Deep brain stimulation in Parkinson's disease

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Ther Adv Neurol Disord
(2009) 2(6) 379–391
DOI: 10.1177/1756285609339382

Abstract: During the last 15 years deep brain stimulation (DBS) has been established as a highly-effective therapy for advanced Parkinson's disease (PD). Patient selection, stereotactic implantation, postoperative stimulator programming and patient care requires a multi-disciplinary team including movement disorders specialists in neurology and functional neurosurgery. To treat medically refractory levodopa-induced motor complications or resistant tremor the preferred target for high-frequency DBS is the subthalamic nucleus (STN). STN-DBS results in significant reduction of dyskinesias and dopaminergic medication, improvement of all cardinal motor symptoms with sustained long-term benefits, and significant improvement of quality of life when compared with best medical treatment. These benefits have to be weighed against potential surgery-related adverse events, device-related complications, and stimulus-induced side effects. The mean disease duration before initiating DBS in PD is currently about 13 years. It is presently investigated whether the optimal timing for implantation may be at an earlier disease-stage to prevent psychosocial decline and to maintain quality of life for a longer period of time.

Keywords: deep brain stimulation, DBS, Parkinson's disease, subthalamic nucleus, STN, GPi, VIM

Introduction

Parkinson's disease (PD) is a disabling chronic neurodegenerative disorder clinically characterized by akinesia, tremor, rigidity, and postural instability, caused mainly by dopaminergic neuron degeneration of the substantia nigra [Hughes *et al*. 1992]. Levodopa and a number of dopamine agonists are available for a dopamine-replacement therapy resulting in an effective relief of motor symptoms in the early stage of the disease. However, this treatment is eventually hampered by the increasing occurrence of motor complications, such as wearing-off and sudden-off phenomena as well as troublesome hyperkinesias [Goetz *et al*. 2005]. Prior to the introduction of Levodopa [Birkmayer *et al*. 1961], surgical lesional procedures – in particular pallidotomies and thalamotomies – were applied as ultima ratio for treatment of refractory symptoms. The result was an improvement of symptoms, but often at the risk of irreversible and severe side effects like dysarthria or hemiparesis. Bilateral surgery dramatically increased complications and was therefore rarely performed.

Deep brain stimulation (DBS) of the motor thalamus, the ventral intermedius nucleus (VIM), was first used in 1986 to treat medically refractory tremor in PD [Benabid *et al*. 1987]. DBS of various basal ganglia nuclei has since developed into a highly-effective treatment for several movement disorders. In PD, DBS of the internal globus pallidus (GPi) and the subthalamic nucleus (STN) were found to be effective and safe targets.

Compared with surgical lesioning procedures, chronic DBS used with the standard stimulation parameters for PD leads to no, or only minimal, tissue damage [Pilitsis *et al*. 2008; Kuncel and Grill, 2004; Burbaud *et al*. 2002; Haberler *et al*. 2000] and is therefore largely reversible. Furthermore, unlike lesioning, bilateral DBS can be implemented without significantly increasing side effects. It is possible to adjust stimulation parameters postoperatively and in the course of the disease. In different randomized controlled trials DBS showed a better functional outcome with fewer side effects [Esselink *et al*. 2004; Schuurman *et al*. 2000] and therefore almost completely replaced lesional surgery in industrialized nations. However, due to economic restrictions in particular countries, lesioning still might be the only option.

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Patient selection

The selection of appropriate patients is of particular importance and individual risk *versus* benefit ratio has to be carefully assessed. DBS in parkinsonian syndromes is thought to be successful only in idiopathic PD including monogenic parkinsonism [Moro *et al*. 2008]. With the exception of tremor which often shows a varied response, dopaminergic medication is highly effective for the treatment of all cardinal motor symptoms but leads to long-term motor complications like wearing off and/or disabling dyskinesias. Prevalence of overall levodopa-induced motor fluctuations after a mean of 5 years of treatment reaches up to 50%, increases with the duration of the treatment and is especially high in younger patients [Le Witt, 2008; Ahlskog and Muenter, 2001; Olanow *et al*. 2001; Rascol *et al*. 2000]. Symptoms best controlled by DBS can be classified into (a) levodopa-sensitive OFF symptoms; (b) levodopa-induced dyskinesias; and (c) tremor.

Concerning STN-DBS, the principal response to dopaminergic medication has the highest predictive value for a good and persistent motor outcome with stimulation [Pahwa *et al*. 2006; Kleiner-Fisman *et al*. 2003; Benabid *et al*. 2002; Charles *et al*. 2002; Welter *et al*. 2002; Krack *et al*. 1998]. Symptoms that are resistant to dopaminergic medication are typically also resistant to DBS. Patients, therefore, should achieve an improvement of at least 30% in the preoperative levodopa-test measured by the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. The OFF score should be performed after an interruption of antiparkinsonian medication for at least 12 hours and the ON score in the best clinical state after administration of a single suprathreshold levodopa-dose, which is typically 1.5 times the effective levodopa morning-dose equivalent [Langston *et al*. 1992]. An improvement of more than 50% would be desirable as a direct correlation of preoperative levodopa responsiveness and outcome after STN-DBS has been shown [Kleiner-Fisman *et al*. 2003; Welter *et al*. 2002]. Lower preoperative levodopa-response has been associated with a decline in postoperative cognitive screening tests [Smeding *et al*. 2006]. OFF phases should cover more than 25% of the awake time and should have a minimum severity of 30/108 points on the UPDRS motor score [Hilker *et al*. 2009]. Peak-dose-hyperkinesias and biphasic dyskinesias as well as OFF-dystonia respond well to DBS [Krack *et al*. 1999]. Severe disabling tremor is the only symptom which, up to 80–90%, shows an excellent response to DBS, even when resistant to levodopa. Tremor is therefore a good target symptom for STN-DBS [Krack *et al*. 1997].

Freezing of gait, postural instability or dysarthrophonia persisting during best medical-ON state revealed no significant improvement after STN-DBS [Charles *et al*. 2002; Welter *et al*. 2002]. Atypical parkinsonian syndromes, e.g. multiple system atrophy or progressive supranuclear palsy, show at best slight and transient improvement and should not be treated with DBS [Lang *et al*. 2006]. Autonomic dysfunctions in an early stage suggest an atypical parkinsonism and, if present, must be critically reviewed. Although there is evidence that bladder function in PD can be slightly improved by DBS [Herzog *et al*. 2006], it is currently no main target for the indication of DBS.

Another important parameter for prediction of outcome is age. Biological age shows an inverse correlation with improvement of motor function and a positive correlation with perioperative complications even in experienced and specialized centers [Weaver *et al*. 2009; Voges *et al*. 2007; Charles *et al*. 2002, Welter *et al*. 2002].

Finally, prior to implanting DBS electrodes for chronic stimulation, evaluation of cognitive function and neuropsychiatric symptoms is of crucial importance. Manifest dementia and/or psychiatric disorders like psychosis or depression persisting during ON, or personality disorders are contraindications for DBS.

Inclusion and exclusion criteria are as follows:

Inclusion

(1) clinically idiopathic PD
(2) significant improvement with regard to dopaminergic medication (>30%)
(3) refractory motor fluctuations or tremor
(4) only minor symptoms during ON-state

Exclusion (relative)

(1) biological age over 75 years
(2) severe/malignant comorbidity with considerably reduced life-expectancy
(3) chronic immunosuppression

(4) distinct brain atrophy
(5) severe psychiatric disorder (cognitve deficits/ dementia, frontal-dysexecutive syndrome, manifest psychosis, depression, substance abuse, personality disorder)

Target points

Currently STN is the main target nucleus for DBS in PD. All cardinal symptoms that principally respond well to levodopa, including akinesia, rigidity, tremor, and postural instability can be effectively treated by STN-DBS. The best outcome might be achieved by stimulation of the dorsolateral motor part of the STN [Herzog *et al.* 2004; Voges *et al.* 2002], but there is evidence that stimulation of the zona incerta also results in good improvement [Plaha *et al.* 2006]. STN-DBS should usually be performed bilaterally to alleviate motor symptoms on both sides and allow for optimal reduction of medication [Kumar *et al.* 1999].

DBS of GPi shows an immediate and significant reduction of levodopa-induced disabling dyskinesias. The effect on OFF-symptoms might be less pronounced [The DBS for PD study group, 2001]. However, the excellent reduction of dyskinesias allows a further increase of dopaminergic medication and consecutive improvement of motor symptoms. In previous studies comparing STN-DBS with GPi-DBS there were no significant differences in motor outcome between these targets [Okun *et al.* 2009; Weaver *et al.* 2005; The DBS for PD study group 2001; Burchiel *et al.* 1999], but there are several reasons which favor STN for the majority of PD-patients. First, GPi-DBS does not allow for a reduction of medication [Volkmann *et al.* 2004]. Second, with regard to OFF-symptoms, a weakening of improvement after GPi-DBS over the years has been described [Volkmann *et al.* 2004]. Also, GPi-DBS commonly requires higher settings which results in shorter battery life-spans [Volkmann *et al.* 2001]. A large randomized, prospective multicenter study including 255 patients and directly comparing STN- and GPi-DBS with best medical treatment is currently being conducted [Weaver *et al.* 2009]. For the first 6-month period of the trial the two target groups were pooled into one DBS group which does not allow comparison of the efficacy between the two targets. However the second phase of the study will directly compare the improvement of STN-DBS and GPi-DBS and will shed further light on this issue.

In a majority of PD-patients VIM-DBS leads to an immediate and almost complete suppression of tremor [Benabid *et al.* 1996], but has no effect on akinesia and rigidity. Therefore, VIM-DBS is only rarely performed in PD but may sometimes still be an option in older patients with unilateral tremor-dominant PD.

The pedunculopontine nucleus has recently aroused interest as a new target for DBS in PD [Stefani *et al.* 2007]. However, the benefit was limited within the small patient group and until now this procedure remains experimental.

Perioperative management

Pre- and intraoperative procedure

Preparation begins several days before surgery with the reduction of the dopamine agonist. Levodopa should be withdrawn on the eve of the operation. During surgery awake patients should be kept in an appropriate OFF-condition as an experienced movement disorders specialist has to evaluate the effect of DBS by test stimulation intraoperatively.

Localization of the target point is based on stereotactic coordinates [Schaltenbrand and Wahren, 1977, Schaltenbrand and Bailey, 1959; Talairach *et al.* 1957] and adapted individually using image fusion of cranial magnetic resonance imaging (cMRI) and cranial computed tomography (CCT) [Schuurmann *et al.* 1999; Starr *et al.* 1999]. Direct visualization of the target nucleus by high-resolution MRI with a voxel size $<1.5\,mm^3$ and high contrast requires axial/coronar T2 and/or inversion recovery sequences and might be superior to indirect target point calculation [Andrade-Souza *et al.* 2005; Vayssiere *et al.* 2002].

For further verification of the electrode position, intraoperative analyses using different neurophysiological techniques have to be performed. Test stimulation in the target area to identify the site of the best therapeutic effect is usually performed by an experienced movement-disorders specialist. Furthermore, mapping the side effects – e.g. oculomotor dysfunction, tetanic contractions, paresthesia, nausea, etc. which may occur during co-stimulation of neighbouring nuclei or fibers – helps to identify the borders of the target nucleus.

The correct positioning of the electrodes can be improved by the use of multitrajectory microelectrode-recording (MER) to register the characteristic activity patterns of the cells in the different nuclei [Hamani *et al*. 2005; Lozano *et al*. 1998]. On the other hand, there is a debate whether MER may increase the risk of cerebral hemorrhages [Hariz, 2002; Palur *et al*. 2002; The DBS for PD study group, 2001].

The tip of the final DBS-electrode used for chronic stimulation has four contacts and each of them can be activated separately for stimulation. This allows for a minor modification of the stimulated area, even if the electrode is already implanted. Intra- and postoperative controls of electrode position using stereotactic x-ray, CCT, or cMRI for correct targeting are indispensable. After implantation of the electrodes they are connected to the pulse generator which is implanted subcutaneously at an infraclavicular or abdominal site.

Postoperative care and stimulator settings

The postoperative adjustment of stimulator settings in STN-DBS remains time-consuming. Usually, stimulation parameters and medication have to be adapted reiteratively. Post-surgery an immediate and significant improvement of symptoms may occur without activating the stimulator. This clinical improvement is attributed to a microlesioning effect and disappears in the course of time. It can last up to several months but in most cases diminishes in the first days and weeks. Once the microlesioning effect has faded, all four electrode contacts should be tested carefully and the contact with the best effect and highest-threshold for side effects be selected for chronic stimulation. In the following days and weeks, stimulation amplitude will be increased successively, paralleled by a gradual decrease of levodopa dosage, until a good mobility is achieved with no significant dyskinesias [Volkmann *et al*. 2006, 2000]. Typical stimulation parameters for chronic DBS are monopolar stimulation, voltage 2.5–3.5 V, impulse duration 60–90 μs and frequency 130–180 Hz. Several issues have to be taken into account when adapting the stimulator settings. Depending on the side effects occurring during chronic stimulation, it may become necessary to change to bipolar stimulation or activate a different contact. Stimulation-induced dyskinesias may occur with a delay after parameters have been increased, that is, major changes should be avoided in the late evening or before the weekend. Occasionally, it is difficult to distinguish OFF-associated dystonia and stimulation-induced dystonia. In these cases, the stimulation effect in the OFF-condition has to be re-evaluated. Furthermore acute effects on mood and subjective well-being following STN-DBS are well-known phenomena [Funkiewitz *et al*. 2003; Schneider *et al*. 2003]. Overly rapid changes of stimulation parameters may even directly induce affective phenomena, e.g. mirthful laughter or pathological crying [Wojtecki *et al*. 2007; Krack *et al*. 2001]. Should the dopaminergic medication be reduced too rapidly, disabling mood disturbances may occur which may require medical intervention [Okun *et al*. 2003].

Because of the complexity of STN-DBS the patient's outcome improves if a movement disorders and DBS specialist programs the device, and if implantation and postoperative patient care is performed in a specialized center [Moro *et al*. 2006].

Programming the devices for GPi-DBS and VIM-DBS is less complex as the medication does not have to be adapted. Once the active contact with the best efficacy/side effect profile has been selected, it is usually possible to increase the parameters faster than with STN-DBS. VIM-DBS stimulation parameters are similar to those used in STN-DBS, while GPi-DBS often requires higher amplitudes and/or impulse duration [Deuschl *et al*. 2002; Volkmann *et al*. 2000].

If standard stimulator settings are used, the capacity of the battery is exhausted after 4–6 years and a surgical replacement of the battery becomes necessary. Recently, a new stimulation device has been introduced which allows wireless recharging of the battery without surgery.

Clinical outcome

Several studies have shown significant improvement of motor function after bilateral STN-DBS or GPi-DBS in advanced PD [Krack *et al*. 2003; The DBS for PD study group, 2001; Limousin *et al*. 1998; Volkmann *et al*. 1998,]. STN-DBS results in a mean reduction of OFF-symptoms of 60% and in most cases the dopaminergic medication can be reduced significantly which leads to a reduction of disabling dyskinesias by about 60% [Krack *et al*. 2003; The DBS for PD study group, 2001]. DBS of the GPi shows an immediate reduction of levodopa-induced

disabling dyskinesias of about 80% [Volkmann *et al.* 2004]. UPDRS motor-score was improved from 37% (GPi) to 49% (STN) after surgery and the percentage of time with good mobility and without disabling dyskinesias was more than doubled [The DBS for PD study group, 2001]. These results are consistent with findings in other studies and were finally confirmed in a large prospective, randomized, multicenter study showing a 41% improvement of motor function 6 months postoperatively [Deuschl *et al.* 2006]. This study was also the first to show a significant advantage of DBS compared with best medical treatment and a significant improvement in quality of life. During a 6-month follow-up period a generic quality of life scale (SF-36) showed an improvement of 22% and a disease-related quality of life score (PDQ-39) revealed an overall improvement of 25% in the DBS group. Regarding PDQ-39 subscores, improvements of 24–38% were recorded for mobility, activities of daily living (ADL), emotional well-being, stigma, and bodily discomfort [Deuschl *et al.* 2006]. Similar results were found in a recent large controlled trial where patients were randomized into STN-DBS or GPi-DBS or best medical treatment [Weaver *et al.* 2009]. Although older patients were included in the study (25% aged 70+ years) an improvement of the OFF-time UPDRS motor score by 29% was observed in the DBS group. Overall the PDQ-39 score improved by 17% [Weaver *et al.* 2009].

Long-term observations after STN-DBS showed an improvement in UPDRS motor scores of 66% at 1 year and 54% at 5 years after implantation [Krack *et al.* 2003]. This slight decrease in motor improvement after 5 years likely reflects disease progression. While reduction of levodopa-induced dyskinesias after GPi-DBS seems to remain significantly reduced, OFF-period motor symptoms and motor fluctuations gradually decline [Volkmann *et al.* 2004], with improvements in ADL scores lost after the first year. Replacement of GPi electrodes into the STN can restore the initial benefit and result in a significant reduction of dopaminergic medication [Volkmann *et al.* 2004]. Another multicenter trial found sustained improvement in motor function over a period of 4 years after STN-DBS as well as GPi-DBS [Rodriguez-Oroz *et al.* 2005].

The long-term follow-up of VIM-DBS revealed effective control of tremor 6 years postoperatively while axial symptoms worsened. The initial improvement in ADL-scores at the 1 year follow-up disappeared after 6 years [Hariz *et al.* 2008]. Table 1 gives an overview of studies investigating the clinical outcome of DBS.

It remains unclear currently whether DBS exerts neuroprotective effects. Several studies have shown a lasting effect, of at least 4–5 years in duration, with marked improvement of motor function [Visser-Vandewalle *et al.* 2005; Kleiner-Fisman *et al.* 2003; Krack *et al.* 2003], but they have been unable to demonstrate any influence of DBS on progression and the natural course of the disease [Krack *et al.* 2003]. In a imaging study using positron emission tomography (PET), a continuous decline of dopaminergic function under effective STN-DBS was shown which was comparable with the natural progression [Hilker *et al.* 2005]. However, recent animal studies show a saving of dopaminergic cells after STN-DBS which might lead to a slowing of disease progression [Wallace *et al.* 2007; Temel *et al.* 2006].

Complications and side effects

In recent years, improvements of cerebral imaging techniques have greatly increased the safety of functional neurosurgery, but surgery-related complications remain a possibility. The most severe complication of DBS surgery is intracerebral hemorrhage (ICH) which is reported to occur in 0.2–5% (Table 2). The degree of hemorrhages varies from asymptomatic ICH to severe ICH resulting in significant and persistent neurological deficits or death. A large variability in the number of postoperative infections ranging from 1.8–15.2% of cases is reported [Oh *et al.* 2002; Limousin *et al.* 1999]. Infections most commonly occur in the area surrounding the pulse generator [Voges *et al.* 2007; Lyons *et al.* 2004; The DBS for PD study group, 2001] (Table 2). Treatment with systemic antibiotics and local surgical-lavation usually suffices, but in severe cases the implanted device has to be removed to prevent further spreading of the infection [Voges *et al.* 2007]. Other hardware complications include lead breakage or malfunction of the pulse generator [Voges *et al.* 2007; Lyons *et al.* 2004]. Table 2 summarizes the complications related to electrode implantation and hardware reported in trials including more than 100 patients.

Decrease of cognitive function was initially assumed to occur especially in older patients or those with preoperative cognitive deficits

Table 1. Clinical outcome after subthalamic nucleus/internal globus pallidus deep brain stimulation.

	Number of patients	Follow-up (years)	Improvement UPDRS* II (%)	Improvement OFF-UPDRS* III (%)	Decrease OFF-time (%)	Increase ON-time w/o dyskinesia (%)	Improvement PDQ-39[$] (%)
Original studies:							
Krack *et al.* 1997	15	1		71			
Kumar *et al.* 1998	7	1	30	58	80	200	
Limousin *et al.* 1998	20	1	58	60	72.7		
DBSPDSG 2001	96	0.5		51	61	270–229	
Volkmann *et al.* 2001	16	1		67			
Pahwa *et al.* 2003	19	2.3	27	28	61		
Krack *et al.* 2003	49	5	66–49	66–54			
Rodriguez-Oroz *et al.* 2005	49	3	43–28	50–39	56–43	260–265	
Fraix *et al.* 2006	95	1	48	57		192	28
Deuschl *et al.* 2006	156	0.5	39	41	64	237	24
Weaver *et al.* 2009	255	0.5		29	42	171	17
Reviews and meta-analyses:							
Hamani *et al.* 2005	471	5	58–42	56–49			
Kleiner-Fisman *et al.* 2006	921	>0.5	50	52	68.2		34.5

*Unified Parkinson's Disease Rating Scale.
[$]Parkinson's Disease Questionnaire.

Table 2. Complication after STN-/GPi-DBS related to surgery and hardware.

	Number of patients (leads)	Follow-up (months)	Haemorrhage (%)	Infection/ erosion (%)	Hardware complications (%)
Original studies:					
Binder *et al.* 2003	357 leads	60	3.1		
Temel *et al.* 2004	108 (178)	42.6 ± 22.5		3.8	
Blomstedt and Hariz, 2005	119 (161)	mean 40		3	17.3
Deuschl *et al.*2006	78 (156)	6	1.9	3.8	1.3
Goodman *et al.* 2006	100 (181)	mean 4	2	4.7	11.5
Voges *et al.* 2006	262 (352)	36.3 ± 20.8	0.2	5.7	13.9
Seijo *et al.*2007	130 (252)	37	6.92		3.84
Kenney *et al.* 2007	319 (507)	10	1.5	4.4	4
Tir *et al.* 2007	103 (206)	1	5.8	6.8	3.9
Sillay *et al.* 2008	420 (759)	6			4.5
Weaver *et al.* 2009	121 (242)	6	0.8	9.9	6.6
Reviews and meta-analyses:					
Hamani *et al.* 2005	471		2		9
Hamani and Lozano, 2006	922		2.8	6.1	11.4
Kleiner-Fisman *et al.* 2006	921		3.9	3.6	4.5
Videnovic and Metman 2008	1154 (2205)		3.8	2.9	5

[Alegret *et al.* 2001; Dujardin *et al.* 2001; Trepanier *et al.* 2000]. Recently, it was shown that, while there is a selective decrease in frontal cognitive functions, in particular executive functions, DBS of the STN does not reduce overall cognition [Witt *et al.* 2008; Smeding *et al.* 2006]. Moreover, modulation of cognitive circuits using STN-DBS has been shown to be frequency dependent: high-frequency DBS leads to a reduction of verbal fluency, while low-frequency DBS at 10 Hz results in an improvement of verbal fluency [Parsons *et al.* 2006; Wojtecki *et al.* 2006].

In the postoperative period transient depressive or mania-like symptoms are frequently found and should be carefully monitored and may sometimes require symptomatic treatment. An overly rapid postoperative withdrawal of dopaminergic medication should be avoided in order not to induce apathy [Funkiewitz *et al.* 2004;

Volkmann *et al.* 2001]. Furthermore STN-DBS might lead to increased emotional lability [Smeding *et al.* 2006]. Most neuropsychiatric symptoms seem to be transient and, in addition to depression, include hypomania, impulse control disorders, hypersexuality, or apathy and might need an adaptation of stimulation parameters and/or dopaminergic medication [Deuschl *et al.* 2006; Funkiewitz *et al.* 2004; Krack *et al.* 2003; Houeto *et al.* 2002]. Another more serious concern is a higher than expected occurrence of attempted and completed suicide following DBS. Retrospective analysis revealed completed suicide of 0.45–1% and attempted suicide of 0.9–2% following STN-DBS, clear motor improvements notwithstanding [Soulas *et al.* 2008; Voon *et al.* 2008]. Postoperative suicide attempts were associated with being single, a history of impulse-control disorder or compulsive medication use and postoperative depression or apathy. This increased risk of suicide makes a careful psychiatric preoperative screening and postoperative follow-up very important.

It still is a matter of debate whether the occurrence of psychiatric complications might be target-point dependent. While psychiatric complications are previously described to be less frequent and less severe in GPi-DBS than STN-DBS [Videnovic and Metman, 2008; Rodriguez-Oroz *et al.* 2005], a recent prospective, randomized study comparing unilateral STN- and GPi-DBS found no significant differences regarding effects on mood and cognition [Okun *et al.* 2009].

Stimulation induced side effects occur if electrode placement is suboptimal and neighboring structures and fibers are co-stimulated. However, they might also occur as a result of current flow to neighboring structures after increasing the stimulation parameters. Depending on anatomical location, typical side effects include dytharthophonia or hypophonia, tetanic muscle contractions, paresthesias, oculomotor dysfunction, visual phosphenes, nausea, dizziness, dystonia, dyskinesia, or even a worsening of bradykinesia [Deuschl *et al.* 2006; Guehl *et al.* 2006; Volkmann *et al.* 2006; Krack *et al.* 2002]. Weight gain is also common after STN-DBS and might be the consequence of a significant reduction of dyskinesias by DBS [Videnovic and Metman, 2008; Macia *et al.* 2004]. Adverse mood effects occurred more ventrally in both STN- and GPi-DBS which might be caused by stimulation of nonmotor associative or limbic circuits within the nucleus [Okun *et al.* 2009]. Single cases of pathological crying and mirthful laughter induced by STN-DBS have also been reported indicating a potential involvement of ponto-cerebellar or limbic pathways of the basal ganglia-cortical circuits for the psychomotor regulation [Wojtecki *et al.* 2007; Okun *et al.* 2003; Krack *et al.* 2001].

Despite the clear improvement of motor function, activity of daily living and quality of life, STN-DBS often fails to result in a successful social re-adjustment in the patient's personal, family or professional life [Schüpbach *et al.* 2006]. Therefore, careful preoperative psychosocial preparation and postoperative psychosocial care are increasingly being recognized as essential parts of patient management [Schüpbach *et al.* 2006].

Mechanism of action of DBS

Current hypotheses on the action mechanism of DBS include depolarization blockade [Beurrier *et al.* 2001], synaptic inhibition [Dostrovsky *et al.* 2000], synaptic depression [Urbano *et al.* 2002], stimulation-induced disruption of pathological network activity [Montgomery and Baker, 2000], and stimulation of afferent axons projecting to the STN [Gradinaru *et al.* 2009]. Depolarization blockade and synaptic inhibition are likely to explain the similarity between the therapeutic benefit of DBS and lesional surgery. Recordings of decreased somatic activation in the stimulated nucleus favor these hypotheses [Dostrovsky *et al.* 2000; Benazzouz *et al.* 1995]. However, the increased output of projection neurons does not seem to be mediated by these phenomena [McIntyre *et al.* 2004a, 2004b; Hashimoto *et al.* 2003]. Another and currently favored hypothesis is that DBS overrides abnormal spike train patterns by an unphysiological, high-frequency pattern, and thereby masks pathological signals, which cause dysfunction of the remaining elements of the basal ganglia-thalamo-cortical and brainstem motor loop [Garcia *et al.* 2005]. The exact nature of the abnormal signals and the interaction between stimulation-induced neuronal responses and intrinsic brain activity remains elusive, but abnormalities of the firing rate and pattern of basal-ganglia neurons, changes in oscillatory activity and excessive synchronization at multiple levels of the motor loop have been proposed as pathophysiological correlates of motor symptoms in PD [Brown and Eusebio, 2008; Montgomery and Gale, 2008; Hammond *et al.* 2007;

Schnitzler and Gross 2005; Hutchison *et al.* 2004; Bergman and Deuschl, 2002].

Outlook/Perspectives

In PD, DBS is currently primarily used to treat severe motor fluctuations or tremor in advanced stages. At that stage, most patients not only show severe impairment in mobility and quality of life but have already experienced psychosocial decline. Once deprived, restoration of mobility does not always result in a return of independency [Schüpbach *et al.* 2006]. Therefore DBS may be considered as a treatment to be used in earlier stages to protect patients from social isolation. There is evidence that the outcome of motor functions is better and the complication rate is lower when DBS is performed earlier in younger patients [Schüpbach *et al.* 2007]. A larger clinical trial is required to address the question whether, compared with best medical treatment, surgery could be advantageously performed at an earlier stage of the disease to improve quality of life and help maintain independency for a longer period of time.

Conflict of interest statement

L.W., M.S. and A.S. have occasionally received honoraria from Medtronic for lecturing at conferences or consulting work.

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