Bilateral deep brain stimulation of subthalamic nucleus in patients with Parkinson's disease

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Ioannou, Nefeli

Dekan:	Professor Dr. I. B. Autenrieth
1. Berichterstatter:	Privatdozent Dr. S. Breit
2. Berichterstatter:	Professor Dr. C. Schwarz

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List of abbreviations

PD	Parkinson's Disease
STN	Subthalamic nucleus
GP	Globus pallidus
GPi	Internal Globus pallidus
SN	Substantia nigra
SNr	Reticular part of Substantia nigra
SNc	Compact part of Substantia nigra
BDI	Beck's Depression Inventory
MMSE	Mini-Mental State Examination
UPDRS	Unified Parkinson's Disease Rating Scale
DBS	Deep Brain Stimulation
IPG	Implanted Pulse Generator
MRI	Magnetic Resonance Imaging
CT	Computer Tomography
PET	Positron Emission Tomography

Introduction

What is Parkinson’s disease?

Parkinson's disease (PD) is a progressive and chronic neurodegenerative disorder of the central nervous system. It is the second most common neurodegenerative disease and it affects 2-3% of the population that are above the age of 65 [poewe2017]. The etiology is unknown and no cure exists up to now, but some treatment options including medication and surgery are provided as to manage the symptoms of the disease. The pathogenetic mechanism of PD implicates the malfunction and eventually apoptosis of dopamine producing cells in the Substantia Nigra (SN). This has as a result the failure of the production of the neurotransmitter dopamine, which is essentially the chemical messenger that sends information to the parts of the brain that control movement and coordination. Thus, a patient with PD has decreased dopamine levels inside the brain, hence signals or messages are delivered to the motor-responsible areas erroneously, causing various motor or non-motor disorders to the affected patients.

History of Parkinson’s disease

Evidence for treatments of PD exist since early 5000 BC in the Indian medical practice, with no evidence when the disease was first "discovered". The first detailed medical essay on PD originates in 1817, a publication entitled "An Essay on the Shaking Palsy", written by the Medical doctor James Parkinson, in London, UK [parkinson2002]. The essay shone light on the disease and established it as a recognized medical condition. The research involved the observation of 6 subjects by James Parkinson. Three of them were his patients in his own medical practice in London and the remaining three were people that he observed in the streets. The symptoms of the disorder were clearly documented in the essay, which he described as "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the

senses and intellect being uninjured". Thus, three of the four main symptoms of the disease were described: tremors, rigidity and postural instability. He even theorized that the symptoms are caused by a problem in the medulla of the brain. The intention of the essay was to encourage other people in the medical community to study this disease. But it was not until 60 years later that this essay attracted the attention it was supposed to. Neurologist Jean Martin Charcot and colleagues distinguished the disease from other neurological disorders and truly recognized the significance of the condition and named it Parkinson's disease [goedert2017].

Epidemiology of Parkinson’s disease

Epidemiological studies [tysnes2017] have as measures the incidence and the prevalence of PD. PD is the second most common neurodegenerative disorder, after Alzheimer's disease. It is estimated that 1 million patients in the USA are affected by the disease . World wide estimates vary from 15 patients in every 100000 people in China to 657 in 100000 in Argentina. This number is expected to increase threefold in the next 50 years, as the lifetime of the population increases [tysnes2017].

The incidence describes the new cases of PD in a given time period. The measurement of incidence is very difficult as many patients may have had the disease but the symptoms have manifested clinically very slowly. The numbers vary from 1.5 in 100000 in China to 20 in 100000 in US.

Age is the most important factor affecting the onset of the disease. The incidence increases with age, however, the onset of the disease can appear at any age. The median age of onset is at 62.4 years for idiopathic PD and the cases for an onset before the age of 40 is 10 %, with onset before the age of 30 being very rare. Prevalence also increases with age. In the range of 50 - 90 years the prevalence is strongly increased. It affects 0.3 % of general population of US and 3 % people older than 65 [tysnes2017].

The disease is present worldwide, in all populations and is found to be more common in populations in Europe and North America (100-350 in 100000). It is assumed to be more prevalent in the Caucasian race. It is generally one-fifth or one-tenth common in

African-American or Asian populations. Recent studies have come to the conclusion that environmental factors are more important than racial ones, as it was found that the prevalence was the same in African-American populations and White populations living in the same geographical area [tysnes2017].

Etiology of Parkinson's disease

The combination of both environmental and genetic factors is considered to be strongly linked with the development of PD, however there cause is still unknown. There are many hypotheses surrounding the topic: free radicals, accelerated aging, environmental toxins and genetic predisposition are some probable pathogenetic factors. The single biggest risk factor of PD is advancing age, with men having a slightly elevated risk than women. Family history also plays an important role, since people with an affected first-degree relative have a double risk for developing the disease. Caffeine consumption and cigarette smoking are reported to present a reduced risk of developing PD, but they are not recommended as strategies to avoid PD, and also the negative impact of smoking in general health is enormous compared to the slight possible reduction in risk of developing PD [tysnes2017].

Physical trauma, exposure to chemicals and infections, as well as nutrition are factors that are believed to affect the developing of PD. Consistent findings show that rural living, agricultural work and exposure to well water increase the risk to develop PD. Hence, pesticides and herbicides may contribute to the disease [tysnes2017]. Environmental toxins, such as MPTP can cause the same symptoms to animal models as PD.

Studies in 2005 [klein2012, brice2005] found that a single mutation in the gene LRRK2 represents an important fraction of PD. Further studies are being conducted to discover the relation between genes and PD. A very recent study, released in the beginning of 2009 [gitler2009] found a connection between genetic and environmental causes of PD. A genetic interaction was found between two Parkinson's disease genes, namely the alpha-synclein and PARK9. Through their research, they determined that the PARK9

protein can protect cells from manganese poisoning, that is a significant environmental risk factor for developing PD. It is prevalent in occupations such as mining, welding and steel manufacturing. Excessive exposure to manganese causes the manganese to attack the nervous system producing motor symptoms. The alpha-synuclein protein that is normally found in brain is then forced to misfold and form clumps.

Pathophysiology of Parkinson's disease

The neurophysiologic cause, in accordance to the main neuropathologic findings, in PD is the failure of the responsible cells in the brain to produce the substance dopamine. The production of dopamine occurs prominently by the dopaminergic neurons in the midbrain, more specifically in SN. SN belongs to a group of brain structures, namely the basal ganglia that is innervated by the dopaminergic system and is considered to be the main location inside the brain that is affected by the disease.

Physiology

Basal Ganglia (Figure 1) is a group of nuclei that are present in the brains of vertebrates. The main components are the SN, subthalamic nucleus (STN), globus pallidus (Gi) and striatum (which consists of the caudate nucleus and putamen). The basal ganglia are responsible for a variety of functions, such as motor control and learning. Experimental studies show that they exert an inhibitory influence on a number of motor systems [purves2012]. The release of this inhibition gives rise to the activation of the corresponding motor system.

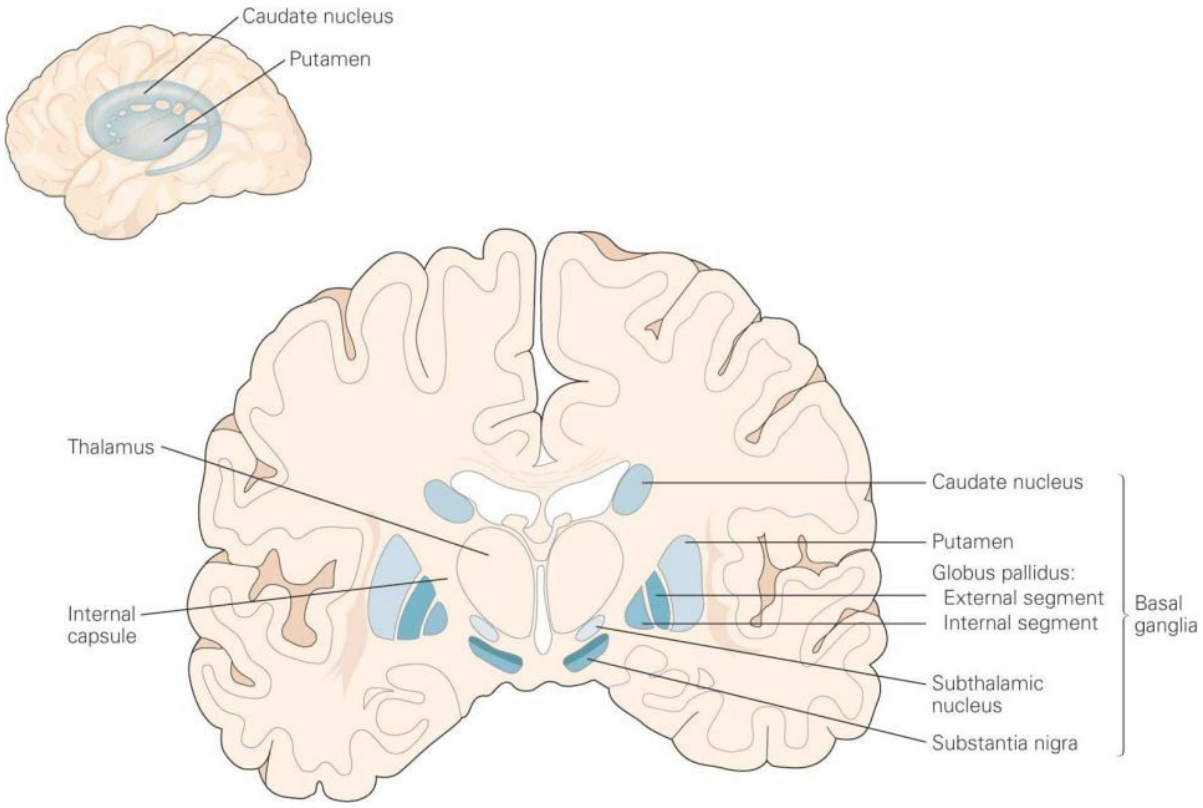


Figure 1. The human brain as viewed from the side, showing the position of the basal ganglia [nieuwenhuys1981].

Figure 1 shows the flow of the neural signals within the basal ganglia. The striatum is the largest component of the basal ganglia and is the main recipient of signals from brain areas external to the basal ganglia, such as the cerebral cortex. The reticular part of the substantia nigra (SNr) and the internal segment of the globus pallidus (GPi) are the primary sources of output signal, with the majority resulting in the thalamus. The striatum then projects directly and indirectly (via STN) to GPi and SNr. Substantia nigra consists of two parts: SNr and the compact part (SNc). The former functions similarly to the globus pallidus, while the compact part sends modulatory dopaminergic input back to the striatum and other structures.

There are three key pathways within the basal ganglia (Figure 2): First, the direct pathway which has two GABAergic inhibitory links in a row (Striatum through GPi/SNr to Thalamus) so that activation of the striatum disinhibits or releases the motor thalamus. Second, the indirect pathway that works in opposition to the direct one, in the sense that the added link through the STN excites the direct pathway inhibitory function. Third is the striatonigral pathway to the SNc which forms a loop with the dopamine-containing nigrostriatal pathway which degenerates in PD.

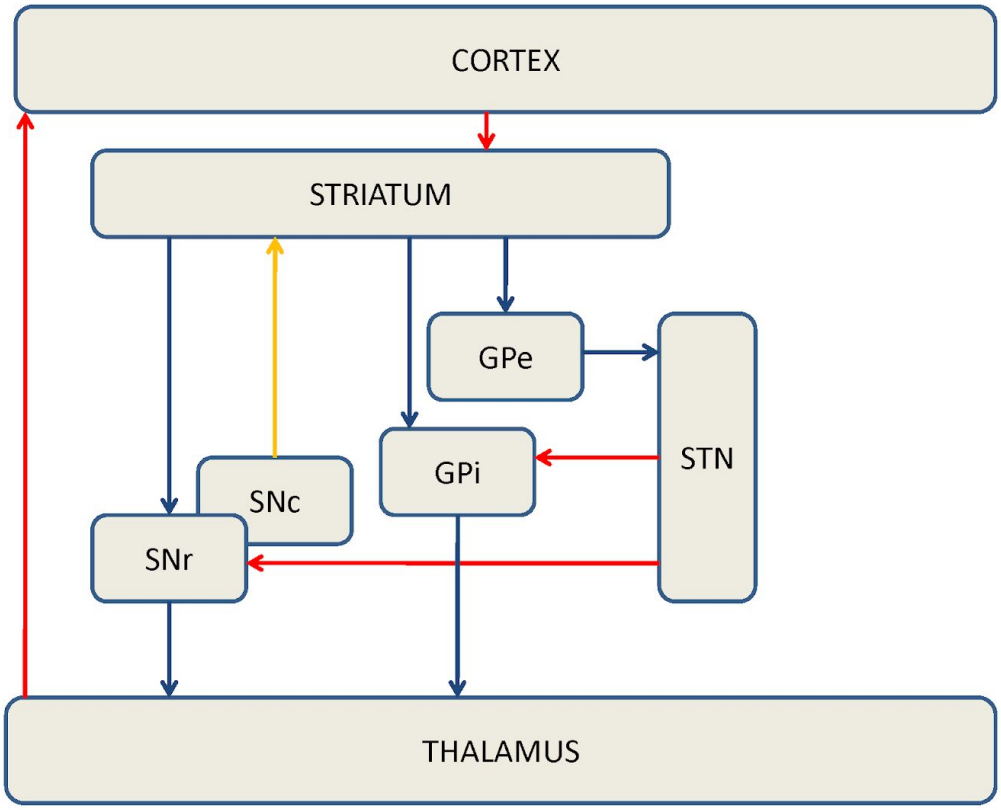


Figure 2. Neuronal pathway in a normal brain.

This system of nuclei, neurons, neurotransmitters constructs a complicated communication network. Dopamine is the chemical neurotransmitter that its lack inside the brain leads to PD. Dopamine is created in SN and helps with the transmission of

messages to the striatum, which initiates and control the movement and balance. The proper dopamine messages help the muscles of the body to operate smoothly and to be precisely controlled [galvan2008]. When a dopamine message is required, SNr gathers a cluster of dopamine particles at the end of the nerve cell until it releases it to the synapse. A neighbouring nerve cell collects this dopamine particles into pockets. This process is called stimulation. The neighbouring cell will now perform the same procedure as to concentrate its own dopamine particles into clusters and hence stimulate further nerve cells to pass the signal [galvan2008]. An important step in this procedure, is that the receiving cell breaks the used and the excess (that may not fitted into a pocket) dopamine particles into MAO-B. This break down of the dopamine particles is crucial to the fine tuning of both coordination and movement.

Pathology

In PD, the cells in SNr responsible for the production of dopamine start to decrease in number. As a result, the dopamine production decreases and hence the amount of available dopamine falls down. The enzyme MAO-B also continues to deplete any dopamine that is present in the synapse. In terms of the circuits mentioned above, the nigrostriatal dopaminergic projection originating in SNr degenerates and leads to a striatal dopaminergic deficit. This circuit would normally modulate the excitatory influence of the cortical afferents on the striatal projection neurons. This dopamine deficiency leads through a cascade of activity changes to an increased neuronal activity of the STN and conversely of the GPi/SNr as the two pathways that performed inhibitory effect stop working properly. As a result of this pathway disruption, the smooth operation of muscles is consequently prevented.

Symptoms of Parkinson’s disease

Motor symptoms

The cardinal symptoms of PD are manifested as motoric signs. They develop due to the fact that the function of the areas of the brain that control motoric movement and

coordination fail to work normally due to the lack of sufficient levels of dopamine in the corresponding centers as explained earlier . The most common of the motor symptoms are: tremor, rigidity, gait/postural instability, bradykinesia and akinesia [goetz2008].

Bradykinesia is the most characteristic clinical feature of PD. It manifests itself with slow movements. It includes various levels of voluntary movement such as planning, initiation and execution - the performance of sequential and simultaneous tasks are also affected. The symptom initially manifests itself as general slow movement and slow reaction times in daily life. Most of the times these include difficulties in performing tasks that require fine motor control, e.g., buttoning, using utensils etc. Further manifestations include loss of spontaneous movements and gesturing, drooling (due to impaired swallowing) monotonic and hypophonic dysarthria, loss of facial expression, or most commonly "masking", decreased blinking and reduced arm swing while walking. The later stage of bradykinesia is akinesia, in which the patients essentially lose their ability to move. Micrographia is also one of the manifestations of bradykinesia and is a result of the decreased amplitude in movement and it points out the alteration of the life of the patients by showing their reduced ability to write in a good and recognizable fashion, as their handwriting becomes small and cramped.

Tremor is mainly distinguished as rest, action and postural tremor. Rest tremor is the main tremor evident in PD and is also one of the most common symptoms in PD and - like bradykinesia - is also very easily recognizable. It occurs when a body part is completely rest against gravity. The tremors occur unilateral with a frequency of 4 - 8 Hz and most often occur at the distant part of the limp. They tend to spread from one hand to the other and can also involve the tremor of the lips, chin, jaw and legs but rarely the head or voice. Rest tremor characteristically disappears with voluntary action and sleep. Postural tremor occurs when the patient assumes a horizontal outstretch position, i.e., a position against gravity. This tremor increases with voluntary action, as opposed to rest tremor, which decreases with movement. The last and least of tremor categories is the action tremor (or kinetic) which occurs during voluntary movement. The tremor of early PD is most often intermittent, and may not be noticeable to others. In fact, about half of

patients with PD report a sensation of internal tremulousness in the limbs or body that is unrelated to the presence of observable tremor [shulman1996]. However, as the disease progresses, tremor usually becomes evident.

Rigidity arises due to stiffness in the joints and increased muscle tone. Rigidity combined to an underlying tremor are evident as a passive movement of the limb (flexion, extension or rotation about a joint). It can occur at the neck, shoulders, hips or at the wrists and ankles. Voluntary movements of the contralateral limb usually increase rigidity and for that reason are useful in diagnosing the symptom. Rigidity is often associated with pain - painful shoulder is one of the most frequent manifestations of PD. Rigidity of the neck and trunk result in conditions such anterocollis or scoliosis and postural deformities can occur due to this symptom. Other skeletal abnormalities that may occur due to rigidity are extreme neck flexion (dropped head, bent spine) and truncal flexion (camptocormia).

Postural instability is in general a late manifestation of PD and it most commonly has a late onset. It occurs due to loss of postural reflexes and it is the most common cause of falls causing usually hip fractures.

Another form of akinesia (loss of movement) is freezing, or motor blocks. This is a very common and evident symptom of PD. It most commonly affects the legs while moving, but can also affect the arms and eyelids. It manifests as sudden and transient inability to move and is also a very common cause of fall. There are five subtypes of freezing: start hesitation (hesitation when beginning to walk), turn hesitation, hesitation in tight quarters, destination hesitation and open space hesitation.

Parkinsonian gait is a distinctive unsteady walk. The parkinsonian patients tend to lean backward or forward in an unnatural fashion and develop a stooped, head-down, shoulders-dropped stance. The walking tends to occur in small shuffling steps, a symptom of PD called festination.

Dystonia is a neurological movement disorder, occasionally appearing as a symptom of PD. It appears as sustained muscle contractions which cause twisting and repetitive movements or abnormal postures.

Bulbar dysfunction can be manifested by dysarthria, hypophonia, dysphagia, sialorrhoea. These symptoms can sometimes be more crucial than tremor and akinesia as they can be more disabling. Speech disorders such as monotonous, soft and breathy speech with variable rate and difficulty of finding the correct words are also usual manifestations. Dysphagia owes its onset in the gradual inability to swallow or by prolongation of laryngeal or oesophageal movement.

Parkinsonian patients can also experience respiratory disturbances, and these can of restrictive or obstructive nature. The obstructive pattern is usually related to rigidity, cervical arthrosis or restricted range of motion in the neck. The restrictive pattern may be related to chest wall rigidity.

All the motor problems of the parkinsonian patient result to significant problems in the patient's daily life. Problems arise in otherwise routine everyday activities, such as talking, walking, writing, wearing clothes, cutting food, feeding, performing the common hygiene actions, driving, arising from a chair, turning in bed. This list is very long, underlying the difficulties of these patients to perform the most simple everyday actions.

The progression of the disease is unpredictable and the speed and severity of the symptoms vary for each person.

Non-motor symptoms

The non motor symptoms of PD include cognitive and neurological disorders, autonomic dysfunction, sensory and sleep difficulties. Features of autonomic dysfunction include orthostatic hypotension, sweating dysfunction, sphincter dysfunction and erectile dysfunction.

Neurological disorders are depression, apathy, dementia, anxiety and hallucinations. Patients may exhibit obsessive-compulsive and/or impulsive behavior e.g., craving, binge eating, compulsive foraging, hypersexuality and pathological gambling.

Sleep disturbances may arise due to nocturnal tremors, physical discomfort related to stiffness or rigidity, inability to roll over in bed, bladder problems, restlessness and painful dystonia. A common experience in patient is vivid dreams and hallucinations,

acting out violent nightmares. This problem is called "REM sleep disorder". Another common problem is the "sleep-wake reversal pattern" in which there is a tendency of sleeping too much during a day and then developing insomnia at night.
Restless leg syndrome is also very common to produce sleep disorders due to the irresistible urge to move one's body, as to stop uncomfortable sensations.
Sensory symptoms such as olfactory dysfunction, pain, paresthesia, akathisia, oral pain and genital pain are frequent but are often not recognised as parkinsonian symptoms.

Fluctuations

Motor fluctuations occur very commonly to patients having PD. They are characterized by frequent switches in the patients between "on" and "off" periods, meaning periods that the patient may react good to the medication and periods that still experiences the symptoms of PD.

Diagnosis of Parkinson’s disease

There is no standardized method for diagnosing PD so far. The diagnosis is mainly based on clinical impression, with no physiologic or blood tests for confirming the diagnosis. The common way of providing a diagnosis for the disease is through clinical neuropathologic examination. It is generally accepted that bradykinesia, plus tremor or rigidity are the necessary symptoms for diagnosing idiopathic PD. The good response to dopaminergic therapy is an important criterion for the diagnosis.
Neurodiagnostic imaging techniques such as conventional MRI and CT-scan are insufficient for providing a diagnosis for PD while Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) may be useful in providing an early diagnosis for PD [martinwieler2008).
Another test showing whether a patient has Parkinson's disease, is using the Unified Parkinson’s Disease Rating Scale (UPDRS), which is explained in "Methods" chapter. The patients are given a dose of levodopa (e.g., carbidopa-levodopa 25/250 mg) or subcutaneous apomorphine (1.5 to 4.5 mg). If the UPDRS score is significantly

improved 20 minutes to one hour after the administration of levodopa or apomorphine, this provides a sign that the patient has the disease.

Medical treatment of Parkinson's disease

Handling of the symptoms through medications, surgery or both is used at present to ease the quality of life of PD patients. Levodopa, COMT inhibitors, dopamine agonists and MAO-B inhibitors [oertel1997] are the main groups of medications that are used to control the motor symptoms.

There are two phases that usually separate the progression of PD. The first phase usually relates to the development of a disability. Pharmacological treatment is then used in order to relieve the symptoms. The second phase relates to the development of complications due to the continuous administration of levodopa. In the first phase the aim is the equilibrium between reduced dopaminergic therapy and good management of symptoms. MAO-B inhibitors and dopamine agonists are usually administered before the levodopa (or L-dopa) in order to delay the L-dopa related complications. Gradually, medication stops controlling the symptoms and deep brain stimulation (or some other form of surgery) are used as last resorts.

Levodopa

Levodopa is a precursor of the neurotransmitter dopamine and works by replacing dopamine when the brain cells in the SN are no longer able to produce if an individual has the PD. Levodopa can cross the blood brain barrier, in contrast to dopamine that can not. Hence, despite the fact that dopamine was first synthesized in a laboratory in 1910, in London, UK by George Barger and James Ewens only 50 years later, levodopa was synthesized and could actually be used for treatment of Parkinson's disease [fahn2008]. Hornykiewicz, after measuring the levels of dopamine in people with PD published a monumental paper on the depletion of dopamine in the caudate and putamen nuclei of patients with both of these conditions, but not in patients with other brain disorders such as Huntingtons chorea [hornykiewicz1998]. Later, Hornykiewicz

[hornykiewicz2008] published a major review article positing that striatal dopamine deficiency is correlated with most of the motor symptoms of PD.

Over the next years the dopamine pathways in the brain were mapped and the nigrostriatal pathway was discovered. Also the dopamine in the nigra of animals was found to be reduced when the nigra was injured.

The treatment with L-dopa began in 1960, when intravenous injections of the drug to patients having PD produced significant but transient effects in the patients. In the coming years, treatments with L-dopa produced contradictory effects to patients and doctors began questioning its effect.

The patients experienced nausea and vomiting and could not tolerate high doses of the levodopa since only 5-10 percent of the drug crosses the blood-brain barrier while the remainder metabolizes to dopamine elsewhere, causing the adverse events. In 1967, a new technique for administering the drug, produced by George Cotzias removed these undesirable effects. The key was to administer the drug gradually. This diminished the gastrointestinal side effects. In the following years, the benefit of levodopa to PD patients was verified with various studies [fahn2008].

Nowadays, dopa decarboxylase inhibitors are used in combination with levodopa in order to help prevent the metabolism of L-Dopa before reaching the dopaminergic neurons. Such combinations are carbidopa/levodopa (e.g., Nacom) and benserazide/levodopa (e.g., Madopar).

Despite the dramatic benefit on treating patients with levodopa, the drug has also weaknesses. A lot of patients start having their symptoms reemerging during the day after being treated for half year. Many patients also develop dyskinesias. Motor fluctuations and psychiatric symptoms start to appear as well. As a fact, levodopa reduces effectively the cardinal symptoms of PD, often for long periods of time, hence the quality of the daily lives of patients are improved to a major extent. Chronic levodopa treatment causes complications to patients (such as levodopa induced dyskinesias) and finally the use of the drug results no effect. Furthermore many of the symptoms that do not respond to L-dopa treatment, such as non-motor symptoms,

speech difficulties and cognitive decline are the symptoms that are most disabling in PD. Thus, although treatment with levodopa is the most effective symptomatic treatment, the developing of dyskinesias and also the decision on whether to start early or late treatment need to be addressed.

COMT inhibitors

COMT inhibitors are drugs that inhibit the action of catechol-O-methyltransferase, an enzyme involved in degrading neurotransmitters. The drugs are used in combination with levodopa for the treatment of PD. Entacapone is a commonly used COMT inhibitor. Entacapone combined with carbidopa and levodopa are commercially found under the trade name Stalevo. COMT inhibitors are important if the patients have “on”/”off” fluctuations, as it increases the “on” period. In addition COMT inhibitors prolong the effect of levodopa, reducing the pulsatile dopamine receptor stimulation and thus contribute to delaying the appearance of fluctuations during the course of the disease.

Dopamine agonists

Dopamine agonists bind to dopaminergic post-synaptic receptors. Hence they have a similar effect to levodopa. It was originally used as a complementary therapy to levodopa, reducing the on/off fluctuations and dyskinesias. They are finally used on their own as an initial therapy and as a way to delay the motor symptoms and avoid the motor complications caused by levodopa treatment. When used in later stages, they are effective in reducing the off periods. Dopamine agonists include pramipexole, ropinirole, pergolide, bromocriptine, apomorphine and others.

They produce mild side effects, such as nausea, constipation, hallucinations, insomnia. But, they can control worse symptoms than levodopa in the early stages, while delaying the motor complications so they are preferred from levodopa as an earlier treatment. At higher doses they are related to a variety of impulse control disorders.

Apomorphine is one of the most commonly used dopamine agonists. It is non-orally administered and may be used to reduce off periods and dyskinesia in late PD. It is

administered by intermittent injections or continuous subcutaneous infusions with side effects being among others confusion and hallucinations.

MAO-B inhibitors

MAO-B inhibitors (selegiline and rasagiline) block the metabolization of dopamine in the basal ganglia, leading to increased amount of neurotransmitter. Thus, reducing the MAO-B results in higher quantities of levodopa in the striatum. They improve motor symptoms and delay the need for levodopa treatment. Efficiency in later stages of the disease is reduced. The MAO-B inhibitors have potential neuroprotective effect [mandel2005] and this is the main reason they are prescribed, rather than symptomatic effects that are poor compared to other medication.

Deep brain stimulation

The practice of surgery for psychological or neurological disorders has long been present in medicine. The famous lobotomies of 40s and 50s are examples of such techniques that promised treatment to the patient. Ablative brain surgeries, which are the surgical ablations by burning or freezing brain tissue were used to treat such kind of disorders. These ablative techniques started declining due to the high morbidity and various post surgical complications. After the development of levodopa-based treatment, the operation of ablative surgeries further declined. But observations of various adverse events due to the continuous administration of levodopa lead the researchers back to the search for new surgical treatments as to avoid medication, and Deep Brain Stimulation (DBS) evolved as a solution for this.

DBS started in France, in 1987 [benabid1987]. The first reports of DBS being used to treat PD was in 1993 [pollak1993]. As an official treatment of Parkinson's disease, DBS was adopted in early 2000. A rough estimate of the patients being treated with DBS worldwide, gives a number of about 75000 people. The new technique is minimally invasive and does not destroy the brain tissue, but sends electrical pulses with

electrodes that are implanted in the regions that are believed to cause PD (Figure 3 shows a typical DBS system).

There are various factors making DBS attractive for PD treatment: (1) no destruction of brain tissues needed, (2) it is reversible in the sense that it does not preclude the use of future treatments, (3) stimulation parameters can be tuned post operatively as to improve efficacy and reduce any side effects that might develop, (4) in contrast to ablative procedures, it can be safely performed bilaterally. Furthermore, performing the surgery leads to reduced administration of levodopa hence the levodopa induced complications, e.g., dyskinesias, are also reduced [breit2004].

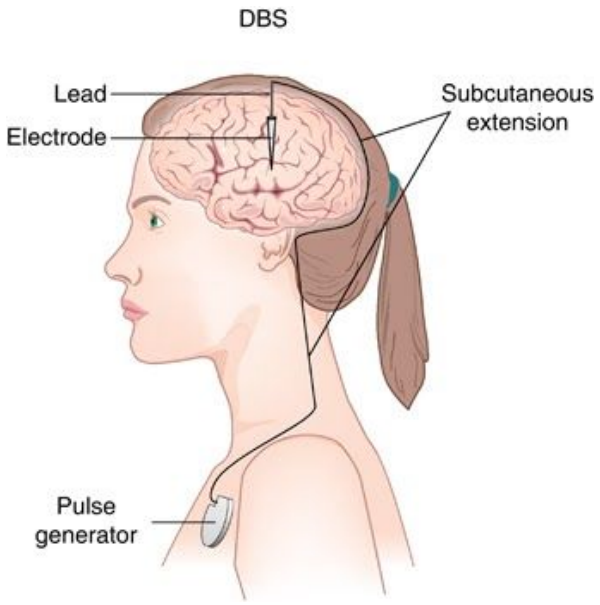


Figure 3. Typical Deep Brain Stimulation system [rosa2012].

Target brain regions for DBS

Experimental studies [blesa2012] using animal models underlined the effects of nigral degeneration and dopamine deficiency in Parkinson's disease and their role in the disruption of the normal operation of the according neural pathways. This irregular operation of the pathways include: (a) the excessive STN excitation of the GPi and (b) excessive GP inhibition of the thalamus.

These studies made clear that the regions in the brain that play a significant role in the cause of PD are STN and GPi. So extensive experimental work was conducted as to accurately specify these regions inside the brain and stimulate them, as to restore these nuclei to their normal function. This technique is highly region specific, so precise sites for conduction of DBS are important to be known.

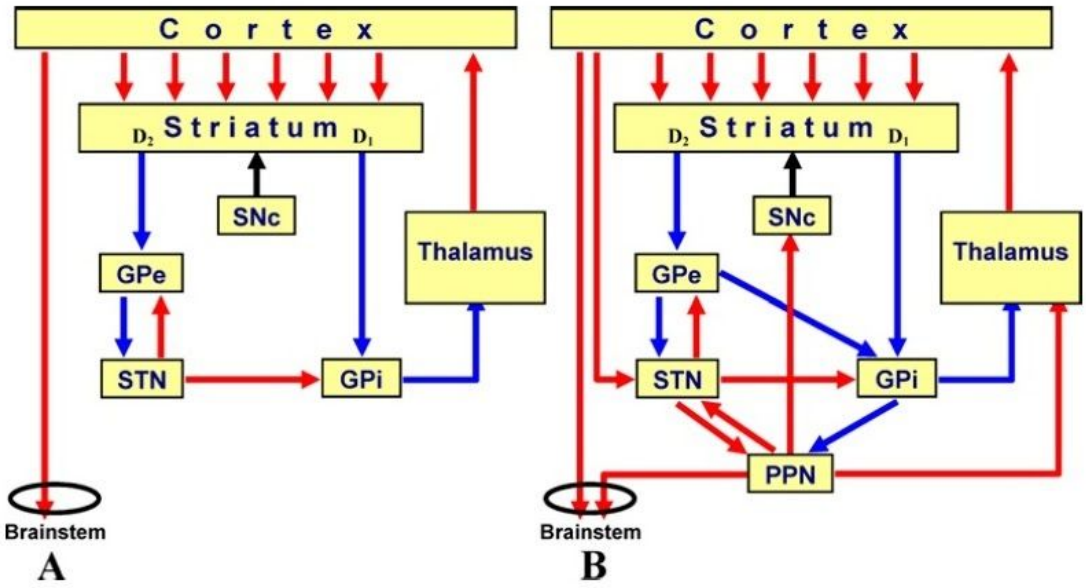


Figure 4. Basic (left) and extended (right) basal ganglia-thalamocortical circuitries under normal conditions [breit2004].

Figure 4 shows the basic and extended basal ganglia-thalamocortical circuitries under normal conditions. The motor circuit connects the motor cortical areas and the primary somatosensory cortical areas with the dorsolateral putamen. The dopamine deficiency in the parkinsonian state lead over a cascade of activity changes to an increased neuronal activity in STN and GPi-SNr. High frequency stimulation in these areas leads to inhibition of the neuronal activity, leading to improvement of PD symptoms, with the effect being always reversible.

Figure 5. Stimulating electrodes located in the subthalamic nucleus (STN) and in globus pallidus GP (Source: www.wikipedia.org).

STN is the region being mostly used - and also used in this thesis - because it reduces the cardinal motor symptoms of PD maximally, more than any other target region up to date [deuschl2006]. It also leads to reduced need for administration of levodopa (in contrary to stimulating the GPi which is not associated with reduction of levodopa requirement) in parallel to the conduction of DBS and is one of the main advantages of performing the surgery, since levodopa induced dyskinesias are also reduced. Figure 5 shows the position of the STN and GPi in the brain, together with the location of the electrodes providing the neurostimulation.

DBS system and procedures

The DBS system consists of three components: the implanted pulse generator (IPG), the lead, and the extension. The IPG is a battery-powered neurostimulator encased in a titanium housing, which sends electric pulses to the brain to interfere with neural activity at the target site. Such neurostimulators are Activa PC neurostimulator (Medtronic) and Kinetra (Medtronic). These devices can provide bilateral stimulation. The lead is a coiled wire insulated in polyurethane with four platinum iridium electrodes and is placed in one of three areas of the brain. The lead is connected to the IPG by the extension, an

insulated wire that runs from the head, down the side of the neck, behind the ear to the IPG, which is placed subcutaneously below the clavicle or in some cases, the abdomen. The accurate implantation of the electrodes in the established regions inside the brain is essential. Imaging techniques such as MRI, CT and ventriculography are used for pre-operational targeting. The implantation of electrodes is done by a stereotactic procedure while the patient is not being anaesthetized, but awake, with the patient being with no medication for about 12h before the operation.

An electrophysiological exploration is needed before the implantation of the final electrodes. This exploration is divided into two steps: (1) micro-recordings and (2) test-simulation. The first step, the micro-recordings, are performed to identify specific firing patterns along traversed brain regions. It is mainly used to identify the STN borders. The patient is subject to the increased risk of hitting a blood vessel, an increased operation time and sometimes the possibility of gaining very limited information. However, it leads to increased confidence and in correct target localization due to refined target region characterization.

Test simulation is an intraoperative stimulation at various sites along the trajectory. This is done to access if there is any symptomatic improvement occurred such as suppression of rigidity and tremor. Another reason for conduction of test stimulation is to detect any threshold above which side effects are induced due to current spreading in adjacent brain structures. The stimulation electrode can provide monopolar or bipolar stimulation and t has four sites by which stimulation can be achieved. Bipolar stimulation is achieved by having two contacts along the electrode active, one being the positive pole and one the negative, while for monopolar stimulation, the case of the stimulator is positive and one of the contacts negative (Figure 6). Monopolar stimulation produces a current in which the electrons diffuse from one site which is negatively charged through the brain. This stimulation might affect a larger area, especially if the current density is high. Concentric bipolar stimulation produces a concentrated current in which current runs from the negative to the positive pole.

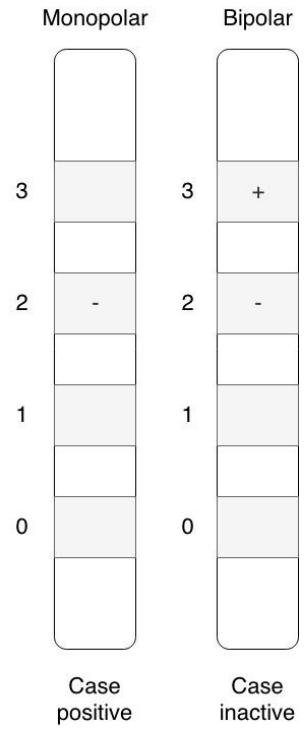


Figure 6. Monopolar and bipolar stimulation. For monopolar stimulation, one of the 4 contacts is negative, with the case being positive. For bipolar stimulation, one of the 4 contacts is positive and one negative.

Post operative localization of stimulation of most effective contacts within the STN have showed that the most effective site is the anterodorsal part of STN [breit2004].

The stimulation parameters used are 120 - 180 Hz frequency of stimulation, 60 - 200 μs pulse width and 1 - 5 V stimulation amplitude for treatment of tremors, and 20 Hz for the treatment of dyskinesias. A problem occurs to patients showing symptoms of tremor and dyskinesias as well. In that case a compromise in the frequency has to be found.

Bilateral DBS of STN might improve the UPDRS scale in off period by 50% - 90% describing a major improvement of the symptoms. Most features are improved if patients responded well beforehand with levodopa treatment.

Preoperative levodopa response of the patient is a strong and robust predictor of postsurgical improvement after DBS of the STN [louis2001]. In almost all cases, the outcome of the surgery can be as good as the best preoperative levodopa response. This means that all the symptoms that do not response to levodopa treatment are

unlikely to improve following the surgery. But this does not alter the need for use of DBS. In a lot of cases the levodopa treatment is being limited due to various adverse events. Hence, DBS of STN will probably produce a better response to the subtherapeutic levodopa dosage.

The mechanisms that cause symptoms improvement induced by DBS are not fully understood. It is evident that the frequency of stimulation is a key factor to the success and that high frequency stimulation effectively and interestingly mimics the effects of ablation in various brain structures. There are various hypotheses that are investigated and are the candidate explanations for the success of DBS, though there is no crucial evidence pointing directly to any of them [mcintyre2004].

Adverse events

Adverse events are typically related to factors as : (1) surgery, (2) hardware failure, (3) stimulation problems. Unmet expectations, problems with social adaptation after dramatic improvement of motor functions are also secondary adverse effects. Two studies [umemura2003, oh2002] with a total of 360 patients (288 with PD), that had DBS showed that within one month of the procedure, 0.6 percent resulted to death and permanent neurologic complications to 2.8 percent. Infections was at 5.6 percent, hemorrhage in 3.1 percent of the patients confusion/disorientation in 2.8 percent, seizures in 1.1 percent. Other complications that were below one percent are not mentioned. A systematic review in 2006, that included 29 studies of STN DBS with 778 patients [kleinerfisman2006] showed the following results: transient confusion and intracerebral hemorrhage were the most common adverse events (15.6 and 3.9 percent respectively). Infections were present in 1.7 percent of patients and seizures in 1.5 percent. The percentage of death cases was minimal. Both of these group studies elucidate the fact that complications and adverse events in STN DBS are present, but serious adverse events (leading to death or neurological problems) are very uncommon. In the same studies, the hardware complications were also reviewed. Lead replacement due to fracture, migration or malfunction, lead repositioning due to misplacement, extension wire replacement due to fracture or erosion, IPG replacement due to

malfunction, allergic reaction to the hardware were some of the complications that existed. A systematic review [kleinerfisman2006] showed the same variety of hardware complications. The rapid development of DBS technology constantly leads to the reduction of such complications.

Neurostimulation related problems included paresthesia, dysarthria, eyelid opening apraxia, hemiballismus, dizziness, dyskinesia and facial contractions. These were results from the same group of four studies. These problems were in general mild and could easily be resolved with proper adjustment of the stimulation parameters. The most common adverse events induced by the stimulation were dysarthria, gain weight, depression and eyelid opening apraxia [kleinerfisman2006].

Purpose of the study

The primary purpose of this retrospective, unblinded and long-term study is to assess the efficacy and safety of bilateral DBS of STN in a set of parkinsonian patients that respond well to levodopa treatment using review of patient records. The cohort of patients in this study is not pre-selected, but it includes subsequent patients eligible for DBS surgery. Several patients were excluded from the study for objective reasons. A set of measures, primarily UPDRS, was used to characterize the efficacy of the treatment, and the adverse events were monitored in order to assess the safety. The study was conducted in a single clinical center in Tübingen, Germany.

Methods

Patients

The inclusion criteria for the patients in the study were clinically diagnosed idiopathic Parkinson's disease [hughes1992], disease duration longer than 5 years, age between 25 and 80 years, UPDRS score ≥ 30 in medication "off" condition, a stable medication Parkinson treatment for at least one months before surgery and written informed consent.

The exclusion criteria were strong depression (Beck's Depression Inventory > 25), cognitive impairment (Mini-Mental State Examination < 25), acute psychosis, surgical contraindications, severe internal diseases, e.g., immunodeficiency, non-curative malignant diseases, severe neurological disorders (epilepsy, brain surgery, brain trauma, brain infarction), previous treatment with DBS or lesion of basal ganglia nuclei, lack of consent or existing care, lack of ability to understand the purpose and course of the study and participation in other clinical trials.

Procedure

Deep brain stimulation

All patients received bilateral implantation of electrode leads in the STN. After the surgery following stimulation parameters are set and optimized by a trained movement disorders specialist in order to obtain optimal clinical results and avoiding side effects: (1) stimulated contact(s), (2) stimulation type (monopolar or bipolar stimulation), (3) stimulation amplitude, (4) stimulation frequency, (5) pulse width of stimulation. Over the time, taking into account the evolution of the symptoms and the course of the disease, further optimization of the stimulation parameters might be necessary.

Patient visits

The clinical assessment was performed for each patient at baseline (before surgery) and at one, two, three and four years after surgery during the regular inpatient stays and the following measures have been assessed: UPDRS, Beck Depression Inventory (BDI), Mini-Mental State Examination (MMSE), Dysphagia, Dysarthria, adverse events, medication and stimulation.

Outcome measures

Unified Parkinson's Disease Rating Scale (UPDRS)

The most common way to assess the variety and severity of problems endured by a patient with PD is through the use of the UPDRS. The aim of this scale is to provide a

comprehensive evaluation of the disability and impairment related to the PD [goetz2008]. The UPDRS was originally developed in the 1980s and since then it has become the standard clinical rating scale for Parkinson's disease. For clinical trials assessing new treatments for PD, the UPDRS scale has been used to determine the treatment related benefits. Its adaptation as the standard clinical rating scale for PD is due to its several strengths, including its wide utilization, its application across the clinical spectrum of PD, its nearly comprehensive coverage of motor symptoms, and its clinimetric properties, including reliability and validity.

One of the core advantages of this rating scale, compared to some previous ones, is that it was developed to capture multiple aspects of PD. It has four subscales/sections complemented with the modified Hoehn and Yahr staging (part 5) and the Schwab and England ADL (part 6) scales. Section I assesses non-motor activities of daily living, namely mentation, behavior and mood. The scores are taken by interview and are based on the patients' experiences and consists of 4 items that get a score between 0 (normal) to 4 (severe) with 16 points being the maximum. Section II assesses motor activities of daily living for both "medication on" and "medication off" conditions. It contains 13 items that get a score between 0 (normal) and 4 (severe) with maximum score 52 points and as with section I, the scores are taken by interview. Section III is the most interesting subscale of UPDRS as it contains the motor examination taken by a specialized physician at scheduled visits of the patients at the examination centers. It contains 14 items that can result in 23 scores as different sides and body parts are separately evaluated. The maximum score is 108. This section is evaluated in medication "on" and "off" conditions combined with stimulation "on" and "off" conditions. Furthermore the items in sections III can be grouped together in order to provide separate scores for the categories: a) gait, b) tremor, c) rigidity, d) akinesia. Section IV assesses the complications of the treatment and they are taken by a specialized physician as well. It contains 11 items and the scoring is irregular compared to sections I - III. The scores for the items can take the values 0 to 4 and 0 or 1 and the maximum score is 23 points. The maximum score for UPDRS I-IV is thus 199 points.

The modified Hoehn and Yahr staging (UPDRS V) scale is used to describe the symptom progression of Parkinson's disease. It has 7 stages: 0 to 5 and in addition 1.5 and 2.5. Stage 0 indicates no sign of the disease and stage 5 indicates wheelchair bound or bedridden unless aided.

The Schwab and England ADL scale (UPDRS VI) measures a person's ability to perform everyday life activities in terms of speed and independence. It has 10 scores in terms of percentages with 0% indicating vegetative functions such as swallowing and 100% completely independent with ability to all activities without slowness, difficulty or impairment. In this study, the UPDRS VI scores are not taken into account due to the lack of sufficient results.

L-Dopa test

The severity of motor Parkinson's symptoms (UPDRS III) is evaluated using the L-Dopa test. The assessment of the UPDRS III score on the medication "off" condition started in the early morning after stopping L-Dopa and COMT inhibitors overnight (at least 12 hours). All dopamine agonists other than cabergoline were discontinued at least 24 hours before the test. Patients with cabergoline were switched to other drugs at least 1 week before the test. The dwell time in the med "off" state was a few hours and may be accompanied by an impairment of motor function or the occurrence of tremor. Patients did not receive their first morning dopaminergic drug dose as usual immediately after getting up, but only after completion of the examination in the med "off" state, i.e., with a delay of a few hours. The L-Dopa dose for the test was 1.5 to 2 times the individual L-Dopa equivalent dose in the morning. For later evaluations, the same dose should be used pre- and postoperatively. Clinical evaluation of the UPDRS III score in the medication "on" state was performed at a time interval with the best therapeutic effect. For this, the symptoms should be stable for at least 10 minutes and both the patient and the investigator agreed that the best medication "on" condition of the patient has been achieved.

Mini-Mental State examination (MMSE)

The MMSE is a 30 point questionnaire that is used regularly in clinical trials in order to measure cognitive impairment. It is used to screen for dementia. Though it is best suited for Alzheimer's disease, it has been widely used for screening patients with PD [folstein1975].

Dysphagia

Dysphagia can be defined as inefficient or unsafe transfer of food, liquid or saliva from the mouth into the stomach [tjaden2008]. Complications of this disorder include aspiration pneumonia, malnutrition, and dehydration. The first complication, aspiration pneumonia, is one of the major causes of death in PD. Hence, early identification and management of swallowing abnormalities is crucial for reducing the likelihood of these complications that negatively impact health status and quality of life [tjaden2008].

Dysarthria

Damage in the central of peripheral nervous system can cause the disorder of dysarthria. The major manifestation of dysarthria is spoken communication and is associated with a loss in the muscular control that is relevant for speech. Reduced comprehensibility is arguably the most significant functional limitation of dysarthria, with voice and speaking rate being also limitations that affect a person's ability to communicate in a normal way [tjaden2008].

Beck Depression Inventory (BDI)

BDI is a 21 question multiple-choice self-report inventory that is one of the most frequently used psychometric tests for measuring the severity of depression [beck1961].

Adverse events

Adverse events related to the surgical procedure, the implanted device and the bilateral STN stimulation were monitored and categorized as transient and permanent. Care was

taken to distinguish between adverse events related to the progression of PD and the ones related to DBS.

Data management and analysis

The data were stored in Microsoft access databases using a custom input software that created the tables in the databases. The databases were then converted to comma-separated values (csv) using the open source software mdbtools (https://github.com/brianb/mdbtools). The data were then processed using the programming language python with the data analysis / scientific computing libraries: pandas, numpy, scipy, matplotlib, seaborn.

The alpha was set to 0.05, and all the inferential tests were two-tailed. The significance levels of the statistical tests are shown using the asterisk notation: $p< 0.05$: *, $p < 0.01$: **, $p<0.001$: ***, no significance: **ns**.

The results are presented in an exploratory data analysis manner and further statistical tests were conducted when appropriate. All the observations were checked for normality and outliers were discarded.

In the study the primary endpoint is the UPDRS III scores. The difference in UPDRS III as the years progress is asserted with three different treatments: 1) med “off”/stim “off” (as control), 2) med “on”/stim “off”, 3) med “off”/stim “on” and 4) med “on” / stim “on” compared to the preoperative med “off” condition, that serves as a baseline. Med “off”/”on” describes treatment with/without levodopa equivalent medication respectively and stim “off”/”on” describes inactive/active bilateral STN stimulation respectively.

Due to the dependency of the observations, paired t-tests were conducted up to 4 years after the surgery, always comparing with the baseline scores. Due to missing observations occurring at random for some years, only a subset of the patients was compared. These scores were collected by specialized physicians using structural neurological tests and are the most reliable results in the study.

The tables presenting the results show the mean scores, that are calculated by taking the scores from all available patients at each year. The standard deviations are presented in brackets and the significance levels are also reported.

The UPDRS III items were segmented into different groups and separate hypotheses were asserted, comparing the subscores for the four different treatments versus the subscores for the baseline. These subgroups are: a) Left/right/dominant. These are the particular items in the UPDRS III section that are side-specific. The dominant side is the left or right side that has the worst UPDRS III score, b) Gait, c) Tremor, d) Rigidity, e) Akinesia.

Results

Demographic data

The demographic data are summarized in Table 1. In this study, 94 patients were included. These individuals comprised patients that received the operation and had data for at least one of the post operative assessments between years 1 and 4 after the operation. The average age at surgery was 64.0 ± 8.0 years with a disease onset at 48.9 ± 10.0 years (this average was calculated based on a subset of patients because of missing data). The disease duration, which is calculated as the number of years between the surgery and the year that the operation took place was 14.8 ± 6.1 years (again, this average is based on a subset of the patients because of missing data).

The percentage of parkinson types in the patients are 38% equivalent, 38% akinetic/rigid and 24% tremor/dominant . Five patients out of the 94 passed away during the post operative assessment period for reasons not related to surgery or PD.

Number of patients	94
Age at surgery (years)	64.0 ± 8.0
Disease onset (years)	48.9 ± 10.0
Disease duration (years)	14.8 ± 6.1
Parkinson type	Equivalent (38%), akinetic/rigid (38%), tremor/dominant (24%)
Gender	Male: 55, Female: 39
Levodopa equivalent dosage (mg)	950 ± 770

Table 1. Summary of the demographic data.

Stimulation parameters

Table 2 summarizes the stimulation parameters of the STN. As shown in the table, the type of the stimulation was monopolar for the majority of the patients along all the 4 post-op intervals after the operation. The stimulated contact is given in the table below. The mean value of the stimulation amplitude is given together with the standard deviation. In the study, the amplitude took values from 0.5 V to 7 V.

Post-op Interval (years)	**1**	**2**	**3**	**4**
Polarity Right (Monopolar, Bipolar) - occurrence	84%, 16%	90%, 10%	82%, 18%	86%, 14%
Polarity Left (Monopolar, Bipolar) - occurrence	88%, 12%	91%, 9%	87%, 13%	86%, 14%
Main contact Right - medianopear	2	2	2-3	2
Main contact Left - median	2	2	2	2
Stimulation amplitude Right (V) - mean, (sd)	3.1 (1.2)	3.0 (1.2)	3.3 (1.3)	3.0 (1.4)
Stimulation amplitude Left (V) - mean, (sd)	3.3 (1.2)	3.1 (1.2)	3.4 (1.3)	3.2 (1.1)
Stimulation frequency (Hz) - median (occurrence)	130 (85%)	130 (82%)	130 (85%)	130 (86%)
Pulse width Right (μs) - median	60	60	60	60
Pulse width Left (μs) - median	60	60	60	60

Table 2. Summary of the stimulation parameters for right and left electrodes.

The stimulation frequency describes the frequency of the stimulation pulse, in Hz. The median value is noted (130 Hz), together with the occurrence percentage. Values spanned a range from 120 Hz to 180 Hz. A frequency of 130 Hz was used in more than 80% of the patients in all 4 post-op intervals that were studied.
Finally the pulse width had median value 60μs for all the post-op intervals.

Motor disability scores (UPDRS III)

Total scores

The UPDRS III scores were collected before brain operation (baseline), 1, 2, 3 and 4 years after surgery. The results are summarized in the graphs below.

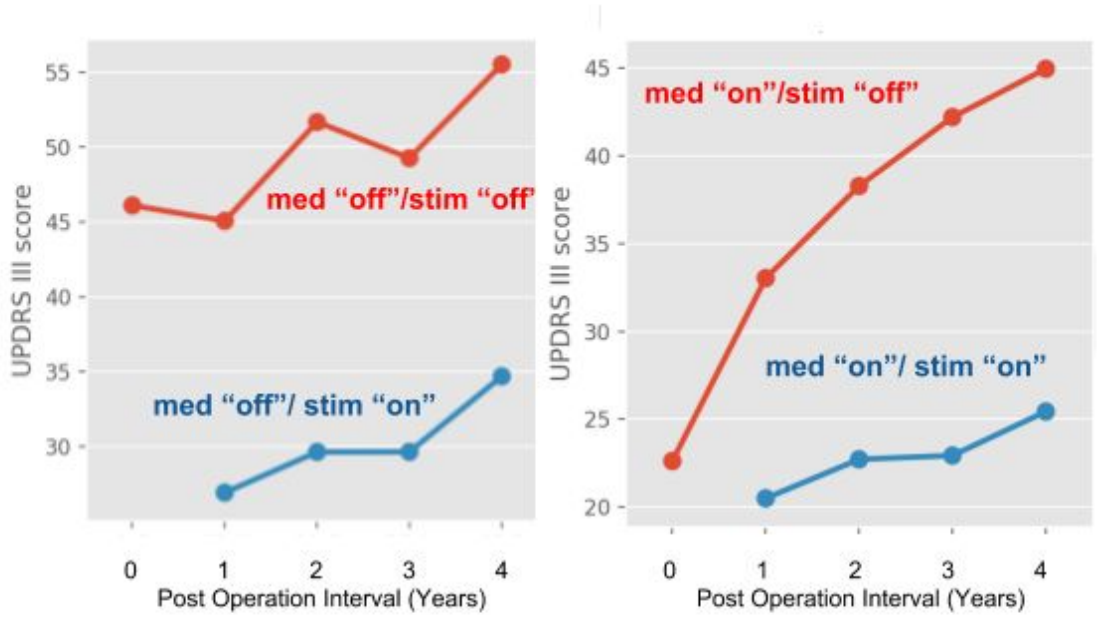


Figure 7. Left: Evolution of UPRDS III scores with stim "on"/"off", keeping the med "off". Right: Evolution of UPRDS III scores with stim "on"/"off", keeping med "on".

In Figure 7 (left), it is shown that with the treatment med "off"/stim "off", the scores are approximately constant over the follow up period of the 4 years. The treatment med "off"/stim "on" leads to a positive effect in the UPDRS III scores, as they drop down significantly. No data point is shown at baseline for med "off"/stim "on" or med "on"/stim

“on” since at baseline, the patients did not have the electrodes implanted. Despite the standard baseline with med “off”, med “on” is also considered as a comparison.

Figure 7 (right) displays that med “on”/stim “off”, the UPDRS III scores get increasingly worse over the period of 4 years, suggesting that with the medication only, one can not alleviate the motor symptoms. On the other hand with the treatment med “on”/stim “on”, the UPDRS III scores are kept low and approximately constant over the period of three years. At baseline, administration of medication only is enough to achieve alleviation of motor disability symptoms and the score at baseline is similar to the med “on”/stim “on”, treatment over the course of 4 years.

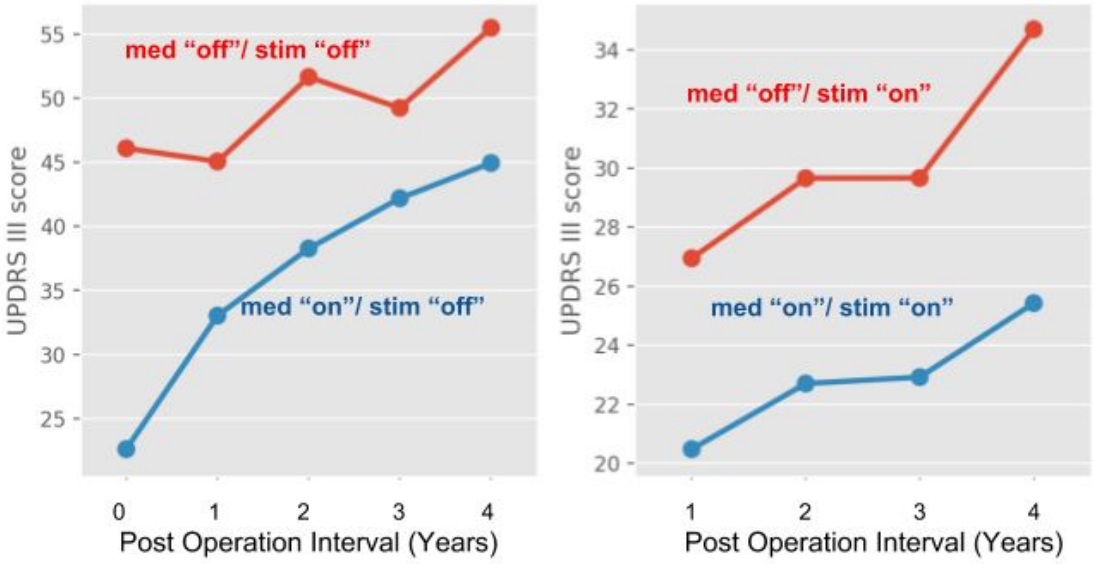


Figure 8 Left: Evolution of UPRDS III scores with med “on”/ stim “off” and med “off”/stim off”. Right: Evolution of UPRDS III scores with med “on”/ stim “on” and med ”off”/stim “on”.

Figure 8 displays the results in a different way, by keeping the stimulation in the “off” or “on” condition and varying the medication condition.

Figure 8 (left), shows med “off”/stim “off” and med “on”/stim “off”. One can see, in the same manner as before, that when the treatment is med “on”/stim “off”, the UPDRS III

scores are initially low but get worse every additional year and at four years, they approach med “off”/stim “off” scores. On the other hand, as shown in Figure 8

	Before surgery	**After surgery (years)**							
	baseline	**1**		**2**		**3**		**4**	
Stimulation/ Medication		**stim “off”**	**stim “on”**	**stim “off”**	**stim “on”**	**stim “off”**	**stim “on”**	**stim “off”**	**stim “on”**
med “off”	46.1 (16.0)	45.1 (15.4)	27.0 (12.2)	51.7 (20.3)	29.7 (13.2)	49.3 (17.3)	30.0 (15.8)	55.5 (16.8)	34.7 (12.9)
Baseline comparison			**-41%**		**-36%**		**-35%**		**-25%**
Significance level over preop. med “off”			***		***		***		**
Significance level over preop. med “on”			ns		ns		ns		**
med “on”	22.6 (10.7)	33.0 (14.1)	20.5 (9.6)	38.3 (17.7)	22.7 (12.1)	42.2 (18.2)	22.9 (12.6)	45.0 (15.2)	25.4 (12.2)
Baseline comparison			**-56%**		**-51%**		**-50%**		**-45%**
Significance level over preop. med “off”		***	***	***	***	*	***	ns	***
Significance level over preop. med “on”		***	ns	***	ns	***	ns	***	ns

Table 3. Total UPDRS III scores. The baseline comparison is shown . The significance levels compared to preoperative med “off” and med “on” treatments are shown respectively for all the available treatments except the med “off”/stim “off” one.

(right), keeping the stimulation in the “on” condition, the UPDRS III scores are significantly lower with the treatment being med “on”/stim “on” or med “off”/stim “on”, up to the 4th year.

In Table 3, the mean UPDRS III scores in yearly intervals up to four years after the surgery are shown. The mean scores and standard deviations (in brackets) are given for all four different treatments. There is a significant decrease in percentage UPDRS III scores for the treatment med “on”/stim “on” of 50% and 45% for the years 3 and 4 respectively, compared to the baseline. The improvement is also evident for the med “off”/stim “on” condition, which shows a percentage reduction of 35% and 25% for years 3 and 4 respectively.

The UPDRS III scores are compared to med “off” and med “on” treatments before surgery and the significance levels for both are shown.

Compared to the preoperative med “off” treatment, there is a significant reduction in the UPDRS III scores ($p < 0.001$) with the med “on”/stim “on” treatment, up to 4 years after surgery. The med “off”/stim “on” treatment also shows significant reduction in the mean scores up to 4 years after surgery. The significance of the tests is $p<0.001$ except in year 4, where the significance is lower ($p<0.01$). The med “on”/stim “off” treatment shows lower UPDRS III scores with significance $p<0.001$ at the 1st and 2nd year after surgery with the significance level in year 3 being $p<0.05$. In year 4, the mean score does not show a significant difference, indicating that treatment based only on medication does not have a long term positive effect in handling the motor symptoms of Parkinson’s disease.

Compared to the preoperative med “on” treatment, which is very successful in the early stage of the disease but not long term, the same treatment is not effective after surgery, as it results in a significant ($p<0.001$) increase in the mean UPDRS III scores. Comparing the med “off”/stim “on” treatment with the preoperative med “on”, there is no change in the scores up to the 3rd year and a significant increase ($p<0.01$) in year 4. The med “on/stim “on” treatment shows no change in the mean scores with respect to preoperative med “on”, indicating a successful relief of symptoms up to 4 years after the surgery.

Right, Left, Dominant sides

		Before	After surgery (years)							
		baseline	1		2		3		4	
Side	**Stimulation/ Medication**		**stim "off"**	**stim "on"**	**stim "off"**	**stim "on"**	**stim "off"**	**stim "on"**	**stim "off"**	**stim "on"**
Dominant	**med "off"**	17.8 (6.1)	17.1 (5.6) ns	9.8 (4.4) *** **-45%**	19.4 (7.6) ns	10.3 (4.8) *** **-42%**	18.7 (7.0) ns	10.7 (6.1) *** **-40%**	20.7 (7.2) ns	11.5 (4.2) *** **-35%**
	med "on"	9.0 (4.6)	12.8 (5.9) ***	7.7 (3.9) *** **-57%**	14.1 (7.3) ***	7.9 (4.6) *** **-56%**	16.4 (7.6) *	8.1 (5.0) *** **-55%**	16.7 (6.4) ns	7.8 (4.0) *** **-56%**
Right	**med "off"**	15.5 (6.3)	15.3 (6.0) ns	8.5 (3.6) *** **-45%**	16.6 (8.4) ns	8.6 (4.5) *** **-45%**	16.0 (6.5) ns	9.2 (6.6) *** **-41%**	18.7 (6.7) ns	9.4 (4.0) *** **-39%**
	med "on"	7.6 (4.3)	10.5 (5.5) ***	6.0 (2.9) *** **-61%**	12.9 (6.9) ***	6.6 (4.0) *** **-57%**	13.8 (7.8) ns	6.9 (4.7) *** **-55%**	14.5 (6.5) ns	6.4 (3.8) *** **-59%**
Left	**med "off"**	15.5 (6.9)	14.4 (5.8) ns	8.7 (4.7) *** **-44%**	17.3 (7.4) ns	9.4 (5.1) *** **-39%**	16.3 (6.9) ns	9.3 (5.5) *** **-40%**	17.7 (7.7) ns	10.6 (4.7) ** **-32%**
	med "on"	7.6 (4.7)	11.5 (6.1) ***	7.0 (4.2) *** **-55%**	12.4 (7.0) ***	7.2 (4.8) *** **-54%**	14.1 (7.4) ns	7.3 (4.3) *** **-53%**	14.0 (6.7) ns	7.1 (4.1) *** **-54%**

Table 4. Subscores for "dominant", "right" and "left" sides. Baseline comparison and significance levels are shown.

A breakdown of the UPDRS III subscores concerned with the different sides (left, right) together with the dominant side of the disease (that is the side affected mostly by the disease) is shown in Table 4.

In this case, the subscores are compared only to the preoperative med “off” condition. The observations follow the ones of total UPDRS III subscores, that show that administering only medication does not relieve the Parkinson’s disease symptoms after the 2nd year. In year 3, the med “on”/stim “on” treatment shows a 55% decrease on both the dominant and right side and 53% decrease on the left side. In year 4, the med “on”/stim “on” treatment shows a similar decrease in the UPDRS III subscores, with the 56%, 59% and 54% decreases on the dominant, right and left sides respectively. Med “off”/stim “on” treatment also shows a significant improvement in the UPDRS III subscores, with a reduction of 40% and 35% for the dominant side for years 3 and 4 respectively, 41% and 39% for the right side for years 3 and 4 respectively and 40% and 32% for the left side for years 3 and 4 respectively.

Gait, Rigidity, Tremor, Akinesia

The tremor subgroup (Figure 9) contains the UPDRS items associated with action and resting tremor. Tremor shows the highest percentage decrease compared to the other subgroups, with a 57% decrease in year 3 and 67% decrease in year 4 of the treatment med “on”/stim “on” over the baseline. Treatment med “off”/stim “on” also shows a large decrease: 48% in year 3 and 43% in year 4.

The gait subgroup (Figure 10) contains the following items: “arise from chair”, posture, postural stability, gait and body bradykinesia. The gait scores decrease by 43 % and 21% for the years 3 and 4 respectively for the med “on”/stim “on” treatment and 28% and 1% (not significant decrease) for years 3 and 4 respectively for the med “off”/stim “on” treatment. Evidently, med “off”/stim “on” treatment provides substantially lower percentage decrease for this particular subgroup, with no significant decrease at four years.

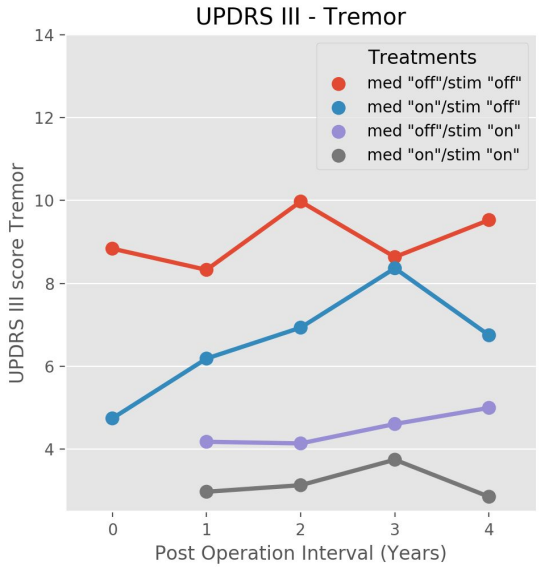
The akinesia subscores (Figure 11) show 45% percentage decrease for year 3 and 40% for year 4, for the med “on”/stim “on” treatment, over the baseline. The med “off”/stim “on” treatment shows lower percentage decrease, 35% in year 3 and 20% for year 4 over the baseline.

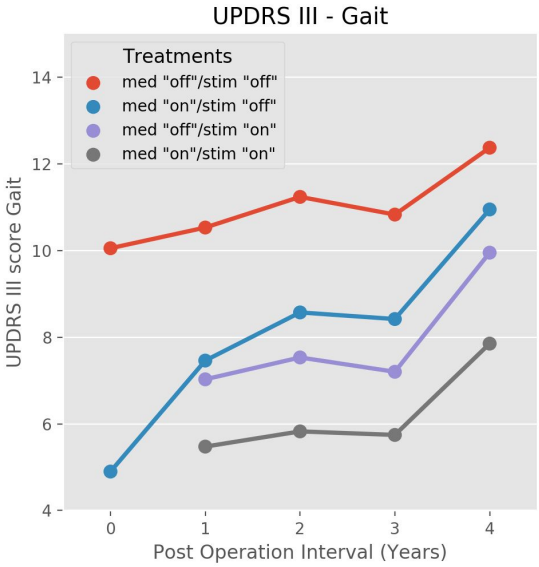
The rigidity scores (Figure 12) show 45% and 50% percentage decrease for years 3 and 4 respectively, for treatment med “on”/stim “on”. The treatment med “off”/stim “on” results in 22% (not significant decrease) and 34% percentage decrease for years 3 and 4 respectively. The percentage decrease in year 3 for med “on”/stim “off” is not significant, in contrast to the scores for years 1, 2 and 4 for the same treatment.

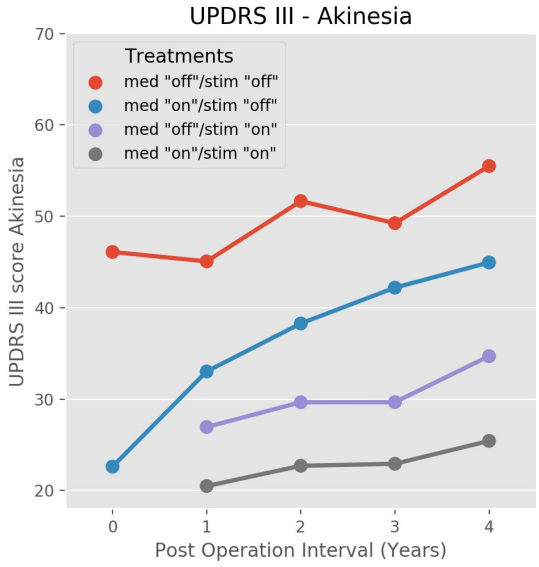
		Before surgery	**After surgery (years)**							
		baseline	**1**		**2**		**3**		**4**	
UPDRS III subgroup	**Stimulation/ Medication**		**stim “off”**	**stim “on”**	**stim “off”**	**stim “on”**	**stim “off”**	**stim “on”**	**stim “off”**	**stim “on”**
Tremor	**med “off”**	8.8 (6.2)	8.3 (5.6) ns	4.2 (2.8) *** **-52%**	10.0 (6.1) ns	4.1 (3.1) *** **-53%**	8.6 (6.0) ns	4.6 (4.3) *** **-48%**	9.5 (5.5) ns	5.0 (2.3) * **-43%**
	med “on”	4.7 (4.0)	6.2 (5.3) ***	3.0 (1.8) *** **-66%**	7.0 (5.5) * **-65%**	3.1 (2.7) ***	8.4 (5.4) ns	3.8 (2.8) *** **-57%**	6.8 (4.9) ns	2.9 (1.6) * **-67%**
Gait	**med “off”**	10.0 (4.3)	10.5 (4.6) ns	7.0 (4.1) *** **-30%**	11.2 (5.5) ns	7.5 (4.4) *** **-25%**	10.8 (5.3) ns	7.2 (4.0) ** **-28%**	12.4 (4.0) ns	9.9 (4.7) ns **-1%**
	med “on”	4.9 (2.6)	7.5 (3.8) ***	5.5 (3.0) *** **-45%**	8.6 (4.9) **	5.8 (3.9) *** **-42%**	8.4 (4.7) *	5.7 (3.8) *** **-43%**	10.9 (4.4) ns	7.9 (4.0) ** **-21%**

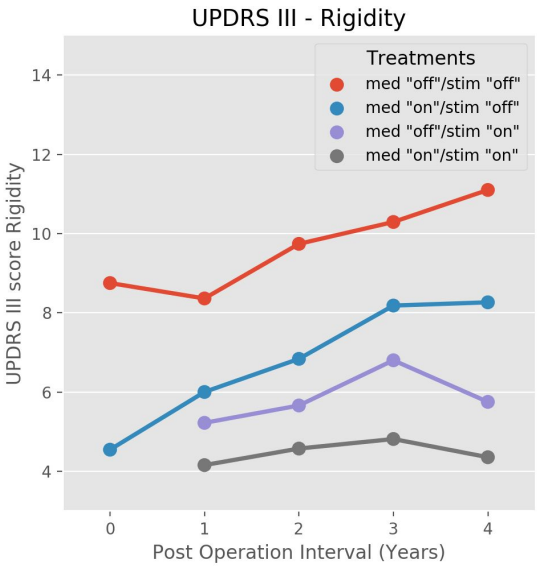
(Table 5 continued)		**Before surgery**	**After surgery (years)**							
		baseline	**1**		**2**		**3**		**4**	
UPDRS III subgroup	**Stimulation/ Medication**		**stim "off"**	**stim "on"**	**stim "off"**	**stim "on"**	**stim "off"**	**stim "on"**	**stim "off"**	**stim "on"**
Akinesia	**med "off"**	16.6 (6.5)	16.4 (6.4) ns	10.4 (5.2) *** **-37%**	18.9 (7.2) ns	11.4 (5.9) *** **-31%**	16.6 (6.5) ns	10.8 (7.3) ** **-35%**	20.0 (7.3) ns	13.2 (6.4) * **-20%**
	med "on"	8.8 (4.7)	13.0 (5.7) ***	8.5 (4.5) *** **-49%**	14.8 (7.6) *	9.0 (5.3) *** **-46%**	15.8 (7.3) ns	9.2 (5.9) *** **-45%**	16.6 (7.6) ns	9.9 (6.2) *** **-40%**
Rigidity	**med "off"**	8.8 (4.3)	8.3 (3.4) ns	5.2 (3.0) *** **-41%**	9.7 (4.5) ns	5.5 (3.3) *** **-38%**	10.3 (3.8) ns	6.8 (4.2) ns **-22%**	11.1 (4.2) *	5.8 (3.4) * **-34%**
	med "on"	4.5 (3.0)	6.0 (3.2) ***	4.2 (2.4) *** **-52%**	6.8 (4.3) **	4.6 (3.7) *** **-48%**	8.2 (3.8) ns	4.8 (3.0) *** **-45%**	8.3 (4.0) ns	4.4 (2.4) *** **-50%**

Table 5. UPDRS III subscores for groups: Tremor, Gait, Akinesia, Rigidity. The subscores are shown up to 4 years after the operation. The percentage decrease of the med "on"/stim "on" compared to the preoperative med "off" are shown.









Figures 9-12. UPDRS III symptom specific groups. Figure 9 (top left): Tremor. Figure 10 (top right) Gait. Figure 11 (bottom left): Akinesia. Figure 12 (bottom right): Rigidity.

Medication related complications (UPDRS IV)

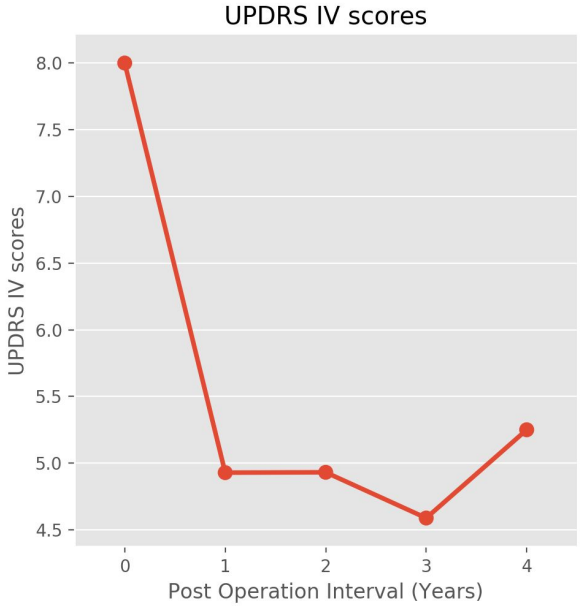


Figure 13. Medication related complications (UPDRS IV) scores.

	Before surgery	**After surgery (years)**			
	baseline	**1**	**2**	**3**	**4**
UPDRS IV score	8.0 (4.0)	4.9 (3.8) * **-39%**	4.9 (3.5) * **-39%**	4.6 (4.0) ** **-43%**	5.3 (4.2) * **-34%**

Table 6. Medication related complications (UPDRS IV scores) for 4 years after brain surgery.

The summary of the UPDRS IV scores (Figure 13, Table 6), that describe the complications introduced due to levodopa (baseline) and levodopa in conjunction with DBS for 1, 2, 3 and 4 years afters surgery show an abrupt decrease, with a p-value < 0.05 at year 1, 2 and 4 and p-value < 0.01 at year 3. The scores after the 1st year are

compared with the scores at baseline (only levodopa). The substantial decrease of the related complications (43% in 3rd year and 34% in 4th year) are very beneficial for the quality of life of each patient.

Motor activities of daily living (UPDRS II)

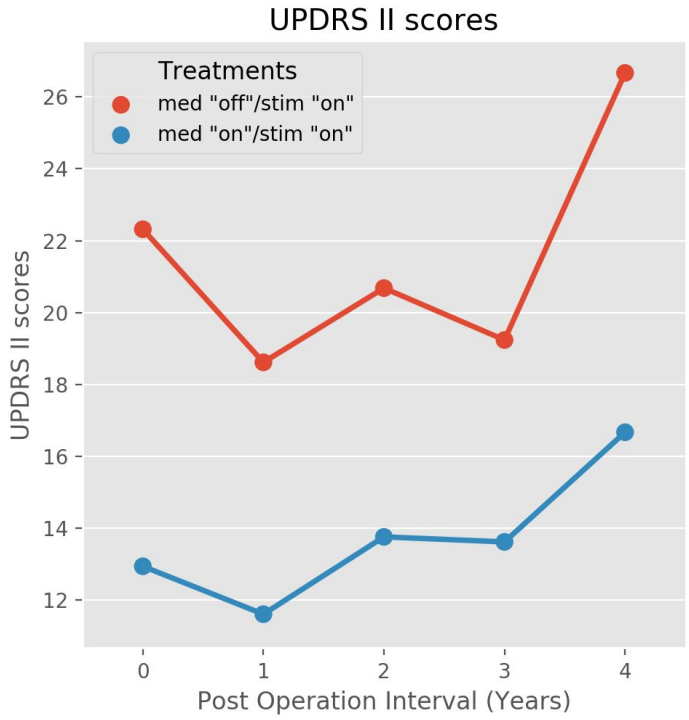


Figure 14. Sum of UPDRS II scores for med “on”/stim “on” and med “off”/stim “on”. At baseline (year 0), the scores shown are for med “off” and med “on” conditions.

Table 7 summarizes the motor activities of daily living, as reported by the patients and depicted graphically in Figure 14. The stimulation state is “on” for all the years following brain surgery and the treatment is compared to baseline (in this case stimulation is “off” as the DBS system has not been implanted yet. Years 3 and 4 show a drop in the scores of 39% and 25% (not significant result, however the sample size at this point

was very small, so the result is not reliable), when compared to the baseline med “off” condition.

	Before surgery	**After surgery/stim ”on” (years)**			
Medication condition	**baseline**	**1**	**2**	**3**	**4**
med“off”	22.3 (8.9)	18.6 (8.5) * **-17%**	20.7 (7.7) * **-7%**	19.2 (8.3) * **-14%**	26.7 (8.3) ns **+20%**
med “on”	12.9 (5.9) ***	11.6 (6.5) *** **-48%**	13.8(6.1) *** **-38%**	13.6 (5.6) *** **-39%**	16.7 (7.2) ns **-25%**

Table 7. The motor activities of daily life (UPDRS II) scores, with med“off” and med “on”. The stimulation is always in the “on” state and the baseline treatment is med “off”.

Non-motor activities of daily living (UPDRS I)

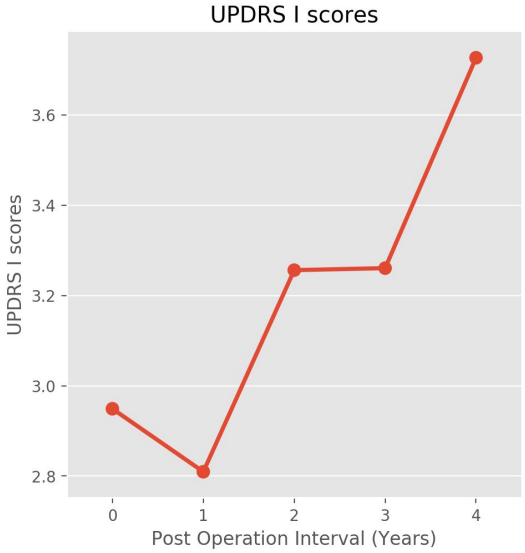


Figure 15. Left: Shows the sum of UPDRS I scores up to the 4th year after operation.

	Before surgery	After surgery (years)			
	baseline	**1**	**2**	**3**	**4**
UPDRS I score	2.9 (1.9)	2.8 (1.6) ns **-3%**	3.3 (2.0) ns **+14%**	3.3 (2.0) ns **+14%**	3.7 (2.7) ns **+28%**

Table 8. UPDRS I scores.

Figure 15 above shows the scores for the items in the UPDRS 1 part of the UPDRS scale, that includes: mentation, thought disorder, depression, motivation/initiative.

Table 8 shows that there is no significance increase in the UPDRS 1 scores, indicating that during the follow-up period of four years after surgery, there is not a further significant impairment in the non-motor activities of the daily living. The table shows an increase of 14% and 28% for 3rd and 4th years after surgery respectively, however the increase is not significant.

Levodopa equivalent intake

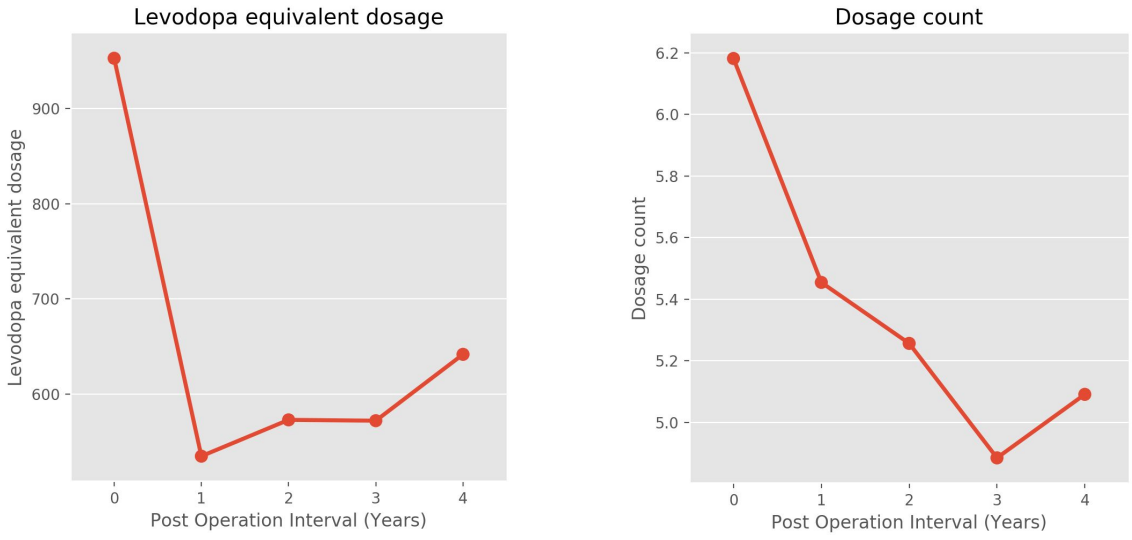


Figure 16. Left: Levodopa equivalent dosage up to the 4th year after operation. Right: Levodopa equivalent number of distinct dosage up to the 4th year after operation.

	Before surgery	After surgery (years)			
	baseline	**1**	**2**	**3**	**4**
Levodopa equivalent dosage (mg)	950 (770)	540 (250) *** **-43%**	570 (280) *** **-40%**	570 (250) ** **-40%**	640 (270) * **-33%**
Dose count	6.2 (1.6)	5.5 (1.6) * **-11%**	5.2 (1.8) *** **-16%**	4.9 (1.6) *** **-21%**	5.1 (1.4) * **-18%**

Table 9. Levodopa equivalent dosage and dose count.

Figure 16 and Table 9 show the levodopa equivalent dosages (see methodology for explanation). Compared to before surgery, the levodopa equivalent dosages is shown to significantly drop (significance levels are $p<0.001$ for years 1 and 2, $p< 0.01$ for year 3 and $p<0.05$ for year 4). As it is shown in the figure there is a highly pronounced transient drop observed on the 1st year after surgery, with a slight, not significant increase (compared to year 1) after that. The average percentage decreases of Levodopa equivalent dosages over the baseline are 40% in the 3rd year and 33% in the 4th year.
The dosage count shows a significant decrease compared to before surgery as well. The significance levels are $p<0.05$ for years 1 and 4, $p<0.001$ for year 2 and $p<0.01$ for year 3. The percentage decrease compared to the baseline is 21% and 18% for years 3 and 4 respectively.

Hoehn and Yahr staging scale (UPDRS V)

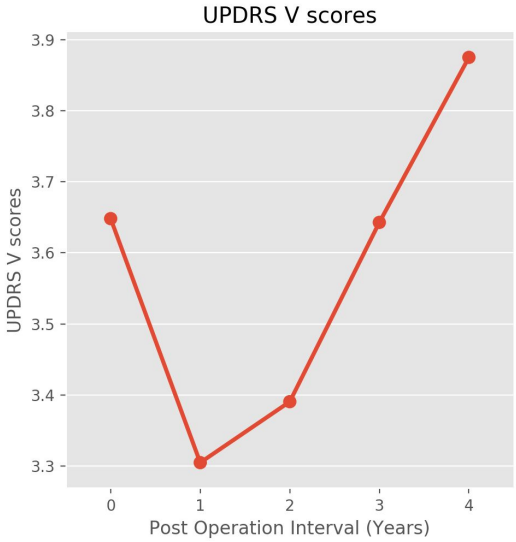


Figure 17. Hoehn and Yahr staging scale (UPDRS V)

	Before surgery	**After surgery (years)**			
	baseline	**1**	**2**	**3**	**4**
UPDRS V score	3.6 (0.8)	3.3 (0.8) ***	3.4 (0.7) ***	3.6 (0.6) ns	3.9 (0.8) ns

Table 10. UPDRS 5 scores.

The UPDRS 5 scores (Figure 17, Table 10) are in the range of 3 to 4 over the 4 years after surgery. The scores represent *mild to moderate parkinson's disease, some postural instability, physically independent* to *severe disability, still able to walk or stand unassisted* respectively. The scores are significantly lower in year 1 and 2 and then they show no significant change in year 3 and 4 over the baseline

MMSE and BDI scores

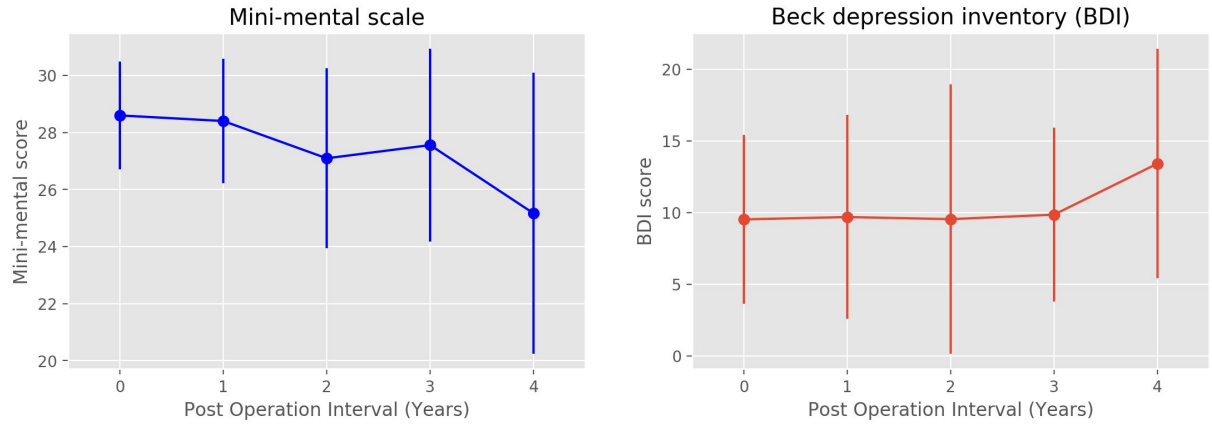


Figure 18. Left: Mini-mental state examination scale, showing no significance difference in the scores within the follow up period. Right: Beck depression inventory scale, showing no significance difference in the scores within the follow up period.

The results for the MMSE do not show a significant change in year 1 compared to the baseline, then they show a decrease for years 2 and 3 ($p<0.05$) and a more significant decrease in year 4 ($p<0.01$).

Scores below 23 indicate cognitive impairment. As it is shown in Figure 18 (left) above, the mean score in years 2 and 3 after operation is at ~27 points, with a standard deviation of ~3 points, indicating a score of 24 at one standard deviation away from the mean (in the negative direction). Hence, even though the t-test shows a decrease in the 2nd and 3rd compared to pre-operation, this decrease in the MMSE score is not translated to a serious cognitive impairment. However, for the 4th year after the operation the decrease is higher, with a mean score of 25 and a standard deviation of 5.This indicates that some cognitive impairment is evident in year 4 after surgery.

No significant change in the BDI is observed when compared to baseline (Figure 18 left). Scores in the range 0 to 13 points indicate minimal depression and scores in the range of 14 to 19 indicate mild depression. The score before operation is at a 9.5 ± 5.5. Thus the mean score falls well in the region of minimal depression, and that is carried

forward unchanged up to 4 years after operation as far as the paired t-test is concerned. A higher increase in the mean score occurs in the 4th year, with the mean score being at the boundary of minimal/mild depression, but the majority of the patients would fall in the minimal/mild depression region, as scores in the range of 20-28 (moderate depression) or 29 - 63 (severe depression) are far away from the range of values observed.

Dysphagia, Dysarthria

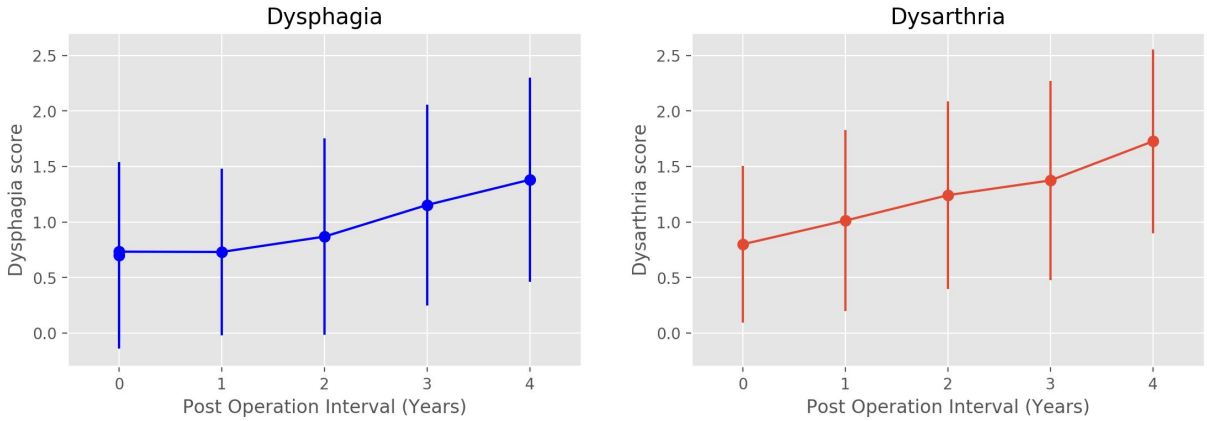


Figure 19. Dysphagia (left) and dysarthria (right) scores for the 4 year follow up after surgery.

The dysphagia and dysarthria scores (Figure 19) have been transformed from categorical to numerical in order to facilitate the scoring. None, mild, moderate and severe dysphagia categories have been assigned the numerical scores 0, 1, 2, 3 respectively.

For dysphagia, there is no significant change compared to the baseline for 1, 2 years, there is an increase ($p<0.05$) at year 3 and a more significant increase at year 4 ($p<0.01$). The baseline dysphagia mean score is at 0.6 indicating a none to mild dysphagia. In year 3, the mean score increases to 1.1, that translates to predominantly mild dysphagia. In year 4, the mean score increases again to 1.4, which falls in the mild/moderate category.

Dysarthria scores have the following progress: in year 1 the increase has significance $p<0.05$, for year 2 $p<0.001$, for year 3, $p<0.01$ and for year, $p<0.001$. The baseline preoperative dysarthria score is at 0.5 indicating none/mild dysarthria induced symptoms, 1 at year 1, indicating mild dysarthria, 1.3, 1.4, and 1.7 in years 2, 3 and 4 respectively, indicating mild/moderate dysarthria.

Adverse events

The adverse events related to the surgical procedure, the implanted device and the bilateral STN stimulation are summarized in Table 11.

Most of the adverse events related to the surgical procedure were not serious, except intracerebral hemorrhage with persistent disability that is reported in 3 patients. Intracerebral hemorrhage was additionally observed in 2 patients, but with no persistent disability. Ischemic stroke was observed in 1 patient. Nine patients experienced a transient postoperative delirium. Common complications that may occur in any surgical procedure and narcosis, such as pulmonary artery embolism and vocal cord dysfunction were observed in 1 patient for each complication. Subdural hematoma was observed in 1 patient. One patient had symptomatic bleeding detected in MRI. Wound healing problems caused a transient complication in 1 patient and a permanent complication in 1 patient. Electrodes were repositioned in 4 patients in total, in 2 patients due to misplacement and in 2 patients due to dislocation. The stimulation generator had to be replaced in 1 patient due to infection.

Permanent eyelid-opening apraxia, a common adverse effect of DBS, was observed in 5 patients. Moderate psychiatric adverse events, such as psychosis, hypomania, apathy, and impulsive aggressive behavior were observed in a very small number of patients, as shown in Table 11. Finally, weight gain was reported in 1 patient.

Type of adverse event	Transient	Permanent
Related to surgery and device		
Intracerebral hemorrhage	2	3
Ischemic stroke		1
Asymptomatic bleeding detected on MRI	1	
Delirium	9	
Pulmonary embolism	1	
Vocal cord dysfunction	1	
Subdural hematoma	1	
Wound healing problem	1	1
Electrode misplacement	2	
Electrode dislocation	2	
Infection of the stimulator	1	
Related to STN stimulation		
Eyelid-opening apraxia		5
Psychosis	2	
Hypomania	2	1
Impulsive aggressive behavior	1	1
Weight gain		1
Apathy	4	3

Table 11. Adverse events related to surgery, device or STN stimulation.

Discussion

The main result of this study shows that bilateral DBS of STN provides long term improvement of UPDRS III scores in patients with advanced Parkinson's disease in both medication "off" and "on".

The overall UPDRS III during neurostimulation markedly improved with and without medication, with the improvements over baseline sustained for the entire follow-up period of 4 years after surgery. When comparing UPDRS III score during neurostimulation with medication, to the preoperative med "on" condition, no significant change was observed, meaning that treatment with neurostimulation in conjunction with medication remained quite stable over the 4 years of follow-up. On the contrary med "on"/stim "off" treatment gave continuously worse scores compared to the preoperative med "on". This underlines the importance of bilateral DBS, as the medication alone could not provide a sustained improvement in the UPDRS III scores.

The improvement in the UPDRS III subscores related to the body sides (left, right, dominant) is evident with a significant decrease in the scores for med "off"/stim "on" and med "on"/stim "on" over baseline. The fact that there is a remarkable reduction on the side affected most dominantly by PD is highly important for the quality of life of the parkinsonian patients.

Furthermore, for all UPDRS III symptom-specific subscores: gait, rigidity, akinesia and tremor, a significant improvement was observed.

Resting and action tremors can be significantly benefited from bilateral DBS in the STN, with the results showing the highest decrease compared to the other UPDRS III symptom-specific subscores. As tremor is a very disabling motor symptom of PD, reducing the quality of life of an individual in several ways, its effective alleviation using bilateral STN DBS with or without medication is a very important relief in an individual's quality of life.

Gait subscores show that it is important to use medication together with DBS for the alleviation of gait related parkinsonian symptoms, since the decrease in the gait

subscore is much higher with the med “on”/stim “on” treatment compared to med “off”/stim “on”. In the 4th year, the gait subscore in med “off”/stim “on” returns to the preoperative values.The worsening of the gait disorders is consistent with the the finding that symptoms such as gait disorder, postural instability and dysarthria are in a category of symptoms which respond less well to levodopa treatment [bonnet1987] and result from increasing severity of cerebral non-dopaminergic lesions [agid1991].

Akinesia and rigidity UPDRS III subscores with med “on”/stim “on” and med “off”/stim “on” show a sustained improvement up to 4 years after surgery, compared to baseline.

A significant decrease in UPDRS IV is observed. This is most likely due to the reduction of the levodopa equivalent dosage administered to the patients. The dyskinesia-related pain and disability together with off-periods related with levodopa medication are critical factors affecting a patient’s everyday life, and the reduction of such complications is a major advantage in the patients’ quality of life. Thus, it is evident that the stimulation of STN makes possible a substantial reduction in the dose of dopaminergic treatment.

Motor activities of daily living (UPDRS II) show a marked decrease when compared to baseline, a result consistent with the improvement shown in UPDRS III scores.

Both levodopa equivalent dosage and the number of single levodopa doses were significantly decreased. Reducing the daily levodopa dosages is beneficial due to the reduction of the medication related side effects. The reduction of the number of single daily dosages is also beneficial for the comfort of the individuals.

Non-motor activities of daily living (UPDRS I: Mentation, behavior and mood) show no significant change compared to the baseline.

Hoehn and Yahr staging scale shows a transient decrease in the PD state in the 1st and 2nd year of the follow up, followed by a return to the preoperative values in the 3rd and 4th year, indicating that the measure of the PD stage shows in essence no change by the end of the follow-up period, compared to baseline.

The MMSE scores remain in the preoperative values up to the 3rd year after surgery and decline in the 4th. Despite the decline in the 4th year, the mean MMSE score indicates a normal pre- and post - operative cognition.

The BDI scores remain in the preoperative values up to the 4th year of the follow up, indicating that depression does not worsen. However, the mean score up to the 3rd follow up year indicates minimal depression and in the 4th year the mean score falls at the boundary of minimal/mild depression. The tendency towards worsening of depression is common as PD progresses [marsh2013].

Dysphagia score in year 3 and 4 after operation is at the mild and mild/moderate categories respectively, thus, dysphagia is developed in the patients in this study. The fact that development of dysphagia occurs after the 3rd year suggests that it is a complication not clearly linked to neurostimulation, as dysphagia is commonly observed during the progression of PD. Dysphagia causes major reduction in the quality of life of individuals and it is observed in 80% of patients with PD, with difficulty in swallowing being the most affecting problem caused by PD. The swallowing impairment causes complications in the medication intake, malnutrition and can lead to aspiration pneumonia, that is one of the major cause of death in PD. In order to make the quality of life of the patients better, early identification and management of swallowing abnormalities is crucial for minimizing the likelihood of the complications that can impact the life of the patients in a negative manner.

For dysarthria, there are significant increases in the mean scores starting in year 1, compared to the baseline. This is consistent with literature findings, indicating that dysarthria precedes dysphagia [tjaden2008]. It also suggests there might be a stronger link between the development of dysarthria and neurostimulation, though dysarthria is also common as PD progresses. Reduced comprehensibility is considered the most significant functional limitation of dysarthria which affects 90% of patients with PD. However, a person's ability to communicate in a way that is considered normal can be affected due to voice and speaking rate, also affected by dysarthria.

Adverse events related to surgical procedure, device and stimulation were observed, similarly to data from other groups. These effects were carefully monitored in order to distinguish the ones that were related to the stimulation with the ones that are common adverse events of PD. These adverse events might have an impact in the activities of

daily living, thus the quality of life of the individual patients, however, the number of patients that experienced serious adverse events was very small. Three percent of the patients experienced serious permanent disability due to brain hemorrhage during surgery, a result in line with other studies [beric2001, buhmann2007, kleinerfisman2006]. Moderate transient adverse events, such as delirium, psychosis, aggressive impulsive disorder, hypomania or apathy were not frequent. Eyelid-opening apraxia [krack2005], which is very common in STN stimulation [kleinerfisman2006] was more frequent (5 patients) but still very low compared to the total number of patients (94) in the cohort. Weight gain is frequently reported in the literature [barichella2003, krack2005], but was not common in this study.

In conclusion, this study demonstrates the efficacy of bilateral STN stimulation in patients with advanced PD. The results are aligned with previous studies of patients treated with bilateral STN stimulation [schüpback2005, krack2003, deuschl2006]. Moreover, the safety of the treatment, which was assessed by carefully monitoring the adverse events, was in the acceptable range, similar to results from other studies [beric2001, buhmann2007, kleinerfisman2006].

Summary

Ninetyfour patients with advanced Parkinson's disease were assessed retrospectively one, two, three and four years after bilateral surgery for Deep Brain Stimulation of the subthalamic nucleus. The patients were treated with bilateral subthalamic nucleus stimulation and assessed under different conditions with levodopa ("medication on") and without levodopa ("medication off") with use of the Unified Parkinson's Disease Rating Scale and were compared with the preoperative "medication off" condition. In addition, the symptoms depression, cognition, dysphagia and dysarthria were monitored during the follow-up period. One year after surgery, the motor disability scores showed a neurostimulation induced improvement of 56% and 41% in the "medication on" and "medication off" conditions respectively. Four years after surgery, accompanied with the progression of Parkinson's disease, the improvement was at 45% and 25% in the "medication on" and "medication off" conditions respectively. The neurostimulation induced improvement was 57% and 45% over baseline at one year after surgery on the body side dominantly affected by Parkinson's disease in the "medication on" and "medication off" conditions respectively. At four years, the improvement was sustained at 56% in "medication on" and slightly reduced to 35% in "medication off". Symptoms tremor, akinesia and rigidity showed a markedly sustained improvement in "medication on" condition, with the improvement at four year being 57%, 40% and 50% respectively. The improvement was at 43%, 20% and 34% in "medication off" condition. Gait showed a sustained improvement only up to three years (43% at year 3) in "medication on" condition, with the improvement in "medication off" being 28% at three years. The medication related complications were markedly improved, with the improvement at one year being 39% and at four years being 34%. The motor activities of daily life showed a significant improvement of 39% and 14% in "medication on" and "medication off" conditions respectively up to three years after surgery. Levodopa dosage was drastically decreased by 33% at four years. Depression scores did not worsen during the follow-up period. Cognitive performance showed slight but significant decline in the

fourth year. Mean scores for dysphagia and dysarthria increased at four years after surgery.

Persistent adverse events related to the brain surgery were observed in 3% of the patients. A few patients experienced eyelid-opening apraxia.

In conclusion, this study demonstrates the efficacy of bilateral stimulation of the subthalamic nucleus in patients with advanced Parkinson's disease. The results are aligned with previous studies. Moreover, the safety of the treatment, which was assessed by carefully monitoring the adverse events, was in the acceptable range, similar to results from other studies.

Zusammenfassung

Vierundneunzig Patienten mit fortgeschrittener Parkinson-Krankheit wurden retrospektiv jeweils ein, zwei, drei und vier Jahre nach einer bilateralen tiefen Hirnstimulations-Operation des Nucleus subthalamicus untersucht. Die Patienten wurden unter der bilateralen Nucleus subthalamicus Stimulation mit Levodopa ("medication on") und ohne Levodopa ("medication off") unter Verwendung der Unified Parkinson's Disease Rating Skala bewertet und mit dem präoperativen "medication off" Zustand verglichen. Zudem wurden während der Nachbeobachtungszeit Symptome einer Depression, Kognition, Dysphagie und Dysarthrie überwacht. Ein Jahr nach der Operation zeigte die motorische Einschränkung eine durch die Neurostimulation-induzierte Verbesserung von 56% unter "medication on" und 41% unter "medication off" gegenüber dem Ausgangswert. Vier Jahre nach der Operation lag die Verbesserung der motorischen Einschränkung, mit dem Fortschreiten der Parkinson-Krankheit, bei 45% bzw. 25% unter "medication on" bzw. "medication off ". Auf der von der Erkrankung stärker betroffenen Seite betrug die Verbesserung ein Jahr nach der Operation auf 57% unter "medication on" und 45% unter "medication off". Im vierten Jahr nach der Operation konnte eine annähernd gleichbleibende Verbesserung von 56% unter "medication on" verzeichnet werden sowie eine Reduktion auf 35% unter "medication off". Die Symptome Tremor, Akinesie und Rigor zeigten eine auch noch im 4. Jahr deutlich anhaltende Verbesserung von 57% (Tremor), 40% (Akinesie), 50% (Rigor) unter "medication on" respektive von 43%, 20% bzw. 34% unter "medication off". Das Gangbild zeigte nur bis zum dritten Jahr (43% im dritten Jahr) eine dauerhafte Verbesserung unter "medication on" wobei eine Verbesserung unter "medication off" auf 28% gesehen wurde. Komplikationen im Zusammenhang mit der Medikation wurden deutlich reduziert, wobei die Verbesserung nach einem Jahr bei 39% und im vierten Jahr bei 34% lag. Die motorischen Aktivitäten des täglichen Lebens zeigten bis zu drei Jahre nach der Operation eine signifikante Verbesserung von 39% bzw. 19% unter "medication on" bzw. "medication off". Die benötigte Levodopa-Dosis sank nach vier Jahren drastisch um 33%. Der mittlere Depressionswert blieb während des gesamten

Beobachtungszeitraumes unverändert. Die kognitive Leistung war bis zum dritten Jahr unverändert, im vierten Jahr jedoch verschlechterte sie sich. Die mittleren Werte für Dysphagie und Dysarthrie stiegen vier Jahre nach der Operation an.

Anhaltende Nebenwirkungen im Zusammenhang mit der Gehirnoperation wurden bei 3% der Patienten beobachtet. Einige Patienten erlitten eine Augenlid-Öffnungs-Apraxie.

Zusammenfassend belegt diese Studie die Wirksamkeit der bilateralen Stimulation des Nucleus subthalamicus bei Patienten mit fortgeschrittener Parkinson-Krankheit. Die Ergebnisse stimmen mit ähnlichen Studien überein. Darüber hinaus lag die Sicherheit der Therapieform, die durch sorgfältige Überwachung der Nebenwirkungen beurteilt wurde, im akzeptablen Bereich, welches den Ergebnissen anderer Studien entspricht.

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Die statistische Auswertung erfolgte nach Anleitung durch PD Dr. Sorin Breit eigenständig.

Ich versichere, das Manuskript selbstständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Die Datenrecherche für die vorliegende Dissertation wurde selbstständig durchgeführt.

Signed _____ (Nefeli Ioannou)

on _____ in Berlin

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