Long term clinical disease progression in patients with Parkinson's disease after STN Deep Brain Stimulation

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Abbreviations

3D	Three dimensional
ADL	Activities of daily life
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BRW	Brown-Roberts-Wells
COMT	Catechol-O-methyl transferase
CRW	Cosman-Roberts-Wells
CSF	Cerebrospinal fluid
CT	Computed tomography
DBS	Deep brain stimulation
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders III, revised
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FOG	Freezing of gait
FSS	Fatigue Severity Scale
GPi	Globus Pallidus internus
GPi-DBS	Deep brain stimulation in the Globus Pallidus internus
HRs	Hazard ratios
L-dopa	Levodopa
LEDD	Levodopa Equivalent Daily Dose
MADRS	Montgomery and Aasberg Depression Rating Scale
MCI	Mild cognitive impairment
MD	Medical Doctor
MMSE	Mini-Mental State Examination
MN	Minnesota
MOA-B	Monoamine oxidase B
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PhD	Philosophiae Doctor
PIGD	Postural instability and gait disorder
SD	Standard deviation
STN	Subthalamic nucleus
STN-DBS	Bilateral deep brain stimulation in the subthalamic nuclei
TM	Trade mark
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS III	Part three of the Unified Parkinson's Disease Rating Scale
VIM	Ventrointermediate nucleus of the thalamus
VOP	Ventralis oralis posterior nucleus of the thalamus

Research groups

The research has been conducted in Oslo and in Stavanger. In Stavanger at The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger Hospital Trust and in Oslo at the Department of Neurosurgery and Department of Neurology, Rikshospitalet (now a part of Oslo University Hospital Trust).

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Summary

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder with severe long-term impact on patients, their caregivers and on the society in general [1]. The treatment of PD is symptomatic. Surgical treatment with chronic high frequency stimulation of the subthalamic nuclei (STN-DBS) has been shown to provide long term symptom relief with few complications in selected patients with PD [2-4].

Aim

The aim of the thesis has been to elucidate the long-term effects of STN-DBS on the development of clinical symptoms in PD.

Materials and methods

All PD patients treated with STN-DBS between 2001-2007 at Rikshospitalet (N=144) and at Stavanger University Hospital (N=28) were prospectively followed with standardized examinations, and all 172 STN-DBS operated PD patients were included in the scientific material for the thesis. As reference we used the patients from a population-based prevalence study conducted with patient recruitment between September 1992 and May 1993, before STN-DBS was available.

Results

We confirm that STN-DBS surgery can be performed with good and stable long time results on dopaminergic motor symptoms. Perioperative mortality was low and the rate of major adverse events low. The non-motor features of PD seem to develop independently of intervention with STN-DBS, as do FOG and falls. Fatigue is observed to develop at a high rate in STN-DBS operated patients after the first year postoperatively.

Conclusions and implications

STN-DBS is a very good treatment option for motor symptoms in selected patients with advanced PD. The benefits of the treatment are limited to motor symptom control as the underlying PD pathology continues to develop in operated patients similar to the natural history of PD. Fatigue seem to develop at a high rate in STN-DBS operated

patients after the first year postoperatively. Our findings are relevant to advising patients both about the indication for, and the timing of, STN-DBS surgery in PD

List of publicized papers

1. Long-term efficacy and mortality in Parkinson's disease patients treated with subthalamic stimulation. Toft M, Lilleeng B, Ramm-Pettersen J, Skogseid IM, Gundersen V, Gerdts R, Pedersen L, Skjelland M, Røste GK, Dietrichs E. Mov Disord. 2011 Aug 15;26(10):1931-4 [5].

2. Progression and survival in Parkinson's disease with subthalamic nucleus stimulation. Lilleeng B, Brønnick K, Toft M, Dietrichs E, Larsen JP. Acta Neurol Scand. 2014 Nov;130(5):292-8 [6].

3. Motor symptoms after deep brain stimulation of the subthalamic nucleus. B. Lilleeng, M. Gjerstad, R. Baardsen, I. Dalen and J. P. Larsen. Acta Neurol Scand. 2015 May;131(5): 298-304. [7].

4. The long-term development of non-motor problems after STN-DBS. B. Lilleeng, M. Gjerstad, R. Baardsen, I. Dalen and J. P. Larsen. Acta Neurol Scand, 2015. Oct;132(4): 251-8. [8].

General introduction

Deep brain stimulation has been available in Norway as a treatment option for PD for 14 years [9]. The promising results from other centres abroad in the late 90-ies were giving new hope to PD patients suffering from severe motor symptoms, fluctuations and drug side effects. International techniques and protocols were adapted at Rikshospitalet, which was first in Norway to offer STN-DBS from 2001. There was a strong consensus among the staff involved at Rikshospitalet that the opportunity of following the STN-DBS patients prospectively should be pursued, and a standardised

set of examinations was established and documented in the medical records from the very beginning. Preoperative evaluations, peroperative procedures and postoperative follow-up were thus planned and conducted in a standardised fashion for all patients. As the Stavanger University Hospital introduced this novel treatment in 2006, similar principles were adapted. A national database for STN-DBS was discussed, and generally agreed on, but was never implemented. In 2009, the Department of Health decided to centralize this (and other) specialized treatment to two centres in Norway, in Oslo and in Trondheim. At that time, the treatment had been offered to Norwegian PD patients for 8 years, and there was a growing need to document the results for the patients. Tapping in to the prospectively registered patient information from medical records, and supplementing with extra follow-ups, we set out to elucidate the long term clinical effects after STN-DBS for our patients. From international literature it was increasingly clear that STN-DBS had great positive effects on dopaminergic motor symptoms in selected PD patients. Rapports indicated good effect over time, with long standing reduction of motor symptoms and reduced need for dopaminergic medication. But the patient materials behind much of the available literature were relatively small, follow-up time was short to medium long, and there was an ongoing debate on the effect of STN-DBS on other aspects of PD like the assumed non-dopaminergic motor symptoms, non-motor symptoms and indeed whether or not STN-DBS could modulate the disease progression itself. On this background it seemed called for to use the materials of prospectively followed-up patients available from Rikshospitalet and Stavanger University Hospital to confirm or examine the positive and lasting motor effects of STN-DBS, and to explore the effect on other clinical symptoms of PD over time after surgery. We also wanted to explore possible disease modulating effects on PD of STN-DBS, by looking at progression of cardinal symptoms after surgery and on cumulative postoperative mortality. The postulate of a potential neuroprotective effect of STN-DBS has been primarily driven by a theoretical concept related to an induction of reduced cytotoxic glutamate release in substantia nigra by the procedure which again leads to less neurodegeneration [10, 11]. Results from early animal studies also lent support to the neuroprotection hypothesis [12-14]. However, no controlled patient studies have provided data to support this

concept and it has therefore been seen as one of the major unanswered research issues related to the STN-DBS procedure [1].

Motor symptoms that have poor or no response to dopaminergic treatment include axial motor involvement causing postural instability and gait difficulties (PIGD) [15, 16], freezing of gait (FOG) and falls. Such symptoms have been shown to have large impact on the daily life of PD patients and for their caregivers [17, 18]. The symptoms increase in PD patients as the disease develops over time, corresponding to the increased number of dispersed lesions in the brain [19]. The PIGD pattern of parkinsonism is associated with a faster rate of cognitive decline and subsequently with an increased risk of dementia [19, 20]. The pathophysiology of PIGD, FOG and falls are likely to be complex, and is not fully understood. Locomotor areas in the brainstem and in the midbrain are believed to be important in the control of balance and gait, and exacerbation of cognitive deficits may also influence the progression of axial symptoms in PD [19]. Dopaminergic cell loss and reduced dopamine outflow are considered less important, leading to the assumption that STN-DBS should not have a major impact on the development of such symptoms, and that they should develop independently in operated patients similar to non-operated patients. This matches with the clinical experience that these symptoms are found to be disabling for patients both on dopaminergic medication and after STN-DBS treatment. However, a meta-analysis of a number of long term follow-up studies after STN-DBS and GPi-DBS (deep brain stimulation in the globus pallidus internus) has indicated acute, positive effects on PIGD symptoms [21].

The progressing incapacitation experienced by PD patients is caused not only by increasing motor symptoms, on which STN-DBS has been shown to have positive effects, but also by a wide range of progressing non-motor symptoms. Common non-motor symptoms in PD include cognitive impairment, neuropsychiatric symptoms, sleep problems and autonomic symptoms. The characteristical progressive dopamine depletion in the nigrostriatal tract cannot directly explain such non-motor PD symptoms, and other brain areas and transmitter systems are assumed to also be affected by PD as these symptoms arise in PD patients. Abnormalities in several

neurotransmitter systems have been found in PD, including in the adrenergic, in the serotonergic and in the cholinergic [22] . Braak et al have advocated a sequential anatomical progression of PD, involving several areas of the brain [23, 24]. According to this theory PD (characterized pathologically by Lewy bodies and α-synuclein pathology) may start out in the brainstem and subsequently spread through the midbrain to mesocortex and finally neocortex. Based on the findings of pathological changes in the brain areas they suggest a staging of PD development from 1-6. The early stages (1 and 2) would be identified by inclusions in the medulla oblongata, pontine tegmentum and the olfactory bulb and anterior olfactory nucleus. Early involvement of olfactory structures could explain the early clinical finding of olfactory alterations in some PD patients, before the manifestation of hallmark motor symptoms [25]. It could also explain the early debut in some PD patients of sleep disorders, an important category of non-motor symptoms in PD [26] .

As non-motor symptoms increase in severity during the natural development of PD, they often play a major role in the total disability of the patients with major impact on the need of care. Cognitive impairment and dementia have been shown to be major factors in decreased functioning in late stage PD [27, 28]. The risk of developing dementia is elevated in PD patients up to six times the risk in the general population with increasing risk with increasing age, and the resulting incidence of dementia amongst PD patients is approximately 10 % per year [29-31].

Since non-motor symptoms in PD are believed to arise as the disease involves non-dopaminergic areas of the brain, they would in principle not be expected to be affected by the electric stimulation in STN-DBS as this procedure is considered a dopaminergic treatment. It has been suggested that the surgical implantation of the electrodes could have lesioning effects, which in turn could also have non-motor effects. However, insufficient knowledge has been available on the development of non-motor symptoms in PD after STN-DBS, despite their major impact on the daily life of many late stage PD patients.

The early history of PD

The history of Parkinson's disease (PD) may be as old as the history of the human brain itself. But surprisingly, the disease seems to have gone unrecognised and unclassified up until modern time. It is unlikely that the reason is that PD arose as a disease only recently. The shorter average life spans in the past centuries may certainly have contributed to a lower prevalence of all diseases with onset late in life, including PD. But still it is somewhat surprising that PD was not recognised as a diagnose earlier. However, symptoms closely resembling parkinsonian cardinal symptoms are mentioned in ancient Egyptian texts, in ancient Hindu texts on traditional, Ayurvedic medicine and by the Greek physician Galen [32]. There have even been studies showing that traditional Ayurvedic herb treatments used for PD have positive effects on PD symptoms [33, 34]. In "Richard II" William Shakespeare lets the Duke of York suffer from "shaking, fumbling and palsy" – the text clearly describes a man with symptoms closely resembling PD [35]. Thus - small, probable imprints of PD on human life can be found way back in history.

The modern history of PD

The modern history of PD as a recognized disease entity is in general view thought to have begun with James Parkinson's famous publication from 1817; "*An Essay on the Shaking Palsy"* [36], although several physicians in the 17th and 18th centuries had described, at least in part, the same symptoms [37].

In his essay, Parkinson described 6 patients, three from his own medical practice and three individuals he had observed on the streets of London. The essay was a systematic description of the cardinal symptoms of the disease later to bear his name. Parkinson described the characteristic resting tremor as opposed to tremor with motion, he had noted abnormal posture and gait difficulties, the paralysis and apparent diminished muscle strength. He also described the progressive nature of the symptoms over time. He wrongly suspected that the origin of the symptoms might be lesions in the cervical spinal cord. As James Parkinson remains one of the great names in the history of neurology, it might be of some interest in this neurosurgical thesis to note that James Parkinson was in fact a surgeon, not a neurologist. His work also provided a clue to the

work of later pioneers in Parkinson surgery, by being the first to report temporary tremor relief in a PD patient (his Case 6) after an apoplectic seizure [36] – an important lead for those surgeons attempting corticotomies to treat tremor in PD over a century later [38].

Many early neurologists picked up on James Parkinson's work, most notably Jean-Martin Charcot who in addition to contributing to the clinical understanding of PD (including defining the three cardinal symptoms of tremor, rigidity and bradykinesia) also suggested the renaming of the disease in honour of James Parkinson [39].

The medical community came closer to understanding the pathophysiology of PD in the early 20th century, as Frederic Lewy in 1912 discovered the Lewy bodies [40] and when Konstantin Tretiakoff in his 1919 thesis described how he observed degeneration and cell loss in the substantia nigra in association with PD [41]. However, the biochemical mechanisms behind the pathophysiology in PD was first further elucidated when the Swedish Nobel Prize laureate Arvid Carlsson in 1957 published his work on dopamine's role as neurotransmitter [42] and Oleh Hornykiewicz's work on describing dopamine's role in PD [43]. Dopamine had been known as a substance since 1911, but levodopa (L-dopa) was first used as a drug in the treatment of PD in 1967 [44]. Based on the work of Georg Cotzias et al. from 1969 L-dopa quickly became the drug of choice for treating PD symptoms [45] . Until L-dopa the only pharmacological treatment for PD was anticholinergics, with limited effect and many side effects.

Epidemiology of PD

PD is one of the most common movement disorders known, matched only by the prevalence of essential tremor [46]. It affects both women and men and the gender distribution is near equal, tough some studies have reported slightly higher prevalence in males [47]. The general prevalence of PD in Norway is about 100-150 patients per 100.000 [48]. Incidence rates vary between studies but seems to be between 8.6 and 19.0 per 100.000 in western countries. Worldwide, about 4 million people are estimated to suffer from PD. The incidence of PD increases with age, and accordingly the prevalence of PD is higher in demographically older populations. Thus, the

prevalence of PD is much higher in *developed* countries as compared to *developing* countries because of the much younger population in the developing countries. The prevalence of PD in people over 65 years is approximately 1-2 %, more than doubling up to a prevalence of 3-5 % in people over 85 years [49]. If PD symptoms occurs before age 50, it is denominated as "early onset". This is the case in approximately 4 % of PD patients [50].

The impact on the society is high, both in direct and indirect cost - but also in the way PD affects the quality of life for many people suffering from PD and for their families.

Pathogenesis

The development of PD is characterised by progressive loss of dopaminergic neurons containing neuro-melanin. The pathogenic causes behind the cell loss are unknown. Possible mechanisms leading to progressive cell loss have been proposed to involve genetic and/or environmental factors: abnormal protein processing involving dysfunction of the ubiquitin-proteasome system, oxidative stress by free radicals, mitochondrial dysfunction, apoptosis, excitotoxity as well as inflammation [51]. The characteristical cell loss in PD takes place foremost in the pars compacta of the substantia nigra. Due to compensatory mechanisms both presynaptic (increased turnover of dopamine) and postsynaptic (increased dopamine receptor sensitivity), symptoms of PD do not develop in patients in the early stages of pathological cell loss [52]. Clinically, the symptoms of PD arise as the striatal dopamine levels drop beyond 40-20 % of the normal levels and cell loss in the substantia nigra exceeds 50 % [53-55]. The time over which the cell loss progresses before clinical onset of PD is unknown and may vary between individuals [56, 57]. The loss of dopaminergic, neuro-melanin containing neurons in the substantia nigra combined with the presence of Lewy bodies, has classically been regarded as the neuropathological and neurochemical hallmarks of PD. Lewy bodies are eosinophilic hyaline inclusions in the cytoplasm of neurons. α-synuclein has been shown to be a central component in Lewy bodies [58]. Lewy bodies are present in surviving neurons of the substantia nigra pars compacta in patients with clinical PD [59]. But Lewy bodies are also found in

other brain areas that also demonstrate cell loss in PD, as well as in the brains of patients with other neurodegenerative diseases. Thus, Lewy bodies may represent a common intracellular feature in some types of neuronal degeneration.

In addition to atrophy of the substantia nigra, cell loss in PD is observed in the cortex, the prefrontal region, in the hypothalamus, the raphe nuclei, in sympathetic ganglia, in locus coeruleus, in the dorsal nuclei of the vagus, in the ventral tegmental area and in the nucleus basalis of Meynert [60, 61]. The finding of widespread cell loss in the brain in PD add to the increasing evidence for involvement in the clinical progression in PD of other pathways than the dopaminergic. Cholinergic, glutamatergic, noradrenergic and serotonergic signal systems have all been shown to be affected in PD patients [22]. Although the classical, cardinal motor symptoms of PD correspond well to impairment of dopaminergic signal pathways, other motor symptoms and non-motor symptoms in PD may well develop by progressively involving other non-dopaminergic signal pathways [62].

Genetics and environmental factors in PD

The risk of PD increases if a close family member develops the disease, by a factor of 3 to 4 as compared to the general risk. And some families have had a history of PD affecting family members over generations. Thus, it has long been suspected that genetic factors play a major role in the pathogenesis of PD in many patients. An important discovery was made in 1997, after studying an Italian family with dominantly inherited early-onset parkinsonism. A mutation (Ala53Thr) on the long arm of chromosome 4, coding for α-synuclein, was found in the affected family members [63]. Later, this and several other mutations associated with the development of parkinsonism were identified at the same locus on chromosome 4, and the locus was subsequently named PARK1 [64]. An increasing number of mutations and loci has later been discovered [65, 66]. Known mutations can explain the development of parkinsonism in a minority of cases, and environmental causes may well be as important in the development of PD. The role of genetics in PD needs further research and elucidation, with the long-term goal of finding new treatment options. For now,

gene therapy for PD seems still far to come. Too little is known about exposition factors increasing the PD risk in the population. A large number of possible factors have been explored. Exposure to pesticides, living in rural areas and long-term consumption of well water have shown a moderately increased risk in a meta-analysis [67]. Interestingly, life style factors like smoking and coffee appears associated with *reduced* risk for developing PD – as opposed to the huge, negative impact smoking has on cardiovascular risk [68].

Pathophysiology

Although the classical model of linear signal pathways in the basal ganglia used earlier to explain the pathophysiology in PD is far too simple [69], it still can be used to understand the basic pathophysiological mechanisms which allow STN-DBS to provide dopaminergic motor symptom control. The classical model suggest that the dopaminergic motor symptoms in PD are caused by nigrostriatal dopamine deficiency in the putamen leading to reduced inhibition of the STN, which in turn increases inhibitory outflow from the STN leading to increased inhibition of thalamocortical pathways supressing movement. DBS with STN as a target would then create a functional lesion, reducing inhibitory outflow from the STN thus alleviating motor symptoms.

Motor symptoms

Parkinsonism is defined as two or more of the four cardinal motor signs; resting tremor, muscular rigidity, bradykinesia and postural abnormalities [70].

The most frequently occurring of these is bradykinesia, in many patients severely impairing activities of daily life (ADL). Bradykinesia also causes the common reduction of facial expression many PD patients experience, and the typical reduction in arm swing when walking.

Tremor is not present in all patients, but up to 70-80% of PD patients have resting tremor in the early disease stages [71]. Resting tremor in the arm and hand with a typical frequency of 4-6 Hz has been named “pill rolling tremor”, and has arguably become the symptom foremost associated with PD in the general public. Tremor in the neck or lower limbs can occur, but is less frequent.

Rigidity is a very disabling symptom, and many PD patients will put it on top of the list of features of PD impairing ADL. Severe rigidity also can cause pain, and many patients will opt to suffer considerable side-effects from drug treatments rather than reverting to a situation in which the prominent PD symptom is severe rigidity.

Postural abnormality as a cardinal symptom in PD, really describes a number of postural changes including abnormal postures in the extremities, in the neck and in the trunk – often associated with rigidity. Abnormal postures can occur early in the course of PD, whereas real postural instability caused by impaired postural reflexes is more common in late stage PD.

Other motor symptoms in PD includes motor symptoms thought to be secondary to the cardinal motor symptoms like dysarthria, hypophonia, dysphagia and sialorrhoea. Motor symptoms thought to be caused by impairment of other signal pathways than the dopaminergic, i.e. non-dopaminergic motor symptoms, include freezing of gait (FOG) and recurring falls. When postural instability and gait impairment dominates, the PD phenotype is known as the PIGD phenotype of PD (postural instability and gait disorder) – a phenotype in which non-dopaminergic motor symptoms may cause severe disability for the PD patient.

Non-motor symptoms

PD patients are likely to develop a wide range of symptoms which do not primarily arise from impaired motor function. Non-motor symptoms in PD include neuropsychiatric symptoms, sleep disorders, sensory symptoms, gastrointestinal symptoms and autonomic symptoms. Recently, fatigue has drawn increased attention

as a non-motor symptom common in advanced PD with a large impact on ADL function level in the individual patient.

Neuropsychiatric symptoms in PD commonly progress during the course of PD, and include depression, apathy, hallucinations, cognitive dysfunction and dementia. Depression in PD may severely reduce the PD patient's quality of life [72]. Development of cognitive impairment and dementia affect both the PD patients and caregivers, and may rapidly increase the caregiver's burden of care. In the long term, up to 80% of PD patients may develop dementia [73, 74].

Autonomic symptoms can manifest in PD patients as bladder disturbances, changes in sweating or orthostatic hypotension.

Sensory symptoms commonly occur in PD, and an early symptom of PD may be olfactory sensory disturbances. Some PD patients suffer from centrally originating pain which may be difficult to alleviate effectively. Visual dysfunction may also arise.

Common gastrointestinal symptoms are constipation, excess salivation (dribbling) and dysphagia.

Sleep disorders can arise in many forms, spanning from insomnia to excessive daytime somnolence.

Medical treatment for PD

From the advent of dopaminergic treatment with L-Dopa in the late 60'ies, a wide range of drugs have been developed and made available for PD patients. Dopamine agonists, monoamine oxidase B (MOA-B) inhibitors, COMT-inhibitors and amantadine are all part of the neurologist's present pharmacological toolbox. A commonly used medication strategy is to combine drugs in order to delay treatment with L-dopa. However, most PD patients will at some point need treatment with L-dopa and most patients subsequently develop motor complications. At that point the option of surgical treatment can be considered.

Other advanced treatment options in advanced PD with motor fluctuations and hyper- and dyskinesias include duodopa and apomorphine. Duodopa is a liquid preparation of levodopa and a decarboxylase inhibitor, and can be administrated by an intra-intestinal pump. The pump itself is then carried externally, but the catheter tip is placed in the duodenum or proximal jejunum. The pump is normally set to deliver a morning bolus and a daytime maintenance dose, supplemented by bolus doses as needed. Apomorphine is a non-selective dopamine agonist used in PD patients with on/off symptoms when other drug regimens no longer can alleviate the situation. Apomorphine is like duodopa delivered by an external pump, but as a continuous subcutaneous infusion. Apomorphine can induce severe nausea and antiemetic medication must be given to patients when using the drug.

Parkinson surgery

The history of surgical treatment of PD is much longer than the history of modern medical treatment for PD. Speelman and Bosch suggested in their 1998 review of the history of Parkinson surgery [75] to divide the history of Parkinson surgery in two main époques; the first being the époque of open surgery from 1912-1947 and the latter being the époque of stereotactic surgery from 1947 [75] – although the delineation between these two époques is not completely clear cut, neither in methodology nor chronology . However, it could at present, 17 years after Speelman and Bosch published their comprehensive review of the history of PD surgery, perhaps be more correct to divide the history in three important époques: Open lesioning (1912-1947), stereotactic lesioning (1947-1991) – and from 1991 onwards, the new époque of Deep Brain Stimulation (DBS).

Open lesioning

René Leriche from 1912 started to perform bilateral cervical rhizotomy in order to relieve PD symptoms [76]. This is likely to have been the first systematic attempt to treat PD symptoms surgically [75]. Rhizotomy had just been introduced in 1911 as a possible way to ease spasticity [77]. Leriche reported some reduction in tremor and improvement in functions of the upper extremity [76]. Unfortunately, Leriche's results

could not be reproduced by other surgeons. Later attempts on open functional surgery aimed the lesioning at different levels of the pyramidal tracts. Corticotomy to treat tremor was introduced by Bucy in 1937 [38], and he later moved on to perform lesioning in the corticospinal tract for PD symptoms. In 1939 Russel Meyers started to perform transventricular surgery on the basal ganglia to reduce PD motor symptoms [75]. The first patient had the head of the caudate nucleus removed, with good effect. Contemporary neurologists was of the opinion that the basal ganglia for all surgical purposes was a zone of "noli me tangere" – a no touch zone – as it was believed to be closely involved in consciousness. The approach was abandoned around 1947 due to the high mortality of the procedure, but it also contributed to the emerging perception of the importance of the basal ganglia in the ethiology of PD and their efferent connections as targets for PD surgery.

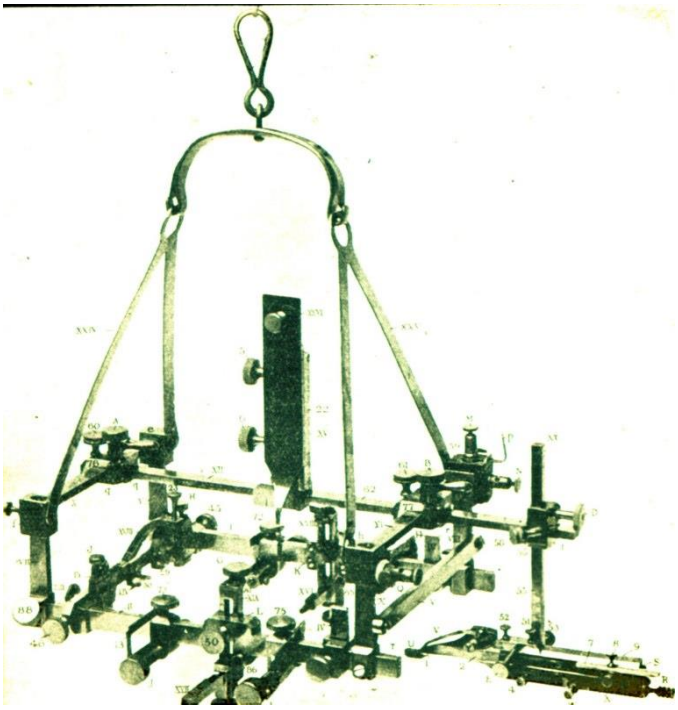
Stereotaxy - the development of the technique

The basic principles of stereotactic surgery are actually fairly simple. The brain is introduced into a fixed, Cartesian (three-orthogonal axis) coordinate system, where all minuscule points in the brain has its own set of unique coordinates. This allows for precise navigation during surgery – if combined with a precise atlas over the location of various brain structures and landmarks from the individual patient or if the coordinate system is fused with the patient's own CT and/or MRI scans. However, the accuracy of stereotactic procedures have always relied on a multitude of sequential steps from preoperative planning to the surgery itself , where any inaccuracy – however minor - in any of the steps can accumulate into a potentially crucial final inaccuracy if left unchecked.

The history of stereotactic surgery has earlier been claimed to have originated with Carl Dittmar (1844-1920) who used a guided system to perform incisions in the medulla oblongata in rabbits at the Institute of Physiology, Leipzig, Germany, described in his 1873 paper [78]. This notion has been challenged by the argument that what Dittmar really invented was a supportive arm to help incisions rather than a device to help guide the surgeon to the anatomical structures [79]. Dittmar's device was never used in humans.

The Russian anatomist Zernov in Moscow on March 22nd 1889 demonstrated an "enchephalometer" [80]. The device was used clinically in humans on several occasions [79, 81]. So was the sequel invention, an instrument called the "brain-topograph" also introduced in Russia, by the neurologist Rossolimo [79]. These early devices were both designed to locate targets for surgery in the human brain. The "brain-topograph" attached to the head with four screws, and bolstered a perforated "helmet" where into a probe could be inserted under guidance. But neither of these devices employed a coordinate system, and thus cannot be regarded as true stereotactic devices.

Consensus is that the first device to be truly stereotactic is the landmark Horsley-Clarke frame from 1908 by Horsley and Clarke [82, 83].



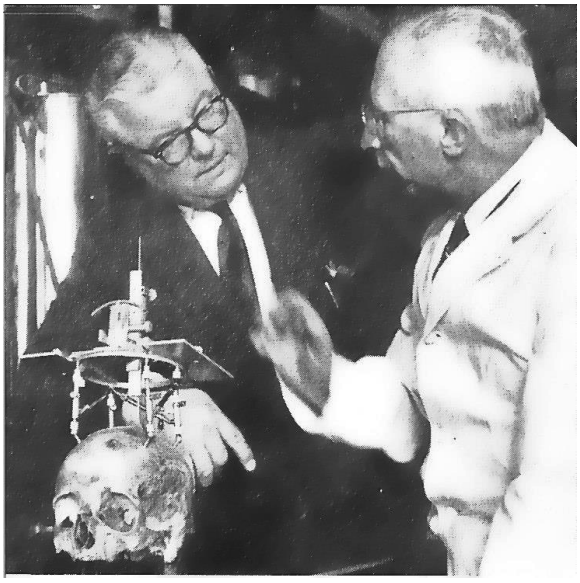
Original Horsley-Clarke instrument

Horsley and Clarke both worked at the University College London Hospital, Sir Victor Horsley as a neurosurgeon and Robert Henry Clarke as a surgeon, anatomist and physiologist. Horsley and Clarke coined the term stereotaxic (their original spelling),

based on their apparatus' ability to lead a moving instrument precisely in a 3D, orthogonal frame of reference. The first version of the frame was constructed for Clarke in 1905 under the name "Clarke's stereoscopic instrument employed for excitation and electrolysis". Horsley and Clarke used this first instrument to do lesioning in the cerebellum in monkeys with electrolytic injections in 1906 [81, 83] before introducing the Horsley-Clarke frame in 1908 in their classical publication in Brain [82]. In this paper they offered a description of the stereotactic instrument itself, an anatomical atlas, and methods on how to perform stereotactic procedures – in their own words: "by this means every cubic millimetre of the brain could be studied and recorded." [82]. The localization of targets relied on the relationships between landmarks on the skull (external auditory canals, inferior orbital rims and midline) and various anatomical structures within the brain. Cranial fixation points established the baselines of a three-dimensional Cartesian stereotactic coordinate system, in which the skull and brain of the experimental animal would then be fixed. The high variability in humans between external skull landmarks and anatomical structures in the brain, rendered the Horsley-Clarke frame and method unusable in humans. Clarke wanted to bring the new technology to use in humans and in 1912 he delivered a patent application for a stereotactic instrument for human use. It is claimed that Clarke's advocacy for moving on to apply stereotaxy in humans alienated him from Horsley and was one of the reasons why their cooperation ended [81]. Regardless, Horsley and Clark contributed significantly to paving the way for stereotactic surgery in humans four decades later, and their frame was used in animal experiments for many years. The original instrument is reported to have been used for the last time in London in the 1950'ies [83].

In 1918 Aubrey Mussen at the Montreal Neurological Institute, Canada designed an improved version of the Horsley-Clarke frame and had it built in London [84]. The concept was based on attaching the frame to the external auditory canals and the infraorbital ridge, and a new stereotactic anatomical atlas Mussen had made. However, Mussen could not find surgeons who would like to try the equipment clinically and it was never tried on humans.

For the next decade and a half the development of stereotactic approaches to the human brain nearly came to a halt. But in 1932 a copy of the original Horsley-Clarke device was built at the Northwestern University Medical School and was subsequently used there by Ranson and Ingram for investigation of nucleus ruber and hypothalamus [85]. The variance between individuals in correspondence between surface landmarks and brain structures remained a challenge, especially in the deeper laying anatomical targets. But in the 1920'ies Walter Dandy had in the meantime invented ventriculography which allowed for the visualization of intracranial anatomic reference points and landmarks. The pineal gland and the foramen of Monro was first used, and upon the subsequent advent of positive contrast for intraventricular use the anterior and posterior commissures were also used as intracranial landmarks. Spiegel and Wycis exploited these new intracranial landmarks when they in 1947 published their first work on stereotactic surgery in humans [86].



Spiegel and Wycis 1959

They used a modified Horsley-Clarke apparatus as setup, and used pneumoencephalograms pre- or intraoperative to localise the pineal gland and the foramen of Monroe. Their objective was to make lesions in the dorsal median nucleus of the thalamus as a less invasive and destructive alternative to the then-popular frontal

lobotomies. However, in their original publication Spiegel and Wycis also suggested other application for stereotactic lesioning in humans, to alleviate pain, drain cystic lesions – and to treat movement disorders [86]. After they made the first stereotactic atlas of the human brain in 1952, the way lay open for trying out new targets and indications. The atlas consisted of a series of photographed coronal brain slices cut at specified intervals in relationship to intracranial landmarks, and with a millimetre reference grid around the borders of each coronal section.

In 1947, the Swedish neurosurgeon Lars Leksell visited Wycis in Philadelphia. Upon his return to Sweden, he in 1949 presented his own stereotactic apparatus which instead of a Cartesian coordinate system employed three polar coordinates (angle, depth and anterior–posterior location). This so-called ‘‘arc-quadrant’’ device provided more flexibility in choosing probe entry point and trajectory. The Leksell frame quickly became the apparatus of choice as the medical society ventured into the era of stereotactic surgery for PD.

Stereotactic lesioning in PD

Initial attempts with deep brain lesioning for tremor and rigidity in PD focused on Globus Pallidus internus (GPi) and the ansa lenticularis as targets. Results differed between centres, but Svennilson et al, from Leksell’s group at Karolinska, reported good effect on tremor, rigidity and functions of daily life in a series of 81 patients treated with pallidotomy [87]. Due to the poor response on tremor in many patients after pallidotomy, new targets were sought. Hassler and Riechert in 1954 introduced new targets in the thalamus which seemed to offer more tremor control in PD and lower risk of complications than the richly vascularized areas of Globus Pallidus and capsula interna [88]. Gradually, into the 1960’ies, most centres turned to perform thalatomies for symptom relief in PD rather than pallidotomy. By 1969 more than 37.000 stereotactic operations had been performed and recorded, most for PD [89]. Overall morbidity was less than 10% and mortality less than 1%. Targets were in the thalamus (VOP, VIM) or in the subthalamic area. Selection criteria had been established, and made 12-15% of PD patients eligible for surgery with expected effect on tremor and rigidity in 80-90 % of operated patients [89].

Despite these convincing results, stereotactic lesioning all but came to a total stop shortly after Cotzias introduced L-dopa [45], with most centres ceasing to perform stereotactic lesioning in PD [75].

Resurgence of stereotactic surgery in the treatment of PD

By the mid-70'ties it was clear that L-dopa therapy could not halt disease progression in PD, and that symptom relief in the long term often required high doses often causing severe side effects. New interest was spurred in thalatomies as a supplement to L-dopa therapy in selected patients, and it was demonstrated that L-dopa therapy did not decrease the known beneficial effects of thalatomy, nor vice versa [90]. In the 70'ties CT scanners were increasingly common in centres worldwide. In 1978 Russel Brown presented a new method of stereotactic localisation of targets, by direct imaging on CT scans of intracranial structures with fiducial markers defining their spatial position [91]. Subsequently, stereotactic localization through neuroimaging rapidly became the standard. It was incorporated in several stereotactic frame systems, notably the Leksell system [92], in the Brown-Roberts-Wells (BRW) [93] and in the Cosman-Roberts-Wells (CRW) system [94]. Globus Pallidus was also revived as a target, with favourable outcomes reported on tremor, rigidity, hypokinesia and also on levodopa induced hyperkinesia [95]. In this period electrical test stimulation was introduced as a way to locate and distinguish specific sites within the brain peroperatively.

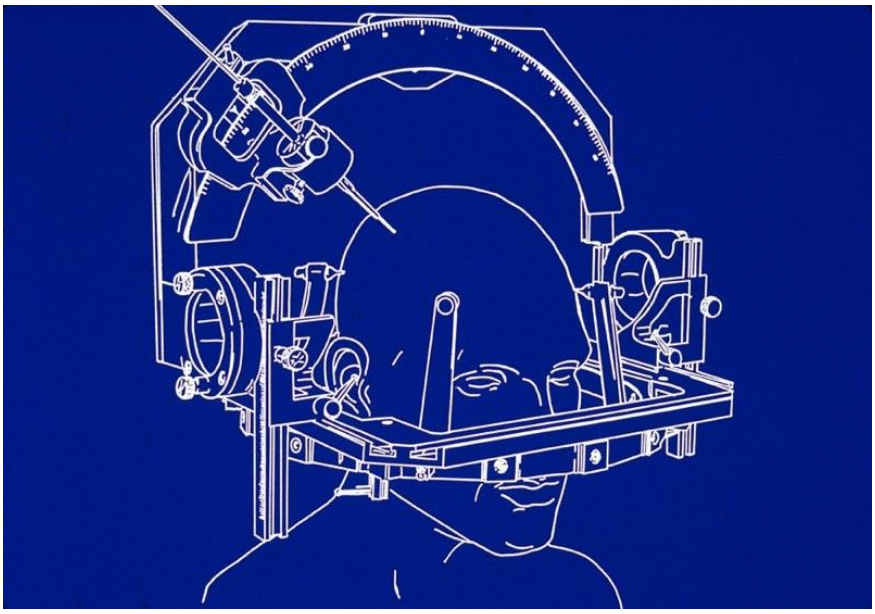


Diagram of the CRW frame setup.

Deep brain stimulation

Deep brain stimulation (DBS) is a technology and a method in which one or two implanted, intracranial electrodes are used to deliver continuous high frequency electrical stimulation to targets in the brain. The basic function of the device resembles that of a heart pacemaker, and the notion “brain pacemaker” has been used in patient education in order to better communicate how the DBS technology really works. DBS has been used to treat movement disorders (PD, essential tremor and dystonia), psychiatric symptoms, chronic pain, obsessive compulsive disorders including Tourette’s syndrome - and epilepsy. Different symptoms are treated with DBS in different targets in the brain.

The high frequency electrical stimulation (>100Hz) has been thought to create a functional, reversible lesion, where the effected neurons are paralyzed and cease to generate axonal outflow. This explanation is likely to be too simple. Many mechanisms for the effect of DBS in the subthalamic nuclei (STN-DBS) have been suggested. Ortodromic axonal stimulation of the cortex has been suspected to be

involved. However, the effect by which DBS works in the brain is not yet fully understood.

The development of DBS

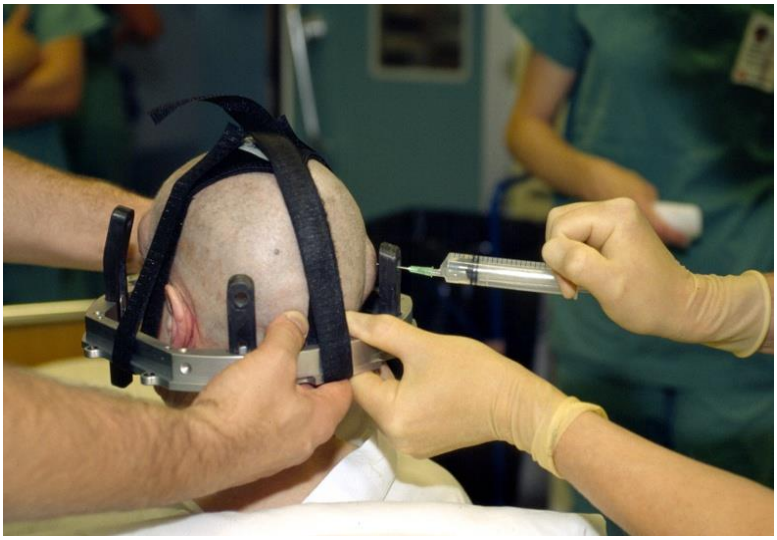
In 1987 the Grenoble-based research group of the neurosurgeon Alim-Louis Benabid and the neurologist Pierre Pollak published their work on continuous high frequency stimulation in the thalamus to treat tremor [96]. The effect of the chronic thalamic stimulation was convincing, but the beneficial effect of the stimulation in the thalamic target was limited to tremor suppression and had no effect on other PD symptoms. In 1990 animal studies in MPTP treated monkeys indicated that dopaminergic deafferentation caused hyperactivity in the STN [97] and that supressing STN outflow by selective lesions could reverse rigidity and akinesia [98, 99].

Alim-Louis Benabid

The Grenoble group built on these results, and in 1994 they published the results of chronic high frequency stimulation in the subthalamic nuclei in two PD patients [100]. The publication led to a rapid spread of the method of STN-DBS and several smaller studies showed promising effect on motor symptoms in PD. By the end of the millennium STN-DBS was established as a proven treatment option in advanced PD. In March 2001 the first STN-DBS for PD in Norway was performed at Rikshospitalet [9].

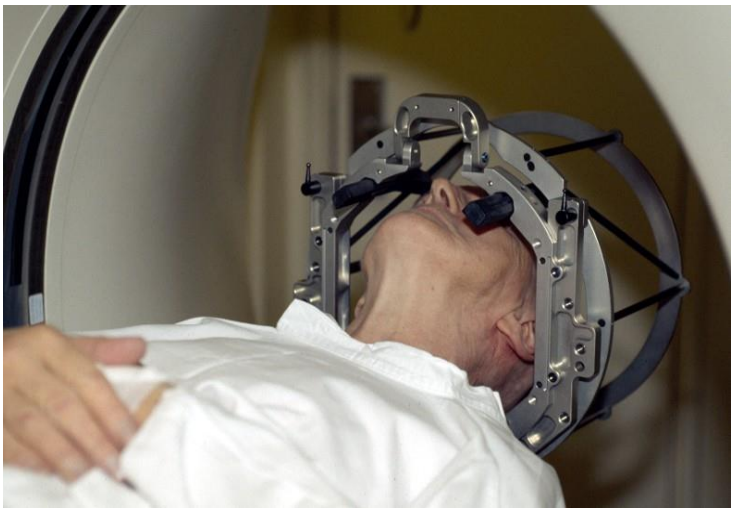
General description of the operative STN-DBS procedure

Preoperative CT and MRI scans are necessary for planning the stereotactic electrode trajectories. MRI is variably conducted before or after the mounting of the stereotactic frame on the patient's head, but the CT scan is always done with the frame mounted to orientate the external markers with the cranial and intracranial structures. The stereotactic frame is mounted under local anaesthesia, and in the CRW system the frame is fixed to the patient's skull by 4 screws.



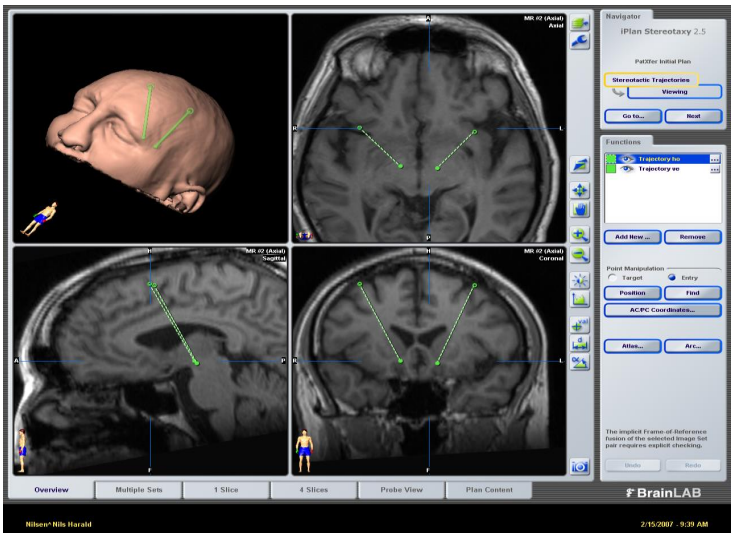
Mounting of the CRW frame, application of local anaesthesia.

If a preoperative MRI scan taken before the mounting of the frame is blurred by movement artefacts, e.g. by tremor, a new MRI is preformed after the patients head is securely fixated in the CRW frame. This is strenuous for the patient, but sometimes necessary in order to secure the required image quality.

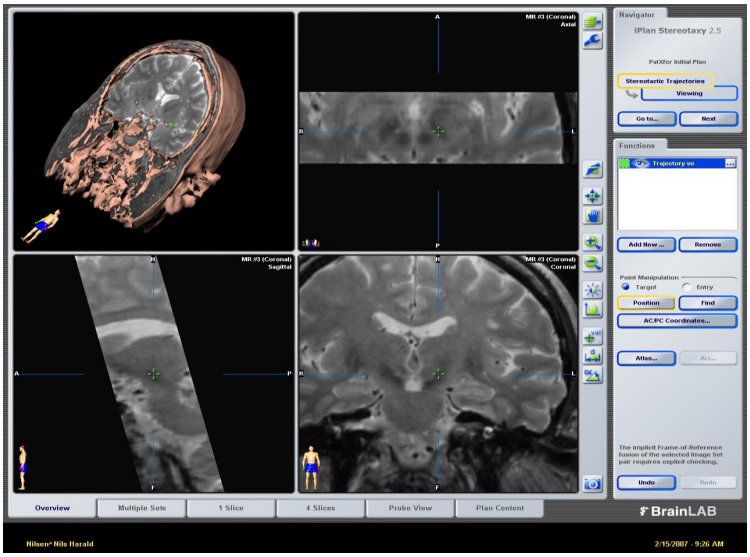


CT scan after mounting of the CRW frame

Planning of trajectory and targets is then done on a computerized planning system, after fusion of the CT and MRI scans. The aim is to place the targets accurately in the dorsolateral sensory-motor part of the STN nuclei, and to plan safe trajectories avoiding the vascularized sulci, visible blood vessels and ependymal ventricular walls. In the STN all neurons with sensorimotor responses are found in the dorsolateral part, and this part of the STN has been the preferred target for STN-DBS [101]. In this part of the STN the neurons seem to be somatotopically arranged. Neurons associated with arm movements are located most lateral, neighbouring more medially placed neurons associated with oromandibular function which are again flanked on the medial side by neurons involved in leg movements [102]. The medial tip of the STN represents its limbic part and is connected to the limbic part of the substantia nigra and the ventral tegmental area [103]. Neurons connected to associative circuits are located ventromedially in the STN [104]. Known complications to chronic STN stimulation include psychiatric side effects [105, 106] and linguistic side effects. Linguistic side effects have been induced in patients by applying test stimulation in the associative part of the STN [107]. Thus, the functional anatomy of the STN may be important in explaining direct, reversible side effects in STN-DBS, and underscores the need for precise targeting during the surgical procedure.

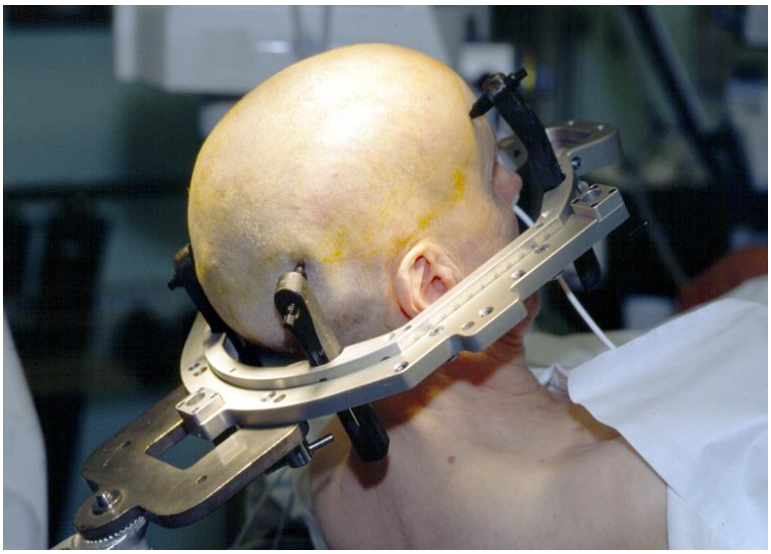


Planning of targets and trajectories in the BrainLAB planning suite, 1



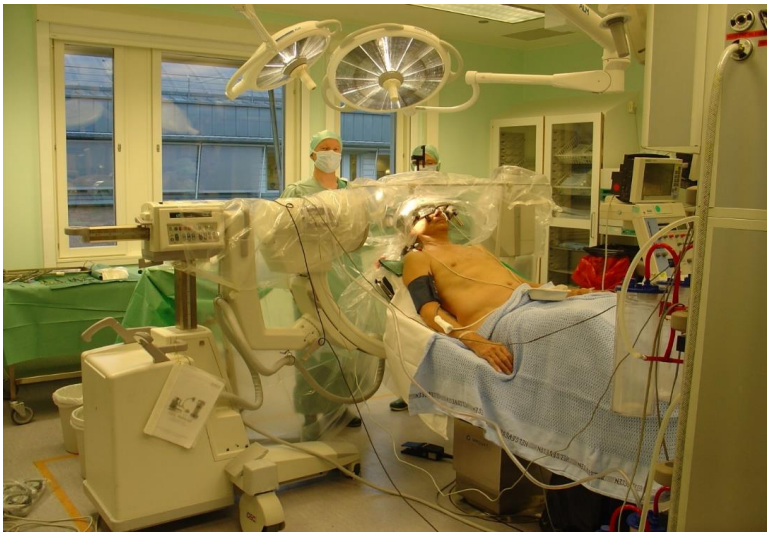
Planning of targets and trajectories in the BrainLAB planning suite, 2

After planning the targets and the trajectories the patient is placed on the operating table in a beach chair position, in order to reduce peroperative CSF loss and brain shift and to make intraoperative neurological examinations possible.



Patient positioned in order to minimize CSF loss

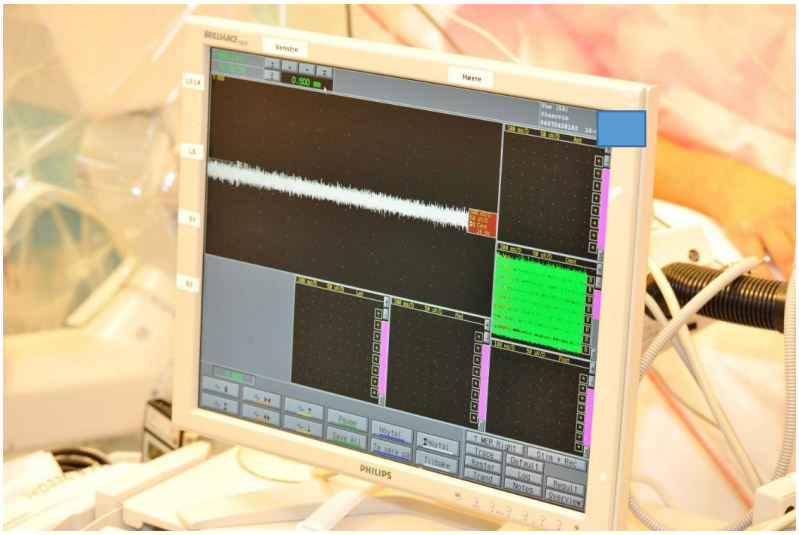
Equipment for fluoroscopy is positioned for recording the electrode positions preoperatively, and the surgical field dressed in sterile draping.



Operative setup

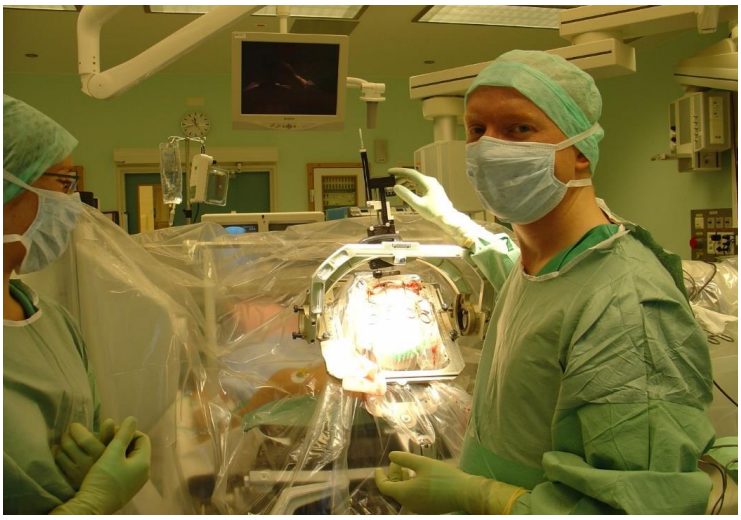
The burr holes in the cranium will normally be placed approximately 2 cm lateral to the midline and 2 cm anterior to the coronal suture. The dura and the arachnoid are incised central in the burr hole, and the underlying gyrus is visualized. Pia is cauterised

in a point to allow entry of the cannula later used for electrode insertion. The first electrode inserted will be the test electrode, with a 20 µm tip allowing electrophysiological recordings from a single neuron.



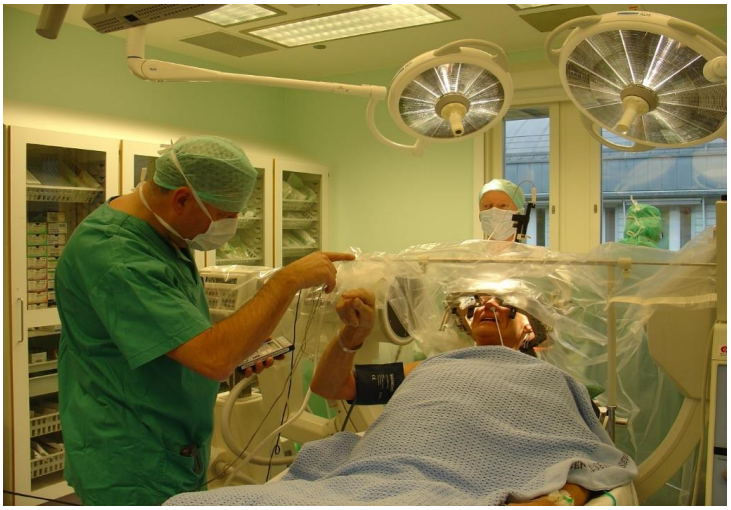
Electrophysiological recordings intraoperatively.

If typical STN recordings are obtained near the planned target, this area is chosen for test stimulation. If not, a new trajectory parallel to the first, but 2 mm apart is tested. Up to five different trajectories can be tested in this setup. When the decision is made on the preferred trajectory, the test electrode for micro electric recordings is removed and replaced by a macro electrode meant for permanent implantation. The permanent intracranial electrodes will normally have multiple poles at the tip with spacing between. In our setup, a permanent lead (Medtronic 3389) with 4 electrodes at the tip and 0.5 mm spacing was used. Test stimulation is then performed from the permanent electrode in different levels in the area of clear STN signal recordings.



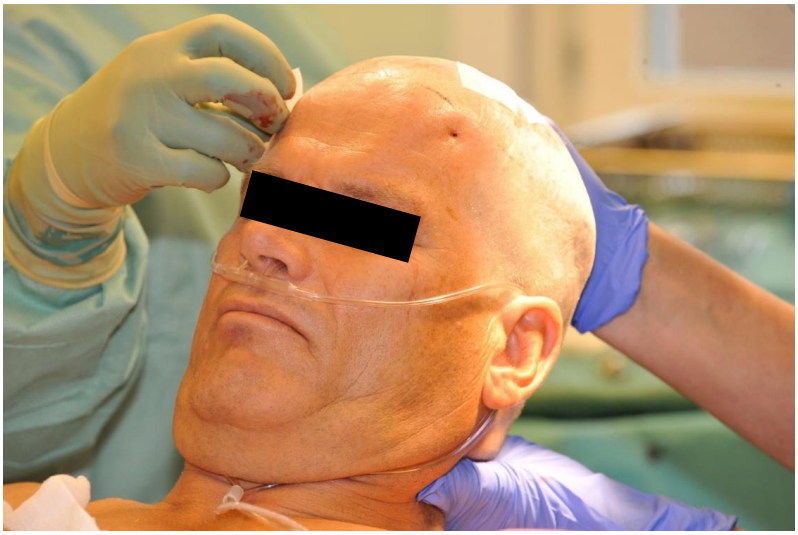
Insertion of the permanent electrode through burr hole under stereotactic guidance from the CRW frame.

Test stimulation is always conducted in concert with clinical testing for effect on motor symptoms and to reveal side effects. If clinical testing confirms the correct and acceptable placement of the permanent electrode, the lead is fixed in this position by permanent implementation of a fixation device attached to the burr hole. The lead position will be recorded with fluoroscopy, as a precaution against later intraoperative shift in the position of the electrode tip. The procedure is repeated on the contralateral side.



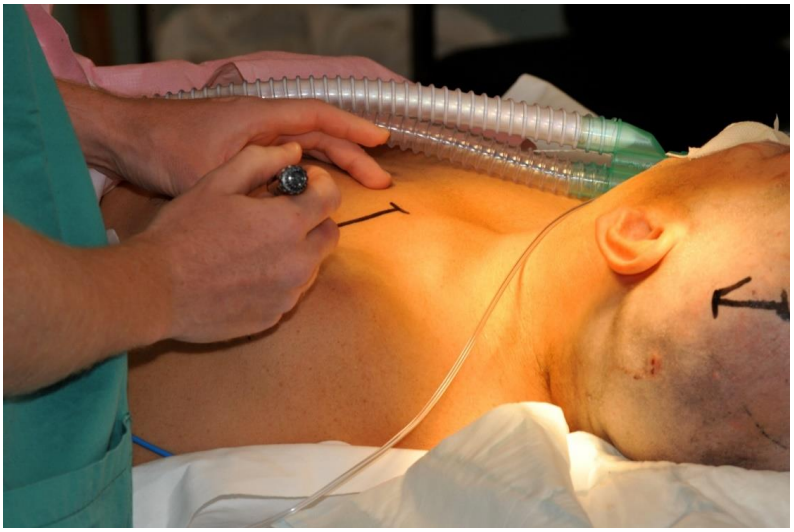
Clinical testing under test stimulation.

After bilateral implantation of permanent electrodes, the lead ends are left subcutaneously posterior to the patient's ear on the side decided for pulse generator implantation. The patient is released from the stereotactic frame, before being placed under general anaesthesia.



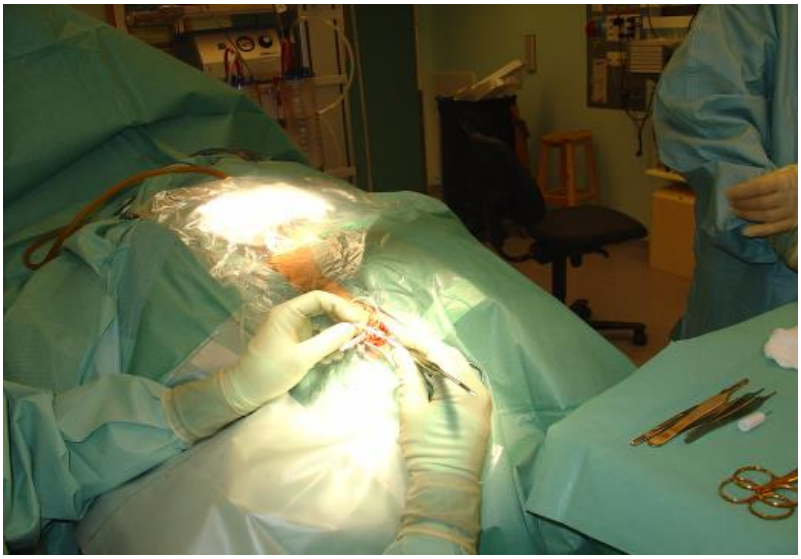
Patient just released from the CRW frame, permanent leads implanted bilaterally.

Under general anaesthesia, a pulse generator (Kinetra, Medtronic) is implanted subcutaneously in the pectoral region, preferably on the off-hand side.



Planning the position of the pulse generator.

Connecting leads are tunnelled under the skin up to the junction point posterior to the patient's ear.



Connecting the intracranial and extracranial leads.

At the end of battery life, non-rechargeable pulse generators must be changed. This requires a small operation in local anaesthesia. Today, rechargeable pulse generators, which can be charged transcutaneously, are becoming more and more common.

All poles on the electrode, and the pulse generator itself, can be set to be positive or negative poles. The voltage, frequency and pulse width of the stimulation current can all be adjusted. Thus, the size and shape of the area of stimulation can be modulated. The objectives are to achieve maximum symptom control with minimum side effects. Over the first months after implantation of a DBS system in PD patients, the voltage of stimulation is gradually increased as dopaminergic medication is gradually reduced.

Aim of the thesis

The overall aim of this thesis has been to investigate the long term clinical development in Parkinson's disease (PD) patients after surgical treatment with continuous high frequency electric stimulation in the subthalamic nuclei (STN-DBS). Important goals have been to study the long-term clinical effects on the various clinical symptoms in PD, including effect of STN-DBS on disease progression and survival as well as the efficacy and safety of the treatment.

We decided to conduct our scientific evaluation of the long term clinical disease progression in patients with PD after STN-DBS by asking four major questions:

1. Could we confirm the stable effect on dopaminergic motor symptoms, the safety of the procedure and reduction of medication reported in a number of small international studies in our large material recruited in the homogenous setting we benefit from in Norway?
2. Could STN-DBS be demonstrated to have any disease modulating or neuroprotective effects in PD, i.e. by halting or slowing down symptom development or reducing mortality?
3. What long term positive or detrimental effects does STN-DBS have on axial motor symptoms in PD?
4. What long term positive or detrimental effects does STN-DBS have on non-motor symptoms in PD?

Through the 4 papers in this PhD we attempt to elucidate these questions systematically.

Materials and methods

The recruitment base for the study populations included in the thesis have been patients with advanced PD treated with STN-DBS. All 144 PD patients treated with STN-DBS at Rikshospitalet from 2001 and until the end of 2007 have been prospectively followed with standardized examinations until the end of 2008. 2001 was when this treatment option first was made available to PD patients in Norway. Likewise, all 28 PD patients operated with STN-DBS at the Stavanger University

Hospital from this treatment was first offered at the hospital in 2003 and until 2006 when the hospital no longer preformed STN-DBS, were also followed prospectively until 2012. The examination program at Stavanger University Hospital was similar to the examination program at Rikshospitalet.

To be eligible for surgery patients had to have a clinical diagnosis of PD, age under 75 years, levodopa-responsive motor symptoms with severe motor complications, and/or resting tremor with unsatisfactory levodopa response. Patients were not considered eligible for surgery if they had dementia, had had major psychiatric illness, had marked atrophy on cerebral MRI or had other general contraindications to surgery. The preoperative examination included an interview, neurological examination, and a levodopa test comparing the UPDRS motor score in the off-medication and best on-medication state. Postoperative evaluations were carried out approximately 3 months after surgery, 12 months after surgery and then annually.

The Regional Committee for Medical and Health Research Ethics in Western Norway approved the studies.

In study 1 all 144 PD patients operated at Rikshospitalet was followed in order to show the clinical outcome and mortality in the long-term after STN-DBS. The patients were examined preoperatively and thereafter at 12 months intervals up to 60 months postoperatively. 131 patients had data preoperatively and at least 1 assessment 12 months after surgery and could be included in the analyses for treatment effect. Descriptive statistics were calculated for baseline demographic and clinical data. Non-parametric tests were used for group comparisons. Possible associations of various demographic and disease/treatment-related factors on treatment efficacy was explored using Mann-Whitney *U* tests and Spearman Rank correlation coefficients, and then studied with regression analyses. To demonstrate mortality over time, Kaplan-Meier survival curves were constructed.

In order to demonstrate differences in the long term clinical development of PD in study 2-4, a reference population of comparable, non-operated PD patients was required. For this purpose a population-based prevalence study conducted with patient recruitment between September 1992 and May 1993 was taken into use [48]. The

prevalence study took place in Rogaland County, Western Norway and used all available sources to identify and include all PD patients in the general population of the county. Hospital files were searched, and general practitioners, nursing homes, district nurses, health workers and the Rogaland Parkinson's Disease society were contacted and cooperated. 245 patients with PD were identified and 239 patients could be included in the subsequent study population. The study population was followed prospectively with standardized examinations in 1997 (144 patients attended) and 2001 (89 patients attended). This sectional population of PD patients was thus followed in the years 1992 through 2001. As such, the patients were followed prospectively in the very last decade before STN-DBS was made available in Norway. By using the same exclusion criteria for surgery on this population as for the operated patients, a reference population of PD patients could be established. The patients in the reference population that were prospectively followed for 8 years were eligible for STN-DBS, but at the time STN-DBS was not a treatment option.

In study 2, the operated patients from Rikshospitalet were compared to the non-operated patients from the reference population with regard to disease progression and survival. Disease progression was measured by changes in motor score on the Unified Parkinson's Disease Rating Scale (UPDRS). Individually age matched groups of patients were established to further increase the likelihood to discover any differences in disease progression or mortality between STN-DBS operated and non-operated. Age was chosen as the variable for matching as previous studies have shown that age is the most important independent risk factor for rapid increase in UPDRS motor score. Differences in development of UPDRS motor scores were analysed using analysis of covariance (ANCOVA) with follow-up time, age and sex as covariates. We examined for differences in mortality using Cox regression to assess different hazard ratios (HRs) for death after baseline.

In study 3 we studied the development of non-dopaminergic motor symptoms in PD patients operated with STN-DBS at Stavanger University Hospital in the period the hospital preformed such surgery, 2003 through 2006. In total 28 patients were operated, and 16 was still alive in 2012 and had sufficient clinical data to be included.

The development of parkinsonism, postural instability and gait difficulties (PIGD), freezing of gait (FOG) and falling was recorded prospectively in these patients preoperatively and at postoperative outpatient controls. Again, the development in the operated patients was compared to the development of the same symptoms in PD patients from the reference population deemed eligible for surgery. For improved reliability of findings, the operated patients were individually matched to comparable non-operated control patients from the reference population, based on their first postoperative control scores by means of propensity scores matching. The propensity scores matching took into account gender, age > 67, levodopa equivalent daily dose (LEDD), total UPDRS motor and ADL (activity of daily living) score and mean UPDRS tremor and PIGD scores, PIGD type,

Selection, surgical procedure, implants and programming in Stavanger and Oslo

The procedures pertaining to STN-DBS treatment in the PD centres of Oslo and Stavanger have been quite similar, both pre-, intra- and post operatively. The procedures for patient selection, the surgical procedure and the post-operative programming algorithm used in Oslo [5] was in general adapted in Stavanger. The criteria for selecting patients for STN DBS were that the patients had a diagnosis of PD, were under 75 years of age, had levodopa-responsive motor symptoms with severe motor complications and/or resting tremor with unsatisfactory levodopa response; and did not have dementia or major psychiatric illness, marked cerebral atrophy on MRI, or other contraindications to surgery. The surgical procedure and procedures for localizing the STN by MRI, intraoperative microelectrode recording and micro- and macrostimulation testing were based on procedures from the major centres in Europe [108].

All patients stopped their dopaminergic medication 24 hours before surgery. No benzodiazepines or similar drugs were administrated in the morning before surgery. After preoperative MR imaging, the patients' head was shaved. A CRW™ stereotactic frame (Radionics, MA, USA) was mounted under local anaesthesia and stereotactic 3D CT imaging was performed with the frame on the patients head. The images were fusioned on the iPlan™ computer-aided neuronavigation system (BrainLAB, Munich,

Germany). The margins of the STN were visualized, the image guided target was placed in the dorsolateral STN bilaterally and the surgical trajectories were planned accordingly, avoiding the ventricles and blood vessels. Burr holes were placed approximately 2 cm anterior to the coronary suture and 2 cm lateral to the midline, under curved incisions in the scalp. The Dura mater was incised, and the underlying Pia mater was punctuated with diathermy over the gyrus in the centre of the burr hole. The phantom in the CRW frame system was used for verification of the surgical setup before inserting the cannula for the electrodes. The localization of the site of the permanent electrode implant (Lead 3389, Medtronic, MN, USA) was refined by a combination of intraoperative microelectrode recordings (LeadPoint™, Medtronic, MN, USA) and intraoperative stimulation. The microelectrodes were introduced one-by-one and recordings were performed from 10 mm above the anatomical target and with 0.5-1 mm steps. Typically, high-frequency, spontaneous, movement related activity and tremor-related cells were identified within the STN. Acute STN-macrostimulation improved contralateral rigidity and akinesia, and suppressed tremor when present. Further microelectrodes were only introduced following insufficient or atypical findings in the first trajectory. The electrodes were fixed to the skull and connected to a Kinetra™ (Medtronic, MN, USA) neurostimulator fully implanted under general anaesthesia. During the weeks after implantation, stimulation parameters were adjusted following usual algorithms for programming [109], gradually increasing stimulation until good effect and no side effects and simultaneously reducing dopaminergic medication.

Results

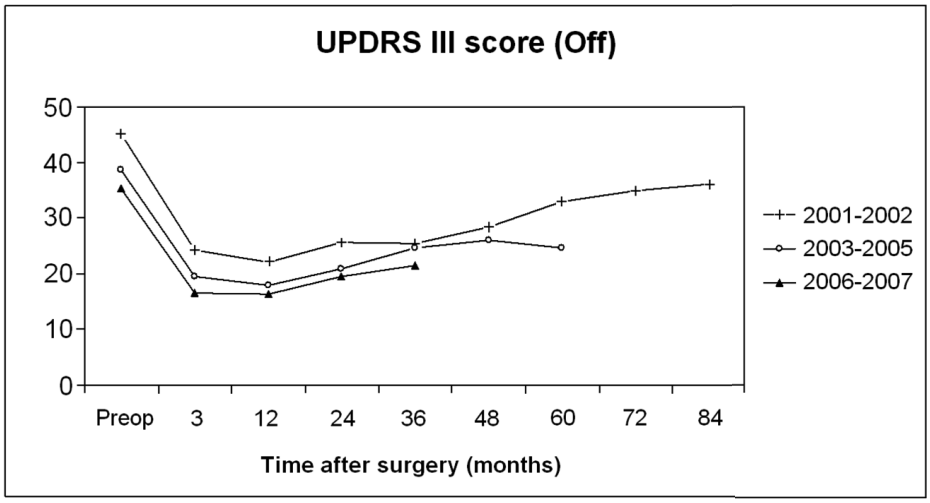
- *Study 1* describe the clinical improvement and subsequent progression in the cardinal, motor symptoms in PD in a very large material consisting of all 144 PD patients operated with STN-DBS at Rikshospitalet in the years 2001 through 2007. The study set out to confirm the stable efficacy of long-term subthalamic stimulation in selected patients with advanced PD.
- *Study 2* investigated the postulated disease modifying or neuroprotective effect of STN-DBS by comparing the rate of deterioration of parkinsonism and mortality over time in two selected and matched groups of patients with PD

with and without surgery. The study investigated both clinical disease progression and mortality in the two study groups.

- *Study 3* examined short- and long-term impacts of STN-DBS on the development of the PIGD (postural instability and gait difficulties) phenotype, FOG (freezing of gait) and falls, comparing the development in matched groups on operated and non-operated patients with PD.
- *Study 4* explored how non-motor problems develop in patients with and without STN-DBS. The study set out to elucidate how non-motor problems of advanced PD develop with and without treatment with STN-DBS, on the presumption that such knowledge could help making the right decisions on *when* to perform this therapy for eligible patients.

Study 1

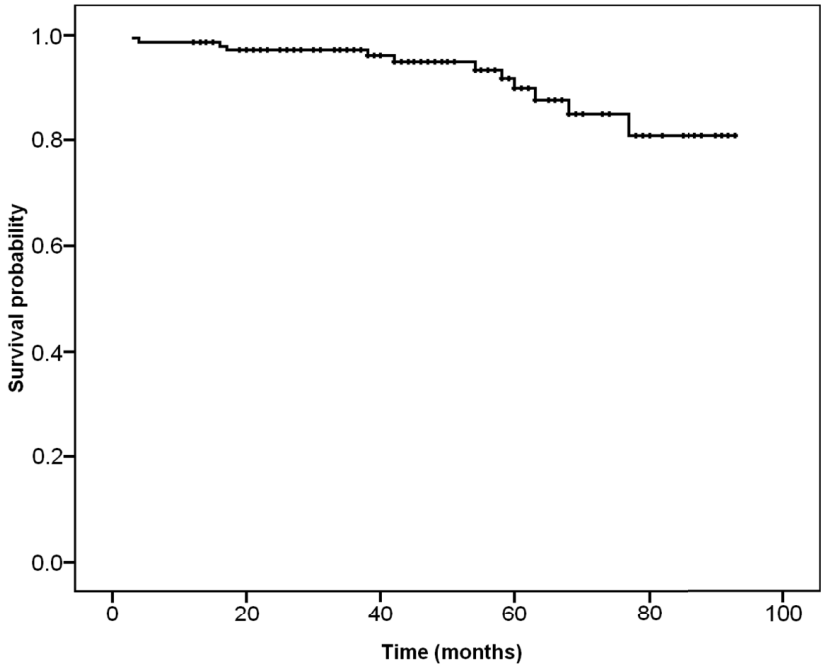
The results in study 1 confirm earlier findings that STN-DBS is an efficient, stabile and safe treatment option for motor symptoms in selected patients with advanced PD [1, 110]. Average improvement on UPDRS motor scores as measured a year postoperatively was 53 % (95% CI 48-57 %)[3]. In 2001-2002 the patients had a mean UPDRS motor score of 45.2 in off-state, as compared to an average score of 35.3 in 2006-2007. This did not affect the effect of the surgery in the patients, the average annual increase in UPDRS III score being 3.2 points[1]. This matches well the annual UPDRS III increase in a contemporary population study (3.3 point average annual increase in UPDRS III) [111]. Peroperative mortality was 0 defined as no mortality during the admission for surgery and within 30 days after surgery. Within the study period two deaths probably related to the surgery occurred among the 144 operated patients (1.4%). We found a total surgical complication rate of 10 %. A reduction in the STN-DBS patients' preoperative off-state UPDRS III scores was observed in the period from 2001 to 2007. The reduction was statistically significant (Kruskal-Wallis, $P = 0.02$).



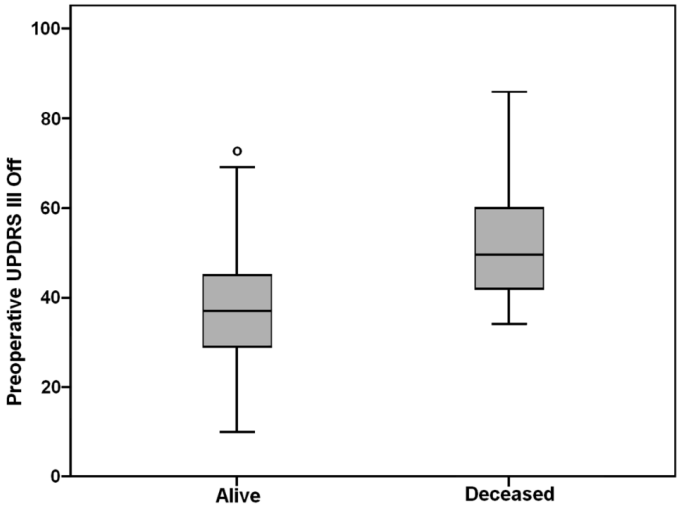
[1]**Figure 1 from study 1:** The development in UPDRS motor score in off during follow-up, patients divided after year of surgery.

Mean LEDD was reduced by 49%. The effect on motor symptoms was shown to be stable over time, and the effect was not associated with gender, age, previous PD surgery, preoperative LEDD, nor the neurosurgeon preforming the procedure. A gradual change in the symptom severity over time in the operated patients was observed, with STN-DBS treated patients in average having more severe symptoms during the first years after the treatment became available in Norway.

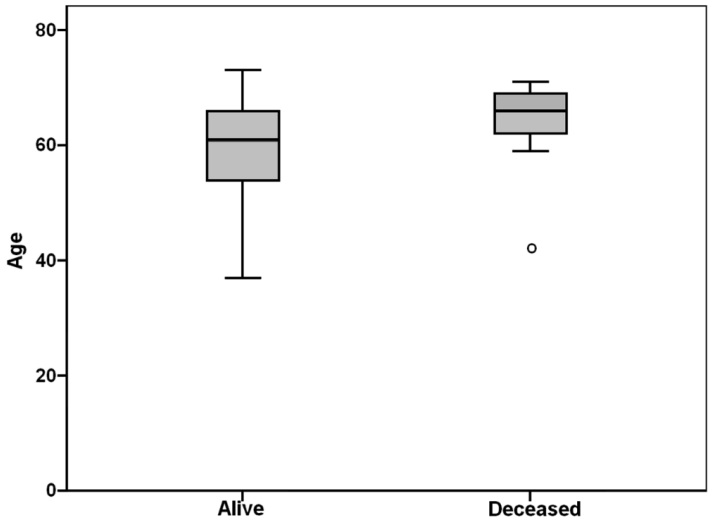
It was observed that two patients from the 144 committed suicide. That gives a suicide frequency of 1.4%, as compared to international reports of a suicide frequency of 0.45% [112]. Overall survival is shown in figure 2 under[2]. There was a trend towards more severe symptoms as measured by UPDRS III in the patients who died during follow-up, as well as a tendency towards higher age at baseline in the patients who died during follow-up[3,4].



[2]**Figure 2, study 1:** Kaplan-Meier curve of patient survival during follow-up.[2]



[3]**Figure 3, study 1:** Distribution of UPDRS III score at baseline for patients alive and deceased at the end of follow-up.



[4]**Figure 4, study 1:** Distribution of age at the time of surgery for patients alive and deceased at the end of follow-up.

[5]Table 1 from study 1.

Table 1. Motor scores, dopaminergic medication, and stimulation parameters during long-term STN-DBS treatment

	Preoperative	12 months	24 months	36 months	48 months	60 months
Number of patients	131	131	110	89	52	32
UPDRS III Off	39.0 ± 13.6	18.4 ± 9.2	21.8 ± 10.1	24.7 ± 11.9	27.0 ± 12.9	28.9 ± 13.9
UPDRS III On	13.2 ± 8.1	12.5 ± 7.5	15.4 ± 9.6	18.1 ± 11.2	19.5 ± 10.4	22.4 ± 14.4
LEDD (mg)	991 ± 462	501 ± 285	539 ± 334	536 ± 369	517 ± 349	525 ± 331
Voltage left (V)	NA	3.3 ± 0.6	3.3 ± 0.6	3.4 ± 0.6	3.3 ± 0.5	3.4 ± 0.5
Voltage right (V)	NA	3.1 ± 0.6	3.3 ± 0.7	3.4 ± 0.6	3.4 ± 0.6	3.3 ± 0.6
Pulse width left (μs)	NA	62 ± 8	62 ± 7	62 ± 7	62 ± 8	64 ± 10
Pulse width right (μs)	NA	61 ± 6	61 ± 8	62 ± 8	61 ± 4	64 ± 10
Frequency (Hz)	NA	158 ± 22	160 ± 27	166 ± 16	170 ± 17	173 ± 17

Data presented are means ± standard deviations of the patients examined at each time.
Abbreviations: LEDD, levodopa-equivalent daily dose; NA, not applicable; UPDRS, Unified Parkinson's Disease Rating Scale.

The results from study 2-4 span various aspects of short and long term clinical symptom development after STN-DBS.

Study 2

In study 2 we found no significant difference between the STN-DSB operated patients and the non-operated patients in the reference group in progression of UPDRS motor scores over time, nor any differences in long-term survival. After age-matching, the results were the same with no significant differences in disease progression between operated and non-operated patients[6]. There were more females in the reference population than in the operated group, but an analysis of variance (ANOVA) could not demonstrate any interaction between gender and annual UPDRS change. Age at baseline was the strongest predictor for mortality, and there was a trend towards higher mortality in the surgery group[7].

[6]Table 1 from study 2

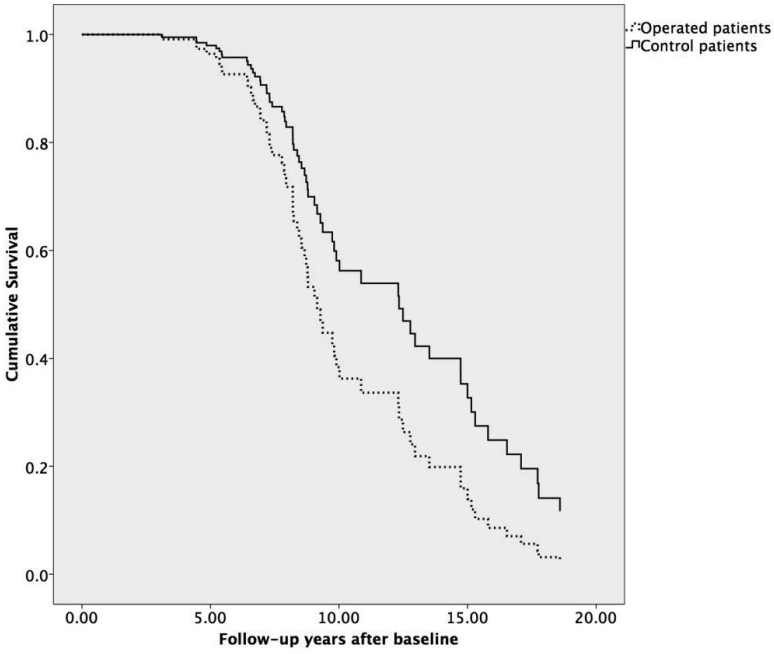
Table 1 Clinical and demographic data of Parkinson's disease (PD) patients with deep brain stimulation of the subthalamic nucleus (STN-DBS) and controls without surgery in the study groups and after individual matching for age of the two patient groups

	PD patients with STN-DBS		PD control group patients	
	Study group	Matched group	Study group	Matched group
No of patients	81	54	90	54
Mean age at baseline, years (SD)	61 (7)	64 (6)	66 (7)	64 (6)
% Females	35	39	52	57
Mean UPDRS follow-up measurement, month (SD)	38 (10)	39 (10)	48 (0)	48 (0)
Mean baseline UPDRS-III score (SD)	15 (8)	18 (9)	20 (11)	26 (13)
Mean baseline LEDD (SD)	448 (262)	433 (226)	537 (305)	581 (341)
Mean UPDRS-III progression pr year (SD)	1.16 (3.60)	1.15 (3.51)	1.43 (3.08)	1.04 (3.34)

LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale. UPDRS-III scores were measured in the medication and stimulation 'on' state. Baseline data for the operated group were obtained 3 months after initiation of STN-DBS.

UPDRS-III scores were measured in the medication and stimulation 'on' state. Baseline data for further disease development in the operated group was scored 3 months after initiation of STN-DBS.

[7]Cox regression on matched patients



Study 3

In study 3 we again demonstrated marked and rapid reduction in UPDRS III scores in patients after STN-DBS, with a reduction in the operated patients' mean UPDRS III score from 27 to 18. Tremor, bradykinesia, rigidity and PIGD showed major improvement after STN-DBS. The two patients in the operated group with preoperative FOG did not experience this at the first follow-up after surgery. The findings are summarized in the table 1 rendered below[8].

[8]**Table 1 in Study 3.**

Table 1 Demographic and clinical data for patients with and without STN-DBS. Data are shown before and after surgery for the operated patients and at baseline for the non-operated patients with PD. Also data for the matched groups are shown. The results are given as mean (SD), unless stated otherwise

	STN-DBS operated, preoperatively, $n = 16$	STN-DBS operated, after surgery, $n = 16$	Reference population, baseline, $n = 62$	Matched STN-DBS operated, after surgery, $n = 12$	Matched from the reference population, $n = 12$
Age, years	60 (8.1)	60 (8.4)	66 (6.7)	61 (8.0)	61 (8.3)
LEDD, mg	960 (220)	740 (380)	520 (250)	740 (290)	720 (220)
UPDRS-II total score	11 (10)*	7.2 (5.1)	8.7 (4.5)	7.8 (5.0)	7.3 (4.0)
UPDRS-III total score	27 (13)	18 (7.5)	18 (10)	17 (6.4)	16 (8.4)
Hoehn and Yahr stage	2.5 (0.6)*	2.1 (0.6)*	2.2 (0.8)	2.1 (0.7)	2.0 (0.7)
Tremor score	3.2 (4.1)*	2.6 (4.1)	4.3 (3.8)	2.3 (3.3)	2.7 (4.5)
Bradykinesia score	12 (7.3)	8.7 (4.5)	8.5 (5.6)	8.0 (4.3)	7.3 (4.4)
Rigidity score	6.1 (3.1)	3.1 (2.6)	2.2 (1.8)	2.5 (2.4)	2.4 (1.9)
PIGD score	3.9 (2.1)*	2.5 (2.0)	2.6 (2.2)	2.8 (2.3)	2.3 (1.9)
PIGD dominance (%)	13 (81)*	12 (75)	28 (45)	9 (75)	8 (67)
FOG (%)	2 (13)*	0 (0)	3 (5)	0 (0)	0 (0)
Falls (%)	3 (20)*	2 (13)	1 (2)	2 (17)	1 (8)

*Based on 15 patients, values missing for one patient.

In the long term, we found that PIGD symptoms dominated in all operated patients at the final visit. FOG and falls also increased during postoperative follow-up, and at last visit approximately 50% of the patients had these symptoms. The development of PIGD score and the proportion with PIGD dominance as well as FOG and falls developed similarly in the historical controls, also after individual matching[9,10]. For tremor and rigidity, there was a minor annual reduction in UPDRS scores for the operated patients whilst the non-operated group showed marked increases during follow-up[10.] Bradykinesia increased in both groups at a similar rate[10].

[9]Table 2 in study 3.

Table 2 Mean PIGD score and proportion of patients with PIGD pattern of parkinsonism, FOG, and falls at baseline (3–6 months after surgery), at 1 year after surgery and at final visit in 2012 (long-term follow-up) for patients with STN-DBS and the same findings for patients in the control cohort at baseline and after 8-year follow-up. Also data for the matched groups are shown. Results are given as mean (SD), unless stated otherwise

	STN-DBS operated (n = 16)	Eligible for surgery from reference population (n = 62)	STN-DBS operated matched (n = 12)	Reference population, matched (n = 12)
Baseline visit				
LEDD, mg	740 (380)	520 (250)	740 (290)	720 (220)
Tremor score	2.6 (4.1)	4.3 (3.8)	2.3 (3.3)	2.7 (4.5)
Bradykinesia score	8.7 (4.5)	8.5 (5.6)	8.0 (4.3)	7.3 (4.4)
Rigidity score	3.1 (2.6)	2.2 (1.8)	2.5 (2.4)	2.4 (1.9)
PIGD score	2.5 (2.0)	2.6 (2.2)	2.8 (2.3)	2.3 (1.9)
PIGD type (%)	12 (75)	28 (45)	9 (75)	8 (67)
FOG (%)	0 (0)	3 (5)	0 (0)	0 (0)
Falls (%)	2 (13)	1 (2)	2 (17)	1 (8)
1-Year visit				
LEDD, mg	840 (470)		830 (250)	
Tremor score	1.6 (2.3)		1.8 (2.6)	
Bradykinesia score	10 (5.1)		9.7 (4.7)	
Rigidity score	4.3 (3.9)		3.6 (2.9)	
PIGD score	4.2 (2.3)		4.3 (2.5)	
PIGD type (%)	14 (88)		10 (83)	
FOG (%)	0 (0)		0 (0)	
Falls (%)	2 (13)		1 (8)	
Long-term follow-up				
LEDD (mg)	910 (320)	700 (430)	870 (330)	1010 (320)
Tremor score	0.7 (1.3)	6.1 (5.3)	0.6 (1.0)	4.4 (3.9)
Bradykinesia score	19 (5.6)	20 (9.2)	19 (5.5)	15 (6.0)
Rigidity score	3.4 (4.4)	5.8 (4.5)	2.5 (3.7)	3.7 (3.7)
PIGD score	9.7 (5.1)	9.4 (5.5)	10 (5.3)	7.4 (3.4)
PIGD type (%)	16 (100)	52 (84)	12 (100)	10 (83)
FOG (%)	9 (56)	31 (50)	7 (58)	7 (58)
Falls (%)	8 (50)	31 (50)	6 (50)	5 (42)

[10]Table 3 in study 3

Table 3 Mean annual change in mean PIGD, tremor, bradykinesia, and rigidity scores, as measured by the UPDRS

	STN-DBS operated (n = 16) Mean 95% CI	Eligible for surgery from reference population (n = 62) Mean 95% CI	P*	STN-DBS operated, matched (n = 12) Mean 95% CI	Reference population, matched (n = 12) Mean 95% CI	P*
PIGD mean score (range 0–4)	0.19 (0.13–0.24)	0.17 (0.14–0.20)	0.639	0.19 (0.12–0.26)	0.13 (0.09–0.17)	0.095
Tremor mean score (range 0–4)	−0.03 (−0.07 to −0.01)	0.03 (0.01–0.42)	0.002	−0.03 (−0.07 to 0.01)	0.02 (−0.03 to 0.08)	0.087
Bradykinesia mean score (range 0–4)	0.14 (0.10–0.19)	0.16 (0.14–0.19)	0.496	0.15 (0.09–0.21)	0.11 (0.06–0.15)	0.204
Rigidity mean score (range 0–4)	−0.00 (−0.06 to 0.05)	0.09 (0.06–0.12)	0.002	−0.01 (−0.05 to 0.04)	0.03 (−0.02 to 0.09)	0.280

*From independent samples t-tests.

Study 4

In study 4, dementia was found to develop over time in both operated and non-operated patients. As dementia is an exclusion criterion for surgery, no patients in the study groups had clinical dementia at baseline. At the final visit 31 % of the patients in

the operated group had developed dementia, and 46 % in the reference group. The average MMSE scores changed from 28.4 3-6 months after surgery to 23.4 at final visit in the STN-DBS group and from 28.3 to 22.6 in the reference population. After individual matching, the results were similar. Sleep disorders as measured by ESS and EDS, as well as insomnia, developed similarly in the operated and non-operated populations. Comparable findings were present for apathy. Depressive symptoms as measured by MADRS score were stable and comparable between the two groups during follow-up. Interestingly, fatigue as measured by FSS score and the proportion of patients with a FSS score ≥ 4 increased significantly in the STN-DBS group from baseline to last visit. At the final visit 87 % of the patients in the STN-DBS group (n=16) had FSS ≥ 4. In the matched groups, the percentage of operated patients (n=12) with FSS of 4 or above also increased. 45% of the STN-DBS patients had an FSS ≥ 4 at baseline, increasing to 75% after one year and at 91% at the final visit. Of the non-operated patients only 55 % had an FSS ≥ 4 at final visit before matching, rising slightly to 67 % after matching. Thus, the comparison of the matched groups also demonstrated a difference in the frequency of fatigue at the final visit. Preoperatively, 25 % of the STN-DBS patients reported hallucinations, but these were gone at the first postoperative visit 3-6 months after surgery as no patients reported hallucinations. During follow-up, hallucinations increased again in the surgery group, and at last visit half of the patients reported hallucinations. In the reference group, 37 % reported having hallucinations. However, after individual matching the difference between operated and non-operated patients disappeared, with 50 % of the patients reporting hallucinations at last visit in both groups.

[11]Table 1 in study 4.

Table 1 Demographic and clinical data for PD patients with and without STN-DBS. Data are shown before and 3–6 months after surgery for the operated patients ($n = 16$) and at baseline for the non-operated patients, that is, the reference population ($n = 62$). Furthermore, data are given for individually matched subgroups of the two patients groups ($n = 12$). The results are given as means (SDs) unless otherwise stated. For scores with missing observations, the numbers of available observations are indicated

	STN-DBS operated, pre-operatively ($n = 16$)	STN-DBS operated, post-surgery ($n = 16$)	STN-DBS operated, matched, post-surgery ($n = 12$)	Reference group, baseline ($n = 62$)	Reference group, matched, baseline ($n = 12$)
Age (years)	60 (8.1)	60 (8.4)	61 (8.0)	66 (6.7)	61 (8.3)
Female gender, no. (%)	10 (63%)	10 (63%)	8 (67%)	33 (53%)	8 (67%)
Disease duration (years)	12.9 (5.7) ($n = 14$)	13.3 (5.6) ($n = 15$)	12.5 (5.1) ($n = 11$)	7.7 (4.9)	10.6 (4.9)
LEDD (mg)	960 (220)	740 (380)	740 (290)	520 (250)	720 (220)
UPDRS-II total	11 (10) ($n = 15$)	7.2 (5.1)	7.8 (5.0)	8.7 (4.5)	7.3 (4.0)
UPDRS-III total	27 (13)	18 (7.5)	16.8 (6.4)	18 (10)	15.8 (8.4)
Hoehn and Yahr stage	2.5 (0.6) ($n = 15$)	2.1 (0.6) ($n = 15$)	2.1 (0.7) ($n = 11$)	2.2 (0.8)	2.0 (0.7)
MMSE	29.1 (1.6) ($n = 15$)	28.4 (3.0) ($n = 15$)	28.2 (3.3)	28.3 (1.8)	28.7 (2.1)
Dementia, no. (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ESS	6.5 (4.3) ($n = 12$)	6.3 (4.3) ($n = 13$)	6.8 (4.8) ($n = 10$)	NA	NA
EDS, no. (%)	NA	NA	NA	2 (3%)	0 (0%)
Difficult night, no. (%)	NA	NA	NA	10 (16%)	1 (8%)
Insomnia, no. (%)	NA	NA	NA	37 (60%)	9 (75%)
Apathy scale	14.7 (4.1) ($n = 12$)	16.9 (5.2) ($n = 14$)	18.0 (4.7) ($n = 11$)	NA	NA
Item 4 UPDRS-I	0.9 (1.3)	0.3 (0.5)	0.3 (0.5)	0.8 (0.8)	0.7 (0.9)
Item 4 UPDRS-I $\geq$ 2, no. (%)	3 (19%)	0 (0%)	0 (0%)	13 (21%)	3 (25%)
MADRS	9.1 (9.1) ($n = 10$)	4.1 (3.0) ($n = 14$)	4.4 (3.1) ($n = 11$)	5.6 (4.2)	5.4 (3.7)
MADRS $\geq$ 15, no. (%)	2 (20%) ($n = 10$)	0 (0%) ($n = 14$)	0 (0%) ($n = 11$)	3 (5%)	0 (0%)
FSS mean	4.1 (1.7) ($n = 11$)	3.7 (1.7) ($n = 14$)	4.1 (1.7) ($n = 11$)	NA	NA
FSS $\geq$ 4, no. (%)	5 (46%) ($n = 11$)	5 (36%) ($n = 14$)	5 (42%) ($n = 11$)	NA	NA
Item 2 UPDRS-I	0.69 (0.87)	0.7 (0.9)	0.1 (0.3)	0.42 (0.69)	0.3 (0.5)
Item 2 UPDRS-I $\geq$ 2, no. (%)	4 (25%)	3 (25%)	0 (0%)	3 (5%)	0 (0%)

STN-DBS, deep brain stimulation of the subthalamic nuclei; LEDD, levodopa-equivalent levodopa dose; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; MADRS, Montgomery and Aasberg Depression Rating Scale; FSS, Fatigue Severity Scale.

[12]Table 2 in study 4.

Table 2 Long-term development of non-motor symptoms for PD patients with and without STN-DBS. Data are collected 3–6 months, 1–1.5 years, and 6–9 years after surgery for the operated patients ($n = 16$), and at baseline and after 8 years for the non-operated patients ($n = 62$). The results are given as means (SDs) unless otherwise stated. For scores with missing observations, the numbers of available observations are indicated

	STN-DBS operated, 3–6 months post-surgery ($n = 16$)	STN-DBS operated, 1–1.5 years after surgery ($n = 16$)	STN-DBS operated, 6–9 years after surgery ($n = 16$)	Reference population, baseline ($n = 62$)	Reference population, 8 years after baseline ($n = 62$)
LEDD (mg)	740 (380)	810 (510)	910 (320)	520 (250)	700 (430)
UPDRS-II total	7.2 (5.1)	9.6 (5.4)	20 (7.3)	8.7 (4.5)	23 (10)
UPDRS-III total	18 (7.5)	22 (10)	33 (12)	18 (10)	43 (20)
Hoehn and Yahr stage	2.1 (0.6) ($n = 15$)	2.1 (0.5) ($n = 14$)	3.2 (0.9)	2.2 (0.8)	3.2 (1.0)
MMSE	28.4 (3.0) ($n = 15$)	28.4 (2.7) ($n = 14$)	23.4 (8.0)	28.3 (1.8)	22.6 (8.0) ($n = 58$)
Dementia, no. (%)	0 (0%)	0 (0%)	5 (31%)	0 (0%)	28 (45%)
ESS	6.3 (4.3) ($n = 13$)	7.5 (3.7) ($n = 11$)	10.1 (7.0)	NA	9.6 (6.6)
EDS, no. (%)	NA	NA	2 (13%) ($n = 15$)	2 (3%)	26 (42%)
Difficult night, no. (%)	NA	NA	2 (13%) ($n = 15$)	10 (16%)	10 (16%)
Insomnia, no. (%)	NA	NA	5 (33%) ($n = 15$)	37 (60%)	32 (52%)
Apathy scale	16.9 (5.2) ($n = 14$)	16.3 (5.9) ($n = 13$)	19.3 (4.4) ($n = 15$)	NA	15.1 (3.3) ($n = 47$)
Item 4 UPDRS-I	0.3 (0.5)	0.8 (0.9)	1.5 (1.2)	0.8 (0.8)	1.4 (1.1)
Item 4 UPDRS-I $\geq$ 2, no. (%)	0 (0%)	3 (19%)	7 (44%)	13 (21%)	25 (40%)
MADRS	4.1 (3.0) ($n = 14$)	6.8 (5.5) ($n = 15$)	5.0 (6.0)	5.6 (4.2)	7.4 (6.2) ($n = 42$)
MADRS $\geq$ 15, no. (%)	0 (0%) ($n = 14$)	2 (13%) ($n = 15$)	1 (6%)	3 (5%)	6 (14%) ($n = 42$)
FSS mean	3.7 (1.7) ($n = 14$)	4.6 (1.5) ($n = 15$)	5.0 (1.6) ($n = 15$)	NA	4.4 (1.8) ($n = 58$)
FSS $\geq$ 4, no. (%)	5 (36%) ($n = 14$)	10 (67%) ($n = 15$)	13 (87%) ($n = 15$)	NA	32 (55%) ($n = 58$)
Item 2 UPDRS-I	0.19 (0.40)	0.50 (0.73)	1.4 (1.2)	0.42 (0.69)	1.2 (1.1)
Item 2 UPDRS-I $\geq$ 2, no. (%)	0 (0%)	2 (13%)	8 (50%)	3 (5%)	23 (37%)

STN-DBS, deep brain stimulation of the subthalamic nuclei; LEDD, levodopa-equivalent levodopa dose; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; MADRS, Montgomery and Aasberg Depression Rating Scale; FSS, Fatigue Severity Scale.

[13]**Table 3 in study 4.**

Table 3 Long-term development of non-motor symptoms for PD patients with STN-DBS and for individually matched PD patients without STN-DBS. Data are collected 3–6 months, 1–1.5 years, and 6–9 years after surgery for the operated patients ($n = 12$), and at baseline and after 8 years for the non-operated patients ($n = 12$). The results are given as means (SDs) unless otherwise stated. For scores with missing observations, the numbers of available observations are indicated

	STN-DBS operated, 3–6 months post-surgery ($n = 12$)	STN-DBS operated, 1–1.5 years after surgery ($n = 12$)	STN-DBS operated, 6–9 years after surgery ($n = 12$)	Reference population, baseline ($n = 12$)	Reference population, 8 years after baseline ($n = 12$)
LEDD (mg)	740 (290)	830 (250)	870 (330)	720 (220)	1000 (320)
UPDRS-II total	7.8 (5.0)	9.8 (5.3)	20.6 (7.8)	7.3 (4.0)	20.5 (5.9)
UPDRS-III total	16.8 (6.4)	20.4 (9.0)	32.8 (11.1)	15.8 (8.4)	30.3 (11.7)
Hoehn and Yahr stage	2.1 (0.7) ($n = 11$)	2.2 (0.4) ($n = 10$)	3.3 (0.9)	2.0 (0.7)	2.8 (0.4)
MMSE	28.2 (3.3)	28.4 (2.8)	23.3 (8.9)	28.7 (2.1)	23.7 (6.4)
Dementia, no. (%)	0 (0%)	0 (0%)	4 (33%)	0 (0%)	6 (50%)
ESS	6.8 (4.8) ($n = 10$)	8.3 (3.4) ($n = 9$)	10.3 (7.3)	NA	7.3 (5.3)
EDS, no. (%)	NA	NA	2 (18%) ($n = 11$)	0 (0%)	5 (42%)
Difficult night, no. (%)	NA	NA	2 (18%) ($n = 11$)	1 (8%)	2 (17%)
Insomnia, no. (%)	NA	NA	4 (36%) ($n = 11$)	9 (75%)	5 (42%)
Apathy scale	18.0 (4.7) ($n = 11$)	17.9 (4.8) ($n = 10$)	18.5 (3.4) ($n = 11$)	NA	14.1 (2.7) ($n = 11$)
Item 4 UPDRS-I	0.3 (0.5)	0.8 (1.0)	1.6 (1.2)	0.7 (0.9)	1.1 (0.9)
Item 4 UPDRS-I $\geq$ 2, no. (%)	0 (0%)	2 (17%)	6 (50%)	3 (25%)	5 (42%)
MADRS	4.4 (3.1) ($n = 11$)	7.4 (5.9)	5.3 (6.9)	5.4 (3.7)	7.7 (4.8) ($n = 10$)
MADRS $\geq$ 15, no. (%)	0 (0%) ($n = 11$)	2 (17%)	1 (8%)	0 (0%)	2 (20%) ($n = 10$)
FSS mean	4.1 (1.7) ($n = 11$)	5.0 (1.4)	5.2 (1.3) ($n = 11$)	NA	4.6 (2.0)
FSS $\geq$ 4, no. (%)	5 (45%) ($n = 11$)	9 (75%)	10 (91%) ($n = 11$)	NA	8 (67%)
Item 2 UPDRS-I	0.1 (0.3)	0.5 (0.7)	1.5 (1.2)	0.3 (0.5)	1.5 (1.0)
Item 2 UPDRS-I $\geq$ 2, no. (%)	0 (0%)	1 (8%)	6 (50%)	0 (0%)	6 (50%)

STN-DBS, deep brain stimulation of the subthalamic nuclei; LEDD, levodopa-equivalent levodopa dose; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; MADRS, Montgomery and Aasberg Depression Rating Scale; FSS, Fatigue Severity Scale.

Discussion

Methodological considerations

The ideal way of studying the long-term clinical effects of STN-DBS would probably be a double blind randomized control trial. Sham surgery has been advocated to document the effect of surgical therapies for PD [113, 114], and has played a role in studying the effect of cell implants to treat advanced PD. However, sham surgery remains highly controversial as a research tool even for novel, experimental treatments [115], and is difficult to perform blinded especially to the investigators. STN-DBS can no longer be regarded as an experimental or exploratory treatment, as it has been an established treatment option for more than a decade and a half. Thus, randomizing patients with advanced PD eligible for STN-DBS treatment to therapy or sham surgery would certainly be deemed unethical in Norway and probably most other countries, under the obligation to offer all patients in a therapy trial the best possible established treatment. To document the effect of GPi-DBS (bilateral deep brain stimulation in the

Globus Pallidus internus) treatment for dystonia, short studies [116-118] have been conducted bypassing these ethical considerations to some degree. Patients deemed eligible for GPi-DBS were included and operated. The patients were then randomized to having the pulse generator switched on, thus receiving active therapy, or to have the pulse generator in stand-by thus receiving no stimulation. The patients were followed for three months comparing the clinical development in dystonia symptoms. A similar approach could be taken to study the effects of STN-DBS in the short term. However, keeping the stimulation off in an implanted system over several years in order to study long-term differences in the development of clinical symptoms caused by STN-DBS would clearly not be ethical given the risk of complications to the surgery to all patients and the potential beneficial effects lost to the patients randomized to stimulation off.

We decided to find the best available substitute for a randomized control trial in order to demonstrate the effects of STN-DBS as an intervention in selected patients. Fortunately, our colleagues at The Norwegian Centre for Movement Disorders had conducted a population-based study in the early nineties [48]. Our colleagues included all PD patients from a Norwegian county at a given time, and followed them prospectively over the following decade with standardised examinations as part of a longitudinal study of disease progression, very similar to the setup later at Rikshospitalet and Stavanger University Hospital for the STN-DBS patients. This created the opportunity to compare the progression of clinical symptoms in two similar populations, in which none of the patients followed in the nineties had the option of STN-DBS, whilst the STN-DBS patients from the following decade were recruited nationwide with all Norwegian patients with PD filling the criteria for surgery in principle had the option of STN-DBS treatment (although some patients were not operated due to limited capacity).

Arguably, this approach brings the studies in paper 2-4 as close to the ideal randomized trial as ethically possible given the ethical and practical considerations above - by being the closest possible setup to a two armed cohort study comparing surgery and best medical treatment to best medical treatment alone. However, this still

gives rise to a number of methodological considerations and shortcomings which could bias our findings.

It is not possible to rule out placebo effects from the surgical intervention in our set-up, although such effects would be expected to occur most frequently in the short-term after surgery. The long follow-up time in this thesis might reduce the impact of placebo effects when regarding long-term results.

When establishing the reference population from the population study in 1992 and 1993, we excluded patients after the same exclusion criteria as for PD patients considered for selection to STN-DBS treatment the following decade. This allowed us to establish a population of PD patients eligible for STN-DBS treatment, from a decade when Norwegian PD patients had no access to such treatment. However, excluding non-operable or non-eligible patients from the reference population does not equal that all patients in the resulting reference population would have been operated if STN-DBS was available as a treatment option at the time. There were some differences between the two populations. Individual matching of patients from the operated and non-operated populations were carried out to mitigate this, and to increase the possibility of uncovering significant differences in long term clinical development [6-8]. The patients in the reference population were on average 5 years older than the operated patients from Rikshospitalet and 6 years older than the operated patients from Stavanger University Hospital. There were also gender differences between the populations, with the percentage of females varying from 35 % in the operated patients from Rikshospitalet, 53% in the reference population and 63% in the operated patients from Stavanger University Hospital. We found higher average LEDD at baseline in the reference population recruited in the last decade of the past millennium (520 mg) than in the operated patients from the first decade in this millennium at Rikshospitalet (448 mg), but lower than in the patients operated within the same time frame at Stavanger University Hospital (960 mg). As the non-operated study population and the two operated populations hail from two consecutive decades, medical treatment options and strategies could have changed over time. This could lead to differences in medical therapy approach in the populations. The differences

were partially mitigated in the two studies in which the individual matching also took LEDD into consideration (study 3 and 4), but still represent potentially confounding factors.

The differences between the two operated populations are also mirrored in the average UPDRS-III scores at baseline in best "on", 27 in the operated patients from Stavanger University Hospital and 15 in the operated patients from Rikshospitalet. It was demonstrated in study 1 that the patients operated in the first years at Rikshospitalet had more advanced PD than the patients operated in the last years of the inclusion period [5]. As the two operated populations have not been compared in this thesis, this heterogeneity has not directly affected our results here, but the possibility that our operated population in study 2-4 may not be fully representative for STN-DBS patients treated worldwide cannot be excluded given the differences between patients operated in Oslo and Stavanger.

In studies 2-4, the materials are made up of relatively few patients especially in the matched groups of patients. Combined with the lack of a blinded and randomized control group, this could have introduced bias in the observed disease development both in the short and in the long term. The small sample sizes would reduce the chances of demonstrating statistical differences between the groups. Further, because only patients with sufficient data could be included there is also a risk of selection bias. The need to include only patients with sufficient data in the long term also meant that patients who died before the end of the 6-9 year follow-up could not be included, thus also introducing a risk of selection bias.

Findings

Overall, we have demonstrated stable long term effect on the cardinal motor symptoms in PD after STN-DBS. The findings of stable, lasting reduction in UPDRS-III scores [5, 6] are supported by lasting reduction in average LEDD and in that stimulation parameters could be kept largely unchanged during a 60 month follow-up [5]. The surgical complication rate was low at 10 % and peroperative mortality were 0[5]. The

surgical complication rate was approximately half of what has been reported in international literature recently [119].

Comparing the progression of PD in operated patients and non-operated eligible PD patients, we found no significant differences supporting a disease modulating effect of STN-DBS [6]. Also, survival rates showed no significant differences which could support a neuroprotective effect of STN-DBS. Indeed, there was a tendency to lower survival in the operated group (p 0.091), adding to the conclusion that STN-DBS does not seem to halt or slow down the natural progression of PD in patients. Our findings match those of other newer long term observational studies [120, 121], increasing the reliability of our results despite the weaknesses stated above in "Methodological considerations". However, a recent study by Ngoga et al compared survival in PD patients eligible for STN-DBS, in two groups of operated patients and patients opting out from surgery after being accepted for STN-DBS [122]. Ngoga et al found significantly reduced mortality in STN-DBS operated patients, as compared to the non-operated. The differences in death from respiratory causes was the underlying significant factor, however, and a neuroprotective effect of STN-DBS was not suggested. Our study could contribute to bring the discussion on an alleged neuroprotective effect of STN-DBS closer to an end. We believe the research focus concerning STN-DBS should now rather be on refining the method and maximizing symptom control, by improving the selection of patients, the timing of the procedure and the management of side effects.

Non-dopaminergic motor symptoms become near ubiquitous in PD patients as the disease progresses over time and the brain lesions become more widespread. The presumably complex pathophysiology behind PIGD, FOG and falls is still not fully elucidated, however. It is likely that locomotor areas in the brainstem and midbrain are involved in control of balance and gait [19], while dopaminergic structures may play a lesser role. Thus, as STN-DBS has been considered a dopaminergic treatment, it would accordingly be expected that STN-DBS would have limited effects on PIGD, FOG and falls. However, we found acute improvement in PIGD symptoms 3-6 months post-surgery, but the acute improvement was followed by long-term

deterioration. 6-9 years after surgery all patients in the operated group had PIGD. 84 % of the non-operated patients had PIGD at last follow-up (8 years after baseline). Thus, no lasting effect on PIGD symptoms from STN-DBS could be demonstrated.

Our work supports that non-motor problems in PD develop independently of interventions with STN-DBS. This could be expected on basis of the traditional view of STN-DBS as a dopaminergic treatment. Still, this knowledge is of importance both for the selection of patients for surgery, for timing surgery and when informing PD patients of the possibilities and limitations associated with STN-DBS.

In our study 4 no patient in any of the groups suffered from mental impairment/dementia at baseline. But after 6-8 years of observation 31 % of the operated patients and 45 % of the non-operated had dementia after the DSM-III-R criteria [123]. When adjusting for the 6 year higher average age in the non-operated group, there is seemingly no influence from the STN-DBS procedure on development of dementia. Our observed rate of dementia development in operated patients match the findings in a recent study following long term development of dementia in 184 STN-DBS operated PD patients [124]. At baseline 23 % of the patients had mild cognitive impairment (MCI), rising to 34 % after 1 year and 40 % after 3 years of follow-up. In the group with MCI at baseline 30 % had developed dementia after 6 years of follow-up. In the group without MCI at baseline 30 % had developed dementia after 11 years of follow-up. No patients developed dementia the first year after surgery, corresponding to our observation. The rate of dementia development also corresponds to earlier studies [29, 31, 125, 126]. Neuropsychiatric symptoms in PD patients is a major cause of distress in caregivers, and dementia is a major contributor to disability and dependence in PD [127, 128]. As dementia develops in a large portion of STN-DBS treated patients similar to non-operated patients, it could support an approach of early surgery in eligible patients with PD in order to give the patients as many independent years as possible after surgery.

Depression has been suggested to be an acute and perhaps indeed a chronic side effect after STN-DBS [1, 129-131]. This suggestion does not find support in our finding as depressive symptoms, as measured with MADRS, decreased from 9.1 on average

before surgery to 4.1 on average after surgery. The later development through follow-up of clinical depression as defined by a MADRS score ≥ 15 was similar in operated and non-operated patients. Reports of depression being induced and perhaps maintained by stimulation seems to hail from the early, pioneering days of STN-DBS and may not be a notable challenge at the present. A possible explanation could be the shift in how dopaminergic medication is reduced postoperatively, as many centres in the beginning quickly withdrew all dopaminergic drugs as opposed to the modern approach where dopaminergic drugs are siphoned off in a more gradual fashion. Sudden withdrawal of dopaminergic medication is known to potentially induce or worsen non-motor symptoms in PD, including depressive symptoms [132].

Sleep disorders, apathy and hallucinations are all disabling symptoms associated with late stage PD. We found these symptoms to develop similarly in operated and non-operated patients, unaffected by STN-DBS. Again, this might support operating eligible PD patients earlier as they will presumably be able to enjoy more years of independent life. The EARLYSTIM study currently being conducted aims to explore the possible benefits of early intervention with STN-DBS [133].

Fatigue, however, could be differently associated with STN-DBS than the other non-motor symptoms we have examined. Fatigue has probably not been fully recognized in patients with PD. In community-based cross-sectional studies approximately 40 % of patients with PD report significant fatigue [134], with as much as a third of patients pointing at fatigue as the symptom most likely to limit them in activities of daily life. Our study 4 demonstrated a surprisingly high incidence of fatigue in patients treated with STN-DBS. 87 % of the SNT-DBS patients had clinical fatigue (FSS score ≥ 4) at final visit. 55 % of the patients in the reference population had clinical fatigue at the end of follow-up. The difference persisted after individual matching. After individual matching 91% of the operated patients had a FSS ≥ 4, compared to 67 % of the non-operated patients. There has not been, as far as we know, any studies on long term development of fatigue after STN-DBS. A recent study found fatigue to be unchanged from preoperatively and until a 6 month follow-up after STN-DBS [135]. This corresponds well with our findings at 3-6 month follow-ups of STN-DBS patients. The

marked rise in fatigue in STN-DBS patients in our study appears between one year after surgery and the final visit. It is possible that our finding indicates a new and important long term side effect from STN-DBS treatment, but this would need further elucidation.

Conclusion

A central conclusion to be drawn on the basis of this thesis is that STN-DBS is a very good treatment option for motor symptoms in selected patients with advanced PD. Further, that the benefits of the treatment are limited to motor symptom control only, and that the underlying PD itself continues to develop in operated patients similar to the natural history of PD. The mechanisms by which STN-DBS mediates the beneficial effects on motor symptoms are still not fully understood. We have demonstrated acute improvements after STN-DBS not only on cardinal, dopaminergic motor symptoms [5, 6] but also on motor symptoms believed to be relatively independent of dopaminergic outflow, such as PIGD [7]. Further, STN-DBS treatment has its side effects and complications like all other treatments. The international literature reports wide variation of infection rates for STN-DBS, seemingly dependent on the definition of a postoperative infection. However, a general surgical complication rate of about 20 %, and an infection rate up to 15% seems to be valid figures [119, 136, 137]. Operative mortality has been reported internationally to be less than 2%, with many centres reporting no mortality at all [119, 136, 138].

We have demonstrated in a large, Norwegian material that STN-DBS surgery can be performed with good and stable long time results on dopaminergic motor symptoms [5-7], with transient beneficial effects on PIGD symptoms, with low perioperative mortality [5] and with a low rate of major adverse events [5]. The non-motor features of PD develop independently of intervention with STN-DBS, as do FOG and falls. The thesis has also described possible long term side effects of STN-DBS not described earlier, as fatigue may seem to develop at a high rate in STN-DBS operated patients after the first year postoperatively [8]. The findings add new information relevant to

advising patients both about the indication for, and the timing of, STN-DBS surgery in PD.

Future perspectives

An increasing variety of leads, pulse generators and other hardware from a growing number of manufacturers are now available. This comes as a result of targeted R&D into DBS medical technology from several major companies in the med-tech sector. The physician and the individual patient have an increasing selection of implantable solutions to choose from, making it possible to make individual choices based on the needs and conditions of each PD patient. E.g. rechargeable and non-rechargeable pulse generators, and leads with different spacing have been available for some time. Recently, leads with the possibility of multiple independent current control have been introduced as a means to adjust the area of stimulation in the brain nuclei with even higher resolution. Innovative technical solutions now being tested and marketed include stimulation planning systems like the Boston Scientific GUIDE system. The system offers a 3D modelling tool to simulate the field of simulation in the individual patient taking into account the relative position of the electrodes in the individual patient in order to engineer precisely the brain area subjected to DBS. It is very likely that innovative improvements to the hardware and software utilized in DBS will continue to accelerate as demand for DBS procedures continue to grow. The number of patients eligible for an increasing variety of DBS treatments will likely grow, in concert with the coming demographic shift in many countries caused by ageing populations. Also for these reasons, we believe that STN-DBS will remain an important treatment option for selected patients with advanced PD for many years to come, despite developments in other novel treatments such as gene therapy and stem cell treatments. Our work supports STN-DBS as an effective, safe and long-term stabile treatment option with low mortality and low complication rates. We find no support for STN-DBS providing disease modulation or deceleration, and we argue that further research on STN-DBS should focus on improving patient selection and refining the treatment as such in order to further improve efficacy and reduce complication rates, perhaps reaching an international consensus on best practice. Much benefit for

STN-DBS patients could probably be gained if variance between centres in treatment efficacy and complication rates could be reduced and results across the institutions performing STN-DBS could be elevated to the level of the best centres internationally. Further, more knowledge on the effects of STN-DBS on a cellular and synaptic level is needed in order to fully understand the effects of the treatment on the PD effected brain. A full understanding of the mechanisms at the synaptic level could further refine the DBS procedures and promote even more innovative developments in DBS associated hardware and software. But it could also be of great value for exploring new pharmacological approaches to PD symptoms.

Our studies serve to contribute in erasing the classical dogma of some motor symptoms being "dopaminergic" and some "non-dopaminergic", or the notion of STN-DBS as being a purely "dopaminergic" treatment. The range of effects by STN-DBS on motor symptoms spans both categories. The possibility of development of severe fatigue as a side effect of STN-DBS in the long term requires further attention, both to clarify whether or not such a side effect really exists - and if so – how to reduce the impact on patients through selection and management of the therapy postoperatively. Exploring the mechanisms by which fatigue could be spawned by STN-DBS would also potentially bring new knowledge both on the physiological effects of STN-DBS, but perhaps also on the central nervous involvement in the development of fatigue.

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I

BRIEF REPORT

Long-Term Efficacy and Mortality in Parkinson's Disease Patients Treated with Subthalamic Stimulation

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ABSTRACT

Background: The objective of this study was to examine the clinical outcome and mortality of long-term deep brain stimulation of the subthalamic nucleus in advanced Parkinson's disease.

Methods: We included all 144 patients (mean age, 60.3 years; mean disease duration, 11.0 years) treated in our center from 2001 to 2007.

Results: Twelve months after surgery, the off-medication Unified Parkinson's Disease Rating Scale motor score was reduced by a mean of 53%, and the annual increase after surgery was 3.2 points. The daily dose of dopaminergic medication was reduced by a mean of 49% and increased only marginally during follow-up. Twelve of the 144 patients died in the study period, including 2 suicides (1.4%). Survival was 97% after 3 years and 90% after 5 years.

Conclusions: The study confirms the stable efficacy of long-term subthalamic stimulation in selected patients with advanced Parkinson's disease. Throughout the study the patient characteristics at time of surgery changed, with less severe disease and shorter disease duration toward the end of the study period. © 2011 *Movement* Disorder Society

Key Words: deep brain stimulation; subthalamic nucleus; mortality; suicide; survival; treatment outcome

Long-term medical management of Parkinson's disease (PD) is frequently complicated by motor fluctuations and dyskinesias. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment in advanced PD, improving all cardinal motor symptoms and treatment-related motor complications.[1,2] In a randomized, controlled study of patients with severe motor complications, STN-DBS was more effective than best medical treatment.[3] Short-term effects have been reported in numerous case series.[4] However, relatively few studies have reported complete long-term data of treatment efficacy and mortality from single centers.

Here we report the findings of a retrospective study of all patients receiving this treatment in our hospital in a 7-year period from the first procedure performed in 2001, with complete analysis of survival. We also show how our practice regarding patient selection has evolved in the study period.

Patients and Methods

Patients

The first 144 patients who received STN-DBS surgery at Oslo University Hospital, from January 2001 to December 2007, were included in this retrospective study. The criteria for STN-DBS were that the patients had a diagnosis of PD, were younger than 75 years, had levodopa-responsive motor symptoms with severe motor complications and/or resting tremor with unsatisfactory levodopa response, and did not have dementia or major psychiatric illness, marked cerebral atrophy on MRI, or other contraindications to surgery. Data were obtained from patient records. The Regional Committee for Medical and Health Research Ethics in South-East Norway approved the study.

Evaluation of Clinical Outcomes

Pre- and postoperative assessment included an interview, neurological examination, and a levodopa-test

Additional Supporting Information may be found in the online version of this article.

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Table 1. Motor scores, dopaminergic medication, and stimulation parameters during long-term STN-DBS treatment

	Preoperative	12 months	24 months	36 months	48 months	60 months
Number of patients	131	131	110	89	52	32
UPDRS III Off	39.0 ± 13.6	18.4 ± 9.2	21.8 ± 10.1	24.7 ± 11.9	27.0 ± 12.9	28.9 ± 13.9
UPDRS III On	13.2 ± 8.1	12.5 ± 7.5	15.4 ± 9.6	18.1 ± 11.2	19.5 ± 10.4	22.4 ± 14.4
LEDD (mg)	991 ± 462	501 ± 285	539 ± 334	536 ± 369	517 ± 349	525 ± 331
Voltage left (V)	NA	3.3 ± 0.6	3.3 ± 0.6	3.4 ± 0.6	3.3 ± 0.5	3.4 ± 0.5
Voltage right (V)	NA	3.1 ± 0.6	3.3 ± 0.7	3.4 ± 0.6	3.4 ± 0.6	3.3 ± 0.6
Pulse width left (μs)	NA	62 ± 8	62 ± 7	62 ± 7	62 ± 8	64 ± 10
Pulse width right (μs)	NA	61 ± 6	61 ± 8	62 ± 8	61 ± 4	64 ± 10
Frequency (Hz)	NA	158 ± 22	160 ± 27	166 ± 16	170 ± 17	173 ± 17

Data presented are means ± standard deviations of the patients examined at each time.
Abbreviations: LEDD, levodopa-equivalent daily dose; NA, not applicable; UPDRS, Unified Parkinson's Disease Rating Scale.

comparing the UPDRS motor score in the off-medication and on-medication states. Postoperative evaluation was carried out 3 and 12 months after surgery and then annually, with the neurostimulator turned on.

Preoperative levodopa response (difference between preoperative UPDRS motor score in the off-medication and on-medication states) and postoperative DBS response (difference between UPDRS motor score off-medication preoperatively and postoperatively on-stimulation) were calculated. The primary outcome variable was the ratio of postoperative response to DBS and preoperative levodopa response. To study changes in antiparkinsonian medication during STN-DBS, the levodopa-equivalent daily dose (LEDD) was calculated as previously published.[3]

Surgery was performed as described in the Supporting Information. Patients were followed until December 31, 2008, or death. The date of death was obtained from the hospital's electronic patient record system. This system is continuously updated with information from the National Population Register of Norway.

Statistical Analyses

Descriptive statistics were calculated for baseline demographic and clinical data. Nonparametric tests were used for 2-group and multiple-group comparisons. Missing postoperative UPDRS motor scores were replaced by the score for the next performed assessment. The possible association of various demographic and disease- and treatment-related factors on treatment efficacy was first explored using Mann–Whitney *U* tests and Spearman Rank correlation coefficients and then studied with regression analyses.

Kaplan–Meier survival curves were constructed using death (any cause) as the outcome. We examined relationships between survival and patient characteristics (sex, age, disease duration, preoperative LEDD, and preoperative UPDRS motor score) using multivariate Cox regression analysis. All statistical analyses were performed using SPSS software version 16.0.

Results

Study Population

Ninety-three of the 144 patients were male (65%), and 51 were female (35%). Mean (SD) age at surgery was 60.3 (7.8) years, and disease duration was 11.0 (4.8) years. Nineteen of the 144 patients had previously been treated with stereotactic surgery. In this group STN-DBS was initiated a median of 6 years (range, 1–13 years) after the first procedure. Preoperative scores and at least 1 assessment 12 months after surgery were available for 131 patients, and these were included in the analyses of treatment effects.

Treatment Efficacy

Mean postoperative follow-up was 3.3 years (range, 1–7 years). UPDRS motor scores off- and on-medication, LEDD, and stimulation parameters during the course of the study are shown in Table 1. Twelve months after surgery, the mean UPDRS motor score off-medication was 18.4 with the stimulator on, compared with a preoperative score of 39.0 ($P < .001$). The average improvement in UPDRS motor scores due to STN-DBS was 53% (95% CI, 48%–57%), compared with a 67% (95% CI, 64%–70%) average improvement due to preoperative levodopa challenge. The mean LEDD was reduced by 49%, from 991 to 501 mg, in the same period ($P < .001$) and increased only marginally during the postoperative period. The mean annual increase of the UPDRS motor score off-medication was 3.2 points (Friedman test, $P < .001$).

The mean ratio of postoperative DBS response versus preoperative levodopa response was 0.80 (95% CI, 0.71–0.89). As incomplete withdrawal of dopamine agonists (DA) may affect the results of the preoperative levodopa test and 79 of the 131 patients (60%) used a DA at the time of the preoperative assessment, this ratio was also calculated separately for DA users and non–DA users. The mean ratio for

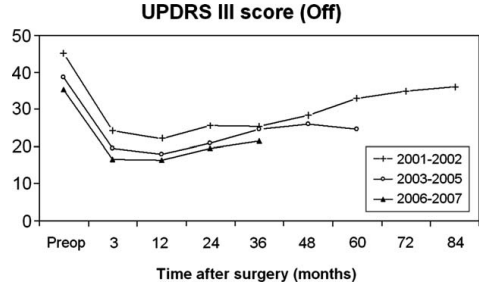

FIG. 1. UPDRS motor scores off-medication during the course of study. The study group was divided in 3 groups depending on the year of surgery. The figure demonstrates the changes in the patients' UPDRS motor scores off-medication during the study period. The reduced preoperative UPDRS motor score between the 3 periods was statistically significant (Kruskal-Wallis, $P = .02$).

the DA users was 0.71, compared with 0.93 in the non–DA user group ($P < 0.02$).

The efficacy of STN stimulation, measured by the ratio of stimulation response versus levodopa response 12 months after surgery, correlated negatively with disease duration and positively with preoperative UPDRS motor scores, but both correlations were weak. We found no association of treatment efficacy with sex, age, previous stereotactic procedures, preoperative LEDD, the neurosurgeon performing the procedure, the number of exploratory tracks, or year of surgery.

Changes in Patient Characteristics

The study group was divided in 3 groups depending on the year of surgery (Fig. 1). The mean preoperative UPDRS motor score was 45.2 among patients operated during the first 2-year period and 35.3 in the last 2-year period. Mean disease duration before surgery changed from 153 months in the first period to 125 months in the last ($P = .09$). There was no difference in mean age at surgery during the study.

Mortality

The preoperative and postoperative mortality rates, defined as the number of deaths occurring during the hospital stay or within the first 30 days after discharge, were 0. Twelve of the 144 patients died during the study period (8.3%), with a median time from surgery to death of 42 months (range, 3–77 months). Survival was 97% after 3 years and 90% after 5 years (Fig. 2).

Two patients died within the first 6 months of causes probably related to the surgical treatment. In addition, 2 of the 144 patients (1.4%) committed suicide, 15 and 16 months after surgery. The remaining 8 of the 12 deceased patients died several years after surgery, presumably of causes unrelated to the surgery. Detailed description of these patients and of severe adverse events are found in the Supporting Information. Deceased and surviving patients were compared for clinical characteristics. The mean age at surgery of the deceased patients was 4 years higher than that of the surviving patients (64.0 vs 60.0 years, $P = .04$; Supporting Fig. 1a). Deceased patients also had more advanced disease at the time of surgery, with a mean preoperative off-medication UPDRS motor score of 52.0, compared with 38.3 in the surviving patients ($P = .006$, Supporting Fig. 1b). In the multivariate analysis, age and preoperative UPDRS motor score were the only significant prognostic factors.

Discussion

Our results support that long-term STN-DBS has a stable effect on motor functions. The average annual increase in off-medication UPDRS motor score was 3.2 points. This is very similar to the annual increase of 3.3 points found in a previous population-based study of PD from Norway,[5] suggesting that an annual increase of this size can be explained by natural disease progression. The stimulation parameters and the dopaminergic treatment were increased only marginally during the first 60 months, further supporting the stable long-term effect of the treatment.[6]

Our investigation was limited by the retrospective nature of the study. However, the number of patients was relatively large, and all patients receiving STN-DBS in our center until the end of 2007 were included consecutively and without exclusions.

We found a survival of 97% after 3 years and 90% after 5 years. Very few previous studies have published long-term survival data after STN-DBS. In a study by Schüpbach and colleagues of 171 consecutive patients, the calculated survival curve was almost identical to our estimate.[7] The only predictive factor for mortality in their study was poorer cognitive function. We found that age and more severe motor disability were predictive factors. These results are not contradictory

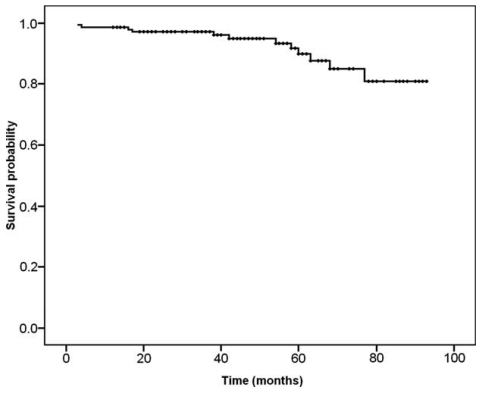

FIG. 2. Kaplan–Meier curve of patient survival. The curve describes survival probability over time. Vertical bars show patients who reached end of follow-up alive.

because age, cognitive function, and advanced motor disability are factors related to mortality in PD.[8] Wider and colleagues found a much higher mortality, with a mean annual mortality ratio of 8.5%.[9] However, this could be related to the higher age at surgery of their patients.

Two of the 144 patients (1.4%) committed suicide. Several previous studies have reported suicides after STN-DBS.[10,11] The suicide frequency has varied between studies, but an international multicenter survey found a frequency of 0.45%.[12] Despite the presence of a progressive disorder and frequent psychiatric comorbidities, previous studies have not found higher suicide rates in PD patients than in the general population.[13] This indicates that either subthalamic stimulation increases the risk, or some of the patients undergoing STN-DBS have increased suicide risk compared with other PD patients. Both theories are supported by recent studies and are not mutually exclusive. A cross-sectional study found increased impulsivity scores in patients treated with STN-DBS compared with patients receiving medical therapy.[14] Several risk factors for attempted and completed suicide after STN-DBS have also been identified, including postoperative depression, being single, early disease onset, and a history of impulse control disorders.[12]

There is an ongoing discussion regarding when in the course of disease, surgery should be performed. Patients who where operated on in the last part of our study had lower preoperative UPDRS motor scores than those operated on during the first 2 years. There are at least 2 probable explanations for this. First, when STN-DBS surgery was established, some of the most severely affected patients with long disease duration were probably among the first to receive treatment. The second explanation is that STN-DBS has become a more accepted treatment and is considered earlier now than some years ago. Results from ongoing studies of STN-DBS earlier in the disease course are awaited to provide further information on the best time to perform surgery.

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II

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ACTA NEUROLOGICA SCANDINAVICA

Progression and survival in Parkinson's disease with subthalamic nucleus stimulation

Lilleeng B, Brønnick K, Toft M, Dietrichs E, Larsen JP. Progression and survival in Parkinson's disease with subthalamic nucleus stimulation.
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Background – Treatment for Parkinson's disease (PD) is symptomatic. Surgical treatment with continuous high-frequency stimulation of the subthalamic nucleus (STN-DBS) is established as a safe symptomatic treatment with long-term beneficial effects. It has been postulated that STN-DBS could halt the progression of PD through a disease modifying or neuroprotective effect. *Objective* – To investigate the postulated disease modifying or neuroprotective effect of STN-DBS by comparing the rate of deterioration of parkinsonism and mortality over time in two selected and matched groups of patients with PD with and without surgery. *Methods* – Group A was derived from all patients who received STN-DSB surgery at Oslo University Hospital, from January 2001 to December 2007. Group B was derived from a prevalence study of PD in the Stavanger area of Western Norway in 1993. The two groups were individually matched and the disease progression measured by Unified Parkinson's Disease Rating Scale-motor scores, and the mortality was compared. *Results* – The mean annual change based on baseline and last observation scores in individually matched groups was 0.97 (SD = 3.57) for the surgery group and 1.04 (SD = 3.33) for the controls and thus not significantly different, $F(1, 104) = .21$, $P = 0.89$. The long-term mortality was also similar in the two groups during long-term follow-up, hazard ratio = 1.76, CL 0.91–3.40, $P = 0.091$. *Conclusion* – This study gives no support to a postulated disease modifying or neuroprotective effect of STN-DBS in patients with PD.

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Key words: modulation; mortality; Parkinson's disease; progression; deep brain stimulation of the subthalamic nucleus

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with great impact on patients, their caregivers, and on the society in general (1). Over the last decade, surgical treatment with continuous deep brain stimulation of the subthalamic nucleus (STN-DBS) has been established as a safe symptomatic treatment with long-term efficacy and acceptable complications (2–7).

Several recent papers have shown that the motor effect of STN-DBS is long-lasting, but the progression of parkinsonism continues (8–11). However, it has also been postulated that STN-DBS could have a disease modifying or neuroprotective effect in PD and thus slow the progression of the disease (1). It has been shown that lesioning of the STN prevents degeneration of the nigrostriatal dopaminergic pathways in the 6-hydroxydopamine rat model (12–14). In addition, it has been hypothesized that glutaminergic STN-mediated neurotoxicity could be an etiological factor in the progressive decline of intact dopamine neurons in the substantia nigra pars compacta and that the reduction in the STN neuronal hyperactivity by inhibition through high-frequency DBS might slow or even halt the progression of neuron degeneration in PD (15, 16).

This hypothesis has been examined by means of serial ^{18}F-flurodopa positron emission

tomography in 30 patients with successful STN-DBS over the first 16 months after surgery (17). Hilker and co-workers demonstrated a continuous decline of dopaminergic function in the range of previously reported data from longitudinal imaging studies in PD. They concluded that they could not confirm neuroprotective effects of high-frequency DBS in the STN. Still, it is considered a major unmet need in the understanding of STN-DBS to further elucidate possible effects on disease progression (1).

The aim of this study was therefore to examine the possible influence of STN-DBS on motor progression by comparing the development of parkinsonism over time in a large longitudinal study of patients with STN-DBS and in a population-based long-term longitudinal study of only medically treated patients. In addition, we investigated the rate of mortality in the two patient series to examine the influence of the procedure on long-term survival.

Material and methods

Patients

We have compared the rate of deterioration of parkinsonism and mortality over time in two selected and matched series of patients with PD. Group A had performed STN-DBS surgery, and group B was without surgery from the time period when such procedures were not routine treatment for the disease.

Group A was derived from all patients who received STN-DBS surgery at Oslo University Hospital between January 2001 and December 2007. The inclusion criteria for surgery were a clinical diagnosis of PD, age under 75 years, levodopa-responsive motor symptoms with severe motor complications, and/or resting tremor with unsatisfactory levodopa response. Exclusion criteria were dementia or major psychiatric illness, marked cerebral atrophy on MRI, or other contraindications to surgery. This patient group was followed annually from surgery until December 31, 2008 or until death. Data for this study were obtained from patient records, as previously published (8). The Regional Committee for Medical and Health Research Ethics in southeast Norway approved the study.

About 144 patients underwent STN-DBS. Severe adverse events directly related to the surgery occurred in 14 patients (10%). These included five extracranial infections, five extracranial hematomas, two seizures, one pulmonary embolus, and one cerebral infarction. None of the patients developed symptomatic intracranial hemorrhages or intracranial infections. Further details concerning these patients are previously published (8).

Group B was derived from a prevalence study of PD in the Stavanger area of Western Norway on January 1, 1993. The crude prevalence rate was 110.9 per 100,000 inhabitants (245 patients). Patient recruitment was described previously in detail (18). All patients were diagnosed by a neurologist of the study group, according to published diagnostic criteria (19). This patient group was prospectively followed up with new examinations 4 and 8 years after prevalence day (20, 21). A subgroup of 22 deceased patients has been assessed neuropathologically after they had given written informed consent. In all subjects, cell loss and synuclein-positive Lewy bodies were found in the surviving neurons of substantia nigra, confirming the clinical diagnosis of PD (22). Tissue processing and staining were performed following standard protocols at the time (23).

Matching procedure

Group A, which comprised of patients who had performed STN-DBS surgery, were selected from the original 144 patients. We included in the analyses patients who had been examined with the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-motor) (24) in the medication 'on' state preoperatively, 3 months postoperatively, and at least at one more study visit giving an observation period of at least 21 months. UPDRS scoring was conducted in a standardized setup in best 'on' state and performed by trained physicians. Two patients died within the first year after the surgical procedure. Eleven patients were either followed at other hospitals or preoperative UPDRS scores could not be identified. Thirty-five patients did not have a UPDRS part III score 3 months postoperatively and/or a repeated score at a later study visit, and 15 patients had an observation period of <21 months and were thus excluded. Accordingly, 81 patients with a complete data set were included in study group A.

Among the 245 patients from the population-based control series, seven were re-diagnosed as not having PD during follow-up, three patients died between prevalence day and baseline examination, two patients refused to participate, and one could not be evaluated due to severe dementia. During the first 4 years of follow-up, 81 had died, one person had moved abroad, and six patients refused participation in the examinations in 1997. Thus, 144 patients had a least two

observations of disease status and were eligible for this study group B.

In the first step of the matching procedure, we excluded all patients from group B that at baseline did not comply with the inclusion and exclusion criteria for patients with surgery in group A. This was age of 75 years or higher, dementia, or major psychiatric illness. After application of the exclusion criteria, 90 patients from group B remained and had valid UPDRS-motor score data at the 4-year examination.

Previous studies have shown that age is the most important independent risk factor for a more rapid progression of the UPDRS-motor score (25, 26). Based on this, we performed a second matching of the two patient groups. In this matching, for each individual from group A was sought an individual from group B with the same age (±3 years) at baseline. This final matching resulted in 54 patients in each patient series.

Demographic and clinical data

In both patient series, we collected data on age at baseline of this study, gender, UPDRS-motor scores in the stimulation 'on' and medication 'on' state, levodopa equivalent daily dose (LEDD) (27), date of surgery, and date of death if this occurred during the study period.

Data analysis

The matching of the two patient groups was based on presurgical data in group A and data from prevalence day (January 1, 1993) in group B. Disease progression as measured by UPDRS-motor scores in the medication (and stimulation) 'on' state was calculated in group A with data from 3 months after surgery as baseline and with the follow-up data from the visit closest to 45 months after baseline (choosing the longest follow-up time whenever there were similar follow-up times around the 45-month follow-up). For group B, calculations of progression are based on data from prevalence day and until the 4-year follow-up visit. Thus, for the patients with surgery, the preferred UPDRS measurement point was at 45 months, and for the controls, it was at 48 months. This was carried out to have similar follow-up times in the two groups, in case of nonlinear UPDRS change with increasing follow-up time.

Disease progression is presented as mean annual change in UPDRS-motor score based on the average change from first to last recorded observations up to 4 years after baseline examinations.

Differences in mean change in UPDRS-motor score between groups A and B, according to both matching criteria, were analyzed using analysis of covariance (ANCOVA) with follow-up time, age, and sex as covariates.

In addition to the evaluation of motor progression, we examined long-term survival in the two patient groups during the observation period from study start and until October 2011. We used Cox regression to assess whether there were different hazard ratios (HRs) for operated versus non-operated patients for death after baseline, while controlling for sex and age at baseline. Separate Cox regressions were performed for complete groups and for groups after individual matching.

Results

Patient group A comprised 81 patients that had been treated with STN-DBS, and the control group B included 90 patients after applying the same inclusion and exclusion criteria as for the operated patients. Table 1 shows demographic and clinical characteristics of the two study groups as well as mean annual progression of UPDRS-motor score. The table also shows these data after the final individual matching according to age at baseline with 54 patients in each group.

Progression of UPDRS-motor score over time

Table 1 shows the annual changes in UPDRS-motor scores in groups A and B. These progression scores were not significantly different when controlling for follow-up time, age, and sex, neither in the matched groups, $F(1, 103) = 1.68$, $P = 0.199$, nor the complete study groups, $F(1, 166) = 2.33$ ($P = 0.129$). Further, to ensure that the higher proportion of female patients in the PD control group did not skew the analysis, we conducted an analysis of variance (ANOVA) in the complete study groups with sex and patient group as fixed factors and annual UPDRS change as dependent variable. Sex did not affect annual UPDRS change ($P = 0.611$), and there was no interaction between sex and patient group with regard to annual UPDRS change ($P = 0.201$).

Long-term survival

In Fig. 1, the calculated survival curves are shown for the complete study groups, based on an observation time of 18 years for all the controls and a mean observation time of 7.5 years

Table 1 Clinical and demographic data of Parkinson's disease (PD) patients with deep brain stimulation of the subthalamic nucleus (STN-DBS) and controls without surgery in the study groups and after individual matching for age of the two patient groups

	PD patients with STN-DBS		PD control group patients	
	Study group	Matched group	Study group	Matched group
No of patients	81	54	90	54
Mean age at baseline, years (SD)	61 (7)	64 (6)	66 (7)	64 (6)
% Females	35	39	52	57
Mean UPDRS follow-up measurement, month (SD)	38 (10)	39 (10)	48 (0)	48 (0)
Mean baseline UPDRS-III score (SD)	15 (8)	18 (9)	20 (11)	26 (13)
Mean baseline LEDD (SD)	448 (262)	433 (226)	537 (305)	581 (341)
Mean UPDRS-III progression pr year (SD)	1.16 (3.60)	1.15 (3.51)	1.43 (3.08)	1.04 (3.34)

LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale. UPDRS-III scores were measured in the medication and stimulation 'on' state. Baseline data for the operated group were obtained 3 months after initiation of STN-DBS.

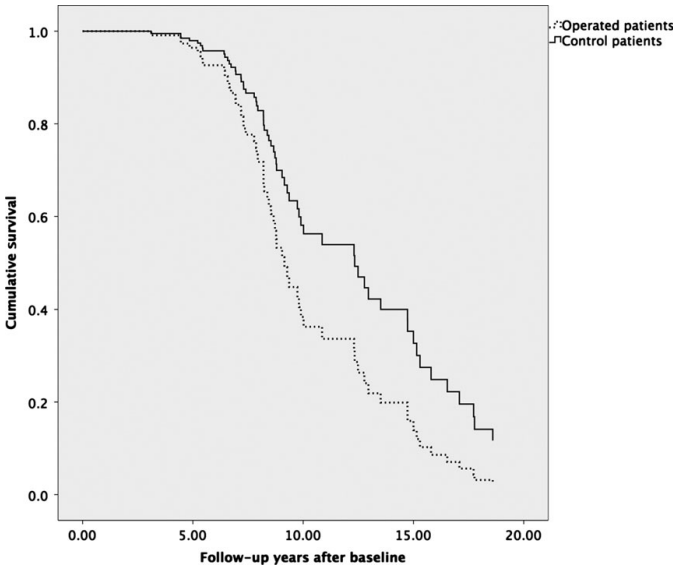

Figure 1. Cox regression curves showing calculated survival for deep brain stimulation of the subthalamic nucleus (STN-DBS)-operated patients based on a mean observation time of 7.5 years and controls with an observation time of 18 years not individually matched for age. Age at baseline and sex were introduced in the calculations as covariates.

on the operated group (SD 1.7). The Cox regression showed that age at baseline was a significant predictor of mortality, with a HR of 1.11, CL 1.07–1.15, $P < 0.001$. There was also a trend toward a higher hazard rate for mortality for the operated patients as opposed to the controls, HR = 1.82, CL 0.99–3.32, $P = 0.052$. Age represented a significant hazard of mortality, HR = 1.15, CL 1.09–1.22, $P < 0.001$. As in the other matching condition, the STN-operated patients showed a trend toward a higher risk of death during the follow-up period, HR = 1.76, CL 0.91–3.40, $P = 0.091$ [with an observation time of 18 years for all the controls and a mean observation time of 7.9 years on the operated group (SD 1.7)].

Discussion

We found in this study that the rate of progression of parkinsonism and mortality was nearly identical in a group of PD patients with deep brain stimulation and in a historical control group from the time period before widespread use of STN-DBS. These findings were further confirmed when performing an individual matching of the groups based on age of the patients at baseline. The results from our study indicate that

STN-DBS treatment in patients with PD does not influence the long-term progression of motor impairment or patient survival. Our study may thus bring an important contribution to the controversy of a possible neuroprotective effect of this procedure.

A potential neuroprotective effect of STN-DBS has been primarily driven by a theoretical concept related to an induction of reduced cytotoxic glutamate release in substantia nigra by the procedure which again leads to less neurodegeneration (15, 16). In addition, results from animal studies have tended to support the neuroprotection hypothesis (12–14). In contrast, there are no data from controlled patient studies that support the validity of this concept and it has therefore been seen as one of the important unanswered research issues related to the STN-DBS procedure (1). Although some studies have shown little disease progression during the first 2 years after surgery (28), other long-term studies show that the clinical syndrome gets worse over time (8–11). In addition, a study using PET scans as outcome measurement could not confirm the experimental data (17) and it has therefore been seen as necessary to address this question through controlled clinical studies. Such trials might, however, be difficult to design and run as the treatment procedure today is established, and it would be considered as unethical to run a prospective randomised controlled study over a sufficient time period.

We have therefore in this study compared the longitudinal development of severity of parkinsonism and mortality in two independent patient cohorts. The operated patients received STN-HFS surgery at Oslo University Hospital, from January 2001 to December 2007, and were followed from surgery until December 31 2008 or until death. The control patients were derived from a community-based group of prevalent cases in Western Norway on January 1, 1993, that has been followed up longitudinally (20, 21) for several years. To ensure comparable patient groups, we applied the same exclusion criteria for the control group as for surgery.

The clinical picture and the rate of progression show large heterogeneity in PD, and several studies have examined factors that can influence disease development. Although several factors are associated with a more advanced disease stage, only age at onset of disease (25) and age at baseline of a study (29) are consistently found as independent risk factors for a more severe progression of parkinsonism. We have therefore further matched the two patient groups by age to overcome this problem. Also with these somewhat smaller, but better matched groups, the findings strongly indicate that the progression is similar in patients with and without STN-DBS.

Parkinson's disease is today recognized as a multisystem brain disorder with a symptomatology that comprises both motor and non-motor symptoms, and measurements that intend to reflect the cerebral progression of the disease are controversial. The longitudinal development of severity of parkinsonism, as measured with the UPDRS-motor score in patients on optimal treatment, is, however, considered as a valid assessment for this (29, 30). Furthermore, we included only patients with at least a 21-month observation period as the first 6–12 months after surgery may not be representative for the long-term disease progression. The baseline time point for calculating progression of parkinsonism was 3 months after the procedure to leave time for adjustment of equipment and medication. Some operated patients would therefore most probably not be optimally treated at this evaluation leading to an underestimation of the disease progression in the surgery group, which further strengthens the main finding of the study.

Although survival is not a direct measurement of disease progression, it was anticipated that this robust end point would give additional value to the evaluation of the objective of this study. It has previously been shown that patients with PD have a moderately increased mortality rate (31), and thus, a higher mortality in any of the study groups would indicate that the disease process would have developed more severely in those patients. We found again no difference between those with and without the STN-DBS treatment when controlling for age and this further strengthens the results related to the primary outcome parameter.

There was small trend toward a higher risk of death during the follow-up period in the STN-DBS group. This could be the result of differences between the two groups despite individual matching. The preoperative LEDD was higher in the STN-DBS group than in the medication group, indicating clinical differences that might influence disease-related mortality.

In this study, we have compared disease progression in two different patient series which made it necessary to use a historical control group and to do post hoc matching of the included patients. This study design has several obvious shortcomings compared with the wanted randomized blinded prospective trial. We still believe that this approach is as close as it is possible to come to run a head-to-head comparison of

progression of parkinsonism and mortality in patients with and without STN-DBS.

The study has other important shortcomings as well. The rather low number of patients and the lack of a blinded and randomized control group could have given a biased picture of disease development both in the short- and long-term perspective. Also, the need to include only patients with sufficient data constitutes a risk of selection bias. In particular, the comparison of the matched groups was carried out based on small samples. The small sample size makes it more difficult to demonstrate any differences between the two groups by statistical analysis. Another weakness of this study is that to include patients with data from long-time follow-up, only patients still alive at the end of the 6- to 9-year observation period have been included, as opposed to patients who died during follow-up. Data on disease duration before baseline were not available for Group A. Not analyzing this variable could add to the risk of selection bias.

However, our results are in line with the newer long-term observational studies carried out on operated patients (9, 10). The results from this study should therefore be valid and fairly robust, despite the above-mentioned shortcomings. Our study together with other recent studies (9, 10) thus strongly argues against a neuroprotective effect of the STN-DBS. Still it is clear that the symptomatic effect of this treatment is well established, and it thus represents an important treatment option in the management of PD.

In conclusion, our study gave no support to the postulated disease modifying or neuroprotective effect of STN-DBS. We found no significant difference between the surgery and non-surgery groups in the mean annual change in UPDRS-motor score, nor in mortality. The absence of significant differences was upheld when controlling for age by individual matching. These findings strongly contradict a neuroprotective or disease modifying effect of STN-DBS. Thus, further research in the field of surgical treatment for PD with STN-DBS may better focus on refining the method and on obtaining even better symptom control, rather than pursuing an alleged disease modifying effect that seems not to exist.

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Conflicts of interests

No conflicts of interest. This study had no funding.

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III

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ACTA NEUROLOGICA SCANDINAVICA

Motor symptoms after deep brain stimulation of the subthalamic nucleus

Lilleeng B, Gjerstad M, Baardsen R, Dalen I, Larsen JP. Motor symptoms after deep brain stimulation of the subthalamic nucleus. Acta Neurol Scand: DOI: 10.1111/ane.12342.

Objectives – Stimulation of the subthalamic nucleus (STN-DBS) is an established treatment with long-term beneficial effects on motor symptoms in patients with Parkinson's disease (PD). The efficacy of STN-DBS on non-dopaminergic motor symptoms remains less elucidated. In this study, we have examined short- and long-term impacts of STN-DBS on the development of the postural instability and gait difficulties (PIGD) phenotype, freezing of gait (FOG), and falls. *Materials and methods* – We collected data from a prospectively followed cohort of patients that had been operated with STN-DBS 6–9 years before final examination and compared our findings to the longitudinal development of the same symptoms in a non-operated, historical reference population. *Results* – During short-term follow-up after surgery, we observed a marked improvement in mean UPDRS-motor score from 27 to 18. We also found clear improvements in tremor, bradykinesia, rigidity, and PIGD scores. However, 6–9 years after surgery, all patients had a dominating PIGD pattern of parkinsonism and 50% of the patients had developed FOG and/or had become recurrent fallers. The disease development in a group of patients with PD from the presurgery period had a similar trajectory as among the operated patients. In addition, mean annual change of both bradykinesia and PIGD scores was nearly identical in both study groups while tremor and rigidity had a significant better development in the operated patients. *Conclusions* – We found that STN-DBS induces an acute improvement of PIGD symptoms. The following long-term development was however characterized by a marked progression of non-dopaminergic symptoms.

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Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is established as an effective and safe treatment option in patients with Parkinson's disease (PD) suffering from motor complications with dopaminergic therapy (1, 2). STN-DBS is documented to have a stabilizing effect on the severity of parkinsonism that seems to be preserved for many years after surgery (1, 3). Still, the procedure's impact on the so-called non-dopaminergic motor problems is not sufficiently clear (1, 4).

Motor symptoms that have poor or no response to dopaminergic treatment include axial motor involvement leading to postural instability and gait difficulties (PIGD) (5, 6), freezing of gait (FOG), and falls. These symptoms are substantially disabling and reduce quality of life in patients and caregivers (7–9). The frequency of these symptoms increases as PD develops in the brain with an increasing number of dispersed lesions (10). In addition, the PIGD pattern of parkinsonism is associated with a faster rate of cognitive decline and increased risk for subsequent dementia (10, 11).

The pathophysiology of PIGD, FOG, and falls are poorly understood and is probably complex. Still, brainstem and midbrain locomotor areas are thought to play a major role in the control of balance and gait (10) and also deficits in cognitive functions may influence the development of these

dominating axial symptoms of PD. On the other hand, the depletion of the dopaminergic system is considered to be less important. If this is true, STN-DBS would be expected to have a limited impact on such symptoms after surgery. But the effects of STN-DBS are not yet clear. A meta-analysis of several long-term studies on bilateral DBS in the STN and the internal globus pallidus internus (GPi) did, however, indicate that the procedures can have acute effects on PIGD (12). It is still assumed from clinical experience that the effects may be small, and in addition, these symptoms would be expected to progress at the same rate as observed in non-operated patients with PD.

We wished to elucidate these issues, and the aims of our study were to examine the short- and long-term impact of STN-DBS on the development of the PIGD phenotype, FOG, and falls in a prospectively followed cohort of patients with PD that had been operated 6–9 years before final examination. Furthermore, we have compared these findings to the longitudinal development of the same symptoms in a non-operated, historical reference population.

Materials and methods

In this study, we have examined prospectively until 2012 the development of parkinsonism, PIGD, FOG, and falling over time in a group of patients with PD who received STN-DBS surgery at Stavanger University Hospital between July 1, 2003 and June 30, 2006. The Regional Committee for Medical and Health Research Ethics in Western Norway approved the study.

The inclusion criteria for surgery in this study were a clinical diagnosis of PD, a positive levodopa challenging test, dyskinesias unresponsive to medical treatment and on/off complications. Exclusion criteria were dementia or major psychiatric illness in the patient's history, marked cerebral atrophy on MRI, age >75 years, or other common contraindications to surgery. A total of 28 patients with PD received STN-DBS implants. Sixteen of them were still alive in 2012 and had sufficient clinical data to be included in this study. Of those excluded, five patients had died 2–6 years after surgery, three did not agree to participate in the follow-up, and in four patients, the device was no longer functioning. The DBS surgery was conducted according to the procedure used by the National Hospital in Oslo, Norway as previously published (3), with an initial improvement in motor function. Trajectories were planned with the target in the dorsolateral, motoric part of the STN bilaterally.

To obtain information on the expected natural history of these symptoms, we have also examined the longitudinal development of parkinsonism, PIGD, FOG, and falls in a comparable group of patients from the time period when STN-DBS were not routine treatment for PD. This group of patients was derived from a prevalence study of PD in the Stavanger area of Western Norway on January 1, 1993. The crude prevalence rate was 110.9 per 100,000 inhabitants (245 patients). Patient recruitment has been described in detail previously (13). All patients were diagnosed by a neurologist of the study group, according to published diagnostic criteria (14).

Among the 245 patients from this cohort, seven were re-diagnosed as not having PD during follow-up, three patients died between prevalence day and baseline examination, two patients refused to participate, and one could not be evaluated due to severe dementia. During the first 4 years of follow-up, 81 had died, one person had moved abroad, and six patients refused participation in the examinations in 1997. Between 1997 and 2001, further 55 patients had died and thus 89 patients completed the 8-year follow-up and were eligible for evaluation in this study.

Among these 89, we first excluded patients according to the same exclusion criteria used for patients evaluated for surgery. This was age of 75 years or higher, dementia, or major psychiatric illness. After application of the exclusion criteria, 62 patients remained. In addition, we did an individual matching of patients in the two groups based on several factors at baseline of the study that could influence the future disease symptoms relevant for this study. The statistical approach and factors included in this matching are described in the Statistics section. This final individual matching resulted in two groups of 12 patients that could be compared for long-term development of parkinsonism, PIGD, FOG, and falls.

Examination program

All patients with STN-DBS surgery were examined preoperatively and 3–6 months postoperatively to evaluate the short-term effects on parkinsonism, PIGD, FOG, and falls. In addition, these patients were examined 1 year after implantation and again in a long-term follow-up during 2011 and 2012. This examination took place 6–9 years after surgery. Patients in the reference group were prospectively followed up with new examinations 4 and 8 years after baseline

(15, 16). All examinations were performed in best 'ON' and with stimulator on, if present.

The examinations performed at each study visit included a semi-structured interview on disease history and drug treatment [the levodopa-equivalent levodopa dose (LEDD) was calculated in mg (17)], the Unified Parkinson Disease Rating Scale (UPDRS) (18) and Hoehn and Yahr stage (19).

Measures of tremor, rigidity, bradykinesia, and PIGD were derived from the UPDRS activity of daily living (ADL) and motor sections. We calculated sum scores and mean per UPDRS item scores for tremor (items 16, 20–21), PIGD symptoms (items 13–15, 29–30), bradykinesia (items 23–26, 31), and rigidity (item 22). Based on the relative severity of tremor vs PIGD symptoms (mean of UPDRS items 13–15, 29–30), motor phenotype was determined as either tremor dominant (TD) or postural instability/gait difficulty (PIGD) phenotype (patients with indeterminate type were classified as non-PIGD), following the classification algorithm proposed by Jankovic et al. (20). FOG was defined as a score of >1 on the UPDRS part II item 14 (freezing when walking), which was measured on a 0 (normal) to 4 (severe) scale. The cut-off was selected to eliminate false positives. Falls were defined as a score of >1 on the UPDRS part II item 13 (falling not caused by freezing), thus primarily targeting recurrent fallers.

Data analyses and statistics

In this study, we examined the short-term effects of STN-DBS by comparing clinical features before and 3–6 months after surgery. The long-term development of symptoms is described in the STN-DBS patients with the clinical status 3–6 months after surgery as the baseline observation and until last observation. Disease development in the reference cohort was calculated from baseline and until 8-year follow-up.

All statistical analysis was performed in SPSS version 20 IBM N.Y., USA. Descriptive statistics for continuous data are presented as means and standard deviations (SDs) and for categorical data as counts and percentages. Confidence intervals (CIs) for means are based on the normal approximation. Observed scores for the STN-operated patients are compared to those of the controls using independent samples *t*-tests.

The STN-operated patients were, based on their 3–6 months postoperative scores, individually matched to comparable controls by means of propensity scores matching (21). The matching routine took into consideration gender (22), being over 67 years of age (yes/no), LEDD, mean UPDRS tremor and PIGD scores, PIGD type (yes/no), total UPDRS-motor score, total UPDRS ADL score, and the interaction between LEDD and all other covariates. The covariates were centered and rescaled as appropriate before being entered into a logistic regression model with outcome STN operated (yes/no). The predicted probabilities or propensities of being in the STN-operated group were then used for individually matching the STN-operated to non-operated controls deemed eligible for operation, by applying a 'greedy' nearest neighbor matching routine based in the SPSS syntax posted online by John S. Painter (23). Due to non-overlapping propensity scores distributions (24), the four of the operated with highest propensity scores were discarded from the matched groups.

Results

Table 1 shows demographic and clinical data for patients with and without STN-DBS. Data are shown before and after surgery for the operated patients ($n = 16$) and at baseline for the non-operated patients ($n = 62$) with PD. Also data for the two individually matched groups ($n = 12$ in both groups) are shown. The mean age for the operated patients was 60 years and with 80% PIGD dominating pattern of parkinsonism. Two patients had FOG and three were recurrent fallers. The non-surgery group was older and had less severe parkinsonism and fewer patients with FOG and falls. After matching, the groups were more similar.

PIGD, FOG, and falls during short-term follow-up

Table 1 also shows the clinical characteristics before and after surgery for the patients that had received STN-DBS implants. We observed a marked improvement in mean UPDRS-motor score from 27 to 18. We also found clear improvements in tremor, bradykinesia, rigidity, and PIGD scores. Only one patient was changed from dominating PIGD to tremor dominant parkinsonism. In addition, the two patients with FOG before surgery, no longer reported this complaint. One of three patients who were recurrent fallers before surgery reported improvement.

PIGD, FOG, and falls during long-term follow-up

Table 2 shows the mean PIGD score and proportion of patients with PIGD pattern of parkinsonism, FOG, and falls at baseline (3–6 months after

Table 1 Demographic and clinical data for patients with and without STN-DBS. Data are shown before and after surgery for the operated patients and at baseline for the non-operated patients with PD. Also data for the matched groups are shown. The results are given as mean (SD), unless stated otherwise

	STN-DBS operated, preoperatively, $n = 16$	STN-DBS operated, after surgery, $n = 16$	Reference population, baseline, $n = 62$	Matched STN-DBS operated, after surgery, $n = 12$	Matched from the reference population, $n = 12$
Age, years	60 (8.1)	60 (8.4)	66 (6.7)	61 (8.0)	61 (8.3)
LEDD, mg	960 (220)	740 (380)	520 (250)	740 (290)	720 (220)
UPDRS-II total score	11 (10)*	7.2 (5.1)	8.7 (4.5)	7.8 (5.0)	7.3 (4.0)
UPDRS-III total score	27 (13)	18 (7.5)	18 (10)	17 (6.4)	16 (8.4)
Hoehn and Yahr stage	2.5 (0.6)*	2.1 (0.6)*	2.2 (0.8)	2.1 (0.7)	2.0 (0.7)
Tremor score	3.2 (4.1)*	2.6 (4.1)	4.3 (3.8)	2.3 (3.3)	2.7 (4.5)
Bradykinesia score	12 (7.3)	8.7 (4.5)	8.5 (5.6)	8.0 (4.3)	7.3 (4.4)
Rigidity score	6.1 (3.1)	3.1 (2.6)	2.2 (1.8)	2.5 (2.4)	2.4 (1.9)
PIGD score	3.9 (2.1)*	2.5 (2.0)	2.6 (2.2)	2.8 (2.3)	2.3 (1.9)
PIGD dominance (%)	13 (81)*	12 (75)	28 (45)	9 (75)	8 (67)
FOG (%)	2 (13)*	0 (0)	3 (5)	0 (0)	0 (0)
Falls (%)	3 (20)*	2 (13)	1 (2)	2 (17)	1 (8)

*Based on 15 patients, values missing for one patient.

Table 2 Mean PIGD score and proportion of patients with PIGD pattern of parkinsonism, FOG, and falls at baseline (3–6 months after surgery), at 1 year after surgery and at final visit in 2012 (long-term follow-up) for patients with STN-DBS and the same findings for patients in the control cohort at baseline and after 8-year follow-up. Also data for the matched groups are shown. Results are given as mean (SD), unless stated otherwise

	STN-DBS operated ($n = 16$)	Eligible for surgery from reference population ($n = 62$)	STN-DBS operated matched ($n = 12$)	Reference population, matched ($n = 12$)
Baseline visit				
LEDD, mg	740 (380)	520 (250)	740 (290)	720 (220)
Tremor score	2.6 (4.1)	4.3 (3.8)	2.3 (3.3)	2.7 (4.5)
Bradykinesia score	8.7 (4.5)	8.5 (5.6)	8.0 (4.3)	7.3 (4.4)
Rigidity score	3.1 (2.6)	2.2 (1.8)	2.5 (2.4)	2.4 (1.9)
PIGD score	2.5 (2.0)	2.6 (2.2)	2.8 (2.3)	2.3 (1.9)
PIGD type (%)	12 (75)	28 (45)	9 (75)	8 (67)
FOG (%)	0 (0)	3 (5)	0 (0)	0 (0)
Falls (%)	2 (13)	1 (2)	2 (17)	1 (8)
1-Year visit				
LEDD, mg	840 (470)		830 (250)	
Tremor score	1.6 (2.3)		1.8 (2.6)	
Bradykinesia score	10 (5.1)		9.7 (4.7)	
Rigidity score	4.3 (3.9)		3.6 (2.9)	
PIGD score	4.2 (2.3)		4.3 (2.5)	
PIGD type (%)	14 (88)		10 (83)	
FOG (%)	0 (0)		0 (0)	
Falls (%)	2 (13)		1 (8)	
Long-term follow-up				
LEDD (mg)	910 (320)	700 (430)	870 (330)	1010 (320)
Tremor score	0.7 (1.3)	6.1 (5.3)	0.6 (1.0)	4.4 (3.9)
Bradykinesia score	19 (5.6)	20 (9.2)	19 (5.5)	15 (6.0)
Rigidity score	3.4 (4.4)	5.8 (4.5)	2.5 (3.7)	3.7 (3.7)
PIGD score	9.7 (5.1)	9.4 (5.5)	10 (5.3)	7.4 (3.4)
PIGD type (%)	16 (100)	52 (84)	12 (100)	10 (83)
FOG (%)	9 (56)	31 (50)	7 (58)	7 (58)
Falls (%)	8 (50)	31 (50)	6 (50)	5 (42)

surgery), at 1 year after surgery and at final visit in 2012 for patients with STN-DBS and the same findings for patients in the control cohort at baseline and after 8-year follow-up. The table also shows the findings in the individually matched cohorts. Among the operated patients, the mean PIGD sum score increased from 2.5 at baseline to 4.2 after 1 year and after 6–9 years to 9.7 (Table 2). At baseline 75% had dominating PIGD, but at final visit all patients had developed this disease pattern. No patients had FOG, and two were fallers at baseline. This was unchanged after 1 year while about 50% of the patients had these manifestations at final visit. The development of PIGD score, and proportion with PIGD dominance were nearly identical in

the historical control group, both seen as a whole group and in the individually matched cohorts.

Table 3 shows the mean annual change in mean score per item of PIGD, tremor, bradykinesia and rigidity in the study period. The mean annual change of PIGD was 0.19 for patients with STN-DBS. The development for the reference population of patients with PD was similar. For tremor and rigidity, there was a small mean annual reduction in scores among the operated patients and a significantly different increase in the control group. Bradykinesia increased at a similar rate in both groups over time.

Discussion

This study shows that STN-DBS induces an acute improvement of PIGD symptoms as measured 3–6 months after surgery. The further disease development is, however, characterized by a marked long-term deterioration of these symptoms. Six to nine years after surgery, all patients had a dominating PIGD pattern of parkinsonism. In addition, 50% of the patients had developed FOG and had become recurrent fallers. For reference, we also examined the disease development in a group of patients from the presurgery period and found that the progression of these dominating non-dopaminergic symptoms had a similar trajectory as among the operated patients with PD. In addition, mean annual change of both bradykinesia and PIGD scores was nearly identical in both study groups during long-term follow-up, while tremor and rigidity had a significant better development in the operated patients. Our findings indicate that STN-DBS improves PIGD symptoms initially, but the further development of these symptoms and FOG and falls seems not to be influenced by persistent stimulation.

Deep brain stimulation of the subthalamic nucleus has ever since its advent delivered impressive results on motor symptoms in PD, improving the level of functioning and quality of life in severely disabled patients with PD. But from reports (12) on long-term follow-up after STN-DBS, it has been increasingly clear that this therapy, although very successful in reducing severe PD symptoms, has its limitations on non-dopaminergic aspects of PD. Our study has investigated one possible shortcoming of STN-DBS – its potential lack of effect on motor symptoms not primarily related to the dopaminergic system. It has been postulated that PD is a disease with several clinical subtypes with variable expressions (20), and thus maybe with different response to STN-DBS. Disability also varies due to the clinical pattern of PD, with the PIGD subtype causing more disability than, for example, tremor dominant PD (20).

Our findings both confirm and extend on the results from a recent meta-analysis of these issues (12). This analysis included 11 studies with UPDRS scores before and beyond 3 years post-surgery (mean 4.5 years). Random effects meta-regression revealed that DBS initially improved PIGD compared to before surgery, but performance progressively declined over time and PIGD was worse than presurgery function within 2 years for patients with STN-DBS. These findings are in line with our results. We found that the PIGD sum score decreased from 3.9 to 2.5 after surgery, but with an increase to 4.2 after 1 year and 9.7 after 6–9 years post-surgery, and the frequency of FOG and falls during long-term follow-up was markedly increased. Furthermore, we have examined the development of PIGD, FOG, and falls in a reference population from the presurgery era and observed a similar rate of progression of these primarily non-dopaminergic symptoms as among the patients with STN-DBS. Taken together, our results and previous studies support an acute effect on PIGD symptoms by STN-DBS but with a marked deterioration of these symptoms and frequency of FOG and falling over time.

There has been a long-standing agreement that stereotactic procedures in the thalami have no effect on non-dopaminergic motor symptoms (25). In contrast, it remains uncertain whether DBS in the STN or GPi truly influence these

Table 3 Mean annual change in mean PIGD, tremor, bradykinesia, and rigidity scores, as measured by the UPDRS

	STN-DBS operated ($n = 16$) Mean 95% CI	Eligible for surgery from reference population ($n = 62$) Mean 95% CI	P*	STN-DBS operated, matched ($n = 12$) Mean 95% CI	Reference population, matched ($n = 12$) Mean 95% CI	P*
PIGD mean score (range 0–4)	0.19 (0.13–0.24)	0.17 (0.14–0.20)	0.639	0.19 (0.12–0.26)	0.13 (0.09–0.17)	0.095
Tremor mean score (range 0–4)	−0.03 (−0.07 to −0.01)	0.03 (0.01–0.42)	0.002	−0.03 (−0.07 to 0.01)	0.02 (−0.03 to 0.08)	0.087
Bradykinesia mean score (range 0–4)	0.14 (0.10–0.19)	0.16 (0.14–0.19)	0.496	0.15 (0.09–0.21)	0.11 (0.06–0.15)	0.204
Rigidity mean score (range 0–4)	−0.00 (−0.06 to 0.05)	0.09 (0.06–0.12)	0.002	−0.01 (−0.05 to 0.04)	0.03 (−0.02 to 0.09)	0.280

*From independent samples t-tests.

symptoms, even though previous studies provide some support (12, 26, 27). The results are far from clear, with the best indications as to some effect on non-dopaminergic motor symptoms related to GPi-DBS in combination with levodopa (12). In this study, we found a rather substantial improvement during the first months after STN-DBS on PIGD score. The observed initial improvement of presumed non-dopaminergic motor symptoms after surgery could have different explanations. It could be caused by effects of STN-DBS outside the dopaminergic system, or the fact that the actual PIGD score (which includes items like walking and gait) may be influenced by increased dopaminergic stimulation and accompanying improvement of general motor function. In addition, a placebo effect related to being treated with surgery might have been responsible for this initial improvement. The results from this study seem not to contribute to the discussions on STN-DBS as a pure dopaminergic treatment or PIGD as pure non-dopaminergic symptoms.

When counseling and advising patients prior to DBS surgery, it is important to inform the patients about benefits as well as limitations of surgical treatment. STN-DBS has proven to be a successful therapy for dopaminergic motor symptoms in PD, but non-dopaminergic features of PD can be just as, or even more so, disabling and detrimental to the patient's and the caretaker's quality of life. Our study adds to the evidence that STN-DBS does not prevent, nor alleviates, the long-term development of non-dopaminergic motor symptoms in PD. This should be taken into the total consideration, and may affect the indication for surgery – especially if a patient already has noticeable non-dopaminergic motor symptoms, or such symptoms contributes significantly to the patients total burden of disease. In addition, in the meta-analysis (12) discussed above it was shown that DBS-GPi in combination with levodopa seemed to preserve PIGD better than DBS-STN during long-term follow-up, although more studies of DBS-GPi and randomized controls were considered necessary.

The study design applied in this study has several important shortcomings. The rather low number of patients and the lack of a blinded and randomized control group could have given a biased picture of disease development both in the short- and long-term perspective. In particular, the comparison of the matched groups was made based on small samples. The small sample size makes it more difficult to demonstrate any differences between the two groups by statistical analysis. Another weakness of this study is that to include patients with data from long time follow-up, only patients still alive at the end of the 6–9 year observation period have been included, as opposed to patients who died during follow-up. Also, the introduction of new treatment possibilities over the intervening decade between the recruitment of the two study groups could affect disease progression and the drug treatment administered to the patients. This could affect the calculated LEDD (17) for the patients of the two groups, but should not affect the observations of changes in LEDD for the individual patient.

Still, our findings seem in line with previous studies on important outcomes like the scores on cardinal signs of PD. We have also made an attempt to include comparative information on how the expected disease development would be in a group of patients without surgery and especially the patients in the individually matched reference group would most probably have been offered surgery if that had been an option at the time. We therefore believe that the results must be regarded as fairly robust despite these shortcomings.

In conclusion, we have found that patients with STN-DBS have acute beneficial effects on PIGD symptoms, but continue to progress thereafter at a similar rate as the general PD population. This information is important when informing patients and may also have consequences for the choice of surgical targets in the individual patients. Still, there is a need for more information on the impact of surgery on PIGD, FOG, and falls by alternative targets.

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Conflict of interests

Bård Lilleeng MD, Michaela Gjerstad MD PhD, Roald Baardsen MD, Ingvild Dalen PhD and Jan Petter Larsen MD, PhD have no potential conflict of interest related to the research covered in the article submitted and has received no funding from external sources.

Authors' roles

Bård Lilleeng, MD: Research project: Conception, Organization, Execution; Statistical Analysis: Design, Review and Critique; Manuscript: Writing of the first draft, Review and Critique. Michaela Gjerstad, MD PhD: Research project: Conception, Organization, Execution; Statistical Analysis: Review and Critique; Manuscript: Review and Critique.

Roald Baardsen, MD: Research project: Conception, Execution; Statistical Analysis: Review and Critique; Manuscript: Review and Critique. Ingvild Dalen, PhD: Statistical Analysis: Design, Execution, Review and Critique; Manuscript: Review and Critique. Jan Petter Larsen, MD, PhD: Research project: Conception, Organization; Statistical Analysis: Review and Critique; Manuscript: Review and Critique.

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The long-term development of non-motor problems after STN-DBS

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Objectives – Stimulation of the subthalamic nucleus (STN-DBS) is an established treatment with long-term beneficial effects on motor symptoms in patients with Parkinson's disease (PD). The long-term development of non-motor problems after STN-DBS is not fully understood. In this study, we have studied how non-motor problems develop in patients with and without STN-DBS. *Materials and methods* – We collected data from a prospectively followed cohort of patients that had been operated with STN-DBS 6–9 years before final examination and compared our findings to the longitudinal development of non-motor problems in a non-operated, comparable reference population. *Results* – In general, the non-motor problems of advanced PD seem to develop independently of treatment with STN-DBS. We found that depressions do not worsen after STN-DBS, and the Montgomery and Aasberg Depression Rating Scale score in operated patients was substantially reduced from pre-operatively to post-operatively. Further, fatigue may represent an important unrecognized side effect of long-term stimulation, as fatigue was found to increase rapidly in operated patients already a year after surgery and continued to increase trough the 6- to 9-year follow-up. *Conclusions* – The non-motor problems of advanced PD seem to develop independently of treatment with STN-DBS. This may influence the strategy for choice of when to perform this therapy for eligible patients.

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Key words: Parkinson's disease; deep brain stimulator; movement disorders; non-motor problems; fatigue; sleep disorders; depression; dementia

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Introduction

Deep brain stimulation of the subthalamic nuclei (STN-DBS) is an effective treatment option in patients with advanced Parkinson's disease (PD) (1). Data from recent long-term studies indicate a persistent effect of stimulation on the cardinal motor symptoms of the disease (1–3). However, the disability of the PD patients deteriorates over time, and this seems caused by both an increase in severity of parkinsonism and the progression of non-motor problems (4–7).

The non-motor symptoms progressing and incapacitating the patients include cognitive impairment, neuropsychiatric symptoms, sleep problems, and autonomic symptoms. The symptoms are thought to primarily develop as the pathology of PD involves non-dopaminergic structures in the brain, and disease progression should be anticipated to develop independently from the STN-DBS procedure. In addition, the implantation of the stimulation electrode itself could potentially have short- or long-term effects on cerebral systems that may impact these non-motor functions both beneficially and negatively.

Cognitive impairment and dementia are major contributing factors for decreased functioning in patients with late-stage PD (4, 5). In a study that followed 14 patients with STN-DBS for more than 9 years, it was found that four of them developed dementia (8), and in another study, one of 20 patients became demented (9). In general, the risk for developing dementia is up to six-fold higher in PD than in non-PD subjects and about 10% of patients with PD develop dementia per year (10, 11). The incidence of dementia increases with age (12), and as patients with STN-DBS usually are younger than the general

PD population, several aspects of the relationship between STN-DBS and dementia need further exploration.

In addition, a number of other non-motor problems are likely to develop in patients with STN-DBS. We have therefore, in this study, prospectively examined the development of dementia and several other important non-motor problems during long-term follow-up of patients with STN-DBS and compared these findings with the longitudinal development of such problems in a non-operated historical reference population.

Material and methods

Study design

In this study, we have examined prospectively, until 2012, the development of cognitive impairment and dementia, sleep problems, apathy, depression, fatigue, and hallucinations over time in a group of patients with PD who received STN-DBS surgery at Stavanger University Hospital between July 1, 2003 and June 30, 2006. We have studied these symptoms prospectively both before and after surgery and during long-term follow-up. The patients were examined before surgery, 3–6 months and 1 year after surgery, and at the final follow-up visit 6–9 years after implantation. In addition, we have compared the observed progression of non-motor symptoms with that of a historical reference population of patients with PD. The reference population was made up by patients eligible for STN-DBS from a prevalence study (13), in which the patients were followed prospectively from 1993 to 2001, that is, in the time period before STN-DBS became a routine treatment option. The operated patients and the reference population were two independent cohorts from two consecutive decades, but both cohorts had prospective follow-up and largely overlapping examination programs at study visits. The Regional Committee for Medical and Health Research Ethics in Western Norway approved the study.

Patients

Twenty-eight patients with PD received STN-DBS implants during the inclusion period. In 2012, at follow-up, 16 patients were still alive and had sufficient clinical data to be included in this study. Five patients had died, and three did not agree to participate in the follow-up. In four patients, the device was not functioning, and for these four patients, no follow-up data were available.

The inclusion criteria for surgery in this study were a clinical diagnosis of PD, dyskinesias unresponsive to medical treatment, and on/off complications. Exclusion criteria were dementia or major psychiatric illness in the patient's history, marked cerebral atrophy on MRI, age > 75 years, or other common contraindications to surgery.

The DBS surgery was conducted according to the procedure used by the National Hospital in Oslo, Norway, as previously published (2). Trajectories were planned with the target in the dorsolateral, motoric part of the STN bilaterally.

In addition to the patients with STN-DBS, we established a reference population of patients that was derived from a prevalence study of PD in the Stavanger area of Western Norway on January 1, 1993. The crude prevalence rate was 110.9 per 100,000 inhabitants (245 patients). Patients were recruited through a search in the patient records at the hospital covering the region, with letters to all general practitioners in the study area and through cooperation with the local Parkinson Association. The prevalence study and the recruitment of the population have been described in detail previously (13). All patients were diagnosed by a neurologist of the study group, according to published diagnostic criteria (14). Among the 245 patients from this cohort, seven were rediagnosed as not having PD during follow-up, three patients died between prevalence day and baseline examination, two patients refused to participate, and one could not be evaluated due to severe dementia. During the first 4 years of follow-up, 81 had died, one person had moved abroad, and six patients refused to participate in the examinations in 1997. Between 1997 and 2001, further 55 patients had died, and thus, 89 patients completed the 8-year follow-up and were eligible for evaluation in this study.

Among these 89, we first excluded patients according to the same exclusion criteria as used for patients evaluated for surgery. This was age above 75 years, dementia, or major psychiatric illness. After application of the exclusion criteria, 62 patients remained eligible for the study and could thus in principle have been candidates for surgery. Patients in the reference group were prospectively followed up with new examinations 4 and 8 years after baseline (15, 16). In addition, we did an individual matching of patients in the two groups based on several factors at baseline of the studies to obtain a reference cohort of patients that would have had a high probability to be candidates for surgery if this had been an option at the time. The statistical approach and

factors included in this matching are described in the Statistics section. This final individual matching resulted in two groups of 12 patients that could be compared for development of non-motor symptoms (Table 3).

Examination program

The examination performed at each study visit included a semistructured interview on disease history, drug treatment [the levodopa-equivalent levodopa dose (LEDD)] was calculated in mg (17), the Unified Parkinson Disease Rating Scale (UPDRS) (18), and Hoehn and Yahr stage (19).

Cognitive functions were tested using Mini-Mental State Examination (MMSE) (20), and dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, DSM-III-R (21).

Hypersomnia was examined with the Epworth Sleepiness Scale (ESS) (22). In addition, information on excessive daytime sleepiness (EDS), insomnia, and proportion of patients with at least moderately difficulties during the night were available at study end for both operated patients and patients with PD in the reference population. EDS was diagnosed in patients falling asleep at least three times or who were sleeping 2 h or more during daytime.

Apathy was assessed with the 14-item Starkstein Apathy Scale (SAS) (23). SAS scores were not available at baseline in the reference population. In addition, the percentage of patients and controls with apathy were defined with a score of 2 or more on the motivation/initiative item (item 4) of the UPDRS.

Depression was measured with the Montgomery and Aasberg Depression Rating Scale (MADRS) (24), and we present mean scores and proportion of patients with MADRS score above 14 as a suggested cutoff to define a valid measure of major depression (25).

Fatigue was assessed with the Fatigue Severity Scale (FSS) (26), and we calculated both the mean group FSS scores and the percentage of patients with a FSS score ≥ 4 as a measure of having clinical fatigue.

Information on the presence of hallucinations was derived from the UPDRS-I subscore, item 2 (thought disorder). Patients with a score of 2 or more were defined as having hallucinations.

Statistics

All statistical analysis was performed in SPSS version 20, IBM Corporation Armonk, New York, United States. Descriptive statistics for continuous data are presented as means and standard deviations (SDs) and for categorical data as counts and percentages. Proportions were compared between time points within groups using McNemar's test and between groups using the chi-squared test.

The STN-operated patients were, based on their 3–6 months post-operative scores, individually matched to comparable controls by means of propensity scores matching (27, 28). Based on the gender, being over 67 years of age (yes/no), LEDD, mean UPDRS tremor scores, mean UPDRS PIGD scores, PIGD type (yes/no), total UPDRS motor score, and total UPDRS ADL score, each patient's probability or propensity of being STN operated was estimated and used for matching. Due to non-overlapping propensity score distributions (29), the four of the operated with highest propensity scores were discarded, thus giving matched groups of 12 to be compared. Further details regarding the matching process have been previously published (30).

Results

Tables 1 and 2 show the demographic and clinical features of patients with ($n = 16$) and without ($n = 62$) STN-DBS. Data from the operated patients are shown before and 3–6 months, 1 year, and 6–9 years after surgery. Data from the reference population are presented at baseline and at 8-year follow-up. Data for the two individually matched groups ($n = 12$ in both groups) are shown in Table 3.

Among the 16 patients included in the study, five (31%) patients had developed dementia at last visit 6–9 years after surgery according to the DSM-III-R criteria. All five developed dementia between 1 year after surgery and final visit. Among patients in the reference population, 46% had developed dementia. The MMSE scores changed from 28.4 at 3–6 months after surgery to 23.4 at final visit in the STN-DBS group and from 28.3 to 22.6 in the reference population (Tables 1 and 2). In the individually matched groups, the results were comparable (Table 3)

Hypersomnia was not a major problem among the operated patients as measured with ESS, although slowly increasing with age as expected. There was also a similar frequency of EDS and insomnia among the STN-DBS patients as in the reference population. Comparable findings were present for apathy (Tables 1–3).

Mean MADRS score was 9.1 before and 4.1 at 3–6 months after operation. Major depression

Table 1 Demographic and clinical data for PD patients with and without STN-DBS. Data are shown before and 3–6 months after surgery for the operated patients ($n = 16$) and at baseline for the non-operated patients, that is, the reference population ($n = 62$). Furthermore, data are given for individually matched subgroups of the two patients groups ($n = 12$). The results are given as means (SDs) unless otherwise stated. For scores with missing observations, the numbers of available observations are indicated

	STN-DBS operated, pre-operatively ($n = 16$)	STN-DBS operated, post-surgery ($n = 16$)	STN-DBS operated, matched, post-surgery ($n = 12$)	Reference group, baseline ($n = 62$)	Reference group, matched, baseline ($n = 12$)
Age (years)	60 (8.1)	60 (8.4)	61 (8.0)	66 (6.7)	61 (8.3)
Female gender, no. (%)	10 (63%)	10 (63%)	8 (67%)	33 (53%)	8 (67%)
Disease duration (years)	12.9 (5.7) ($n = 14$)	13.3 (5.6) ($n = 15$)	12.5 (5.1) ($n = 11$)	7.7 (4.9)	10.6 (4.9)
LEDD (mg)	960 (220)	740 (380)	740 (290)	520 (250)	720 (220)
UPDRS-II total	11 (10) ($n = 15$)	7.2 (5.1)	7.8 (5.0)	8.7 (4.5)	7.3 (4.0)
UPDRS-III total	27 (13)	18 (7.5)	16.8 (6.4)	18 (10)	15.8 (8.4)
Hoehn and Yahr stage	2.5 (0.6) ($n = 15$)	2.1 (0.6) ($n = 15$)	2.1 (0.7) ($n = 11$)	2.2 (0.8)	2.0 (0.7)
MMSE	29.1 (1.6) ($n = 15$)	28.4 (3.0) ($n = 15$)	28.2 (3.3)	28.3 (1.8)	28.7 (2.1)
Dementia, no. (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ESS	6.5 (4.3) ($n = 12$)	6.3 (4.3) ($n = 13$)	6.8 (4.8) ($n = 10$)	NA	NA
EDS, no. (%)	NA	NA	NA	2 (3%)	0 (0%)
Difficult night, no. (%)	NA	NA	NA	10 (16%)	1 (8%)
Insomnia, no. (%)	NA	NA	NA	37 (60%)	9 (75%)
Apathy scale	14.7 (4.1) ($n = 12$)	16.9 (5.2) ($n = 14$)	18.0 (4.7) ($n = 11$)	NA	NA
Item 4 UPDRS-I	0.9 (1.3)	0.3 (0.5)	0.3 (0.5)	0.8 (0.8)	0.7 (0.9)
Item 4 UPDRS-I ≥ 2, no. (%)	3 (19%)	0 (0%)	0 (0%)	13 (21%)	3 (25%)
MADRS	9.1 (9.1) ($n = 10$)	4.1 (3.0) ($n = 14$)	4.4 (3.1) ($n = 11$)	5.6 (4.2)	5.4 (3.7)
MADRS ≥ 15, no. (%)	2 (20%) ($n = 10$)	0 (0%) ($n = 14$)	0 (0%) ($n = 11$)	3 (5%)	0 (0%)
FSS mean	4.1 (1.7) ($n = 11$)	3.7 (1.7) ($n = 14$)	4.1 (1.7) ($n = 11$)	NA	NA
FSS ≥ 4, no. (%)	5 (46%) ($n = 11$)	5 (36%) ($n = 14$)	5 (42%) ($n = 11$)	NA	NA
Item 2 UPDRS-I	0.69 (0.87)	0.7 (0.9)	0.1 (0.3)	0.42 (0.69)	0.3 (0.5)
Item 2 UPDRS-I ≥ 2, no. (%)	4 (25%)	3 (25%)	0 (0%)	3 (5%)	0 (0%)

STN-DBS, deep brain stimulation of the subthalamic nuclei; LEDD, levodopa-equivalent levodopa dose; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; MADRS, Montgomery and Aasberg Depression Rating Scale; FSS, Fatigue Severity Scale.

was found in two before and none patients 3–6 months after implantation (Table 1). During follow-up, the severity of depressive symptoms was rather stable and comparable to the observations in the reference group (Tables 2 and 3).

Fatigue before surgery and after surgery was unchanged as measured with mean FSS score and proportion of patients with a score of 4 or more on this scale (Table 1). Surprisingly, these measures showed a clear deterioration during follow-up (last visit vs 3–6 months after surgery ($P = 0.008$), and as compared to the reference patients at final visit ($P = 0.025$). At the final visit, 87% of the patients with STN-DBS had a mean FSS score of 4 or above. Only 55% of the patients from the reference population had clinical fatigue after 8 years of follow-up (Table 2). In the matched groups, the percentage of operated patients with FSS of 4 or above also increased notably from 45% at baseline, to 75% after a year and peaked at 91% at the final visit. The percentage of patients in the matched non-operated group with FSS at or above 4 upon the final visit was 67%. Thus, the comparison of the matched groups also demonstrated a difference in the frequency of fatigue at the final visit.

Four of the patients with STN-DBS reported hallucinations before surgery but none 3–6 months after (Table 1). During follow-up, 50% of the patients in the surgery group had hallucinations as compared to 37% in the reference population (Table 2). After the matching, this difference disappeared, with 50% of the patients experiencing hallucinations in both groups at the final visit.

Discussion

This study shows that PD patients with STN-DBS have a rather stable long-term motor function, but a substantial proportion of them develop dementia and cognitive impairment during follow-up. Further, we have in this study examined the short- and long-term progression of several non-motor problems among operated patients and found that these problems develop in general as in non-operated patients with PD. Fatigue was, however, found to increase over time more than expected and depressive symptoms were markedly improved by initiation of STN-DBS. Our results underscore that the surgical procedure is a treatment of motor symptoms

Table 2 Long-term development of non-motor symptoms for PD patients with and without STN-DBS. Data are collected 3–6 months, 1–1.5 years, and 6–9 years after surgery for the operated patients ($n = 16$), and at baseline and after 8 years for the non-operated patients ($n = 62$). The results are given as means (SDs) unless otherwise stated. For scores with missing observations, the numbers of available observations are indicated

	STN-DBS operated, 3–6 months post-surgery ($n = 16$)	STN-DBS operated, 1–1.5 years after surgery ($n = 16$)	STN-DBS operated, 6–9 years after surgery ($n = 16$)	Reference population, baseline ($n = 62$)	Reference population, 8 years after baseline ($n = 62$)
LEDD (mg)	740 (380)	810 (510)	910 (320)	520 (250)	700 (430)
UPDRS-II total	7.2 (5.1)	9.6 (5.4)	20 (7.3)	8.7 (4.5)	23 (10)
UPDRS-III total	18 (7.5)	22 (10)	33 (12)	18 (10)	43 (20)
Hoehn and Yahr stage	2.1 (0.6) ($n = 15$)	2.1 (0.5) ($n = 14$)	3.2 (0.9)	2.2 (0.8)	3.2 (1.0)
MMSE	28.4 (3.0) ($n = 15$)	28.4 (2.7) ($n = 14$)	23.4 (8.0)	28.3 (1.8)	22.6 (8.0) ($n = 58$)
Dementia, no. (%)	0 (0%)	0 (0%)	5 (31%)	0 (0%)	28 (45%)
ESS	6.3 (4.3) ($n = 13$)	7.5 (3.7) ($n = 11$)	10.1 (7.0)	NA	9.6 (6.6)
EDS, no. (%)	NA	NA	2 (13%) ($n = 15$)	2 (3%)	26 (42%)
Difficult night, no. (%)	NA	NA	2 (13%) ($n = 15$)	10 (16%)	10 (16%)
Insomnia, no. (%)	NA	NA	5 (33%) ($n = 15$)	37 (60%)	32 (52%)
Apathy scale	16.9 (5.2) ($n = 14$)	16.3 (5.9) ($n = 13$)	19.3 (4.4) ($n = 15$)	NA	15.1 (3.3) ($n = 47$)
Item 4 UPDRS-I	0.3 (0.5)	0.8 (0.9)	1.5 (1.2)	0.8 (0.8)	1.4 (1.1)
Item 4 UPDRS-I ≥ 2, no. (%)	0 (0%)	3 (19%)	7 (44%)	13 (21%)	25 (40%)
MADRS	4.1 (3.0) ($n = 14$)	6.8 (5.5) ($n = 15$)	5.0 (6.0)	5.6 (4.2)	7.4 (6.2) ($n = 42$)
MADRS ≥ 15, no. (%)	0 (0%) ($n = 14$)	2 (13%) ($n = 15$)	1 (6%)	3 (5%)	6 (14%) ($n = 42$)
FSS mean	3.7 (1.7) ($n = 14$)	4.6 (1.5) ($n = 15$)	5.0 (1.6) ($n = 15$)	NA	4.4 (1.8) ($n = 58$)
FSS ≥ 4, no. (%)	5 (36%) ($n = 14$)	10 (67%) ($n = 15$)	13 (87%) ($n = 15$)	NA	32 (55%) ($n = 58$)
Item 2 UPDRS-I	0.19 (0.40)	0.50 (0.73)	1.4 (1.2)	0.42 (0.69)	1.2 (1.1)
Item 2 UPDRS-I ≥ 2, no. (%)	0 (0%)	2 (13%)	8 (50%)	3 (5%)	23 (37%)

STN-DBS, deep brain stimulation of the subthalamic nuclei; LEDD, levodopa-equivalent levodopa dose; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; MADRS, Montgomery and Aasberg Depression Rating Scale; FSS, Fatigue Severity Scale.

and that the non-motor problems will cause important impairments as the disease develops also for these patients. These findings may indicate that optimal benefits from STN-DBS are achieved when treating younger patients and by starting earlier when motor problems dominate.

Patients with PD may experience a multitude of different non-motor symptoms as the disease progresses (4, 5). This study has examined the development of several important such symptoms among patients with STN-DBS in both short- and long-term follow-up. In accordance with previous reports (10, 11, 16, 31), we found that five of 16 patients became demented 6–9 years after surgery and with a mean MMSE score of 23.4 at last study visit. The development of cognitive impairment in the reference population from the presurgery era showed similar or even stronger deterioration. These patients were, however, 6 years older at baseline. The development of cognitive impairment that has an important influence on the life of patient and caregiver and health costs seems not improved by this surgical procedure.

Sleep problems that include insomnia, hypersomnia, and sleep-related symptoms are important complaints in especially late-stage PD (4, 5). The patients in this study also developed these symptoms. Apathy and hallucinations developed to a similar extent both in patients with STN-DBS and patients from the reference population.

Depression has been reported as an acute and even chronic side effect of STN-DBS (1, 32–34). In this study, we observed a marked improvement in depressive symptoms with a mean MADRS score of 9.1 before and 4.1 after surgery. The MADRS score was varying and similar during follow-up among both the STN-DBS and the reference patients. These findings indicate that previous warnings related to depression and even suicide were primarily based on observations in the early, establishing phase of STN-DBS therapy.

Fatigue is an under-recognized symptom in patients with PD. Previous studies have, however, shown that in community-based cross-sectional populations about 40% of patients with PD have significant fatigue (35), and one-third of the patients report fatigue to be the symptom most likely to limit their daily life activities (35). In this study, we found surprisingly that 87% of the patients with STN-DBS had fatigue at final visit compared to 55% in the reference population, and already 1 year after surgery, 67% had a FSS score at ≥ 4. The difference was seen also after matching, with the percentages of patients with a FSS score ≥ 4 at 91% and 67% at the final visit in the operated and non-operated groups, respec-

Table 3 Long-term development of non-motor symptoms for PD patients with STN-DBS and for individually matched PD patients without STN-DBS. Data are collected 3–6 months, 1–1.5 years, and 6–9 years after surgery for the operated patients ($n = 12$), and at baseline and after 8 years for the non-operated patients ($n = 12$). The results are given as means (SDs) unless otherwise stated. For scores with missing observations, the numbers of available observations are indicated

	STN-DBS operated, 3–6 months post-surgery ($n = 12$)	STN-DBS operated, 1–1.5 years after surgery ($n = 12$)	STN-DBS operated, 6–9 years after surgery ($n = 12$)	Reference population, baseline ($n = 12$)	Reference population, 8 years after baseline ($n = 12$)
LEDD (mg)	740 (290)	830 (250)	870 (330)	720 (220)	1000 (320)
UPDRS-II total	7.8 (5.0)	9.8 (5.3)	20.6 (7.8)	7.3 (4.0)	20.5 (5.9)
UPDRS-III total	16.8 (6.4)	20.4 (9.0)	32.8 (11.1)	15.8 (8.4)	30.3 (11.7)
Hoehn and Yahr stage	2.1 (0.7) ($n = 11$)	2.2 (0.4) ($n = 10$)	3.3 (0.9)	2.0 (0.7)	2.8 (0.4)
MMSE	28.2 (3.3)	28.4 (2.8)	23.3 (8.9)	28.7 (2.1)	23.7 (6.4)
Dementia, no. (%)	0 (0%)	0 (0%)	4 (33%)	0 (0%)	6 (50%)
ESS	6.8 (4.8) ($n = 10$)	8.3 (3.4) ($n = 9$)	10.3 (7.3)	NA	7.3 (5.3)
EDS, no. (%)	NA	NA	2 (18%) ($n = 11$)	0 (0%)	5 (42%)
Difficult night, no. (%)	NA	NA	2 (18%) ($n = 11$)	1 (8%)	2 (17%)
Insomnia, no. (%)	NA	NA	4 (36%) ($n = 11$)	9 (75%)	5 (42%)
Apathy scale	18.0 (4.7) ($n = 11$)	17.9 (4.8) ($n = 10$)	18.5 (3.4) ($n = 11$)	NA	14.1 (2.7) ($n = 11$)
Item 4 UPDRS-I	0.3 (0.5)	0.8 (1.0)	1.6 (1.2)	0.7 (0.9)	1.1 (0.9)
Item 4 UPDRS-I ≥ 2, no. (%)	0 (0%)	2 (17%)	6 (50%)	3 (25%)	5 (42%)
MADRS	4.4 (3.1) ($n = 11$)	7.4 (5.9)	5.3 (6.9)	5.4 (3.7)	7.7 (4.8) ($n = 10$)
MADRS ≥ 15, no. (%)	0 (0%) ($n = 11$)	2 (17%)	1 (8%)	0 (0%)	2 (20%) ($n = 10$)
FSS mean	4.1 (1.7) ($n = 11$)	5.0 (1.4)	5.2 (1.3) ($n = 11$)	NA	4.6 (2.0)
FSS ≥ 4, no. (%)	5 (45%) ($n = 11$)	9 (75%)	10 (91%) ($n = 11$)	NA	8 (67%)
Item 2 UPDRS-I	0.1 (0.3)	0.5 (0.7)	1.5 (1.2)	0.3 (0.5)	1.5 (1.0)
Item 2 UPDRS-I ≥ 2, no. (%)	0 (0%)	1 (8%)	6 (50%)	0 (0%)	6 (50%)

STN-DBS, deep brain stimulation of the subthalamic nuclei; LEDD, levodopa-equivalent levodopa dose; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; MADRS, Montgomery and Aasberg Depression Rating Scale; FSS, Fatigue Severity Scale.

tively. To our knowledge, fatigue has not previously been examined in long-term follow-up of patients with STN-DBS. In a recent study, fatigue was found to be unchanged from before and till 6 months after surgery (36) in line with our findings 3–6 months after implantation. Our observation of a marked increase of fatigue over time may thus represent a new important side effect during follow-up of patients with STN-DBS that warrants further exploration.

Taken together, the results from this study show that patients with STN-DBS develop the same pattern of incapacitating non-motor symptoms as in the general PD population. This may have implications for the evaluation of which patients are the most suitable for such therapy. Higher age and duration of disease are the two most important factors that drive the appearance of non-motor problems in PD and as these problems develop in patients with advanced disease, motor problems become less important for level of functioning and quality of life. In consequence, the benefits from STN-DBS are thus highest in patients with low age at disease onset and in the earlier disease stages. The findings from this study therefore support the concept of neurostimulation at an earlier stage of PD than previously advocated. This is also being investigated in the EARLYSTIM study (37).

This study has several important shortcomings. A rather low number of patients and that we only included patients that were still alive and with a functioning STN-DBS device at the end of the 6–9 years observation period may challenge the representativeness of our findings. In addition, we did not have a blinded and randomized control group, and at some study visits, we had missing data or only data – especially for sleep problems – at the final follow-up visit. This could have given an incomplete or biased picture of disease development both in the short- and long-term perspective and with the small sample size making it more difficult to demonstrate any differences between the groups by statistical analysis. The individually matched groups of operated and non-operated patients could have increased the possibility of uncovering significant differences. We did, however, not find any further differences in the long-term development of clinical symptoms when comparing the matched groups. Furthermore, several factors besides the effects of STN-DBS like a possible placebo effect or changes in the dopamine replacement therapy could influence the outcome (38, 39). Reduction in dopamine therapy could induce improvement in non-motor side effects of the drugs or, in some cases, lead to a dopamine agonist withdrawal syndrome with worsening of non-motor problems (40).

Still, the observed results on motor function are in line with previous reports, and we have also made an attempt to include information on how the disease was expected to develop in a reference population of patients with PD without surgery. We therefore believe that the results may be important and valid despite these shortcomings. Another strength of our study is the wide range of the examined non-motor problems that also resulted in an observation of fatigue as a possible important side effect in long-term follow-up of patients with STN-DBS.

We have in this study examined the long-term development of specific non-motor symptoms after STN-DBS. In addition, it could have been important to study the development of the holistic impact of non-motor problems on the lives of patients with PD (41) that have been operated with STN-DBS. The use of instruments like the non-motor symptoms scale (42) could have added to the value of this study.

In conclusion, we have in this study found that in general the non-motor problems of advanced PD develop independently of treatment with STN-DBS. This may influence the strategy for choice of when to perform this therapy in the disease development of the individual patient. In addition, we found importantly that depression do not worsen after STN-DBS but improves mood substantially after surgery. Furthermore, fatigue may represent an important unrecognized side effect of long-term stimulation.

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Conflict of interest

Bård Lilleeng, MD, Michaela Gjerstad, MD PhD, Roald Baardsen, MD, Ingvild Dalen, PhD, and Jan Petter Larsen, MD, PhD have no potential conflict of interests related to the research covered in the article submitted.

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Authors' contributions

Bård Lilleeng, MD (corresponding author) involved in conception, organization, and execution of the research project; design and review and critique of the statistical analysis; and writing of the first draft and review and critique of the manuscript. Michaela Gjerstad, MD PhD involved in conception, organization, and execution of the research project and participated in review and critique of the statistical analysis and manuscript. Roald Baardsen, MD involved in conception and execution of the research project and participated in review and critique of the statistical analysis and manuscript. Ingvild Dalen, PhD involved in design, execution and review and critique of the statistical analysis and manuscript. Jan Petter Larsen, MD, PhD involved in conception and organization of the research project and participated in review and critique of the statistical analysis and manuscript.

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