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Tuomo Erola

DEEP BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS IN PARKINSON'S DISEASE

A CLINICAL STUDY

FACULTY OF MEDICINE,
DEPARTMENT OF NEUROSURGERY,
DEPARTMENT OF NEUROLOGY,
UNIVERSITY OF OULU

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A clinical study

Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Auditorium 1 of the Department of Surgery, Oulu University Hospital, on May 12th, 2006, at 12 noon

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Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been gaining importance in the treatment of advanced Parkinson's disease. This study was undertaken to evaluate the beneficial effects of bilateral STN stimulation on patient's clinical symptoms and quality of life related to the potential risks and side effects of the treatment.

A consecutive series of 42 patients operated on for Parkinson's disease with STN DBS in Oulu University Hospital were included. A subgroup of these patients was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), neuropsychological tests, and Health Related Quality of Life (HRQoL) instruments i.e. the Parkinson's Disease Questionnaire (PDQ-39) and the Finnish version of the Nottingham Health Profile (NHP). The costs of the treatment were calculated from the perspective of the health care provider. The possible effects of bilateral STN-operation on cardiovascular autonomic function were analyzed by measuring various time- and frequency domain indexes as well as non-linear indexes of heart rate variability (HRV) from 24-hour EKG recording before and 12 months after the operation.

This study showed that STN DBS significantly improves the clinical symptoms and HRQoL of parkinsonian patients. The dyskinesia and clinical fluctuation scores were reduced very significantly in the UPDRS IV subscale. The clinical fluctuations were reduced by 53 %. After DBS best motor response (UPDRS III) scores also improved significantly. The HRQoL measured with both instruments improved significantly. Improvement was seen in the PDQ-39 summary index and the subscales of activities of daily living, emotional well-being, stigma and bodily discomfort. Only communication became worse during the follow-up. There was a statistically significant improvement in the score of the subscales of NHP measuring problems with energy, sleep, emotional reactions and social isolation. One patient died from pulmonary embolism and another contracted a late postoperative intracerebral hemorrhage leading to a permanent deterioration of her neurological condition to the bedridden stage. Other complications were much milder.

Clinical improvement and improvement in HRQoL were positively correlated. STN DBS does not influence tonic autonomic cardiovascular regulation. The incremental costs of performing bilateral STN DBS in Finland compared to preoperative medical treatment amounted to an average of 25 591 EUR per patient during the first postoperative year.

The majority of parkinsonian patients experienced significant and long lasting relief in their motor symptoms and an improvement in HRQoL following STN stimulation.

Keywords: autonomic nervous system, cost-benefit analysis, deep brain stimulation, Parkinson disease, quality of life, subthalamic nucleus, treatment outcome

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Abbreviations

AC	Anterior Commissura
ADL	Activity of Daily Living
ANS	Autonomic Nervous System
CAPIT	Core Assessment Program for Intracerebral Transplantation
CAPSIT	Core Assessment Program for Surgical Interventional Therapies
CT	Computed Tomography
DBS	Deep Brain Stimulation
EKG	Electrocardiography
GABA	Gamma Amino Butyric Acid
GPe	Globus Pallidus Externum
GPi	Globus Pallidus Internum
HF	High Frequency
HFS	High Frequency Stimulation
HR	Heart Rate
HRQoL	Health Related Quality of Life
HRV	Heart Rate Variability
LEDD	Levodopa Equivalent Dose
LF	Low Frequency
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic Resonance Imaging
NHP	Nottingham Health Profile
PC	Posterior Commissura
PET	Positron Emission Tomography
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Questionnaire
PPN	Pedunculopontine Nuclei
SD	Standard Deviation
SNc	Substantia Nigra Pars Compacta
SNr	Substantia Nigra Pars Reticulata
STN	Subthalamic nucleus
UPDRS	Unified Parkinson Disease Rating Scale

Vim	Ventral Intermediate Nucleus
VLF	Very Low Frequency
WAIS	Wechsler Adult Intelligence Scale

List of original publications

This thesis is based on following articles, which are referred to in the text by their Roman numerals:

I Erola T, Heikkinen ER, Haapaniemi T, Tuominen J, Juolasmaa A & Myllylä V (2006) Efficacy of Bilateral Subthalamic Nucleus (STN) Stimulation in Parkinson's Disease. Acta Neurochirurgica 148: 389-394.

II Erola T, Karinen P, Heikkinen E, Tuominen J, Haapaniemi T, Koivukangas J & Myllylä V (2005) Bilateral subthalamic nucleus stimulation improves health-related quality of life in parkinsonian patients. Parkinsonism and Related Disorders 11: 89-94.

III Erola T, Karinen P, Heikkinen E, Tuominen J, Haapaniemi T, Myllylä V & Koivukangas J (2006) Bilateral subthalamic nucleus deep brain stimulation: The direct costs compared to the effects. Annals of Neurosurgery 6: 1-7.

IV Erola T, Haapaniemi T, Heikkinen E, Huikuri H & Myllylä V (2006) Stability of long term heart rate variability after subthalamic nucleus deep brain stimulation. Submitted for publication.

Contents

1 Introduction

During recent years high frequency (100–200 Hz) deep brain stimulation (DBS) has mostly replaced stereotactic lesioning procedures, such as thalamotomies and pallidotomies, in the surgical treatment of various movement disorders. Its clinical effects are comparable with the best results achieved by irreversible lesions. The concomitant side effects are generally fewer and milder due to the reversible and adjustable nature of DBS (Caparros-Lefebvre *et al.* 1999a).

The exact mechanism of action of the DBS is not known. In Parkinson's disease (PD), increased neuronal activity in the subthalamic nucleus (STN) and globus pallidus internum (GPi) have been found to influence motor dysfunction. High frequency DBS simulates the effects of a lesion without destroying brain tissue (Haberler et al 2000). This is thought to be achieved at the neuronal level by induction of membrane potential blockade, by direct inhibition of the neural cell by activation of an inhibitory loop, by jamming of a feedback loop, and/or by blockade of intracellular biochemical cascades (Benabid 2002).

There are several reports describing beneficial clinical effects achieved by long-term DBS therapy on relatively small patient series. A full picture of the advantages compared to potential complications and side effects is harder to find from these studies. Both the pros and cons of DBS therapy were considered in a multicenter study investigating the effects of bilateral STN DBS and Gpi DBS on patients suffering from advanced PD. This prospective, double blind, crossover study was conducted during 1995-99, and included the participation of 18 medical centres from all over the world (The DBS for Parkinson's Disease Study Group, 2001). The conclusion was that both STN and Gpi DBS are associated with significant improvement in patients with severe Parkinson's disease and showing a good response to levodopa.

The effects of STN DBS on neuropsychological performance are thought to be nominal and/or transient. The most common findings have been improvement in self reported symptoms of depression and diminished verbal fluency. Changes in cognitive abilities, memory, attention, and frontal executive functions are noted to be inconsistent in most cases. Participants older than 69 years of age appear to be at greater risk for deterioration after the operation. These studies are considered to provide preliminary support for the cognitive and neurobehavioral safety of STN DBS, so that the possibility

of minor, transient neuropsychological inefficiencies does not seem to outweigh the obvious motor benefits (Woods *et al.* 2002, Funkiewitz *et al.* 2004).

In addition to classical parkinsonian disability, there are also many other symptoms causing distress for PD patients. These symptoms include autonomic disorders, weak or stiff limbs, communication problems, sleep disorders, painful spasms, social embarrassment, fatigue and problems with activities of daily life (Martinez-Martin 1998). These symptoms may also relate to a depressive disorder (Marsden 1994) and lead to a considerable decline in the self-estimated health related quality of life (HRQoL).

The impact of the STN-DBS therapy on antiparkinsonian medication is not fully established. On the basis of their one year follow-up of 18 consecutive patients receiving STN-DBS therapy, Thobois and coworkers (2003) stated that this treatment allows a major reduction and simplification of Parkinson medication, an opinion that is commonly accepted. The magnitude of levodopa reduction has varied from 19 % up to 81 % in different publications (Krack *et al.* 1998a, Kumar *et al.* 1998, Limousin *et al.*1998, Moro *et al.* 1999, Pinter *et al.* 1999, Houeto *et al.* 2000, Molinuevo *et al.* 2000, DBS-PD-SG 2001, Lopiano *et al.* 2001, Østergaard *et al.* 2001, Volkmann *et al.* 2001, Tavella *et al.* 2002).

The present study was designed to clarify the relatively controversial field of DBS in Parkinson's disease in a Finnish population since there are no previous studies on DBS performed in Finland. The effects and complications of the treatment as well as the patients´ own view of their health was taken into consideration. An analysis of costs and effects was regarded as important because of the high cost associated with DBS.

2 Review of the literature

2.1 Parkinson's disease

2.1.1 Epidemiology, pathology and etiology

James Parkinson was the first to describe the eponymous disease, which is nowadays commonly referred as idiopathic Parkinson's disease. The descriptive article "An essay on the shaking palsy" was published in 1817 (Parkinson 1817), and the diagnosis is still predominantly based on the disease's clinical assessment. The most common characteristics of PD are rest tremor, bradykinesia, muscular rigidity and postural instability (Hughes 1992). Therapeutic response to levodopa supports the diagnosis (Olanow *et al.* 2001). The classification of Parkinson's disease as one distinct disease entity has, however, recently been questioned (Calne 2001). There are other diseases with parkinsonian symptoms resembling idiopathic PD (Daniel & Lee 1993, Gelb *et al.* 1999, Jankovic *et al.* 2000, Goldstein 2003). In addition to the development and implementation of diagnostic clinical assessments, there is a need for available objective markers to aid physicians in the differential diagnosis of idiopathic PD (Piccini & Whone 2004). Functional neuroimaging holds the promise of improved diagnosis and allows assessment in early disease (Piccini & Whone 2004).

The accuracy of the diagnosis of PD varies from 73 to 92 percent depending on the clinical criteria used (Rajput & Rodilsky 1991, Hughes *et al.* 1992, Daniel & Lees 1993, Litvan *et al.* 1998, Jankovic *et al.* 2000). The overall age-adjusted annual incidence of PD in world-wide studies ranges from 9,4 to 22,1 per 100 000 and the estimated prevalence from 59 to over 200 per 100 000 population (Marttila 1983, Rajput 1992, Zhang & Roman 1993, Errea *et al.* 1999). With intensive case-finding methods involving in-person screening, the incidence become higher with rates increasing from 30 per 100 000 person-years in subjects aged 55 to 65 years, to 440 per 100 000 person-years for those aged 85 years or more (de Lau *et al.* 2004). In Finland the age-adjusted incidence was 14.9 and the age-adjusted prevalence 166 per 100 000 in a study by Kuopio *et al.* (1999).

Before the levodopa period the annual incidence rate was 16.6 and prevalence 120.1 per 100 000 population (Marttila 1974).

Age is considered to be the most important predictive factor in Parkinson's disease; most people develop PD between 50 and 79 years of age (Marttila 1987). The incidence of disease seems to increase with age from 30 per 100 000 at 55 – 65 years of age to 440 per 100 000 at 85 years of age and older (de Lau *et al.* 2004). Gender has not been considered as a risk factor for PD (Rajput & Rajput 2002). However, there are recent data suggesting that even if the overall age-adjusted incidence rate of any parkinsonism is not different in men and women, men seem to have a higher risk for PD (de Lau *et al.* 2004). Uncertainty remains about the prognostic importance of many baseline clinical features in PD. Greater baseline impairment, early cognitive disturbance, older age, and lack of tremor at onset appear to be adverse prognostic factors (Marras *et al.* 2002). Increased mortality risk in Parkinson disease is dependent on disease duration and is only modest in the absence of dementia (de Lau *et al.* 2005).

The main histopathological findings in PD are progressive neuronal loss with associated characteristic cytoplasmic inclusion bodies (Lewy bodies, intracellular inclusions of aggregated alpha-synuclein) in the pigmented nuclei of the midbrain, in many subcortical nuclei and cortex (Goldmann & Tanner 1998, Jellinger 1999). Depletion of melanin containing cells and tyrosine hydroxylase positive cells leads to striatal dopamine deficiency (Forno 1996). Dopamine deficiency correlates with motor problems. Although the cause and pathogenesis of selective loss of dopamine neurons and the accumulation of alpha-synuclein in PD remain elusive, growing lines of evidence from environmental risk factors and early-onset genetics point to a convergence between energy metabolism and the disposal of damaged proteins in the development of PD (Eriksen *et al.* 2005). These findings suggest that impairments in mitochondrial and ubiquitin-proteasome system function can significantly contribute to the pathogenesis of PD (Eriksen *et al.* 2005).

In addition to the dopaminergic system, PD also affects the serotonergic raphe nuclei, the noradrenergic nucleus ceruleus, the cholinergic nucleus basalis of Meynert and many peptidergic brainstem nuclei. Lewy bodies have also been found in sympathethic and parasympathethic neurons, in the adrenergic medulla, in the thalamus, hypothalamus and in the olfactory bulb (Den Hartog Jager & Bethlem 1960, Jellinger 1991, Wakabayashi & Takahashi 1997, Jellinger 1999). Thus, PD widely affects the monoaminergic system, peripheral parts of the autonomic nervous system (ANS) and the central autonomic network causing many clinical and functional symptoms.

PD affects not only the monoaminergic system. Incidental cases of idiopathic Parkinson's disease may show involvement of both the enteric nervous system and the dorsal motor nucleus of the vagus nerve (Braak *et al.* 2003). This observation, combined with the working hypothesis that the stereotypic topographic expansion pattern of the lesions may resemble that of a falling row of dominos, prompts the question whether the disorder might originate outside of the central nervous system, caused by a yet unidentified pathogen that is capable of passing the mucosal barrier of the gastrointestinal tract and, via postganglionic enteric neurons, entering the central nervous system along unmyelinated preganglionic fibers generated from the visceromotor projection cells of the vagus nerve (Braak *et al.* 2003).

2.1.2 Medication

The neurochemical basis for the treatment of PD is dopamine deficiency in the nigro-striatal system (Ehringer & Hornykiewics 1960, Utley & Carlsson 1965). That finding has led to the introduction of levodopa treatment and a marked improvement in PD motor symptoms and increased life-expectancy in parkinsonian patients (Cotzias *et al.* 1967, Uitti *et al.* 1993). Levodopa does not halt the progression of disease, but has remained the most effective treatment for PD since its implementation. Long-term use of levodopa is, however, a bit problematic because of adverse effects such as fluctuations and dyskinesias. After five years of treatment, approximately 50 % of patients develop these long-term complications (Rinne 1987, Miyawaki *et al.* 1997). Levodopa has been suspected to be toxic for dopaminergic neurons, although this has not been shown in humans (Olanow *et al.* 2004). Increasing evidence suggests that motor complications are related, at least in part, to the short half-life of the drug (and its potential to induce pulsatile stimulation of dopamine receptors) rather than to specific properties of the molecule (Olanow *et al.* 2004). For these reasons alternative treatment options have been sought especially for younger patients.

Dopamine agonists such as ropinirole, bromocriptine, pergolide, cabergoline and pramipexole have shown to be effective monotherapy in the early stages of the disease (Rinne *et al.* 1997, Shannon et al 1997, Watts 1997, Rascol *et al.* 1998a). The quite common side effects of dopamine agonists are nausea and vomiting, constipation and postural hypotension (Grimes & Lang 1999). Also pleuritis, pulmonary fibrosis and valvular heart fibrosis have been described with ergot agonists bromocriptine, cabergoline and pergolide (Rinne 1981, Pritchett *et al.* 2002). With non-ergot agonists ropinirole and pramipexole these problems have not been described reliably.

The best way to initiate dopaminergic therapy for early Parkinson disease is unclear. Initial treatment with dopamine agonist seems to result in lower incidences of dyskinesias and wearing off compared to initial treatment with levodopa (Holloway *et al.* 2005). Initial treatment with levodopa seems to provide better symptomatic control (Holloway *et al.* 2005). Levodopa is still recommended as initial treatment for elderly patients and for patients with several diseases.

Selegiline and rasagiline, irreversible inhibitors of monoamine oxidase B, are preclinically neuroprotective, but a substantial neuroprotective effect has not been demonstrated (The Parkinson Study Group 1993, Olanow *et al.* 1995, Mytilineou *et al.* 1997). MAO-B inhibitors do not appear to delay disease progression but may have a beneficial effect on motor fluctuations (Macleod *et al.* 2005). At present MAO-B inhibitors can be used in the treatment of early Parkinson's disease, but further randomized controlled trials should be carried out to clarify, in particular, their effect on motor complications and deaths (Biglan *et al.* 2006).

Patients with symptoms interfering with normal daily life activities are recommended to be treated symptomatically. Yet no drug has been shown to halt or slow down the progression of the disease.

2.1.3 Quality of Life

Early terminology referred to qualitative aspects of diseases and treatment using concepts such as “quality of life”, “health status”, “well-being” and “functional status” (Karnofsky & Burchenal 1949, Calman 1984, Shumaker & Naughton 1995). Calman provided possibly the most quoted definition of quality of life, as being "the gap between the patients’ expectations and their achievements: small gap meaning high quality of life" (Calman 1984). To make this broad concept more relevant to health care, the term 'health-related quality of life' (HRQoL) was proposed. Self-care and activities of daily life (ADL) are normally included in the operational definition of HRQoL (Wiklund 1990, Jenkinson *et al.* 1995, Coulthard-Morris *et al.* 1997, Berzon 1998).

In addition to the main motor parkinsonian symptoms, there are many other manifestations that may cause distress for PD patients (Martinez-Martin 1998). All these symptoms may worsen HRQoL of the patients. A number of studies have made attempts to evaluate HRQoL in PD (Shindler *et al.* 1993, Chrischilles *et al.* 1998, Hobson *et al.* 1999, Karlsen *et al.* 1999, Koplas *et al.* 1999, Karlsen *et al.* 2000, Schrag *et al.* 2000, Kuopio *et al.* 2000, The Global Parkinson’s disease survey 2002). Along with the use of general scales (Karlsen *et al.* 2000, Hagell *et al.* 2000, Hariz *et al.* 2003) PD-specific scales have been developed in order to detect specific aspects of the disease affecting HRQoL (Peto *et al.* 1995, Schrag *et al.* 2000, Gray *et al.* 2002). Disease specific instruments have been designed to describe the parkinsonian patient’s subjective well-being more adequately than generic instruments (Jenkinson *et al.* 1999). The most widely used of these is the Parkinson’s Disease Questionnaire (PDQ-39), which has been demonstrated to have relatively good reliability and validity in PD (Jenkinson *et al.* 1995, Jenkinson *et al.* 1997, Jenkinson *et al.* 1999, Bushnell & Martin 1999).

Compared with an age-matched group of healthy individuals, parkinsonian patients show higher levels of distress in all measured dimensions of HRQoL using the NHP as an instrument (Karlsen *et al.* 1999). Especially depression seems to influence HRQoL, but also sleep disturbances and low independency are significant (Karlsen *et al.* 1999, Schrag *et al.* 2000, The Global Parkinson’s disease survey 2002). Progression of PD correlates with an increase in the patient's perception of pain, in perceived physical disability, social isolation and emotional constraint (Karlsen *et al.* 2000). Differences between male and female patients are not found in PD groups with respect to HRQoL (Schrag *et al.* 2000).

2.1.4 Autonomic nervous system dysfunction

PD may contribute to several autonomic manifestations, but severe autonomic failure preceding typical PD is uncommon (Benarroch 1997, Bannister & Mathias 1999). The most common clinical manifestations of autonomic dysfunction in PD are abnormalities in gastrointestinal and urinary functions, postural dizziness, hypersalivation, seborrhoea and impotence (Ludin *et al.* 1987, Turkka 1987, Sandroni *et al.* 1991, Niimi *et al.* 1999). Also, postprandial hypotension and disturbances of breathing are mentioned in the literature (Micieli *et al.* 1987, Niimi *et al.* 1999).

Autonomic nervous system dysfunction has been shown to significantly influence HRQoL in parkinsonian patients (Magerkurth *et al.* 2005). PD seems to be not only a movement disorder with dopamine loss in the nigrostriatal system of the brain, but also a dysautonomia, with norepinephrine loss in the sympathetic nervous system of the heart (Goldstein 2003). Recently, cardiac sympathetic dysfunction in PD has been postulated on the basis of decreased cardiac uptake of sympathoneural imaging tracers (Amino *et al.* 2005). Furthermore, the extent of involvement of the cardiac sympathetic nerves seems likely to be equivalent to that in the central nervous system, including the nigrostriatal dopaminergic system (Amino *et al.* 2005).

The prevalence of autonomic symptoms in PD has been reported to vary from 76 % to 93 % (Spiegel *et al.* 1969, Turkka 1987, Singer *et al.* 1992, Magalhães *et al.* 1995). The symptoms are reported to be especially severe in patients with bilateral signs, pronounced bradykinesia and rigidity, and milder in patients with unilateral signs (Spiegel *et al.* 1969, Marttila 1974). The duration and severity of the disease have also been thought to be associated with the degree of clinical autonomic failure (Turkka 1987), although this was not confirmed by a recent study (Magerkurth *et al.* 2005).

2.2 Surgical treatment of Parkinson's disease

Already in the middle of the 20th century it was noticed that surgery of the globus pallidus relieves symptoms of Parkinson's disease (Meyers 1951). Neurosurgery of the basal ganglia was performed as early as 1939 by Meyers with notable improvement in the motor symptoms of Parkinson's disease, but with a high mortality rate of 12% (Meyers 1942). Due to the severe adverse effects of this traditional open surgery, it did not achieve popularity. However, this finding was the basis for pallidotomies after implementation of a new operation technique, stereotaxia. The development of stereotactic frames made it possible to restrict the size of lesions and confirm the accurate target of surgery even during the operation (Cooper & Bravo 1958, Svennilson *et al.* 1960).

In the beginning of the 1950´s, pallidotomy was the most popular target for the treatment of PD, but later thalamotomies replaced this technique as a somewhat safer and more effective treatment (Laitinen 1966). Especially, destruction of the ventral intermediate nucleus (Vim) proved to be effective as a treatment of contralateral tremor for years. As much as 90 % of patients did get a good to moderate relief on their symptoms (Fox *et al.* 1991). Thalamic cells in Vim lose their ability to produce discharges causing a tremor in the same rhythm as the electric output of the nucleus. Later this hypothesis was proven to be false, but destruction of Vim is still useful in some conditions (Lentz *et al.* 1995, Schuurman *et al.* 2000).

The primary indication for thalamotomy is still tremor, as in the 1960´s (Selby 1967). Gait disturbances and bradykinesia are not relieved by thalamotomy. The most common complications of unilateral thalamotomies are hemiparesis, ataxia and speech disturbances. Bilateral thalamotomies may provoke severe gait disturbances and aphonia (Fox *et al.* 1991).

Bilateral pallidotomies are debatable operations, because mortality is increased (Shannon *et al.* 1998, Samuel *et al.* 1998) and over 25 % of patients suffer long-term

speech disturbances, difficulties in swallowing and deterioration of cognitive abilities (Jankovic *et al.* 1995, Giller *et al.* 1998).

Several studies from the era of lesional stereotaxy have briefly commented on some neuropsychological sequelae of subthalamotomy. Those studies describe a long-term decrease in spontaneity, initiative, satiability and environmental interest combined with an increased interest in food (Andy *et al.* 1963). In the 1960s subthalamotomies were abandoned because of concerns regarding adverse events (hemiballismus) due to small STN lesions (Henderson & Dunett 1998).

In the late 1960's levodopa was introduced, and the interest in surgical treatment options for PD decreased remarkably. A new interest in pallidotomies was aroused in 1992, when Lauri Laitinen noticed that posteroventral pallidotomy relieved not only PD symptoms, but also peak phase levodopa induced dyskinesias (Laitinen *et al.* 1992).

The development of pathophysiological models of PD indicated also that the STN may be a promising target for surgery (Albin *et al.* 1989, DeLong 1990). Unfortunately, ablative surgery of the STN was associated with several adverse effects such as difficulties in swallowing and deterioration of cognitive abilities. STN lesions are also described to be related with fatal hemiballismus (Vidakovic *et al.* 1994). Later this connection was questioned in a review article (Guridi&Obeso 2001), but the STN has remained a primary DBS target.

DBS was primarily used in combination with thalamotomy in patients with bilateral PD (Benabid *et al.* 1987) to avoid the adverse effects of bilateral thalamotomies. Later studies showed Vim DBS to be as effective as thalamotomy, but with less risks (Schuurman 2001). Like thalamotomy, Vim DBS is effective for tremor, but has minor effects on other parkinsonian symptoms (Benabid *et al.* 1996, Koller *et al.* 1997). DBS does not affect the origin of tremor, as symptoms are restored immediately after cessation of years of continued high frequency stimulation (HFS) (Pollak *et al.* 1997).

The development of the DBS technique also enabled bilateral treatment, and made safe targeting of the STN possible (Limousin *et al.* 1995, Limousin *et al.* 1998, Krack *et al.* 1998, Olanow *et al.* 2000).

In the beginning of this century ventriculography was considered to be "the golden standard" to localise the STN. The STN was normally localized using an atlas of brain structures and pre-existing data obtained by teams experienced in STN stimulation (Benabid *et al.* 2000). The coordinates of the target are referenced to a line drawn from the anterior commissura (AC) to the posterior commissure (PC). Later also 3D magnetic resonace imaging (MRI) reconstruction was introduced to replace the invasive ventriculography. Neither of these procedures takes into account possible individual variations in the STN localization with regard to the AC-PC-derived positions. Therefore, also direct identification of the STN by MRI with adequate sequences seemed to be a suitable method. However, the direct identification using MRI proved to be most inaccurate method when intraoperative microrecording was used to determine the reference point (Cuny *et al.* 2002).

Because of the inherent imprecision of imaging techniques used, intraoperative stimulations are unanimously regarded as a crucial part in localizing the optimal target. Further, microrecordings performed on multiple parallel trajectories are also considered by some neurosurgeons mandatory to improve the localization of the optimal target site (Alterman *et al.* 1999, Carlson and Iacono 1999b, Mobin *et al.* 1999). The requirements

for exact positioning of the DBS electrodes on the STN seem, however, to be groundless, as the extent of STN neuronal activity recorded along the trajectory has no effect on the postoperative clinical outcome (Houeto *et al.* 2003).

STN DBS is considered effective in evidence-based medical review updates (Goetz *et al.* 2005). The preoperative percentage improvement in UPDRS motor scores with antiparkinsonian medications and UPDRS motor score in the medication "on" state at baseline seem to be the strongest clinical predictors of responsiveness to bilateral STN DBS (Pahwa *et al.* 2005).

2.3 Pathophysiological basis of surgery in PD

The last decade has provided substantial advances in the understanding of PD pathophysiology and in its medical as well as surgical treatment, mainly because of the development of better animal models. Particularly the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of PD has provided the opportunity to understand changes in basal ganglia functions in PD (DeLong 1990). Even if the clinical characteristics of PD do not only constitute motor manifestations, the motor circuit in the basal ganglia is most important in the understanding of the cardinal features of PD and the rationale of its surgical treatment.

2.3.1 Current model of the function of the basal ganglia

Motor problems correlate with striatal dopamine deficiency and are the main target of all therapeutic approaches. The motor circuit is somatotopically organized; the leg is represented dorsally and medially, the face ventrally, and the arm in between, with a more lateral distribution (Herrero *et al.* 2002). This circuit connects both the motor areas and the primary somatosensory areas with the dorsolateral putamen (Fig. 1). Excitatory glutamatergic afferents of the cortex synapse with gamma-amino butyric acid (GABA) neurons and also with the cholinergic neurons. GABA neurons are striato-pallidal projections and cholinergic neurons are interneurons. The dopaminergic projection of the nigrostriatum is mainly directed to GABAergic output neurons. Basal ganglia activity is controlled by means of a direct and indirect circuit. The direct circuit is an inhibitory pathway from striatum to globus pallidus internum (GPi). The indirect circuit is an excitatory striato-Gpe-STN-Gpi projection (DeLong 1990, Albin *et al.* 1989). Due to the dual action of dopamine on striatal GABA efferent neurons, it is believed that the direct and indirect circuits can have opposite effects on basal ganglia output structures. To make it simple, inhibition of the Gpi/SNr neural firing facilitates movements, whereas increased neuronal activity inhibits movements.

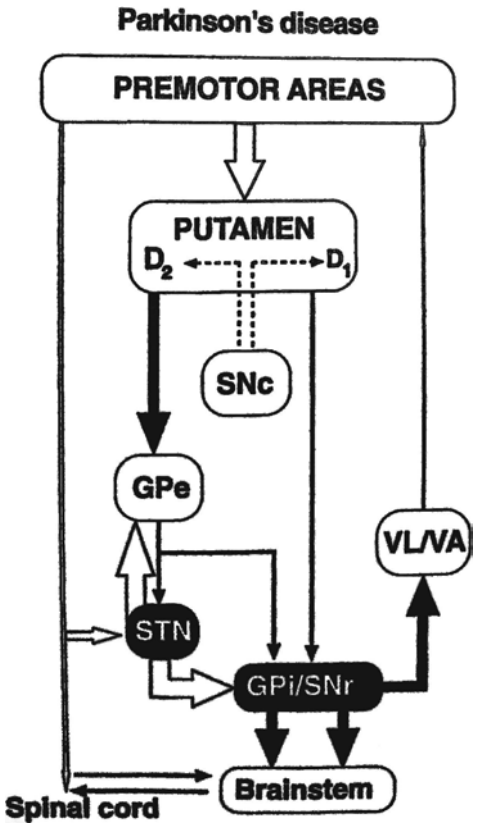

Fig. 1. Striatal dopamine deficiency (broken lines) provokes a series of functional changes in the basal ganglia circuitries. Disinhibition of the indirect striatal neurons (D2) leads to a decrease in the Gpe activity that induces an overexcitation of the STN and consequently of the GPi and SNr. Decreased activation of D1 GABA striatal neurons giving rise to the direct circuit leads to disinhibition of the GPi and SNr and reinforces hyperactivity through hyperinhibition of brainstem and ventrolateral (VL) and ventral anterior (VA) parts of the thalamus. Black arrows-inhibitory projections; white arrows-excitatory projections. Hyperactivity of the nuclei is represented in black (STN, GPi and SNr) (Reprinted with permission from Obeso *et al.* 2000c).

2.3.2 Pathophysiology of the basal ganglia in PD

Dopamine deficiency leads to several functional changes, which have a net effect of increased neuronal activity of the STN (Berman *et al.* 1994). The increased activity of the STN is considered to be the functional hallmark of PD (Obeso *et al.* 1997, Wichmann *et al.* 1996). The mechanisms underlying the STN hyperactivity according to the present model are presented in the previous chapter, but the concept can be summarized as follows: decrease of nigrostriatal dopaminergic activity reduces inhibition on the GABA-

enkephalin neurons increasing their activity and overinhibiting the GPe. The inhibitory tone from GPe on the STN is reduced leading to increased neuronal activity of the STN (Fig 1.). Excessive activity in the STN produces augmented neuronal activity in the GPi and SNr. Therefore, in the parkinsonian state the GPi and SNr are disinhibited through the direct pathway and overexcited by the indirect circuit (Fig 1.) The end result of the hyperactivity of GPi/SNr is overinhibition of the motor thalamus and brainstem nuclei. This gives rise to brady- and hypokinesia by inhibiting movement initiation and execution as well as the performance of sequential tasks and the frequency of repetitive movements.

Hyperactivity in the STN-GPi-SNr projections is relatively well established also in patients with PD using intraoperative microrecording and examining the response to apomorphine (Lozano *et al.* 2000, Vitek J *et al.* 2000). In addition, imaging studies (PET, MRI) and electrophysiologic studies (EEG) before and after administration of levodopa (Jenkins *et al.* 1992, Rascol *et al.* 1998b) or the basal ganglia surgery (Ceballos-Baumann *et al.* 1994, Limousin *et al.* 1997, Limousin *et al.* 1999) clearly support this model. On the other hand, we have to admit that this classical model does not fit with every experimental and clinical finding. Probably this model needs re-evaluation or even revision in the near future.

2.3.3 Pathophysiology of dyskinesias

The current knowledge of the origin of dyskinesias (for example chorea-ballism) is based on the previous model (Crossman 1987, Albin *et al.* 1989, DeLong 1990, Obeso *et al.* 1997). STN hypoactivity reduces discharge frequency in the GPi (Hamada & DeLong 1992) and the decreased firing pattern results in the delivery of erroneous signals to the thalamus and later to the cortex (Vitek & Giroux 2000). In the dyskinetic state the STN is overinhibited (Crossman 1987) either pharmacologically, as in tardive dyskinesia, or as a result of focal striatal lesions, as in Huntington disease. It has been assumed, that both levodopa induced dyskinesias (LID) and hemichorea-ballism share a common pathophysiologic origin (Crossman 1990), because levodopa induced dyskinesias in the MPTP monkey have been associated with a 50 % decrease in mean firing frequency in the GPi (Filion *et al.* 1991).

To summarize, the basal ganglia is currently understood as a highly organized network with multiple cortical loops and circuits (Shink *et al.*1996), which probably provide a stabilizing function (Obeso *et al.* 2000b). Thus, the basal ganglia system probably works like a non-linear system based on several codes, not only on firing rate code (Obeso *et al.* 2000b). This seems to be an explanation of why lesioning or a blockade of specific basal ganglia nuclei does not always cause the predicted outcome (Marsden & Obeso 1994).

2.3.4 Motor improvement after basal ganglia surgery

Reduction of the STN and GPi/SNr overactivity should be accompanied with better motor response. Experimental studies, in which the STN of MPTP monkeys has been

lesioned with kainic acid or ibotenic acid, have strongly supported the classic model of basal ganglia pathophysiology. In these studies the STN lesion has been associated with a striking motor benefit including better performance of speed demanding motor tasks, increased spontaneous activity and abolition of postural tremor (Bergman *et al.* 1990, Aziz *et al.* 1991, Guridi *et al.*1996). Also, symptoms in the ipsilateral limbs were moderately relieved by these unilateral lesions. Dyskinesias provoked by the lesion were nominal or did not exist at all. Also, a lesion of the GPi by administration of excitotoxin in MPTP monkeys resulted in a permanent motor improvement (Guridi *et al.* 1996). Injection of a GABA agonist (muscimol) to reduce reversibly GPi neuronal activity improved motor response but only when the injection was administered in the sensorimotor region of the nucleus (Wichmann *et al.* 1994).

In parkinsonian patients, pallidotomy reduces bradykinesia, rigidity and tremor especially in the limbs situated contralaterally to the lesion (Baron *et al.* 2000, Fine *et al.* 2000). Intraoperative microelectrode recording in the GPi and STN has confirmed the somatotopic organization in humans similar to that described in monkeys (Guridi *et al.* 1999). Also, high-frequency discharges of a large proportion of neurons have been found, agreeing with current model (Hutchinson *et al.* 1998, Vitek *et al.* 1998).

Pallidotomy is, at best, a limited method of reducing the cardinal features of PD. Daily levodopa doses need to be maintained or even increased after prolonged follow-up (Baron *et al.* 2000, Fine *et al.* 2000). This could be partly explained with unilaterality of pallidal lesions. On the other hand, bilateral pallidal stimulation seems to have a similar outcome, i.e. alleviation of the severity of off-medication parkinsonism possibly reaching a 50 % reduction with no reduction of levodopa and dopamine agonist requirement compared to baseline amounts (Kumar 2000, Rodriquez-Oroz *et al.* 2005, Anderson *et al.* 2005).

In contrast to pallidal lesions STN stimulation provides a more overt antiparkinsonian effect allowing a significant reduction in the daily levodopa dose (Krack *et al.* 1998a, Kumar *et al.* 1998, Limousin *et al.*1998, Moro *et al.* 1999, Pinter *et al.* 1999, Houeto *et al.* 2000, Molinuevo *et al.* 2000, DBS-PD-SG 2001, Østergaard *et al.* 2001, Lopiano *et al.* 2001, Volkmann *et al.* 2001, Tavella *et al.* 2002, Thobois 2003, Rodriquez-Oroz *et al.* 2005, Anderson *et al.* 2005). This is in concordance with some neurophysiologic and PET data indicating that STN DBS activates motor areas to a greater extent than does GPi DBS (Brown *et al.* 1999, Guridi *et al.* 1999) suggesting that the pathophysiologic origin of PD depends not only on the cortico-basal ganglia-cortical motor loop, but also involves other circuits. This suggestion especially concerns the pedunculopontine nuclei, which is heavily interconnected with basal ganglia, the thalamic parafascicular nucleus, and the spinal cord (Parent *et al.* 1999). Lesioning of PPN in monkeys leads to transient akinesia (Kojima & Takada 1997).

2.3.5 Dyskinesia decrease in basal ganglia surgery

Hemichorea-ballism has been associated with a reduction in basal ganglia inhibitory output according to the original basal ganglia model (Crossman 1987, Albin *et al.* 1989, DeLong 1990). Unquestionably STN-lesions cause hemichorea-ballism in many cases in

both humans and monkeys (Guridi & Obeso 1997). MPTP monkeys also encounter dyskineasias as a consequence of a STN lesion, but less frequently and with milder severity (Bergman *et al.* 1990, Aziz *et al.* 1991, Guridi *et al.* 1996). Unilateral GPi lesions are asymptomatic in humans, but cause moderate dystonic postures in monkeys (Carpenter *et al.* 1950). Bilateral GPi lesions in humans are associated with dystonia, akinesia and gait disturbances (Bhatia & Marsden 1994), but pallidal lesions do not manifest as hemichorea-ballism. In parkinsonian patients pallidotomy abolishes levodopa induced dyskinesias without any significant motor deficit (Narabayashi *et al.*1984, Limousin *et al.* 1999). Pallidotomy also relieves hemiballism caused by STN lesions in both humans and animals (Carpenter *et al.* 1950, Suarez *et al.* 1997, Vitek *et al.* 1999).

These observations indicate, that the classic pathophysiological model does not explain every aspect of the origin of dyskinesias (Crossman 1987, Albin *et al.* 1989, DeLong 1990). The data we have so far suggest that dyskinesias result from a particular pattern of firing rate in the GPi (Vitek & Giroux 2000, Obeso *et al.* 2000a). On the other hand, reduced firing rate in GPi is associated with the pathophysiology of levodopa induced dyskinesia (Papa *et al.* 1999, Fillion 2000), but cannot be regarded as the only factor of its origin (Olanow & Obeso 2000). Thus, all parkinsonian motor features cannot be explained only by neuronal hyperactivity.

2.3.6 Mechanisms of deep brain stimulation

Deep brain stimulation (DBS) at high frequency is an effective tool in the treatment of PD as well as other movement disorders. There is still debate on the mechanism(s) underlying the effect of high frequency stimulation (HFS) (Benabid 2002, Dostrovsky & Lozano 2002, Vitek 2002a). The first studies using electrical stimulation were based on a concept that stimulation activates the stimulated region. Later on, the concept has been that stimulation leads to decreased output from the stimulated nucleus. This is supported by data showing similar effects of DBS and lesionary surgery in the GPi and STN (Limousin et al 1995, Gross *et al.* 1997). Also, PET studies have shown similar changes in cortical metabolic activity after GPi DBS and traditional pallidotomy (Davis *et al.* 1997, Limousin et al 1997). In addition to the clinical outcome, neurophysiological observations also support these conclusions (Boraud *et al.* 1996, Dostrovsky *et al.* 2000, Beurrier *et al.* 2001, Wu *et al.* 2001, Dostrovsky & Lozano 2002).

However, some data supports the hypothesis that stimulation leads to activation of the stimulated structure. GPi microdialysis studies during STN stimulation have shown increased levels of glutamate (Windels *et al.* 2000). Also, increased activation of GPi is seen during STN stimulation in MPTP monkeys coincidentally with improvement of parkinsonian symptoms (Hashimoto *et al.* 2001). In addition, inhibition of thalamic activity is reported during HFS in the GPi indicating increased output from the stimulated site (Montgomery *et al.* 2001). One example of neuronal activation is microstimulation-evoked movement. In multiple sites in the neuronal system including the motor cortex (Stoney *et al.* 1968), thalamus (Vitek *et al.* 1996) and deep cerebellar nuclei (Schultz 1979) involuntary movements can be provoked by electrical stimulation.

One possible explanation for inconsistency between data is that while neuronal activity near the stimulating electrode decreases, neurons farther away may be activated. Thalamic in vitro stimulation has shown a complex pattern of activation and inhibition of neurons at different distances measured from the stimulation site (Schlag &Villablanca 1968). Similar distance dependent activation and inhibition has been proposed for nerve fibers (Ranck 1975). This could explain the fact that, contrary to the original PD model (Albin *et al.* 1989, DeLong 1990, Obeso *et al.* 2000c), GPe stimulation leads to improvement of parkinsonian motor signs (Vitek *et al.* 1998, Yelnik *et al.* 2000). Furthermore, axons may fire independently of the soma during stimulation (Grill 2001), and electrical stimulation may lead to excitation of neuronal pathways (Ranck 1975).

In one of the earliest DBS studies a beneficial effect on tremor in the thalamic ventralis intermedius nucleus was obtained with frequencies above 60 Hz with a maximal benefit between 150 and 1 000 Hz (Benabid *et al.* 1991). The Grenoble group also noted that voltages below 3.6 V generally allowed tremor to be controlled when combined with frequencies >130 Hz. In addition, the lower voltages prolonged the life span of the implantable pulse generator battery. When STN stimulation was introduced in 1993 (Pollak *et al.* 1993), the combination of previous experience of thalamic stimulation and clinical practice enabled a general guideline for implantable pulse generator settings to be drawn up. That experience has later shown that the voltage is the most important factor in ameliorating the parkinsonian symptom triad (Rizzone et al 2001, Moro *et al.* 2002). There is not any general recommendation to optimal voltage, which is highly dependent on the patient, possibly due to the placement of the electrode. However, voltages over 3 V are very seldom needed.

Bradykinesia and tremor have shown no improvement at frequencies below 50 Hz, while rigidity starts improving at 33 Hz and continues to improve with a maximum benefit at 185 Hz (Moro *et al.* 2002). A broader pulse width has shown a more substantial improvement in clinical symptoms but effects are not as clear as for the voltage or the frequency. This favors the use of a narrow pulse width, 60 μseconds, a setting which also has a beneficial impact on energy consumption (Moro *et al.* 2002).

In conclusion, the actual mechanism of HFS cannot be explained in a simple model. Taking into consideration the anatomic complexity of the basal ganglia structure, the proximity of several fiber pathways of varying sizes, shapes and neurophysiological properties, it is quite amazing that DBS is so effective and consistent in the treatment of movement disorders.

2.4 Impact of subthalamic nucleus deep brain stimulation

2.4.1 Effect on motor performance

From the very beginning, STN DBS has proven to be effective in alleviating the motor symptoms of PD (Limousin *et al.* 1995, Limousin et al 1996, Limousin *et al.* 1997, Krack *et al.* 1998). The improvement after bilateral STN surgery was comparable with the results for unilateral GPi pallidotomy (Dogali *et al.* 1995, Iacono *et al.* 1995a, Baron *et*

al. 1996, Fazzini *et al.* 1997, Johansson *et al.* 1997, Kishore *et al.* 1997). Of the motor signs, akinesia and rigidity responded best to STN DBS. On the other hand, dyskinesias did not alleviate to the same extent as in pallidotomies, if medication was not reduced (Limousin 1998). In contrast to unilateral pallidotomy, patients were able to reduce their levodopa intake after STN DBS (Limousin *et al.* 1995, Krack *et al.* 1998).

For objective assessment of DBS surgery in PD, standardized rating scales of motor function and disability have been utilized. The most common set of rating scales is the core assessment program for intracerebral transplantation, CAPIT (Langston *et al.* 1992) and later core assessment program for surgical interventional therapies, CAPSIT (Defer *et al.* 1999), including the Unified Parkinson's Disease Rating Scale (UPDRS) as a major rating scale. This scale has four subscales: I, mentation, behavior, and mood; II, activities of daily living (ADL); III, motor examination; and IV, complications of therapy. The ADL and motor examination subscores are often reported separately from the total score. The UPDRS total score, the sum of subscales I, II and III, may vary from 0 (no symptoms) to 176 (most disabled). As the symptoms of PD fluctuate considerably depending on the medication, ratings must always be performed in either the medication on or medication off state.

Table 1. The change in the UPDRS scores after bilateral STN DBS (medication off), publications with less than 10 patients are excluded.

Author	No. of patients	Follow-up (months)	UPDRS motor score reduction (%)	Reduction (%) of dyskinesias	Reduction (%) of medication
Limousin, 1998	20	12	60	55	50
Fraix, 2000	24	12	67	73	81
Houeto, 2000	23	6	67	77	61
Molinuevo, 2000	15	6	66	80	80
Bejjani, 2000	10	6	64	-	-
DBS Study Group, 2001	96	6	51	74	37
Volkmann, 2001	16	12	60	83	65
Lopiano, 2001	16	3	57	71	72
Alegret, 2001	15	3	57	-	58
Tavella, 2002	47	24	63	90	81
Thobois, 2002	18	6	55	76	66
Østergaard, 2002	26	12	64	86	19
Romito, 2002	22	18	50	-	60
Spottke, 2002	16	12	66	-	-
Pahwa, 2003	33	12	28	-	57
Kleiner-Fisman, 2003	25	12	39	69	38
Esselink, 2004	20	6	49		33
Mean	26	10	57	76	57

- = not reported

One of the first studies on bilateral STN DBS described UPDRS motor scores to improve only 10 % postoperatively when the patient's medication was "on" (Limousin et al 1998).

This data was achieved by administration of levodopa plus benserazide after drug withdrawal overnight. Relatively low rates of improvement in similar study set ups have been confirmed by several authors (Molinuevo 2000, Houeto 2000, Volkmann 2001, Lopiano 2001, Tavella 2002). On the other hand, in studies on patients continuing their own medication, a better outcome than a 10 % reduction in motor scores has been described also in the "on" medication state (UPDRS III score improvement by 26 – 55 %) (DBS-PD-SG 2001, Østergaard 2001, Spottke 2002). These studies have reported improvement by 51 – 66 % in UPDRS III score in the off-medication state.

The reported reduction in dyskinesias has varied from 55 to 91 % (Limousin 1998, Pinter 1999). Stabilization of the motor condition is also expressed by a reduction of off-periods, varying from 60 to 89 % (Pinter 1999, Molinuevo 2000, DBS-PD-SG 2001).

The decreased motor complications of medical therapy result in decreased energy expenditure in parkinsonian patients (Macia *et al.* 2003). Due to the fact that energy intake does not change significantly, STN DBS induces a significant weight gain (Macia *et al.* 2003). However, also other causes leading to weight gain cannot be excluded, and it is conceivable that most of the patients "normalize" their weight towards their premorbid status, even if nutritional counselling before the intervention to prevent rapid and/or excessive weight gain is recommended (Barrichella *et al.* 2003).

The effect of STN DBS on verbal fluency is a complex issue. Several neuropsychological studies have reported diminished verbal fluency after STN DBS (Ardouin *et al.* 1999, Saint-Cyr *et al.* 2000, Alegret et al 2001, Volkmann *et al.* 2001), whereas studies show improvement in oral force control (Gentil *et al.* 1999, Pinto *et al.* 2003). One has to remember, that the production of fluent speech is an elaborate system, which might be disturbed by bilateral STN stimulation.

Recently, follow-up results of four to five years of STN DBS have been published (Krack *et al.* 2003, Rodriquez-Oros *et al.* 2004, Schupbach *et al.* 2005). So far the results of long-term treatment are practically equal to those with shorter follow-up, even though the STN DBS does not seem to influence the progression of the disease. Similar motor and cognitive decline is seen in patients with STN DBS as in those without it (Schupbach *et al.* 2005).

2.4.2 PD medication

One of the clearest advantages of STN DBS as compared to GPi stimulation is reduction of medication (Krack *et al.* 1998, Limousin *et al.* 1995). STN DBS is thought to exacerbate the peak phase levodopa induced dyskinesias if medication is not reduced, and that may encourage the patients treated by STN DBS to diminish the levodopa dose more actively than those with GPi DBS. GPi stimulation, instead, relieves peak levodopa induced dyskinesias (Bejjani *et al.* 1997, Gross *et al.* 1997, Iacono *et al.* 1995b). There is also some evidence that STN stimulation might relieve dyskinesias without reduction in medication, but these observations have not been confirmed (Vitek 2002b).

The dose reduction of medication following STN DBS has varied greatly from 19 to 81 % (Østergaard 2001, Tavella 2002) expressed as levodopa equivalents (LEDD) (Wilding *et al.* 1991, Lozano *et al.* 1995, Krack *et al.* 1998b). The largest study published

so far demonstrated a 37 % reduction in LEDD (DBS-PD-SG 2001) (Table 1). One explanation to the high variation could be differences in preoperative levodopa dosage (Østergaard 2002); lower doses seem to diminish less than high ones. The use of dopamine agonists preoperatively varied in different studies and this may have affected the results because of variable levodopa doses. However, the main goal of the operation is not to diminish the medication, but to relieve symptoms of the disease, especially clinical fluctuations and levodopa induced dyskinesias. The combined use of STN stimulation and decreased medication is crucial for achieving optimal treatment results after the surgery.

2.4.3 Effect on quality of life

The improvement of motor symptoms of PD alone may not reflect the overall therapeutic effect of the surgical operation. Social isolation, cognitive impairment and depression may have greater impact on quality of life than the motor symptoms (Schrag *et al.* 2000, GPDS Steering Committee 2002). In addition, surgical side effects (Limousin *et al.* 1998) or neuropsychological (Hariz *et al.* 2000, Saint-Cyr *et al.* 2000) and behavioral disturbances of surgery and STN stimulation might mitigate the effect of diminished motor symptoms. Surprisingly few studies have evaluated the effects of STN DBS on HRQoL so far.

The first publication describing the effect of bilateral STN DBS on quality of life was performed in Aarhus, Denmark (Just & Østergaard 2002). This study presented a consecutive series of 11 patients treated with DBS of the STN with a follow-up of 6 months. The results were compared with a similar group of patients (n=13) awaiting surgery. The group used a disease specific scale of HRQoL, the PDQ-39 (Peto *et al.* 1995). The results showed significant improvement in dimensions of mobility, ADL, stigma, bodily discomfort and the summary index describing the overall HRQoL.

Lagrange *et al.* (2002) conducted a study to assess the HRQoL after STN DBS using another disease specific rating scale, the PD Quality of Life (PDQL) (de Boer *et al.* 1996). The follow-up was similar to the Aarhus study, 6 months, and the authors found an improvement in all aspects of quality of life, including motor (48%), systemic (34%), emotional (29%) and social (63%) dimensions. The number of patients in this study (n=60) was relatively high compared with other studies focusing on the HRQoL during DBS.

Recently, it has been noticed that physical aspects of quality of life are enhanced by bilateral STN stimulation, while mental items such as emotional well-being, social support, cognition and communication do not necessarily improve (Drapier *et al.* 2005). This is not surprising taking into consideration both the nature of the disease and criteria for the operation. Even if the follow-up period of most studies is relatively short, the effect of STN DBS on quality of life seems to last as long as motor improvement is present (Lezcano *et al.* 2004, Lyons & Pahwa 2005).

2.4.4 Neuropsychological functions

The first published report on neuropsychological effects following STN DBS describes 24 individuals diagnosed with idiopathic PD (Limousin *et al.* 1998). In that series several patients demonstrated transient neuropsychological fluctuation, but had recovered within 2 weeks postoperatively. Neuropsychological test batteries emphasizing frontal/executive functions and global cognitive abilities showed mostly unchanged performances 1 year after surgery. One patient displaying impaired cognition at baseline demonstrated a decline in frontal/executive functioning.

The same group of investigators has later published a similar follow-up study with a consecutive series of 77 patients and three years follow up (Funkiewiez 2004). The results agreed with the previous observations, and no global deterioration was observed. However, a minor increase in apathy scores was observed, while depression scores mildly improved.

In another series there were 49 parkinsonian patients, who underwent bilateral STN DBS (Ardouin *et al.* 1999). Preoperatively all patients were free of neuropsychological dysfunctions. The postoperative evaluations were done at 3 and 6 months. At the stimulator-on stage, the patients showed improvement in several cognitive measures, but also exhibited reduced verbal fluency. At the stimulator-off stage, a slight reduction was reported in visual associative learning. 21 of 25 cognitive variables were statistically unchanged in the STN group, and the pattern of declines and improvements was described as “sprinkled haphazardly” by the authors.

Pillon *et al.* (2000) published an extensive work using the same patient series as Ardouin 1999 and 14 additional relatively young patients without significant cognitive or mood disturbances. These patients were evaluated preoperatively and 3 months and 12 months postoperatively. Postoperative evaluations were performed with the stimulator both on and off using parallel tests whenever possible to minimize practice effects. Stimulator settings were adjusted 15-30 minutes before evaluations. Stimulation of the patients resulted in an improvement in self-reported depression, visual attention, Trail Making Test (a measure of divided attention, visuomotor tracking and processing speed), simple and choice reaction time and spatial working memory. Even if significant, the changes were reported to be less than 1 SD. Categorical fluency performance reduced both stimulation on and off as did letter fluency. After 3 months the verbal free recall was reduced, but recovered to the baseline level by the 1-year follow-up.

In a similar study setting by Jahanshahi *et al.* (2000) 7 bilateral STN patients were evaluated after a 12 hour withdrawal from medication. STN stimulation improved the results of the trail making test, a visual serial attention task and a measure of selective visual attention. On the other hand, visual associative learning declined.

Saint-Cyr *et al.* (2000) reported results on 11 patients who underwent bilateral STN DBS and were divided into two age-groups: six persons older than 69 and five younger than 69 years. The patients were assessed preoperatively and 3 and 12 months postoperatively. The fact that all the patients did not take part in every evaluation diminished the reliability of this study. At the 3-month follow-up, patients demonstrated a decline in finger tapping, set alternation, lexical fluency and verbal/nonverbal memory. The patients in the older age-group demonstrated mood improvement, but also declines in

cognitive processes such as working memory, phonemic fluency, susceptibility to interference, associative learning, speed of processing and bimanual coordination under divided attention. Recognition of novel designs and simple motor speed improved over time, but only learning based to multiple trials recovered to the baseline level during follow-up. The authors concluded that elderly patients are at greater risk for cognitive decline. The authors also expressed their concern about whether elderly patients would benefit from the operation.

The precise nature of the role of STN in neuropsychological functions is not fully understood. At any rate, it is clear that the STN plays a role not only in motor functions, but also in cognition and emotion. In animal models the STN has been shown to influence attention (Maurice *et al.* 1998, Baunez *et al.* 1995). For patient selection a neuropsychological evaluation helps to exclude the possible comorbid psychiatric conditions or dementing illnesses (Petersen *et al.* 2001). In addition, an assessment of the patient's support network and psychosocial environment may reveal some risk factors speaking against surgery (Perozzo *et al.* 2001).

2.4.5 Complications

Due to the small number of patients in the studies published it is hard to get a full assessment of potential risks of STN DBS and about complications which have actually occurred. The complications can be divided to surgical complications, hardware related complications and other complications including neuropsychological impairments.

A prospective study in 18 centers using STN DBS treatment for Parkinson's disease was conducted between the years 1995-1999 (DBS-PD-SG, 2001). 96 parkinsonian patients were enrolled in this study for bilateral operations. Six of these patients developed a complication during the first surgical procedure (two intracranial hemorrhages, one hemiparesis, one confusion, one lack of response and one improper lead placement). During the six-month follow-up 8 patients did not participate in all of the postoperative evaluations (two got an infection in the leads, five withdrew their informed consent, and one patient died).

Another study with 81 consecutive patients (Lyons *et al.* 2004) included data from 155 completed and 5 aborted surgical procedures. There were no serious surgical complications resulting in death or permanent neurological deficit. Only one patient had an intracranial hemorrhage which did not lead to any neurological deficit. The incidence of milder complications was as follows: 26.2 % had hardware complications including lead migration, lead fracture, extension erosion, extension fracture and implantable pulse generator malfunction. 12.5 % had misplaced leads, 3.7 % had infections demanding removal of the pulse generator, and 2.5 % had infections requiring system removal. In a recent series of 100 PD patients there were reported 7 device infections, 1 cerebral infarct, 1 intracerebral hematoma, 1 subdural hematoma, 1 air embolism, 2 wound hematomas requiring drainage, 2 skin erosions over implanted hardware, 3 periprocedural seizures, 6 brain electrode revisions, postoperative confusion in 13 patients, and 16 battery failures (Goodman *et al.* 2006). Of the 100 patients, there were no surgical deaths or permanent new neurological deficits (Goodman *et al.* 2006).

Transient adverse effects after operation are common. Some groups have reported dysarthria, paresthesias, diplopia and a tonic contraction contralateral to the side of stimulation in almost all patients (Kumar *et al.* 1998, Kleiner-Fisman *et al.* 2003). This is probably due to the search for maximal effect of stimulation. More persistent complications are scalp cellulitis and scalp electrode erosion as a result of lead infection. Most of these problems are treated by removal of the implanted material and by antibiotic treatment. The frequency of these infections varies from none to 16 % (Molinuevo *et al.* 2000, Kleiner-Fisman *et al.* 2003).

Worsened balance or gait has also been reported in some patients. Minor worsening is relatively common in up to 16% of the patients (Pahwa *et al.* 2003) and is controlled with stimulator adjustments; however sometimes retraction of the leads is needed (Østergaard *et al.* 2002).

Hariz *et al.* (2000) described the postoperative course of a successful STN DBS operation highlighting neuropsychological impairments as a noteworthy complication for STN DBS. A 53-year old man became agitated 1 day postoperatively and was confused even 2 weeks after surgery. Four weeks after surgery he expressed marked improvement in akinesia, tremor, gait, freezing and dyskinesias. Unfortunately, this success was combined with depicted aphonia, increased salivation and worsening of cognitive functions. Two months postoperatively he expressed disrupted sleep, fatigue, a depressed mood, apathy and subjective dyspnea. Also, dyspraxia was noted at the 6-month follow-up. Although motor control was adequate one year postoperatively, a decline in memory functioning was noticed, as well as speech deficits characterized by poor articulation and rigidity. The decline in memory functioning resembled dementia and speech deficits were also expressed as dysphonia and dysarthria.

Some other case reports emphasize synergistic effects of both medication and stimulation on mood and behavior. Especially cases of mania (Kulisevsky *et al.* 2002, Romito *et al.* 2002, Herzog *et al.* 2003) and depression (Berney *et al.* 2002, Doshi *et al.* 2002, Houeto *et al.* 2002, Thobois *et al.* 2002) have been described. These changes are only seemingly contradictory, because mania can be explained by additive psychotropic effects of STN stimulation and dopaminergic treatment, while depression can be related to a decrease in dopaminergic treatment and the loss of the antidepressant effect of levodopa in the same way as for apathy (Funkiewiez *et al.* 2003). These findings emphasize the need to adapt medication and stimulation parameters in the long term (Krack *et al.* 2002).

2.4.6 Cost-effectiveness

PD is thought to be one of the most expensive neurological disorders (Ahlskog 1992). Especially the presence of motor complications due to long term L-dopa use is associated with higher costs for the health care system (Dodel *et al.* 1998). Due to a reduction of the use of levodopa and levodopa equivalents also the costs of antiparkinsonian medication have reduced by 32 % after one year and 39 % after two years following STN surgery (Charles *et al.* 2004).

Despite the medical effectiveness of DBS treatment, the economical effectiveness from different perspectives has to be assessed in order to control the available resources as reasonably as possible (Spottke *et al.* 2002). This is especially important with complex treatment modalities binding up lots of substantial health care system resources.

When both the costs and effectiveness of the treatment are increasing, the efficiency should be assessed by comparing the incremental cost with the incremental outcome (Willan & O´Brien 1996). In most studies, treatments with a cost-effectiveness ratio below US$ 20 000 (EUR 16 600) are considered to be cost-effective (Goldman *et al.* 1991, Hay *et al.* 1991). According to Tomaszewski and Holloway (2001), incremental ratios of up to US$ 50 000 (EUR 41 500) should be considered cost-effective, and ratios greater than US$ 100 000 (EUR 83 000) should be considered as not cost-effective. These calculations also give a recommendation for estimating cost-effectiveness in general, even if the cost-effectiveness depends highly on the instrument used to estimate the effectiveness of the treatment. Therefore, no standard and well accepted threshold criteria for cost-effectiveness have been established.

So far only one prospective cost-effective analysis of bilateral STN DBS has been published. The mean costs per patient were calculated to be EUR 20 410 (Spottke *et al.* 2002). As a consequence of decreased drug consumption, the total annual costs amounted to EUR 16 010 (Spottke *et al.* 2002). The incremental total cost-effectiveness ratio for STN DBS was EUR 3 289 for one unit improvement in the UPDRS III (motor) score.

One retrospective study has been able to also analyse the indirect costs, taking into consideration also the ancillary costs of STN DBS surgery of 46 patients. This study showed that the costs increased by 32 % for the first year and decreased by 54 % for the second year of STN DBS. Drawn together, STN DBS pays off from the second year of stimulation when motor symptoms are significantly improved (Meissner *et al.* 2005).

2.4.7 Ambulatory electrocardiografia and analysis of heart rate variability

Cardiovascular parameters fluctuate from one beat to another under the control of the autonomic nervous system (ANS). The first one to describe the respiratory sinus arrhythmia, i.e. the temporal fluctuations of heart beats related to respiration, was Hales in 1733 (Singer & Underwood 1962). However, more subtle beat to beat fluctuations have received attention only after the development of computers and high resolution electrocardiographic (EKG) recordings. Analysis of heart rate variability (HRV) from ambulatory EKG recording has become an important method for assessment of cardiovascular autonomic regulation.

The time and frequency domain analysis based on linear fluctuations of HR provide useful information about tonic automic effects on the heart (Huikuri *et al.* 1995). However, the periodic oscillations under normal physiologic conditions are insufficient for outlining the changes in HR dynamics (Kaplan & Goldberger 1991, Goldberger 1996). Therefore, methods based on non-linear dynamics and fractal analysis have been introduced to quantify complex HR dynamics and to complement conventional HR measures (Goldberger & West 1987, Denton *et al.* 1990, Pincus & Goldberger 1994).

The time domain analysis of HRV is traditionally based on statistical indices applied to measures of the RR intervals. The most common index is the standard deviation of all RR intervals (SDNN) over a 24-hour period. SDNN mainly reflects the very low frequency (VLF) fluctuation in HR behavior, possibly associated with thermoregulation and peripheral vascular resistance (Rosenbaum & Race 1968). In post myocardial infarction low patient SDNN has been used as a predictor of increased mortality (Kleiger *et al.* 1987).

Spectral analysis of HRV examines the frequency specific oscillations of HR fluctuations and decomposes series of sequential RR intervals into a sum of sinusoidal functions of amplitudes and frequencies (Akselrod *et al.* 1981). The amplitude of the HR fluctuations at different oscillation frequencies is presented as a power spectrum. The most common methods for the transformation of the signals to the frequency domain are Fast Fourier transformation and autoregressive analysis. The power spectrum is often divided into three frequency bands, the boundaries of which are as follows: VLF 0.005 to 0.04 Hz (very low frequency, VLF), 0.04 to 0.15 Hz (low frequency, LF) and 0.15 to 0.4 Hz (high frequency, HF) (Task Force 1996). Sometimes also ultra low frequency <0.0033 Hz is presented. The VLF and LF bands are affected by sympathetic excitation, sympathovagal balance and arterial BP oscillations (Dwain & Eckberg 1997, Pagani *et al.* 1997).

The Poincaré Plot is a geometrical method of HRV analysis. It presents each RR interval as a function of the previous RR interval producing a diagram to be interpreted both visually and quantitatively. In the analysis, the SD of the continuous long-term RR interval variability (SD2) and the instantaneous beat to beat RR interval variability (SD1) are considered (Huikuri *et al.* 1996a, Tulppo *et al.* 1996). SD1 reflects vagal modulation of the HR and has a relatively strong correlation with the HF spectral component. SD2 reflects the magnitude of both the VLF and LF spectral component describing the long-term RR interval fluctuations. The Poincaré method is thought to be more suitable for HRV analysis from uncontrolled ambulatory ECG recordings, because it is not affected by stationary irregularities and trends (Tulppo *et al.* 1996).

Analytic methods derived from non-linear dynamics based on fractal mathematics and chaos theory have opened new approaches for estimating the correlation properties and complexity of the HRV (Goldberger & West 1987, Goldberger 1996). Methods analyzing fractal-like properties have been used to detect abnormalities in RR interval dynamics in various cardiovascular disorders (Bigger *et al.* 1996, Huikuri *et al.* 1998, Mäkikallio *et al.* 1998, Mäkikallio *et al.* 1999a, Mäkikallio *et al.* 1999b). Analysis of the inverse power-law slope (1/f characteristics) has been a better predictor of survival than the traditional risk markers for both elderly people and patients with impaired left ventricular dysfunction (Brouver *et al.* 1996, Ho *et al.* 1997, Huikuri *et al.* 1998). The slope of the power law is especially deep in denervated, transplanted hearts (Bigger *et al.* 1996), and therefore it is thought to be influenced by autonomic input, even if the underlying physiological mechanisms are not exactly understood.

The advantages of 24-hour ambulatory EKG recordings are good reproducibility and especially information concerning low frequency bands of spectral heart rate variability gathered over longer time periods than standard cardiovascular tests can provide (Huikuri *et al.* 1990, Kleiger *et al.* 1987, Ori *et al.* 1992).

Previously, in 24-hour ambulatory EKG recordings the difference between PD patients and healthy subjects has been described most significant in the very-low frequency component of HRV and power-law slope (Haapaniemi *et al.* 2001). HRV components seem to decrease in advanced PD being possibly a marker of increased cardiovascular dysautonomia (Devos *et al.* 2003).

Before this trial, the effect of STN DBS on tonic autonomic cardiovascular regulation had not been studied.

3 Aims of this study

The main purposes of this study was to evaluate the STN DBS as a treatment of Parkinson's disease.

The more specific aims of the individual studies were:

1. To evaluate the clinical outcome after bilateral STN DBS.
2. To assess the impact of bilateral STN DBS on health-related quality of life.
3. To compare the costs of DBS treatment with the possible benefits of surgery.
4. To evaluate the effect of STN DBS on tonic autonomic cardiovascular regulation.

4 Patients and methods

4.1 Patients

This study was carried out at the Departments of Neurosurgery and Neurology, at the University of Oulu, between years 2001 -2005. The study was approved by the Ethics Committee of the Medical Faculty, University of Oulu, and was carried out according to the principles of the Declaration of Helsinki. Every patient gave their informed consent before inclusion in this prospective study. A summary of the patients is presented in Table 2. The patients were sent to our department from all over Finland excluding the Helsinki area.

Table 2. The demographic data of the patients in this study.

Gender	Age	Disease duration, years	Study	Levodopa dose mg	LEDD	Selegiline	Entacapone
F	51	15	retrospective	200	800		
M	61	10	retrospective	400	1550		1000
M	67	12	retrospective °	350	800	5	
M	66	8	retrospective	800	900		1200
F	63	10	retrospective	950	1600	10	
F	73	12	retrospective	100	1300		600
M	62	14	retrospective [1]	200	1200		
M	50	12	retrospective	100	650	10	1200
F	68	16	retrospective	400	550		
M	44	10	I	1000	1000	10	1200
F	70	7	I	350	450		
F	58	15	I	1200	1200		
F	61	15	I[1],II	850	950	5	
F	74	13	I[2],II[2]	500	600		1000
M	56	17	I[1],II	950	1000		
F	44	6	I,II,III	200	1240		
M	47	10	I,II,III,IV		350	5	1200
M	70	12	I,II,III,IV	200	375	5	1000
M	67	12	I,II,III,IV	50	470	10	
M	51	8	I,II,III,IV	300	820		600
M	54	12	I,II,III,IV	1100	1190		400
M	61	7	I,II,III,IV	1000	1350		1200
M	50	12	I,II,III,IV		2205	5	
M	56	8	I,II,III,IV[3]	100	200		1200
F	61	13	I,II,III,IV	800	930	5	
M	52	13	I,II,III,IV	700	820		1000
F	52	8	I,II,III,IV	800	1460		400
F	44	6	I,II,III,IV	300	850	10	600
M	70	32	I,II,III,IV	750	750		1000
F	66	23	I,II,III,IV	650	650		1000
M	65	12	I,II,III	200	700		
M	68	15	I,II,III	500	990	10	1000
M	71	17	I,II,III	400	1250		1200
M	56	9	I,II,III	200	850		1200
M	69	15	I,II,III	150	1050		600
F	51	8	I[4],II[4]	500	1370		
M	65	9	I,II	600	860		
M	71	22	I,II	650	1550		
M	58	14	I[1],II	1000	1600	10	1000
M	56	17	I	250	500		
F	49	10	I	600	740		
M	63	20	I	1100	1300		

° Died in bicycle accident 10 months postoperatively. [1] Infection requiring removal of stimulator material, excluded (F 61 partially removed, excluded only from analysis of surgical outcome using UPDRS rating scale). [2] Died from pulmonary embolism two days postoperatively, excluded. [3]M 58 excluded from study IV due to paroxysmal atrial fibrillation. [4] Intracerebral hemorrhage as surgical complication, died 9 months postoperatively, excluded. LEDD = Levodopa Equivalent Daily Dose (Wilding *et al.* 1991, Lozano *et al.* 1995, Krack *et al.* 1998b): 100 mg levodopa + decarboxylase inhibitor = 140 mg levodopa CR + decarboxylase inhibitor = 10 mg bromocriptine = 10 mg apomorphine = 1 mg lisuride = 1 mg pergolide = 1 mg pramipexole = 6 mg ropinirole = 2 mg cabergoline. M = male. F = female

The patients had idiopathic PD that responded favorably to levodopa fulfilling the Parkinson's Disease Society Brain Bank clinical criteria (Gibbs & Lees 1988). The patient group included every patient operated on with bilateral STN DBS in the Oulu University Hospital during years 2000 – 2003. Patients operated on during year 2000 were included in the retrospective part (general aspects) of this study.

The decision about operative treatment was made in co-operation with the patient's treating neurologist, the operating neurosurgeon and the neuropsychologist. An outpatient visit at our neurosurgical clinic was arranged for all patients some months before the operation to give them pertinent information about the operation, including its anticipated advantages and possible untoward effects. The patients were admitted to our surgical ward two days before the operation for a final preoperative evaluation and an information session.

4.2 Methods

4.2.1 Operation technique

The surgical practice consisted of using Laitinen's stereoguide under local anesthesia complemented with intravenous sedation when necessary. The patients were awake during the procedure, and the ability of speaking and moving were tested repeatedly. Standard ventriculography was used to serve as the anatomical basis for all stereotactic measurements. An intraoperative stereotactic X-ray controlled by permanently mounted X-ray generators was routinely utilized for verifying the position of the implanted DBS-electrodes. The STN was interpreted to be located 3 mm posteriorly from the midcommissural point, 5 mm below it, and 12 mm lateral from the midline. Also, the macrostimulation (Radionics RFG 5S stimulator, Radionics, Burlington, Massachusetts) with a Radionics stimulation electrode (2,1 mm in diameter, 4 mm tip) was used. Without exception, only one trajectory was used for one hemisphere. After having obtained the desired responses, the Radionics electrode was replaced by the Medtronic DBS electrode (model 3387, 1.27 mm in diameter, 11.5 mm active area). Its proper position was confirmed by plain X-ray of the skull in anteroposterior and side projections. The patients took their prescribed PD medication after the operation, when it was safe anesthesiologically.

Further, the effects of the DBS were assessed during the following 20-24-hours by temporary test stimulation (Mattrix, Medtronic, Minneapolis). After the testing period the patients received a permanent pulse generator (Kinetra, Medtronic, Minneapolis). Thereafter, a meticulous adjustment of the stimulation site and stimulation parameters was undertaken during the follow-up, mean 5 days, whenever needed, to optimize the DBS by striving for maximal therapeutic effects and the least possible amount of side effects. Mainly, the pulse width was set at 60 μseconds and the frequency at 160 - 180 Hz with monopolar voltage, and these adjustments were altered only as required.

4.2.2 General aspects

To examine the general aspects of STN DBS, every patient operated on since January 2001 was analyzed retrospectively. The patients were followed up from 18 to 49 months (mean 30 ± 9) and all changes in the stimulation parameters and the medication were registered. The data was collected from patient documents at 6-month intervals. We also recorded how often the patients were admitted to hospital for adjustment of stimulation parameters, what the reason for admission was, and how long the patients had to stay at the ward to reach the optimal benefit from the DBS treatment.

Every patient had a preplanned follow-up visit one month after the operation. Decisions for adjusting the stimulation parameters were made by the neurosurgeon responsible for adjustments, in co-operation with each patient's treating neurologist. This was done if problems appeared that were not being resolved by medical treatment. The adjustments were preferably made in a stable off-medication stage in the morning after 12 hours withdrawal of medication. Consistent attempts were made to find the lowest effective amplitude with the least side effects. The stimulation site was chosen directly after the operation on the basis of the best efficacy and the least side effects, and during the follow-up it was only seldom changed.

As for those patients who participated in the prospective study, the adjustments of the stimulation parameters were accomplished during the hospital stays only when necessary, and if no adjustments were made, the follow-up visits for research purposes were ignored when we analyzed the amount of hospital visits.

4.2.3 Clinical evaluation and neuropsychological tests (Study I)

The effects of the STN-DBS on motor symptoms and activities of daily living (ADL) were evaluated by one and the same neurologist (TH). The patients were evaluated using the UPDRS parts I, II, III and IV. The tests were performed preoperatively and then postoperatively as blinded for the stimulation status, being randomly assigned to be on or off at one of the repeated follow-up examinations at one and 12 months after the operation. The blinding was performed one hour before evaluation and all the evaluations were made at the best medication "on" situation using the patient's own medication, mostly one hour after levodopa intake.

The patients were assessed using a revised version of the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler 1981), the Trail-Making test (Reitan & Davison 1974) and phonetic and semantic verbal fluency tests. Patients were instructed to combine the numbers from 1 to 25 in the Trail-Making A Test, and to join numbers and letters following a number-letter sequence ordered from 1-A to 13 in the Trail-Making B test. The time taken to join the items was recorded. In the phonetic and semantic verbal fluency tests, patients had to supply as many words as they could that begin with the letter p (phonetic clue) and names of animals (semantic clue), with 1 minute for each task. The tests were performed in connection with the clinical evaluation preoperatively and at one month and 12 months postoperatively. The results were evaluated by our neuropsychologist (AJ). Two patients did not want to take part in every

neuropsychological test. Furthermore, two other patients had preoperatively severe clinical fluctuations and one patient had aphonia postoperatively, making the examination impossible. These patients were excluded from the analysis of neuropsychological test results, but not from evaluation of clinical outcome.

To measure changes in intellectual performance, patients performed the Wechsler Adult Intelligence Scale subtests for similarities and block design (WAIS-R). In the test for similarities, the patient looks for similarities in word pairs. This test measures verbal ability for reasoning and conceptualization. In the block design test, patients build figures from blocks according to a model. This test is thought to measure visuospatial perception and visuoconstructive reasoning. For testing memory, the digit span, story recall, recall of two sets of pictures, interfered immediate recall, and ten-word learning tests were used. The test for executive functions was divided into verbal fluency and serial substractions. These tests were chosen for their good reproducibility and general acceptance (Jahanshahi *et al.* 2000, Saint-Cyr *et al.* 2000, Woods *et al.* 2002).

4.2.4 Evaluation of health-related quality of life (Study II)

Two HRQoL instruments, the PDQ-39 and NHP, were used to measure the HRQoL. The disease specific PDQ-39 instrument is a well-known measure of HRQoL in PD, comprising 39 questions with five answer options. PDQ-39 has eight subscales, namely: mobility, ADL, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. In this study the Finnish version of PDQ-39 was used. The results can be expressed either as a summary score of the items of each subscale or as a total score transformed linearly to a 0-100 scale, with higher scores reflecting lower HRQoL (Jenkinson *et al.* 1999). The PDQ-39 has a well established construct validity and a moderate content validity (Peto *et al.* 1995, Jenkinson *et al.* 1999, Marinus *et al.* 2002). In addition, the internal consistency of the subscales is adequate and the reproducibility of the subtests is good, except for the social support subscale (Peto *et al.* 1995). The PDQ-39 seems to be capable of detecting disease deterioration but responsiveness to improvement still needs assessment (Fitzpatrick *et al.* 1997).

The NHP is a generic HRQoL questionnaire developed and tested for its validity and reliability in the UK (Hunt *et al.* 1980) andmany other countries, including Finland (Koivukangas *et al.* 1995). It deals with six aspects of health, namely: pain, energy, sleep, physical mobility, emotional reaction and social isolation. The items are preference weighted, and each item yields a value between 0 and 100 (worst possible health status). The first section of the NHP as the authorised Finnish version of the NHP was used to ensure that the results are comparable with the values of the general population in Finland. The normal population sample consisted of 3600 persons between the ages of 18 and 80 years. The values were also calculated in the different age categories (Koivukangas *et al.* 1995).

Patient data was collected before the operation, one month and 12 months after the operation during hospital visits. The patients themselves gave the written answers to the questions of the PDQ-39 and NHP questionnaires.

The comparison between clinical improvement and improvement in quality of life was performed with the patients who also participated in Study I.

4.2.5 Assessment of the costs (Study III)

This study assessed the direct costs from the perspective of the health care provider. The costs were determined as the charges for drug treatment and the in-patient hospital care. The drug prices were attained from the official Finnish price list (Pharmaca Fennica, 2005) using the largest available package size. The costs of the surgery included the preoperative evaluations, operation theater costs including stimulator material, salaries, anaesthesia and the recovery room costs. The expenditure for a hospital day included all patient related costs such as treatment, examinations, drugs, food and physiotherapy. The prices were derived from the hospital register. The total cost for the hospital stay was calculated by multiplying the total number of days of hospital stay by the mean costs of one day. All currency was converted according to the exchange rates of May 2005: 1 EUR = 1.26 US$.

For evaluating the clinical outcome and HRQoL, the same instruments were used as in Studies I and II.

4.2.6 Autonomic nervous system evaluation (Study IV)

A two channel 24-hour ambulatory EKG recording (Polar Electro electroscanner) was performed on all patients before the operation and 12 months afterwards. During the recording, conducted in the hospital ward, the subjects were encouraged to continue their daily activities.

The EKG data were sampled digitally and transferred from the scanner to a microcomputer for analysis of heart rate variability. All RR interval time series were first edited automatically, after which a careful manual editing was performed by visual inspection of the RR intervals. Each RR interval time series was passed through a filter that eliminates premature beats and artefacts and deletes the filling gaps using previously described methods (Korpelainen *et al.* 1999). In the final analysis of the linear and non-linear components of heart rate variability, 24-hour measurements were divided into segments of 8000 RR intervals, and only segments with >85% sinus beats were included. The mean duration of all RR intervals and the SD of all RR intervals (SDNN) were computed as time domain measures reflecting slow fluctuations of RR intervals. SDNN primarily reflects very low frequency fluctuation in heart rate behavior, possibly reflecting peripheral vascular resistance and thermoregulation (Rosenbaum & Race 1968).

One otherwise successful patient was excluded from the study because of paroxysmal atrial fibrillation, which made the data ineligible for analysis.

The control group consisted of 57 age matched subjects selected from a group of healthy people who were participating in a trial comparing the characteristics of hypertensive and normotensive subjects randomly selected by their social security code

from the population of the city of Oulu (Huikuri *et al.* 1996b). There were 38 males and 19 females in the control group with a mean age of 56±13 years of age. They all underwent a complete physical examination and had no disease or medication affecting the autonomic nervous system (ANS) in their history.

4.2.7 Statistics

For statistical treatment of the results, SPSS-spreadsheet 12.0 was utilized except for study I, in which version 11.5 was used. The patients functioned as their own controls. For comparisons between pre- and postoperative situations and between stimulator on and stimulator off, the one sample t-test for paired data was used. Comparisons over time were made using Friedman's test. Correlations were estimated with Spearman's correlation coefficients. The Mann-Whitney two-sample test was utilised to compare the values of the control subjects and those of the PD patients. Statistical significance was determined at a $p<0.05$ level.

5 Results

5.1 General aspects

The mean stimulation amplitude was 1.8 ± 0.7 V at the time of discharge from the ward (Table 3). The amplitude had to be increased significantly during the first six months of follow-up ($p<0.001$), but after that time-point the changes were not significant.

The pulse width ranged from 60 to 120 microseconds. During the first six months postoperatively, the pulse width had to be increased significantly, but did not change after that (Table 3). The stimulation frequency ranged from 130 Hz to 180 Hz, being typically 160 -180 Hz. We did not find any significant changes to be necessary in stimulation frequency during the follow-up.

The mean preoperative levodopa dose and mean LEDD-dose (Levodopa Equivalent Daily Dose) (Wilding *et al.* 1991, Lozano *et al.* 1995, Krack *et al.* 1998b) diminished significantly after the surgery (Table 3). However, significant further changes were not observed after the first six months.

Table 3. Changes in the medication and stimulation parameters during follow-up.

Time	Operation	6 months	12 months	18 months	24 months
Number of patients	35	35	35	35	27
Amplitude (V)	1.8±0.7	2.6±1.0[1]	2.8±1.2[1]	2.7±0.8[1]	2.8±0.8[1]
Pulse width (μs)	71±14	76±15[2]	76±16[2]	76±14[2]	78±13[2]
Equivalent dose	975±412	824±555[1]	804±555[1]	816±541[1]	722±536[1]
Levodopa dose (mg)	536±337	431±407[2]	406±402[2]	420±400[2]	413±441[2]

Levodopa Equivalent Daily Doses (Wilding *et al.* 1991, Lozano *et al.* 1995, Krack *et al.* 1998b): 100 mg levodopa + decarboxylase inhibitor = 140 mg levodopa CR + decarboxylase inhibitor = 10 mg bromocriptine = 10 mg apomorphine = 1 mg lisuride = 1 mg pergolide = 1 mg pramipexole = 6 mg ropinirole = 2 mg cabergoline (not determined).

The stay at the neurosurgical ward for the DBS implantation operation and the beginning of the stimulation varied from 6 to 17 days (median 8). The reasons for the prolonged duration at the ward were temporary confusion, esophagitis and failed ventriculography

in the first attempt. There was one case in each category. Also, one vocal cord paresis in a 52-year old female was encountered after a successful STN-operation. The reason for this paresis remained unknown, and it was spontaneously resolved in a week.

The eldest patient in our series, a 74-year-old woman, died from a pulmonary embolism during the mobilization phase after otherwise uneventful STN-DBS surgery. Another patient with rapidly progressive and severe PD contracted a late postoperative intracerebral hemorrhage. This led to a permanent deterioration of her neurological condition to the bedridden stage. This patient died 9 months postoperatively. The rate of the major complications including death and permanent deterioration of neurological condition in this series was therefore 4.8 %.

However, other complications were much milder. Three of the patients developed stimulator infections requiring removal of all the stimulator material. Two of these patients did not want to have a surgical procedure after the antibiotic treatment. The third failed to get a lead to the STN in the operation probably due to a former thalamotomy. Additionally, one patient developed a unilateral infection of the scalp wound leading to the removal of the DBS electrode. This patient refused DBS re-operation. These patients were not evaluated postoperatively.

One patient developed an infection around the pulse generator and the extension leads which necessitated the removal of the implanted material except for the DBS electrodes. This was followed by a successful implantation of new equipment after antibiotic treatment. The rate of these hardware related complications was 9.5 %.

Three of the patients developed gait disturbances and two of these also suffered from speech disturbances. These problems were transient as well as limb weakness in one patient and akinesia in another one. In this series, only one patient developed adverse psychiatric effects; a 44-year old male developed hypersexualism three weeks postoperatively. The problem was resolved by reducing the dopaminergic medication within a few weeks. The same patient also later suffered from mild depression, which was treated with medication.

The mean amount and duration of the adjustment visits decreased significantly after the first six months (Table 4). The decrease was also significant after one year as compared to the period of 6 - 12 months. Our series includes a total of 130 visits for stimulator adjustments. Thirty-five of these were routine one-month follow-up visits postoperatively and 95 were arranged in co-operation with the treating neurologist to obtain additional benefit from the DBS. The most common reason for these extra visits was the recurrence of parkinsonian symptoms, or the patient’s wish to still get more advantage from the relatively well functioning DBS treatment (Table 5).

Table 4. Mean number of postoperative follow-up visits and days at the ward.

Parameter	0-6 months	6–12 months	12–18 months	18–24 months	24-30 months	30–36 months
Number of patients	35	35	35	27	17	15
Number of visits	2.2±1,5	0.8±0.9[1]	0.5±0.6	0.2±0.6	0.1±0.2	0.1±0.4[2]
Time at the ward	4.2±3.7	1.3±1.6[1]	1±1.2	0.3±1.1	0.1±0.5	0.1±0.4[2]

[1]$p<0.001$ (compared to 0 -6 months value); [2]$p\leq0.02$ (compared to 6 -12 months value). As a statistical method, the one-sample t-test for paired data was used.

Table 5. Reasons for the non-protocol follow-up visits (35 patients, median follow-up time 27 months).

Reason for follow-up visit	N
Disease related problems	
Recurrence of parkinsonian symptoms	69
Hardware related problems	
Wound revision or infection	4
Depletion of battery voltage	2
Stimulator unintentionally off	1
Stimulation related problems	
Gait disturbances	9
Speech disturbances	5
Limb weakness	3
Akinesia	1
Hypersexualism	1
Total	95

5.2 Clinical evaluation and neuropsychological evaluation (Study I)

Twelve months after the surgery a significant improvement was seen in most subscales of the UPDRS evaluation when the stimulation was on (Table 6). The dyskinesias and clinical fluctuation values reduced very significantly in the UPDRS IV subscale. Clinical fluctuations were reduced by 53 %. Best motor response (UPDRS III) values also improved significantly (31.4 %) due to stimulation.

Table 6. UPDRS scores of 24 PD patients treated with bilateral STN-stimulation, medication and stimulation on.

Parameter	UPDRS items no.	Max. value	Score before surgery	1 mo after surgery	12 mo after surgery
M, B & M	1 – 4	16	3.6 ± 2.2	3.0 ± 2.4	3.1 ± 2.7
ADL	5 – 17	52	20.0 ± 6.3	14.0 ± 6.4	16.2 ± 8.0[2]
Motor	18 – 31	108	34.7 ± 16.5	24.3 ± 14.9	23.8 ± 15.1[2]
Dyskinesias	32 – 35	13	4.9 ± 2.6	1.8 ± 1.9	2.3 ± 2.5[1]
Fluctuations	36 – 39	7	4.1 ± 1.4	2.5 ± 1.5	2.5 ± 1.9[1]
Complications	40 – 42	3	0.9 ± 0.9	0.8 ± 0.8	0.5 ± 0.6
H & Y	43	5	2.9 ± 0.7	2.8 ± 0.7	2.6 ± 0.9

[1] $p<0.01$ using Friedman's test; [2] $p<0.05$ using Friedman's test. M, B & M = Mentation, Behaviour & Mood. H&Y = Hoehn & Yahr staging (Hoehn & Yahr 1967)

The mean impulse generator voltage needed to achieve therapeutic benefit was 2.7 ± 1.1 (mean ±SD). As for other impulse generator settings, the mean pulse width (± S.D.) was 77 ± 16 and the mean frequency (± S.D.) was 171 ± 13.

When comparing motor function during stimulator on and stimulator off situations, we found a clear improvement during the stimulator on condition in the severity of tremor, rigidity and akinesia (Table 7). These parameters also improved in comparison to preoperative results. However, the change in the UPDRS scores assessing speech and postural stability was not significant.

Table 7. UPDRS motor scores of 24 PD patients treated with bilateral STN stimulation, on medication.

Score	UPDRS item no.	Max. value	Preop. score	1 month stim. on	1 month stim. off	12 month stim. on	12 month stim. off
Speech	18	4	2.0 ± 0.8	1.3 ± 1.0	1.5 ± 1.0	1.7 ± 1.1	1.9 ± 1.1
Tremor	20 - 21	28	5.0 ± 5.5	2.8 ± 3.6	5.1 ± 5.8	2.1 ± 3.2[2]	5.8 ± 6.0
Rigidity	22	20	6.6 ± 5.1	4.5 ± 3.5	7.2 ± 4.3	4.1 ± 3.9[2]	6.7 ± 4.2
Akinesia	23 – 26	32	13.1 ± 6.5	9.5 ± 6.3	13.1 ± 5.1	9.2 ± 5.4[1]	14.5 ± 6.3
Gait	29	4	1.0 ± 0.6	0.7 ± 0.9	1.2 ± 1.0	1.0 ± 0.8[2]	1.4 ± 1.0
Post. stabil.	30	4	1.0 ± 1.0	1.0 ± 1.1	1.1 ± 0.9	0.9 ± 0.9	1.0 ± 1.0

[1]$p<0.001$ (comparison between stimulation on and stimulation off); [2]$p<0.005$ (comparison between stimulation on and stimulation off). One sample t-test for paired data.

The changes in the neuropsychological test scores were also minor and not significant, except for the verbal fluency test results (Table 8). These showed significant deterioration: preoperatively, the patients were able to name 21 ± 7 (mean ± SD) animal names in a minute, but only 15 ± 9 after 12 months STN DBS ($p=0.003$).

Table 8. Comparison of neuropsychological test results of 19 patients preoperatively and postoperatively.

Measure	Preoperative	1 mo after surgery	12 mo after surgery
WAIS-R[1] IQ	96.4 ± 8.8	95.6 ± 9.4	95.4 ± 9.9
Trail-Making A Test	101.2 ± 75.3	101.3 ± 73.4	99.8 ± 81.6
Trail-Making B Test	299.9 ± 188.2	280.2 ± 200.4	301.1 ± 179.2
Phonetic verbal fluency	10.5 ± 5.2	9.0 ± 4.6	7.8 ± 5.0[2]
Semantic verbal fluency	21.1 ± 7.2	15.2 ± 8.2	14.9 ± 9.3[3]

[1] WAIS-R indicates revised version of Wechsler Adult Intelligence Scale (Wechsler 1981); [2] $p<0.05$; [3] $p<0.005$ using Friedman´s test.

5.3 Health-related quality of life (Study II)

Table 9 shows the PDQ-39 scores preoperatively, one month and 12 months postoperatively. Significant improvement was seen in subscales of ADL, emotional well-being, stigma and bodily discomfort. Also, the PDQ-39 summary index improved significantly. Only communication became worse during the follow-up, whereas mobility improved, but the change did not reach statistical significance.

Table 9. Scores of the PDQ-39 subscales and summary index (±SD) of the 27 patients operated with bilateral STN DBS for PD

PDQ-39	Preoperative mean	1 month mean	12 months mean	p-value
Mobility	53.9±22.8	45.9±26.8	47.6±25.6	p=0.12
ADL	59.0±19.7	46.8±25.0	45.5±27.9	p<0.001
Emotional well-being	41.5±16.4	29.2±17.1	35.6±20.7	p=0.004
Stigma	40.5±23.1	27.9±21.1	28.7±21.3	p=0.001
Social support	32.4±22.5	24.4±21.1	32.1±24.0	p=0.2
Cognition	29.6±18.3	30.0±21.0	26.9±17.9	p=0.5
Communication	38.0±24.6	35.0±23.9	44.1±31.3	p=0.003
Bodily discomfort	51.2±24.3	30.6±18.2	34.0±24.9	p<0.001
PDQ-39SI	46.2±14.8	36.3±17.7	38.9±18.7	p<0.001

ADL = activities of daily life; Friedman's test was used to compare the pre- and postoperative results. PDQ-39SI = PDQ-39 Summary Index

There was a negative correlation ($r=-0.417$, $p=0.031$) between the patient's age and improvement in the PDQ-39 ADL subscale score; younger patients showed a greater improvement between preoperative and 12 months ADL scores than did older ones.

The NHP scores before the treatment and one month and 12 months after the treatment are presented in Table 10. There was a statistically significant improvement in the score of the subscales measuring problems with energy, sleep, emotional reactions and social isolation. There was also a decrease in the score of the subscale measuring problems with physical mobility. However, it did not reach statistical significance.

When the results of the NHP in the PD patients were compared with a control group of an elderly Finnish population, all the dimensions measured by the NHP showed lower HRQoL in the patients with PD than in the control group.

Table 10. Nottingham Health Profile (NHP) scores (±SD) of the 25 patients operated with bilateral STN DBS for PD.

NHP	preoperative mean	1 month mean	12 months mean	p-value	Controls*
Energy	39.9±37.0	31.6±31.7	34.7±30.4	p=0.04	17.5±31.3
Sleep	32.9±27.6	20.5±27.0	26.1±29.3	p=0.02	18.2±27.4
Pain	28.7±33.4	22.8±32.8	22.8±30.7	p=0.2	19.2±27.6
Emotional reactions	30.2±28.3	17.4±23.6	19.8±21.8	p=0.01	6.9±18.2
Social isolation	25.0±29.8	12.3±19.1	21.5±24.0	p=0.04	12.5±21.6
Physical mobility	33.5±21.9	22.9±23.8	32.6±26.0	p=0.07	11.8±19.8

*Finnish elderly population (55-64 years) (Koivukangas *et al.* 1995); Friedman's test was used to compare the patients' preoperative results with the results after 12 months follow-up.

Table 11 presents the correlation between clinical improvement and subscales of the PDQ-39 instrument. We were not able to find any correlation between the NHP subscales and clinical improvement because the NHP dimensions are generic in nature.

Table 11. Correlation between the improvement of the UPDRS subscales and the PDQ-39 subscales.

UPDRS subscale (median improvement)	PDQ-39 subscale correlation	p
	ADL	
UPDRS II (11.1 %)	0.51	0.01
	Mobility	
UPDRS III (21.9 %)	0.44	0.02
	Mobility	
UPDRS IV (46.2%)	0.41	0.03
	PDQ-39 Summary Index	
UPDRS tot. (22.7 %)	0.47	0.01

Correlations were estimated with the Spearman's correlation coefficient method.

5.4 Costs and effects (Study III)

The costs associated with DBS were divided into two categories: surgery and follow-up visits. The average surgery costs included the stimulator, leads and electrodes (Kinetra, Medtronic, 14 346 EUR 18 076 US$); salaries of the employees and use of the operation theater plus the recovery room (2 615 EUR, 3 295 US$); anaesthesia (1 380 EUR, 1 739 US$) and inpatient daily costs (234 EUR, 295 US$ / day). The average length of stay for an operation was 7.9 days per patient, resulting in inpatient daily costs of 1 849 EUR

(2 330 US$). The average surgery cost was 20 142 EUR (25 379 US$) per patient. On average there were three follow-up visits per patient during the first year after the treatment. The total length of the stay in hospital was, on average, 7.1 days per patient. Follow-up visits added a cost of 1 661 EUR (2 093 US$) per patient. Thus, the average total direct costs for the operative treatment per patient was 25 869 EUR (32 595 US$) in the first year.

The patient's need for medication reduced significantly during the follow-up period; a mean daily dose of levodopa (±S.D) 450±310 mg diminished to a mean dose of (±S.D) 320±224 mg one year postoperatively (p=0.031). Also, levodopa equivalent daily doses (LEDD) (Wilding *et al.* 1991, Lozano *et al.* 1995, Krack *et al.* 1998b) reduced from 921±459 mg to 779±488 mg (p=0.007). Our research also showed a significant decrease in mean drug costs during the follow-up (Table 12). The most important factor decreasing costs was the reduction of levodopa doses. The cost for drugs during the one-year period after the treatment was 4 066 EUR (5 123 US$). Mean drug savings as a result of the operation totalled 278 EUR (350 US$) in follow-up period costs per patient.

Table 12. Mean drug costs before and 12 months after STN DBS, EUR.

Source of cost	Baseline, EUR/day	12 Months, EUR/day
Levodopa	1.6±1.4 (n=20)	1.0±0.7 (n=18)
Levodopa CR	1.1±1.4 (n=11)	1.1±1.3 (n=11)
Dopamine agonist	3.7±3.9 (n=14)	3.3±3.7 (n=14)
Selegiline	0.4±0.9 (n=7)	0.4±0.9 (n=7)
COMT-inhibitor	5.2±3.6 (n=15)	4.8±3.5 (n=14)
Amantadine	0.01±0.06 (n=1)	0.01±0.06 (n=1)
Total per day	11.9±6.1 (n=20)	10.4±6.0 (n=20)[1]
Total per year	4343.6±2244.4 (n=20)	3787.7±2195.5 (n=20)[1]

[1]p<0.001 compared to baseline. A paired sample t-test was used for statistical analysis.

The total incremental cost, meaning the difference between the total direct costs of the operative treatment and the savings in drug costs during the same time, was calculated to be 25 591 EUR (32 245 US$) per patient. Based on the UPDRS total score, the incremental cost per one unit improvement was 1 815 EUR (2 287 US$). Using the PDQ-39 summary index, a 3 891EUR improvement in incremental cost per patient was calculated.

5.5 Autonomic nervous system evaluation (Study IV)

Measurements of HR and HR variability of the patient and control groups are presented in Table 13. The spectral measures of heart rate variability and the slope of power law relation were impaired in our patient series compared to healthy subjects. Especially, the very-low frequency component of HRV ($p<0.05$) and the power-law slope ($p<0.01$) differed between PD patients and controls.

There were no significant changes in the time or frequency domain measures of HR variability or the slope of power-law relation in the PD group after the STN operation, although there was a non-significant trend toward lower values of VLF ($p=0.114$) spectral component.

Table 13. Measures of HR and HRV of 13 STN DBS treated patients and 57 control subjects.

Variable	Preoperative	12 months postoperative	Control group
RRI	832±92	844±101	866±108
SDNN	137±36	135±30	160±41
VLF	1073±618	698±523	1701±1997[1-3]
LF	545±248	472±377	918±812
HF	340±333	334±457	500±496
Slope of HRV	-1.4±0.2	-1.4±0.2	-1.3±0.1[2-3]

Values are presented as mean±SD. RRI=RR interval; SDNN=SD of all RRIs; VLF=very low frequency; LF=low frequency; HF=high frequency; slope of HRV=slope of power law relation. [1]$p<0.05$ preoperative values vs. control values; [2]$p<0.01$ preoperative values vs. control values; [3]$p<0.01$ postoperative values vs. control values. A paired sample t-test was used for statistical analysis.

6 Discussion

6.1 Operation technique

The modern practice for exact localization of the target for DBS comprises a fusion of intraoperative images derived from stereotactic CT and MRI, although ventriculography has been the golden standard during this study (Benabid 2000). Especially the direct visualization of the most popular cerebral target, the STN, may be considered as a crucial step for successful DBS. In addition, intraoperative microrecordings have been advocated by some neurosurgeons to be mandatory for truly hitting the tiny (20–30 mm3) STN. The requirements for exact positioning of the DBS electrodes into the STN seem, however, to be controversial, as the extent of STN neuronal activity recorded along the trajectory of the electrode has been shown to have no effect on the postoperative clinical outcome (Houeto *et al.* 2003).

Even the role of the STN itself has been cast into doubt, as the stimulation of its surroundings, especially the center median and parafascilular complex (Caparros-Lefebvre *et al.* 1999b), zona incerta and lenticular fasciculus (Yelnik *et al.* 2003) can improve symptoms of PD. This confusing information about the real target needed to be stimulated for achieving excellent clinical effects resembles the results of Laitinen (1985) concerning the exact localization of the clinically effective target for thalamotomy: there was a separation by as much as 6-7 mm between the targets of world famous stereotactic neurosurgeons. His conclusion can be applied even to the present day DBS by stating that for achieving success, the stimulation has to interrupt the pathways that transmit the increased neuronal activity in the STN and GPi, known to be responsible for motor dysfunction in PD.

A rather simple mode of action for implanting the DBS electrodes without microelectrode recordings and fusion imaging seems to be sufficient for effective long-term stimulation. Our surgical method during the study period 2000-2003 seemed sufficient to guarantee long lasting relief of motor symptoms in the majority of the parkinsonian patients.

According to this study ventriculography, intraoperative macrostimulation, temporary test stimulation via the DBS electrodes, and the meticulous adjustment of the permanent

stimulation parameters compensate for omissions of intraoperative microrecordings and sophisticated image fusions. The problem of MRI is the geometrical distorsion, sometimes even several millimeters, in performing preoperative targeting of the STN (Menuel *et al.* 2005). The distortions can be corrected using appropriate software, but the accuracy for determining midcommissural point is higher in standard ventriculography. On the other hand, the improved accuracy targeting the STN gained by 3-D imaging and microelectrode recording may lead to improved efficacy of DBS surgery. So far, the estimated increased effectiveness of these procedures has not been confirmed.

6.2 General aspects

The STN DBS procedure for severe Parkinson's disease is an efficacious treatment that produces a great advantage for the patients receiving it. Although the DBS treatment places a load on the health care system during the first postoperative months, the need for stimulator adjustments diminishes thereafter.

This study demonstrated that, even though the operation may be associated with severe complications, the adverse effects of STN DBS are mostly mild and reversible. Both the surgery and stimulator adjustments seem to need experience to achieve the best possible results.

The stimulation parameters in the present study were very similar to those published in earlier studies (Benabid *et al.* 2000, Moro *et al.* 2002, Vesper *et al.* 2002). The need for frequent adjustments, especially during the first months, has also been described earlier (Hariz *et al.* 1999, Krack *et al.* 2002). Shortly after the operation, strong currents in the STN tend to cause unwanted dyskinesias, but the patient's tolerance to the current increases when the medication is reduced. This finding is in accordance with previous observations (Krack *et al.* 2002).

The procedure of increasing the stimulation amplitude in Oulu is somewhat more radical than in Broggi's group (2003); sometimes our patients seemed to need higher increases than 0.4 V per adjustment appointment. Since the patients were carefully observed, it has been possible to increase the amplitude even slightly over 1 V per one control period without any complications. To avoid adverse effects, it was found to be useful to observe the patients at the ward overnight after considerable adjustments.

In previously published series of bilateral STN-operations, the antiparkinsonian medication has been reduced by from 19 to 81 % (Krack *et al.* 1998a, Kumar *et al.* 1998, Limousin *et al.* 1998, Moro *et al.* 1999, Houeto *et al.* 2000, Molinuevo *et al.* 2000, DBS-PD-SG, 2001, Lopiano *et al.* 2001, Volkmann *et al.* 2001, Østergaard 2002, Tavella 2002).The reduction in the levodopa dose in this study (26 %) is in the same range as Østergaard *et al.* has reported (2002), being slightly lower than in most publications.

An explanation for this could be lower preoperative levodopa dose used than in many other studies. Most studies report relatively high preoperative doses, but in the Aarhus study, it was only 804 mg (Østergaard 2002). The mean preoperative levodopa dose in our study was 556 mg, reflecting the standard clinical practice in our country. The relatively small reduction in the levodopa dose in this study is in accordance with the

hypothesis, that higher doses of levodopa have a higher probability of being diminished postoperatively than lower ones (Østergaard 2002).

Even if the levodopa reduction is slightly lower than in most publications, the improvement in UPDRS motor scores is comparable with previous publications. Our scores improved 31 % in the "on" medication state, whereas the largest series published so far reported improvement of 26 % (DBS-PD-SG, 2001).

Results of this study suggest avoiding operating on patients far over 70 years of age with severe comorbidity, and not to operate patients suffering from a rapidly progressing or highly advanced PD. Probably part of those patients with atypical, severe clinical course do not have pure Parkinson's disease, but so called Parkinson-plus syndrome (Sjöström *et al.* 2002), which is not recommended to be operated on. An infection or adverse events preventing the long-term use of DBS might not necessarily mean a final setback. The most important factor determining the result of these operations is the selection of the patients. Young patients without any psychiatric problems, suffering from severe PD with motor complications and good response to levodopa, should be considered as STN DBS candidates.

6.3 Clinical and neuropsychological function (Study I)

This study showed that STN DBS significantly improves the motor performance and ADL functions of PD patients also in the medication "on" situation when the patient's own prescription is used.

Previous papers have shown, that UPDRS motor scores improve only 10 % postoperatively when scoring during the "on" phase (Limousin et al 1998). These data were achieved by using an administration of levodopa, plus benserazide after drug withdrawal overnight. Later study settings of that kind have been repeated by several authors (Molinuevo 2000, Houeto 2000, Lopiano 2001, Volkmann 2001, Tavella 2002) and the relatively low rates of motor improvement have been confirmed. In our procedure, we have evaluated the patient´s clinical outcome using their own medication. That is probably the reason why the improvement in the medication "on" situation seems to be relatively high compared with the studies mentioned earlier.

In our study the best motor response (UPDRS III) values also improved 31.4 % due to stimulation. Studies performed in a set-up similar to our study report improvement in the UPDRS III score by 25.8 – 54.5 % in the "on" state (DBS-PD-SG 2001, Østergaard 2001, Spottke *et al.* 2002), which is in accordance with our results. However, the combined use of medication and stimulation is the ordinary state postoperatively, and changes in that situation are meaningful for the patient.

The finding that verbal fluency decreases postoperatively, but no other clearly negative sequelae are observed, is in accordance with several neuropsychological studies (Ardouin 1999, Alegret 2001, Volkmann 2001). The UPDRS scoring was not sensitive enough to capture the decrease in verbal fluency in this patient group, although dysarthria was clinically obvious in some patients. In some cases, the impairment of speech would have been avoided with a lower current, but the patients preferred defects in speech to a decrease in other efficacy of stimulation.

6.4 Health-related quality of life (Study II)

This study showed that STN DBS significantly improves the HRQoL. The improvement of the HRQoL is correlated with clinical improvement. Our data suggests that the PDQ-39 ADL subscale improves in younger patients more than in older ones. Previously, it has been assumed, that young age is a good prognostic factor for a favorable UPDRS outcome of DBS (Charles *et al.* 2002), but we were not able to confirm that.

The PDQ-39 measurements in our patient group showed a significant improvement in the subscale of ADL. A significant improvement was also shown in the subscales of emotional well-being, stigma and bodily discomfort, which has not been reported in earlier studies, possibly due to smaller patient populations (Just & Østergaard 2002). Previously, in a smaller patient series and shorter follow-up, the subscales of mobility, ADL and cognition were shown to improve significantly (Just & Østergaard 2002). In the present study, the improvement in the subscale of mobility was not significant due to a large variation in the results. Furthermore, the improvement of the subscale cognition was only minor.

The results are in line with several neuropsychological studies indicating the neuropsychological sequelae in cognitive function seem to be nominal and / or transient (Woods *et al.* 2002). In accordance with previous reports (Just & Østergaard 2002), our results clearly indicate an improvement of the PDQ-39 single index and the ADL score by STN-DBS.

Our results demonstrate a clear correlation between overall clinical improvement and the HRQoL measured with the PDQ-39 instrument. Surprisingly, the improvement of the PDQ-39 subscale of mobility seemed to have almost as strong an association with the UPDRS IV score, measuring complications of therapy such as dyskinesias and freezing, as with the UPDRS III, measuring motor functions.

The improvement of HRQoL agrees with the knowledge that motor fluctuations cause great distress to PD patients (Pechevis *et al.* 2005), and the STN-DBS is highly effective in diminishing medication, resulting in reduction of dyskinesias. The correlation between clinical improvement of the UPDRS ADL score, and the subjective improvement of the PDQ-39 ADL score, did not reach a statistical significance, possibly due to a relatively small patient population. The correlation of the clinical improvement and the NHP results did not show a statistical significance, probably because the NHP is a generic HRQoL instrument not designed specifically to assess the quality of life in patients with PD (Hunt *et al.* 1980).

The worsening of the communication subscale of the PDQ-39 in our patients was clear. A previous study measuring the HRQoL in STN-DBS showed neither significant improvement nor significant worsening of the communication dimension (Just & Østergaard 2002). On the other hand, this may reflect our own finding of deterioration in verbal fluency.

Our results with the generic NHP show that the HRQoL of the patients with PD is lower than that of elderly people in Finland. The greatest problems for patients are associated with the energy, sleep, emotional reactions and physical mobility dimensions.

6.5 Costs and effects (Study III)

The costs of bilateral STN DBS amounted to an average of 25 869 EUR (32 595 US$) per patient during the one year follow-up period. The total incremental cost, meaning the difference between the total direct costs of the operative treatment and the savings in medical costs during the same time, was calculated to be 25 591 EUR (32 245 US$) per patient. The first year of STN DBS therapy is expensive due to the high cost of the stimulator device. The following years are less expensive, because the stimulator only needs to be replaced after 3 – 5 years (Krack *et al.* 2003, Meissner *et al.* 2005).

The direct costs of STN DBS (25 869 EUR, 32 595 US$) were somewhat higher than in earlier studies: 21 082 EUR (26 563 US$) and 20 410 EUR (25 712 US$) for Spottke *et al.* and Meissner *et al.* respectively. The decrease in medical costs in our study was significant, even though the preoperative levodopa equivalent dose was already lower in our patients than in many other published series (Spottke *et al.* 2002, Meissner *et al.* 2005).

In this study the costs and effects were analyzed on the successful patients only. The costs would have turned out to be higher, if the selection of the patients would have taken into account also the patients with complications. Some costs for the hospital stay could be possibly avoided by adjusting the stimulator on outpatient basis, but this is seldom possible due to long distances and the need for proper follow-up to avoid stimulation related problems.

When formally estimating cost it is of course not adequate to analyze direct costs alone. Indirect costs such as the burden to health care and home care services should also be considered. Also, the estimated life expectancies and the need to replace stimulators over time should be analyzed.

The decision model for lifetime cost-effectiveness of DBS surgery by Tomaszewski and Holloway (2001) suggested that DBS surgery is cost-effective if quality of life improves 18 % or more compared to those receiving best medical management. In the present series the direct costs of DBS surgery were somewhat lower than those in the model of Tomaszewski and Holloway (2001). Also, our clinical experiences indicate that the indirect costs estimated by Tomaszewski and Holloway are valid for our study as well. This allows us to compare changes in quality of life.

The subscale of the PDQ-39 instrument that is most responsive to DBS seems to be stigma (48 % improvement). Also, subscales of ADL (23 % improvement) and bodily discomfort (37 % improvement) clearly exceeded the threshold considered to be cost-effective. Even if the communication subscale worsened, the PDQ-39 summary index improvement was within the range of what is considered to be cost-effective in Tomaszewski's study.

In conclusion, STN DBS therapy seems to be cost-effective, even if we have to admit that longer follow up periods are needed. With acceptable incremental costs we

were able to significantly relieve the motor complications of pharmacotherapy resulting in a better functional outcome and an increased quality of life during one year follow up. Also, we have to remember that the amount of complications is crucial when estimating the effectiveness of the treatment.

6.6 Autonomic nervous system function (Study IV)

According to the present study, the bilateral STN-operation has no significant effect on cardiovascular autonomic function despite functional improvement of the patients. This study is also the first to describe the effect of DBS on 24-hour HRV, and widens our conception of this relatively new treatment modality.

Predictably, diurnal autonomic cardiovascular regulation, as demonstrated by the spectral measures of HRV and the slope of power law relation, was impaired in our PD series compared with healthy subjects in our district. As our group has previously described, the difference between patients and controls was most significant in the very-low frequency component of HRV and power-law slope (Haapaniemi *et al.* 2001).

The physiological background for these HRV indexes is not completely understood. Recent data suggest that daily physical activity might play a major role in long-term HR fluctuations (Tulppo & Huikuri 2004, Roach *et al.* 2004, Bernardi *et al.* 1996). Subjects who are more active have higher values of long term HRV. In light of these observations, one might assume that an increase of long-term HRV indexes in PD patients occurs after STN operation. This improves the physical activity of PD patients. However, an opposite trend towards lower long term HRV indexes was observed. This implies that altered long term HRV may indeed be related to the actual process of PD itself, which impairs the long-term HRV, independent of the patient's physical activity. However, we have to admit, that the improvement of the clinical situation in PD patients does not necessarily mean an increase in physical activity.

The slope of the power-law relation has been proven to be a powerful predictor of death in elderly subjects (Saul *et al.* 1989) and in patients with recent myocardial infarction (Bigger *et al.* 1996). Even though we are compiling data on longer follow-up periods after STN DBS treatment, we do not know the effect of DBS on life expectancy (Krack *et al.* 2003). Our data suggest that the life expectancy is not altered by STN DBS due to stimulation effects on autonomic dysfunction. Naturally, the prognosis of the patients is also affected by many other factors.

Recently, data have been published showing neutral effects of STN DBS on autonomic dysfunction measured by standard cardiovascular reflex tests (Holmberg *et al.* 2005). The advantages of 24-hour ambulatory ECG recordings are good reproducibility and especially information concerning low frequency bands of spectral heart rate variability gathered over longer time periods than standard cardiovascular tests can provide (Kleiger *et al.* 1987, Huikuri *et al.* 1990, Ori *et al.* 1992). In any case, our results are in accordance with previous results indicating that long term STN DBS does not have an effect on tonic autonomic function.

However, we cannot exclude all cardiovascular effects of STN DBS. Due to STN DBS, a transient intraoperative increase of R-R interval has been reported (Kaufmann *et al.* 2002, Thornton *et al.* 2002) as well as a variety of autonomic symptoms (Sauleau *et al.* 2005). Furthermore, there are data suggesting that the dorsal subthalamic nucleus and/or the zona incerta are involved in autonomic control (Benedetti et al 2004). The autonomic nervous system is a complex system and possibly short term effects of STN DBS differ from long term ones.

STN DBS seems to be an effective treatment for motor complications caused by PD, and its neutral effect on tonic autonomic cardiovascular regulation is so far the strongest evidence suggesting that altered autonomic function observed in PD is not merely a result of impaired motor function.

7 Conclusions

In conclusion, STN DBS is an effective treatment of advanced PD. Microelectrode mapping of the subthalamic area does not seem to be essential for a good clinical response. Our rather simplified surgical method for implanting STN DBS significantly improves the motor performance and ADL functions of PD patients.

Our results indicate that quality of life, measured by the generic NHP and the disease specific PDQ-39 instruments, improves in patients with advanced PD after bilateral STN stimulation.

The incremental costs of performing bilateral STN DBS in Finland compared with preoperative medical treatment amounted to an average of 25 591 EUR per patient during the first postoperative year.

The bilateral STN operation has no significant effects on cardiovascular autonomic function despite the functional improvement of the patients, suggesting that impaired autonomic function is related to the PD process itself rather than to motor dysfunction of this disease.

The results of this study encourage the practice of STN DBS surgery. Relatively young patients without any psychiatric diseases, suffering from severe PD with motor complications and initially showing a good response to levodopa, should be considered as STN DBS candidates.

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