeutic complications, fluctuations and dyskinesias, and sensory symptoms. This scale has been validated by evidence-based medicine studies,[33] and is used as a reference standard in preference to other less specific and global scales,[34,35] or those specifically aimed at determining quality of life (eg, the 39-item PD questionnaire [PDQ-39]).[36]

Table 1 provides a summary of the studies that have assessed improvements in symptoms due to STN-HFS. Although it was difficult to obtain the same information from each report, the improvements are globally of the same order of magnitude, which supports the robustness of the procedure, despite differences in the expertise of the various teams and the methods used.

In a meta-analysis of 37 cohorts comprising 921 patients,[49] complemented by a multicentre controlled study of 136 patients and a retrospective analysis over 5 years,[21,22] the estimated decreases in absolute UPDRS II (activities of daily living) and III (motor) scores after surgery in the stimulation-on, medication-off state compared with the preoperative off-medication state were 50% and 52%, respectively. Pairwise comparisons showed that neurostimulation caused significantly greater improvements than drugs alone in PDQ-39 and UPDRS III scores. The mean UPDRS III score improved by 41% in the off-medication state and by 23% in the on-medication state; the UPDRS II score also improved markedly.[22] The STN-HFS improvement in UPDRS III scores, versus baseline values, was reasonably stable over time, decreasing from a 66% improvement at 1 year to 54% at 5 years after surgery, and in additional studies with follow-up periods of 2–4 years was reported to be 43–57%.[43,51–54]

	Patients (n)	Follow-up (months)	Age (years)	Duration of PD (years)	Quality index*		Improvement†			Decrease		
					UPDRS II	UPDRS III	UPDRS II	UPDRS III	Symptoms	LDED	Daily off-time	PDQ-39
Krack et al[7]	15	1–12	57·8 (8·5)	14·2 (4·3)	..	1·04	72·6%	71%	Tremor 87%; bradykinesia 71%; rigidity 67%; dyskinesia 40%	56%	..	..
Kumar et al[37]	7	12	67	14·3	..	1·26	30%	58%	Tremor 82%; bradykinesia 57%; rigidity 68%; gait 49%; dyskinesia 83%	40%	..	80%
Limousin et al[6]	20	12	56 (8)	14 (5)	..	..	58%	60%	Tremor 80%; bradykinesia 60%; rigidity 50%; gait 12%; dyskinesia 55%	50%	..	73%
Pinter et al[38]	9	12	..	..	..	0·75	..	45%	Dyskinesia 91%	60%	..	89%
Houeto et al[39]	23	6	53·0 (2)	14·7 (1)	..	0·94	55%	67%	Dyskinesia 77%	61%	..	..
DBSPDSG[40]	96	6	59·0 (9·6)	14·4 (90)	..	0·91	..	51%	Tremor 56%; bradykinesia 18·9%; rigidity 33%; gait 33%; dyskinesia 74%	37%	..	60%
Lopiano et al[41]	16	3	60·7	15·4	0·98	0·86	68%	57%	Tremor 68%; bradykinesia 61%; rigidity 54%; gait 57%; dyskinesia 71%	72%	..	85%
Volkman et al[42]	16	12	60·2 (9·8)	13·1 (5·9)	..	0·92	..	67%	Tremor 89%; bradykinesia 48%; rigidity 75%; gait 44·4%; dyskinesia 90%	63%	56%	75–100%
Østergaard et al[43]	26	12	59·8 (6·8)	14 (6)	1·1	1·18	64%	64%	Tremor 90%; bradykinesia 55%; rigidity 73%; gait 64%; dyskinesia 86%	19%	..	83%
Simuni et al[44]	12	12	58 (11)	12 (4)	..	0·84	42%	47%	Tremor 83%; bradykinesia 39%; rigidity 32%; gait 52%; dyskinesia 64%	55%	..	37%
Pahwa et al[45]	19	28	58·4	12	..	0·76	27%	28%	Tremor 79·3%; bradykinesia 15·9%; rigidity 26·3%; gait 44·4%	57%	47·2%	..
Krack et al[21]	49	60	55·0 (7·5)	14·6 (5·0)	0·87	0·89	66·1%	65·9%	Tremor 75%; bradykinesia 62·7%; rigidity 73·1%; gait 67·7%; dyskinesia 58%	58·5%	71%	..
Rodriguez-Oroz et al[46]	49	36	59·8 (9·8)	15·4 (6·3)	1·03	0·84	43·1%	49·5%	Tremor 87%; bradykinesia 43·2%; rigidity 59·2%; gait 41·4%; dyskinesia 71·7%	65·6%	56%	..
Hamani et al[47]	471	..	59·3 (8·3)	13·7 (4·5)	0·90	0·86	58–42%	50–49%	Tremor 81%; bradykinesia 52%; rigidity 64%; gait 63%; dyskinesia 73–94%	52%	..	..
Fraix et al[48]	95	12	57 (8)	14 (5)	..	..	48·5% (14·5)	57%	Dyskinesia 74·7%	59·2%	48·1%	28%
Kleiner-Fisman et al[49]	..	..	58·6 (2·4)	14·1 (1·6)	0·81 (0·1)	0·88 (0·1)	49·9% (7·0)	52·3% (4·2)	Dyskinesia 69·1% (7·1)	59·9% (0·9)	68·2% (10·6)	34·5% (15·3)
Deuschl et al[22]	..	..	60·5 (7·4)	13·0 (5·8)	..	..	39%	41·0% (12·3)	Dyskinesia 54%	50%	..	23·9% (13·6)
Goodman et al[50]	28/100	12–48	60·1 (11)	12·8 (5·4)	..	..	29·5%	..	Dyskinesia 60%	..	69%	..

Data are means for age, duration, and quality index. SDs are also given in parentheses for improvement and other categories, if available. *Quality index was calculated as follows: (improvement under stimulation)/(improvement on medication). †Percentage improvement was calculated as follows: [(baseline–after stimulation)/baseline]×100. LDED=levodopa-equivalent doses.

Table 1: Improvements in patients with Parkinson's disease after high-frequency stimulation of the subthalamic nucleus

For rigidity and tremor, the improvement was 70–75%, and for akinesia it was 50%.[21] STN-HFS has a direct effect on dystonia during the off-medication state, which was observed in 71% of patients preoperatively and in only 19% at 1 year and 33% at 5 years. Postural stability and gait also improved, but speech improved only during the first year and then progressively returned to baseline by 5 years. UPDRS II scores also improved, although with a significant worsening over time. Mean postoperative reduction of dopaminergic drugs was 50–56%.[22,49] Levodopa-induced dyskinesias and disability, and their duration were decreased by 69%, 58%, and 71%, respectively,[21] which has a major effect on quality of life.[22,55] These decreases mainly indicate desensitisation due to both long-term stimulation-induced neuronal plasticity and levodopa withdrawal[56–58] afforded by the beneficial effects of STN-HFS; this restores a more normal pharmacokinetic reaction of the striatal dopaminergic receptors and therefore leads to a reduction in dyskinesias, which are thought to be related to the pulsatile administration of levodopa.[59] By contrast with the improvements seen during the off-medication state, motor symptoms during the on-medication state are either only moderately or not improved by STN-HFS.[6,37,46] Moreover, UPDRS III scores neglect the temporal dimension of the improvement, whereby the fluctuating benefits seen after drug intake before STN-HFS are replaced by a stable improvement indicated by an increase of about 47–71% in the time for which patients have a medication-related reduction in motor symptoms.[21,22,45,46,49,50,55]

Speech is generally less improved with STN-HFS than are other parkinsonian signs.[6,21,46] Hypophonia might improve, but dysarthria might be aggravated due to current diffusion to corticobulbar fibres.[60] As a consequence, the patient's satisfaction, particularly with regard to hypophonia and ability to communicate with their family, can decline after surgery. Improvements in sleep architecture and quality have been reported, with an increase in total sleep time (up to 47%),[61,62] resulting indirectly from improvement in night-time akinesia and early morning dystonia. STN stimulation can also be effective for improving bladder control by decreasing detrusor hyperreflexia.[63,64]

After STN-HFS, progression of symptoms over time closely resembles the natural history of PD on medical treatment, but without the motor complications. Therefore, these changes are thought to represent progression of the disease rather than side-effects of stimulation. A longitudinal PET study showed continuous decline of dopaminergic function in patients with advanced PD after clinically effective bilateral STN-HFS, with rates of progression within the range of previous studies of non-stimulated patients.[20]

Improvement in quality of life

After treatment, patients can expect improvements in quality of life. A large randomised controlled multicentre study of 156 patients compared bilateral STN-HFS in combination with drugs versus optimum drug therapy alone over a 6-month period.[22] Neurostimulation resulted in improvements of 24–38% in the PDQ-39 subscales for mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort, and a 22% improvement in the physical summary score of the 36-item short-form questionnaire versus no change in the drug-only group. The mean improvement in PDQ-39 summary index score was 24%, and the dyskinesia scale obtained in patients in the off-medication state was improved by 54%. The total number of adverse events was higher among drug-only patients. This confirmed previous uncontrolled studies on quality of life after STN-HFS, which consistently reported greater improvements in subscores of mobility, activities of daily living, stigma, emotional well-being, and bodily discomfort than in social support, cognition, and communication.[65,66] The quality of life of caregivers also improved.[67]

Drugs and stimulation settings

After surgery, most patients are given dopamine agonists rather than levodopa to avoid the risk of dyskinesia. However, this strategy has not yet been validated by controlled studies. After 5 years of follow-up after STN-HFS, a third of patients had still not resumed levodopa treatment and the decrease in the levodopa-equivalent daily dose (ie, the sum of the doses of the various drugs weighted by their specific equivalent binding coefficient to the dopaminergic receptors) was 67%, similar to that at 1 year; fewer than 1% of patients received no dopaminergic drugs at this time point.[21] The dramatic and early reduction of drug intake might have accounted for some of the complications, such as dysarthria, apathy, and cognitive problems.[21,68]

Monopolar stimulation (amplitude $2 \cdot 9 \pm 0 \cdot 6$ V, frequency 139 ± 18 Hz, pulse duration $63 \pm 7 \cdot 7$ μs) has been used in most patients by most studies, with similar results.[46] There is no indication of habituation and effects are stable over 5 years of follow-up with no increase in stimulation settings needed after the first year.[21] STN-HFS is mostly bilateral, because candidates for surgery usually show bilateral motor symptoms and because the effects of unilateral stimulation are mainly contralateral and do not provide maximum improvement in walking,[5,69] except in some patients with asymmetrical motor symptoms.[70] Postoperative management of dopaminergic drugs might be difficult after unilateral STN-HFS. However, management of the device itself is straightforward, and the batteries can last up to 7 years.[71]

Surgical complications and side-effects

Table 2 summarises the complications that have been related to the surgical procedure. Reviews have produced rather too general a summary,[32,40] and, contrary to data on improvements, outcomes varied widely between centres (table 2),[72–92] which might be due to differences in expertise or methods. However, definitions of complications were

	Patients (n)	Follow-up	Complications (n)	Procedure-related complications	Physical complications	Cognitive/psychiatric complications	Transient/permanent side-effects	Deaths
Beric et al[72]	86	3·5 years	69·8	Hardware 8·8%; stimulation 4·4%	Infection 1·1%	..	?/6	..
Oh et al[73]	79	3·3 months	..	Hardware 25·3%; implantation 8·4% per electrode per year	Haemorrhage 1·26%; infection 15·2%	..	..	..
Pahwa et al[45]	33	28 months	..	Hardware 48·5%; implantation 30·3%; stimulation 42·8%	Infection 4·3%	Depression 1·7%	..	..
Binder et al[74]	357 DBS leads	5 years	..	Implantation 3·1% per electrode	Haemorrhage 2·5%	..	..	..
Krack et al[21]	49	5 years	..	Hardware 6·1%; implantation 57·1%; stimulation 44·9%	Weight gain 83·7% (~5 kg); haemorrhage 4%; infection 2·1%	Confusion 24·5%; depression 2·1%; suicide 2·1%‡	49/10·2	1
Lyons et al[75]	81	17 months	..	Hardware 26·2%; implantation 12·5%	Haemorrhage 1·2%; infection 6·2%	Suicide 0%	1·2/0	..
Temel et al[76]	108	42·6 months	..	..	Infection 3·8%	..	..	..
Okun et al[77]	41	..	..	Hardware 46%	Infection 4·8%	..	..	..
Rodriguez-Oroz et al[46]	49	3 years	47	Hardware 12·2%	..	Cognitive 24·5%; depression 6·12%	18·4	..
Hamani et al[47]	471	..	..	Hardware 9%; implantation 2%; stimulation 19%	..	..	..	..
Hamani et al[78]	922	1–10 years	..	Hardware 11·4%	Weight gain 17·6%; haemorrhage 2·8%; infection 6·1%	Confusion 13·7%; depression 6·8%	19	..
Blomstedt et al[79]	119	136 months	..	Hardware 14·3%	Infection 3·5%	..	..	..
Amirnovin et al[80]	40	4 years	..	Hardware 5%; implantation 2·5%	Haemorrhage 10%	..	..	..
Fraix et al[48]	97	12 months	..	..	Haemorrhage 5·2%	..	..	2·1
Deuschl et al[22]	156	6 months	..	..	Haemorrhage 3·8%	Confusion 5·1%; depression 5·1%; suicide 0·13%	..	..
Kleiner-Fisman et al[49]	921	..	..	Hardware 4·4%	Weight gain 8·4%; haemorrhage 3·9%; infection 1·6%	Confusion 15·6%; suicide 0·1/0·7%§	28	..
Goodman et al[50]	100	1–4 years	74	Hardware 15%; implantation 19%	Weight gain 3%; haemorrhage 2%; infection 7%	Confusion 13%	?/0	..
Voges et al[81]	262	36·3 months	..	Hardware 13·9%; implantation 4·2%	Haemorrhage 0/0·2%;† infection 5·7%	..	0·2/0·4	..
Seijo et al[82]	130	7 years	30	Hardware 1·8%; implantation 12%	Haemorrhage 3·5%	..	..	..
Vesper et al[83]	73	24 months	..	..	Infection 9·6%	..	..	..
Kenney et al[84]	319	10 years	..	Hardware 29·8%; implantation 4%	Haemorrhage 0·3%; infection 4·4%	Confusion 5%; suicide 0·6%¶	..	0·6
Tir et al[85]	103	12 months	..	Hardware 4%; implantation 8%	Haemorrhage 5%; infection 7%	..	..	..
Sillay et al[86]	420	8 years	..	Hardware 4·5%	..	..	..	..
Videnovic et al[87]	928	..	..	Hardware 8·7%; implantation 33·5%; stimulation 57·1%	Weight gain 37·5%; haemorrhage 2/1·2%†; infection 2·8%	Cognitive 18·4%; confusion 10·2%; depression 1·3%	..	..
Alvarez et al[88]	18	3 years	..	Implantation 16·7%*	Infection 1%	..	16·7%‖	..

Data are percentages of patients, but several complications could occur in each patient. Hardware-related complications include hardware revision required, fracture, lead migrations, battery failures, skin erosion, and hardware-related infection; implantation-related complications include misplacement, confusion, hallucinations, seizures, aborted procedures, cerebral infarct, air embolism, and wound haematoma; stimulation-related complications include speech impairments, apathy, and dyskinesias, etc. ?=Transient side-effects unknown. *Severe generalised chorea. †Transient/permanent side-effects. ‡One suicide and seven attempts in the first 49 patients, but still only one suicide in the total series of 350 patients in 11 years. §Attempted suicide/suicide. ¶Unrelated to procedure. ‖Severe dysarthria.

Table 2: Complications after high-frequency stimulation of the subthalamic nucleus in patients with Parkinson's disease

not the same between reports and were not exclusive (a patient might have several complications, each of which might be counted more than once in different categories). None of the studies reported the number of patients who were free of complications. We can therefore provide only a general overview of the common adverse effects, the events that raise concerns, and the preventive measures that can be taken to decrease the risks to which patients are exposed.

Complications related to implantation of electrodes and hardware

Data reported by different teams vary substantially (table 2).[93–98] In a study of 526 consecutive patients (325 patients with STN-HFS, 138 with thalamic DBS, and 63 with DBS of the internal globus pallidus [GPi]),[99] haemorrhages occurred in 8·4% (range 0·2–12·5%) of all DBS cases mostly at the entry point or subcortically, but rarely in the target, and more often in hypertensive patients. 3·4% of this series of patients had asymptomatic haemorrhages, symptoms were transient in 4·4%, and permanent in only 0·6% of patients. MRI is important in the preoperative stage to avoid damage to superficial vessels and penetration of the sulcus, ventricles, and caudate nucleus; MRI can also be useful in the postoperative stage to visualise asymptomatic bleeding. Severe adverse effects leading to permanent neurological after-effects are mainly due to intracranial haemorrhage, which occurred in 2–4% of cases.[40,49]

Other transient or benign complications are common and do not lead to permanent after-effects. About 10% (range 1–36%) of patients were reported to have transient post-operative confusion (from temporo-spatial disorientation to psychosis),[21,100–114] which might be related to intracranial contusion or minimal bleeding, although non-specific factors, such as the long duration of brain surgery and the withdrawal of dopaminergic drugs, might be implicated. Complications in general state, including aspiration pneumonia, pulmonary or urinary infection, thrombophlebitis, and pulmonary embolism, can occur in patients with severe PD. Duration of surgery and the number of electrode passes have been poorly related to clinical outcome and complications,[77,89] but the influence of microelectrode recording is still under debate.[74,77,79,80,89,96] In summary, if the indication is correct, poor outcome of STN-HFS in PD is generally related to either incorrect implantation or to hardware failure.[67]

Hardware-related complications

Several studies report a high incidence of hardware-related complications (range 2·7–50%).[75,106,115–119] Reported infection rates for DBS surgery vary widely, from less than 1% to more than 15% (table 2).[40,47,49,72–75,79–81,83–85,93–95,97,98,120–127] Infections are mostly superficial, and occur in about 1·1–15·2% of published cases[40,47,49,72–75,79–81,83–85,93–95,97,98,120–127] and were seen in about 4·4% of the cases (1·1% were severe, 1·3% were significant, and 1·9% were mild or

benign) in our unpublished series.[99] They typically present within 3 months of surgery, and most often occur at the site of the implanted pulse generator.[40,75,79,81–85,98,125,127] Other complications related to the implant, such as skin erosions, lead breakage, extension wire failure, premature battery consumption, or malfunction of the pulse generator, are common.[73,75,76,78,79,90–92] Such complications led to discontinuation of treatment in 6·1% of 49 patients in a multicentre study with 4 years of follow-up.[92] These side-effects can generally be managed without permanent morbidity, but in the case of infection, the stimulator and related hardware almost always have to be removed.

Discomfort might occur around the extension lead, which can pull in the lateral region of the neck or around the stimulator in the subclavicular area. Scars might be unsightly, and the bump made by the thickness of the cable connector in the parietal region can be visible in bald patients with thin scalps. Flat connectors can be used to minimise this side-effect.

Stimulation-related complications

Although adverse effects due to stimulation are common, those inducing permanent neurological impairment are relatively rare (~3%). In a study that compared two groups of 78 stimulated and medically treated patients,[22] the occurrence of adverse events was not significantly different between the groups, although serious adverse events were significantly more common in those receiving neurostimulation than in those treated with drugs alone. Most adverse events were well known medical problems associated with advanced PD.

Stimulation-induced adverse effects are generally reversible, and can be alleviated by adjusting the settings to produce an acceptable compromise between the absence of side-effects and a suboptimum benefit. Stimulation-induced adverse effects often occur if the electrode placement is suboptimum; they vary according to the anatomic location of the stimulated fibres or neuronal structure, and include dysarthria or hypophonia in 4–17% of patients.[30,43,52,121,128,129] Other side-effects include dysphagia, motor contraction, paraesthesias, eye deviation, gaze deviation, visual flashes, nausea, dizziness, sweating, flushes, imbalance, eyelid opening apraxia, dyskinesias, and discontinuation of the effect of levodopa with worsening of akinesia.[130,131] However, some adverse effects might occur with the progressive increase in voltage necessary to adequately control parkinsonian features. Stimulation-induced dyskinesias can be a sign of accurate placement of the electrodes, and are reversible by decreasing the voltage, the drug dose, or both.[21,22,30,132,133] Most patients with STN or GPi stimulation gain weight (mean 3 kg, maximum 5 kg).[134]

Alterations of higher functions

Most studies reporting cognitive or behavioural deterioration are limited by small sample sizes and do not include PD control groups.[130] Patients who have

behavioural abnormalities after surgery generally had these symptoms before surgery, and the reported abnormal behaviour is clearly not target specific.[131] A high prevalence of confusion and behavioural side-effects has been reported immediately after surgery, but in the long term, cognitive and psychiatric effects are relatively rare.[21]

Patients who were depressed after surgery were usually depressed before.[105] Depression is a common finding in patients who request surgery,[131] and patients with suicidal ideation require close psychiatric follow-up. Preoperative depression, although transiently improved in the first postoperative year, does not change in the long term after STN-HFS, and, in addition to a history of repeated surgery, was found to be a risk factor for postoperative suicide, although was also subject to selection bias.[135] Most of the observed neuropsychiatric symptoms are thought to be transient, treatable, and potentially preventable,[130] and have been reported in up to 25% of cases.[28] In the postoperative period, transient hypomania,[21,22,105] acute sadness,[136] impulsive aggressive behaviour,[21,137] hilarity,[138] or mania might develop,[139,140] commonly due to the combined effects of drugs and STN surgery.[141] Transient depressive episodes with longer follow-up were observed in 17% of patients.[21]

Apathy is part of PD,[142] and is a common finding in patients with PD after STN-HFS.[21,105] Severe apathy related to postoperative withdrawal of dopaminergic drugs can occur, especially in patients addicted to levodopa,[143] and responds to resuming dopaminergic drugs.[105,131] Transient apathy has been reported in 5% of 42 patients who responded to dopaminergic drugs, antidepressants, or both.[21] Apathy did not respond to dopaminergic treatment in 12% of these 42 patients.

Reports on suicides after STN surgery, although rare (0·7% of 921 patients have made suicide attempts, although only 0·1% succeeded),[49] have raised concerns.[6,131,135] Depression and suicidality are multifactorial, related to societal issues, and to changes in treatment, and not specifically related to the procedure.[133] Depression and suicide have been observed after all types of major surgery that have provided patients with significant improvements, and after the release of long-term prisoners.[144–146] These changes in mood after STN-HFS are probably related to changes in surrounding brain structures, but they could represent behavioural patterns induced by an abrupt change in STN limbic activity.[138]

The most frequently observed long-term neuro-psychological change is a decline in word fluency.[109] No short-term global cognitive deterioration has been reported in selected young and non-demented patients.[110,130,147,148] Minor changes in neuropsychological test scores have been reported with limited impact on cognitive function.[114,130] In one series of 42 patients followed up for 5 years, no significant changes were noted in the Beck depression inventory, although the average score on the Mattis Dementia Rating Scale was worse at 5 years, which indicated progressive dementia in three patients, but the changes were not significant.[21]

There are generally no major modifications of personality structure.[149] Mean frontal lobe function tends to decrease slightly over time.[21] After STN-HFS, patients lose their normal ability to take time when faced with decision conflict, and tend to make impulsive decisions.[150] Elderly patients with reduced cognitive function or patients with preoperative cognitive decline are at risk of acceleration of their cognitive decline.[21,151] In the long term, progression of the dysexecutive syndrome can lead to dementia in non-operated patients with PD.[21]

Although there are some risks associated with STN-HFS, as reviewed here, they tend not to be severe and the clinically valuable improvement in motor function means that the benefits of STN-HFS outweigh the risks for many severely disabled patients. Careful selection of candidates should lower morbidity further. However, we are unable to determine from the literature the number of patients who are completely free from all complications. Complications and adverse events might seem more common after surgery involving the STN than other targets (ie, GPi or ventral intermediate nucleus) in some series,[22,46,87] but not in others.[74,152] We cannot conclude whether this is directly related to a differential effect of properties of the STN and GPi, or to other factors, because only one randomised controlled trial has compared the various targets.[152]

Alternatives to STN-HFS
Other targets
STN-HFS mainly improves levodopa-sensitive symptoms. Midline symptoms, dysautonomic symptoms, and gait disturbance unresponsive to levodopa (ie, freezing)[25] are only slightly improved, if at all. Thus, randomised controlled trials are currently underway to compare the outcome of surgery involving the GPi versus the STN, to reassess old targets (ie, centre median–parafascicular complex of the thalamus), and to assess new targets (ie, radiation prelemniscalis, caudal zona incerta, and pedunculopontine nucleus).

Experimental findings suggest that DBS of the mostly cholinergic pedunculopontine nucleus, which degenerates in PD, could improve gait-related motor function if stimulated at low frequency (20–25 Hz) but not at high frequency,[153,154] and human clinical trials of pedunculopontine DBS at these low frequencies have thus been designed. Preliminary results support the basic science assumptions: improvements in gait dysfunction and postural instability have been reported in both on-medication and off-medication states.[26–28] Therefore, low-frequency stimulation of the pedunculopontine nucleus adds to the benefits of STN-HFS by improving gait, but on its own cannot recreate the positive effects of STN-HSF on the typical motor symptoms of PD. The exact anatomical structure to be stimulated is still under debate,[155,156] and the determination of the target might benefit from new imaging procedures.[157] Larger, more extensive, studies are needed and have been initiated, although the results are not yet available.

Ablative methods, which were almost completely abandoned in the post-levodopa era, have again been proposed to solve the problems of the cost, and of the burden for neurologists of parameter adjustments, despite being seen as one of the advantages of DBS. However, the expected high rate of severe complications from ablative surgery should remind us that other solutions to the drawbacks of DBS should be sought.[88]

Cortical stimulation

Experiments to assess chronic cortical stimulation of the motor area of monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism have shown an improvement in PD symptoms.[158] Human clinical trials are being done, the results of which have yet to be reported. However, preliminary results reported to date have been disappointing, and depend on the indications (eg, parkinsonian tremor, dystonia, or post-ictal spasticity).[159,160]

Gene therapy

On the basis of the assumption that the hyperactive STN would deliver increased glutamate excitotoxin to the nigral dopaminergic cells, an adeno-associated virus vector containing an isoform of glutamic acid decarboxylase has been used to transform the glutamatergic STN of rats into a GABAergic structure.[161] This has subsequently led to a clinical trial in patients with PD; preliminary data have shown a clinical improvement and PET evidence of metabolic improvement.[162] Encouraging data have also been reported on the delivery of adeno-associated virus serotype 2-neurturin into the striatum of patients with PD.[163]

Growth factor infusion

Experimental studies in rats and monkeys have shown the therapeutic effects of the glial-derived nerve factor in PD. Chronic infusion of this factor into the striatum of patients with PD has been done and a highly significant improvement was reported.[164–166] However, these findings were not confirmed by a controlled study.[167]

Neural grafts

Over the past few decades, grafting methods have been the focus of an impressive amount of basic research in high-profile laboratories around the world, in addition to several controlled trials in patients with PD. Encouraging, but always partial, results have been reported. Such results show clinical improvement, evidence of dopaminergic reinnervation of the striatum, good survival of the grafted neurons, efficient production of dopamine and increased tyrosine hydroxylase (rate-limiting enzyme in dopamine production) immuno-reactivity. Various types of cells have been used (adrenal gland, mesencephalic fetal grafts, and more recently, epithelial retinal cells). Stem cells are also being investigated, which might be better tolerated

immunologically, but raise their own (oncological) problems. Despite the elegance of this approach, it is still experimental and is not currently available to patients.[168]

Infusion therapy

Levodopa-induced dyskinesias are the main drawback of drug therapy. They are considered to result from a loss of an optimum response by the striatal dopaminergic receptors, induced by pulsatile administration of levodopa.[59] Continuous infusion of dopamine agonists such as lisuride or apomorphine, which produce a more stable and regular dopamine concentration in the brain, clearly decreases the dyskinesias, but induces cutaneous nodules at the site of injection.[169,170] As an alternative to this, use of intraduodenal administration by duodeno-gastrostomy is being investigated and satisfactory results have been reported, despite the invasiveness and discomfort of this method.[171]

New drugs

Pharmaceutical companies are working intensively on designing dopaminergic agonists that would have the beneficial effects of levodopa but without the major complication of dyskinesia. If such a drug could be designed, this would negate the use of surgical approaches such as DBS, as happened with ablative methods when levodopa was introduced.

Unanswered questions and future research

STN-HFS is currently widely thought of as the surgical method of choice for patients with advanced PD. The benefits of STN-HFS are due to combined mechanisms and probably involve several adjacent structures, including the STN itself. To improve the success of the procedure, more selectivity is needed, both at the topographical level with newly designed electrodes and rechargeable batteries, and at the level of stimulation from the pulse sequence to the pulse waveform.[172] All hardware components need to be redesigned, miniaturised, and made more biocompatible and more compact, and should be designed to suppress cables and distant pulse generators via nanotechnology. Although the overall cost of treatment for the life of the implanted pulse generator (~7 years)[71] is lower in implanted patients than in medically treated patients,[48,173] the costs are due to hardware that is needed at the time of implantation and of replacement. New designs need to be cheaper to allow the management of advanced PD, and also need to be available in countries where health-care systems are developing.

The question of the mechanism of action of STN-HFS and whether it has a neuroprotective effect must be addressed both by basic research and clinical trials, including clinical and metabolic assessment of its effects on disease progression, stability, or even regression, in a precisely quantitative manner. Although these trials

might be difficult to design and run, this will be the only way to find out whether this theoretical, and still very controversial, concept has any validity and use in the clinical situation.

The timing of surgery is of great importance. There is global consensus that surgery could be proposed at an earlier stage of disease, as soon as symptoms cannot be adequately managed by drugs, and when the risk-to-benefit ratio has become reasonable. This needs to be shown by large multicentre studies. STN-HFS has better results than GPi stimulation, but seems to have more complications and side-effects. Thus, the best target still needs to be defined through a large and well designed controlled clinical trial. The same strategy must be applied to understand the effects of unilateral STN-HFS, which can apparently have lower morbidity[174] in patients with asymmetric symptoms and can sometimes lead to changes on the ipsilateral side of the body.[175]

The review of the literature on complications and side-effects is difficult to synthesise, because of the variable nature in which they are reported, which is mainly due to a lack of guidelines.[87] All complications or adverse effects should be reported, irrespective of their severity. A qualitative standardised assessment should be defined, ranging from "benign" (ie, not symptomatic, only visible on MRI, not persistent, or do not require reoperation), to "significant" (ie, symptomatic, persistent, or require reoperation, but with no permanent sequelae) and "severe" (ie, symptomatic, require reoperation, hardware revision or ablation, specific treatment, and are responsible for permanent sequelae). We also believe that the number of patients without any complications should be reported. However, long-term adverse events associated with this technique can be considered acceptable in view of the severity of the disability of those patients selected for surgery.

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