Striatal dopamine transporter availability and individual clinical course within the 1-year follow-up of deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease

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1 Introduction

First described by James Parkinson in his “Essay on the Shaking Palsy” in 1817 Parkinson’s disease (PD) is a complex progressive neurodegenerative disease characterized primarily by motor symptoms and a spectrum of neuropsychiatric and other nonmotor symptoms.[44,85] It is a common disorder with a worldwide prevalence of approximately 0.3% in the population over the age of 40 and an incidence of 8-18.6 per 100,000 person years.[15, 45] With a mean age of 70.5 years at diagnosis PD mainly affects the elderly population.[86]

The degeneration of dopaminergic nerve cells in the substantia nigra and hence the dopaminergic depletion in the basal ganglia circuits cause PD. There is no curative treatment for PD available so far, instead symptomatic treatment aims to reduce symptoms and increase the patients’ quality of life. Possible therapeutic methods include pharmacologic and adjunctive as well as surgical treatment, such as deep brain stimulation (DBS). Even when treated with a combination of these, patients still suffer from parkinsonian symptoms and side effects resulting from the therapy may affect patients' quality of life. Thus, treatment of PD is in need of further improvement and therefore ongoing investigation into other therapeutic options is necessary.

1.1 Parkinson’s Disease Pathophysiology

The loss of dopaminergic nerve cells in the substantia nigra pars compacta (SNc) leads to a decrease in available dopamine in the basal ganglia and is responsible for the development of PD. Thus, the connection between the basal ganglia and the thalamus and therefore to the motor cortex is disturbed. The basal ganglia are a complex network consisting of several parts: the substantia nigra, the striatum with the caudate nucleus and putamen, the globus pallidus (globus pallidus internus GPi, globus pallidus externus GPe) and the subthalamic nucleus (STN). Understanding the basal ganglia circuit is essential for understanding the development of motor symptoms in PD. The substantia nigra influences the striatum both excitatory and inhibitory by dopaminergic input to the dopamine receptors.[25] Mainly located in the dorsal striatum, five dopamine receptors are described (D1-D5) with D1 und D2 being most relevant for parkinsonian pathophysiology.[25] There are two output pathways from the striatum named direct and indirect pathway.[25,57]

In the direct pathway the striatal D1 receptors receive excitatory input from SNc. By doing so the striatum directly inhibits GPi and substantia nigra pars reticulata (SNr) by gamma-aminobutyric acid (GABA). Through the indirect pathway SNc sends inhibitory signals to the striatal D2 receptors. The striatum uses GABAergic efferents to inhibit the GPe. GPe affects the STN inhibitory using GABA. The STN gives excitatory efferents using glutamate to GPi and SNr. At this point both pathways end with the GPi pointing to the thalamus und the thalamus affecting the motor cortex excitatory.[25]

In PD the dopaminergic depletion in the nigrostriatal pathway lead to the disinhibition of STN which in turn causes the disinhibition of GPi and SNr. Therefore, an overinhibition of the thalamus develops causing a low excitation of the motor cortex. This change in the basal ganglia circuit is made responsible for parkinsonian motor symptoms such as bradykinesia.[57]

Nevertheless, this description of the basal ganglia circuit is a simplified model and the truth is supposed to be much more complex.

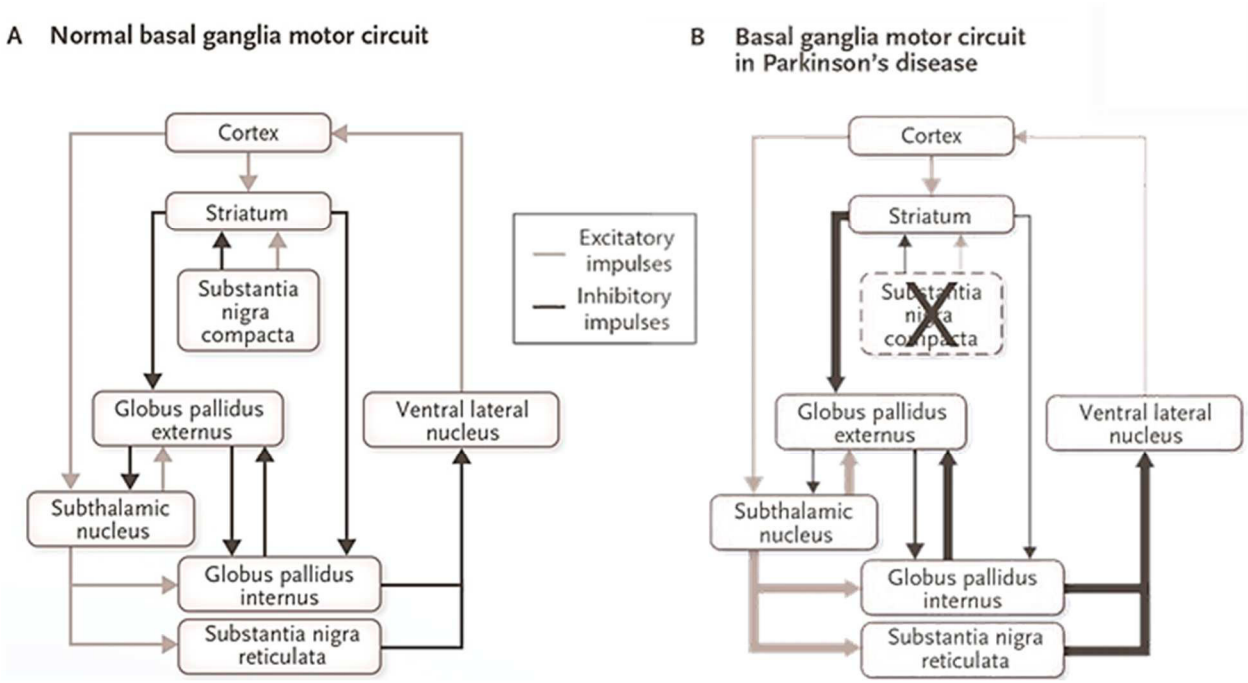

Figure 1. *Model of the normal basal ganglia motor circuit (A) versus pathological basal ganglia motor circuit in Parkinson's disease (B).* Picture from "Deep-brain stimulation--entering the era of human neural-network modulation", New England Jounal of Medicine 2014 Oct 9;371(15):1369-73.

1.2 Parkinson's Disease Clinical Manifestation

PD is characterized by typical motor symptoms and a variety of nonmotor symptoms. The leading motor symptoms are rest tremor, rigidity, bradykinesia as well as postural instability.

Tremor, described as "pill-rolling" tremor, classically appears as a rest tremor which normally decreases with action and is worst at rest.[48] Its frequency lies between three to seven Hertz, most often between four and five Hertz.[19] Tremor is a cardinal symptom of PD since it appears as the first parkinsonian symptom in 70% - 80% of patients and 79% - 100% are affected at some point during disease course.[33] Usually, tremor starts unilaterally with the hand being the most common localization.[74]

Bradykinesia, a general slowness of movement, is the most common symptom of PD as it affects about 80% of patients at the beginning of the disease.[61]

About 75% - 90% of patients experience rigidity during disease course.[74] It starts unilaterally and occurs ipsilaterally to tremor provided tremor is there.[61,60]

Rigidity describes a high resistance to passive movement and can present as cogwheel rigidity or lead-pipe rigidity, for example.[61]

Postural instability means the patients' imbalance and the tendency to fall due to an impairment of postural reflexes.[42] Normally, it affects patients at a later stage during the course of disease.[42]

Apart from those motor symptoms, parkinsonian patients usually suffer from a broad spectrum of nonmotor symptoms, additionally. These can be neuropsychiatric, such as cognitive dysfunction or dementia, but also psychosis, hallucinations and mood disorders. Furthermore, patients report olfactory, autonomic and gastrointestinal dysfunctions as well as pain and sensory disturbances.[44]

1.2.1 Parkinson's Disease Diagnosis

PD is a clinical diagnosis and requires the presence of bradykinesia and either rest tremor or rigidity, the combination of which is defined as parkinsonism.[65,84] Classically, the symptoms show up unilaterally at the beginning and the asymmetry persists as the disease progresses.

Additional diagnostic criteria (supportive criteria) include the positive response to dopaminergic therapy, the occurrence of levodopa induced dyskinesia, the presence of rest tremor of a limb as well as olfactory loss or cardiac sympathetic denervation which can be visualized by iodine-123 ([^{123}I]) labeled metaiodobenzylguanidine (MIBG) scintigraphy.

There are numerous exclusion criteria and red flags making the diagnosis of PD very unlikely.[65,84] According to the Movement Disorder Society the establishment of the PD diagnosis has to be made by an "expert clinician" and requires the presence of parkinsonism plus two or more supportive criteria as well as the absence of exclusion criteria or red flags.[26,65,84]

1.2.1.1 Unified Parkinson's Disease Rating Scale

For the assessment of the severity of symptoms the Unified Parkinson's Disease Rating Scale (UPDRS) is used. It consists of the following 4 parts:

I. Non-motor aspects of experiences of daily living
II. Motor aspects of experiences of daily living
III. Motor examination
IV. Motor complications.

Parts I, II and IV are evaluated in an interview between the clinician and the patient, part III requires a clinical examination.[26] Every question or task is scored with zero to four credits with the following meaning:

- Zero: normal finding
- One: "symptoms/signs with sufficiently low frequency or intensity to cause no impact on function"
- Two: "symptoms/signs sufficiently frequent to cause a modest impact on function"
- Three: "symptoms/signs sufficiently frequent or intense to impact considerably, but not prevent, function"
- Four: "symptoms/signs" that prevent function"[26]

All in all, 199 credits can be reached which means maximal impairment.[26]

1.2.1.2 Imaging

Neuroimaging, such as magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT), is not obligatory to establish the diagnosis, but can be useful to exclude other conditions.[75,80,84] SPECT using [^{123}I] N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([^{123}I] FP-CIT) as a ligand, so called dopamine transporter (DAT) scan (DaTSCAN^{TM}; GE Healthcare) offers the opportunity of striatal DAT imaging. It allows to differentiate between PD and other parkinsonian syndromes with nigrostriatal degeneration from patients without nigrostriatal degeneration, for example with essential tremor or drug-induced parkinsonism where the DAT scan is normal. Therefore it should be applied early in the disease course in clinically unclear cases. [6,37] The discrimination between specific parkinsonian syndromes is, however, not possible.[6,37] For selecting patients for clinical trials, a DAT SPECT that demonstrate dopaminergic degeneration can help to confirm the diagnosis if necessary, too.[43,64]

1.2.2 Parkinson's Disease Subtypes

As described above PD is a disorder with numerous clinical presentations. Of course, not all patients experience the full spectrum of symptoms. Therefore, the disease has been classified into different clinical subtypes according to the most present symptoms.[83] The understanding of the different phenotypes may also be helpful for gaining more information about the pathophysiology and pathogenesis of PD.[83] As the disease progresses a switch between the subtypes is possible.[11]

PD was originally divided into a tremor dominant type and a postural instability and gait difficulty type.[36] Later on these subtypes were renamed into tremor dominant, equivalence and akinetic rigid type based on the UPDRS score.[71] As their names imply the tremor dominant subtype is dominated by tremor whereas the akinetic rigid subtype is mainly associated with bradykinesia and rigidity.[83]

To differentiate between the subtypes is not only important for clinical decisions but also allows a statement regarding the prognosis. The tremor dominant type, for example, goes along with a slower disease progression and less neuropsychiatric symptoms.[36] Moreover, differences in imaging have been noted, e.g. on fluorodopa PET scans and SPECT scans.[88] Some studies have shown a correlation between DAT availability measured by means of SPECT and severity of symptoms in akinetic rigid but not in tremor dominant patients.[16,70]

1.3 Parkinson's Disease Therapy

1.3.1 Pharmacologic Therapy

Pharmacologic treatment of PD is symptomatic only. None of the available medication is proven to be disease-modifying or neuroprotective.[21]

The leading substances are monoaminoxidase-B (MAO-B) inhibitors, amantadine, anticholinergic drugs apart from levodopa and dopamine agonists.[12,18]

MAO-B inhibitors and amantadine are suitable as monotherapy or initial therapy for patients with mild symptoms.[12] Studies have shown that MAO-B inhibitors have a beneficial effect over placebo in terms of reduction of UPDRS motor score as well as the reduction of levodopa intake and motor fluctuations.[35] Similarly, amantadine monotherapy verifiably improves tremor, bradykinesia and rigidity.[73]

Patients under the age of 65 suffering from tremor as the main symptoms without relevant bradykinesia may benefit from anticholinergic drugs. Anticholinergic treatment is also known to cause neuropsychiatric side effects, such as confusion, hallucination and memory impairment, which occur more often among patients aged 65 and older.[38]

Levodopa works best against parkinsonian motor symptoms but its use goes along with a high risk of motor complications, like dyskinesia, dystonia and motor fluctuations and also neuropsychiatric complications.[12,21]

By contrast, dopamine agonists like ropinirole, pramipexole or rotigotine have an intermediate effect on motor symptoms but are associated with less motor complications than levodopa. Nevertheless, dopamine agonists are known to cause somnolence, impulse control disorders and hallucinations.[12,21]

In summary, it can be said that treatment with MAO-B inhibitors, amantadine or anticholinergic drugs only, can be reasonable in younger patients with mild symptoms whereas patients under the age of 65 with moderate symptoms benefit best from levodopa or dopamine agonists as initial therapy.[81] In patients aged 65 or older with moderate symptoms mostly levodopa is used due to its stronger effect on motor symptoms and a low tolerance of dopamine agonists because of their neuropsychiatric side effects.[12,21,63]
In patients suffering from severe symptoms levodopa is the superior therapy regarding quality of life, activities of daily life and motor function.[18]

Motor Complications

Levodopa therapy is commonly accompanied by motor complications like motor fluctuations and dyskinesia. About 40 % of patients report about them after five or more years of levodopa treatment.[1]
These effects are due to the decreasing ability of presynaptic neurons to store levodopa during the course of disease. Also, temporary overstimulation of dopamine receptors is held responsible for motor complications. Furthermore, with 90 minutes levodopa has a relatively short half-life.[22,67]
Motor fluctuations describe the different periods when positive levodopa response alleviates symptoms and when parkinsonian symptoms reoccur. They usually present as so called “wearing-off” phenomenon, about three to four hours after the last dose of levodopa. Unpredictable “off”- periods and failure of “on” response, meaning no positive impact of a dose, are possible. Clinically, freezing of gait or acute akinesia can be observed.[22,67]
Dyskinesia is defined as involuntary movement, e.g. chorea, ballism, dystonia or myoclonus. Dyskinesia can occur anytime, as peak-time dyskinesia in the “on” state or as “wearing-off” dystonia. Diphasic dyskinesia with the first beginning during the “on” state and a second period during the “wearing-off” is possible, too.[68]
There are several possibilities to handle motor complications. Dietary, dose and interval adjustment as well as additional medication should be mentioned as conservative ways. Also, DBS as surgical therapy has to be considered.[22,67]

1.3.2 Surgical Therapy – Deep Brain Stimulation

DBS is a surgical procedure in which electrodes are implanted to special target regions in the brain and connected to a neurostimulator which sends electrical impulses to the selected brain tissue. It is the most often applied surgical therapy in advanced PD.[17] It is completely reversible since in contrast to lesioning procedures it does not destroy brain tissue. The two main targets are GPi and STN. Both methods are equally safe and almost equally effective with DBS of the STN (STN-DBS) leading to a stronger reduction of parkinsonian medication and DBS of the GPi (GPi-DBS) reducing dyskinesia better.[20,58] The best clinical outcome of DBS is comparable to the best levodopa response regarding motor symptoms. DBS does not treat behavioral or cognitive impairment.[97]

1.3.2.1 Patient Selection

Best suitable patients for DBS are PD patients which respond to levodopa therapy but suffer from severe motor complications and therefore experience disability or a decreased quality of life despite optimal conservative treatment.[60,97]

Patients with secondary parkinsonism or atypical parkinsonian disorders do not profit from DBS.[97] Also, frank dementia or severe cognitive impairment are exclusion criteria for DBS.[97] Since DBS is under suspicion to cause increased suicidality patients should be screened for mood disorders and suicidality preoperatively.[89]

1.3.2.2 Operative Technique

Exact preoperative planning and selection of entry and target structures is necessary. Therefore, four bone anchors are placed into the tabula externa in the regions of drill hole trepanation under local anesthesia. Subsequently, patients undergo a 3D MRI (T1w, T2w) and a spiral CT which is required for the production of an individual stereotactic frame. By means of imaging target and entry coordinates are determined.

Intraoperative the stereotactic frame is placed first by using the previously implanted bone anchors. Next, drill holes are trepanned and the dura is incised bifrontally. Afterwards the reference and stimulation electrodes are connected and placed to the target structure. An intraoperative test stimulation shows the best motoric answer and reveals where the permanent electrodes can be placed. After placing the permanent electrodes their lead is connected via a wire to an impulse generator which is implanted in the chest wall, similar to a pacemaker. High-frequency electric stimulation can now begin. Finally, the bone anchors are removed and the wounds closed.[53]

1.3.2.3 Efficacy

Studies have shown that bilateral DBS is superior to conservative management alone in patients with advanced PD and motor complications regarding the motor symptoms.[14,91]

Also, the “EARLYSTIM” trial investigated the efficacy of DBS in relatively young patients with early motor complications. Over the duration of two years 251 levodopa-responsive PD patients with a mean age of 53, a mean duration of disease of eight years and a mean levodopa use over five years were evaluated in two groups: one group undergoing DBS and medical therapy and one group treated by medical therapy alone. Patients suffering from dementia were excluded.[72]

The trial showed that the combination of DBS and medical therapy is superior regarding the self-assessed quality of life, activities of daily living, motor symptoms, levodopa induced motor complications and time with good mobility.[72]

As a predictive factor of success, the response to levodopa should be considered, since symptoms not alleviated by levodopa will most likely not be improved by DBS.[92]

1.3.2.4 Complications

As every surgical procedure DBS is accompanied by several complications, which can be divided in surgical, hardware and cognitive complications. The side effects reported in four studies including 360 patients were reviewed by the American Academy of Neurology showing death in 0.6% and permanent neurologic damage in 2.8% of patients.[8,49,45,48,67] Temporary complications were infection (5.6%) and intracerebral hemorrhage (3.1%) as well as confusion (2.8%) and seizures (1.1%) to name only the most frequent.[8,49,45,67] In a different review of STN-DBS complications the number of patients suffering from transient confusion was reported higher (16%) whereas the share of cases of intracerebral hemorrhage (3.9%), infection (1.7%) and seizures (1.5%) were comparable.[39]

The most frequent hardware complications include malfunction, migration or fracture of the electrodes and wires in about five percent of patients followed by lead misplacement (2-3%) making replacement necessary. Malfunction of the extension wire or impulse generator (4%), infection (2%) and allergic reaction to the implanted material (<1%) have also been reported.[39,62]

Paresthesia, hemiballism, dyskinesia and dysarthria have occurred as stimulation-dependent complications.[39,62] Apart from the increased suicidality DBS seems to cause no significant cognitive adverse effects except from the deterioration of verbal fluency.[4,46,89,96]

1.3.2.5 Mechanism of action

Although a lot of research has gone into understanding how DBS works it is still a highly-controversial topic of debate. Numerous hypotheses exist discussing the impact on neurotransmitters, synaptic plasticity and neuroprotective effects.

First of all, the time course by which DBS alleviates symptoms indicates that multiple processes are involved. For example, tremor improves within seconds, rigidity and bradykinesia within minutes to hours and axial symptoms after hours to days. When stimulation is turned off symptoms reappear in the same time span as they improved with stimulation turned on.

Neurotransmitter hypothesis

Different studies show that DBS influences the basal ganglia circuits due to a change in release of neurotransmitters. So, DBS is supposed to cause a frequency-dependent increase of extracellular glutamate in the GPi in rodents and in the striatum as well as GABA in the SNr in rats.[94,95] The role of dopamine is not entirely clear, since both STN and GPi-DBS have shown to induce a release of dopamine in humans but clinically the impact of DBS seems to be additive to the impact of levodopa which could suggest a dopamine-independent mode of action.[29,52,99] However, different studies present quite different results, some of which deny a striatal dopamine increase altogether.[9,32,54] The effects on neurotransmitter release have been described and summarized to be inhibitory, excitatory or disruptive. The inhibition hypothesis claims STN-DBS causes an inhibition of STN neurons due to depolarization block, inactivation of currents and activation of inhibitory efferents. This hypothesis is in line with the fact that DBS leads to similar effects as lesioning surgery performed in the past. In contrast to this, the excitation hypothesis starts from the assumption that DBS causes increased firing rates in GPi, GPe and SNr neurons through excitatory projections from the STN.[24,54,69] Additionally, studies addressing the effect of DBS on downstream targets most constantly reported efferent axons to be activated.[2,28,66]

A third approach suggests a totally different explanation altogether: the disruption hypothesis states that stimulation changes the neurotransmitter release in the stimulated nucleus generally and therefore leads to a dissociation from in- and outputs so that the pathological information flow is disrupted without causing explicit inhibition or exhibition.[3,13]

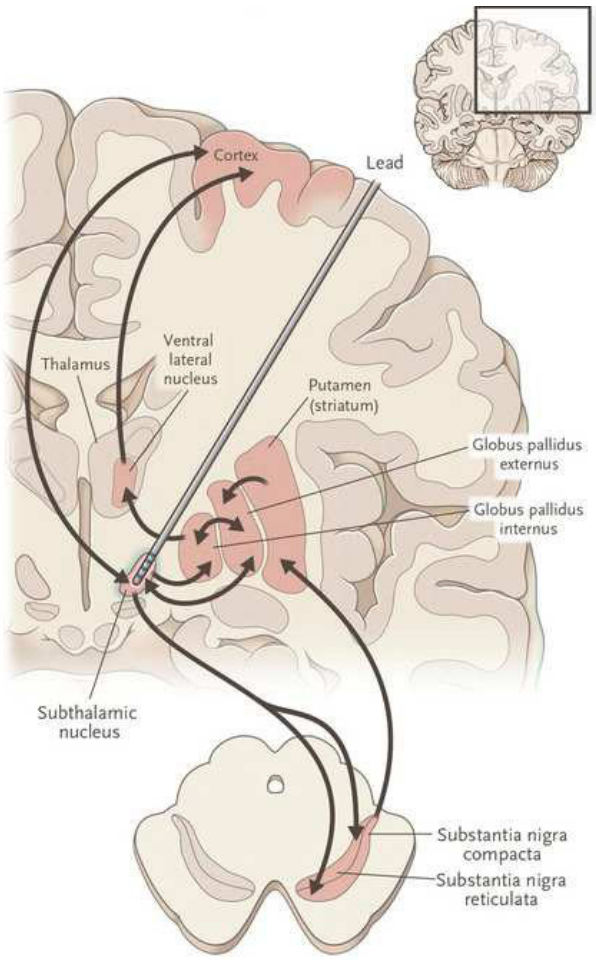

Figure 2. *Deep Brain Stimulation of the subthalamic nucleus influences the pathological basal ganglia motor circuit in Parkinson's Disease.* Picture from "Deep-brain stimulation-entering the era of human neural-network modulation", New England Jounal of Medicine 2014 Oct 9;371(15): 1369-73.

Neurorestorative Approaches

In rats STN-DBS has been revealed to cause different forms of synaptic plasticity in different STN neurons, i.e. short- and long-term potentiation but also long-term depression.[77] Up to this date, however, there has been no evidence showing the same effects for human brains.

Nevertheless, there are some hints for synaptic plasticity in humans: A special glucose metabolism pattern on fluoro-D-glucose (FDG)-PET imaging, named PD-related metabolic pattern, has been observed in PD patients.[98] DBS has been shown to reduce the expression of this pattern and is thus supposed to regularize network activity.[5,23]

Additionally, DBS has been proven to normalize the PD's typically abnormal regional cerebral blood flow.[10,40]

Recently, one patient was examined via functional MRI before and five months after DBS with the result that the brain's structural connectivity changed to values more similar to healthy control probands.[87] Similar to this case report Horn et al. investigated structural connectivity in PD patients treated with STN-DBS using functional MRI as well and showed modulation of connections towards healthy control with stimulation turned on in a resting state.[34]

Since STN-DBS has been reported to increase the survival of SNc neurons in rats DBS has been suggested to have a neuroprotective effect in terms of slowing degeneration of dopaminergic neurons.[50,82] The same neuroprotective effect was found in primates and non-primates in further studies.[76,90] In concordance to this, a neuroprotective growth factor (brain-derived neurotrophic factor) has shown to be induced by STN-DBS in the SN, GPi and motor cortex.[78] However, progression of PD symptoms has been observed despite clinically successful DBS. Furthermore, a PET study reported decrease of dopamine after DBS similar to patients who did not undergo DBS.[31,32] Additionally, a study comparing frozen brain tissue post-mortem from PD patients with and without STN-DBS concerning striatal dopamine showed no difference between both groups not indicating a neuroprotective effect of STN-DBS.[63] All in all, exactly like synaptic plasticity, neuroprotection and specifically its mode of action has to stay a field of active investigation.

Aim of our work

Although DBS is frequently applied in advanced PD the mechanism by which DBS, in particular DBS of STN, works is still not well understood.[17] Specifically, the question whether the restoration of motor function is dopamine mediated plays an important role for clinical therapy planning. Our study investigates whether there is an association to DAT availability preoperatively and whether DBS changes DAT over the duration of one year. In addition, we tried to find correlations between DAT and patient-related parameters, such as age, gender, duration of disease, individual UPDRS scores and PD subtypes. Altogether, the study has the aim to contribute to a better understanding of the basal ganglia's functional anatomy, the impact of DBS on their functionality and the following clinical relevance for patient selection and the patients' outcome.

2 Publication

Striatal dopamine transporter availability and individual clinical course within the 1-year follow-up of deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease

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CLINICAL ARTICLE

Striatal dopamine transporter availability and individual clinical course within the 1-year follow-up of deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease

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OBJECTIVE Degeneration of dopaminergic neurons in the substantia nigra projecting to the striatum is responsible for the motor symptoms in Parkinson's disease (PD). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established procedure to alleviate these symptoms in advanced PD. Yet the mechanism of action, especially the effects of STN-DBS on the availability of striatal dopamine transporter (DAT) as a marker of nigrostriatal nerve cell function, remains largely unknown. The aim of this study was therefore to evaluate whether 1) DAT availability changes within 1 year of STN-DBS and 2) the clinical outcome can be predicted based on preoperative DAT availability.

METHODS Twenty-seven PD patients (mean age 62.7 ± 8.9 years; mean duration of illness 13.0 ± 4.9 years; PD subtypes: akinetic-rigid, n = 11; equivalence, n = 13; and tremor-dominant, n = 3) underwent [^{123}I]FP-CIT SPECT preoperatively and after 1 year of STN-DBS. DAT availability as determined by the specific binding ratio (SBR) was assessed by volume of interest (VOI) analysis of the caudate nucleus and the putamen ipsilateral and contralateral to the clinically more affected side.

RESULTS Unified Parkinson's Disease Rating Scale (UPDRS) III scores improved significantly (mean preoperative on medication 25.6 ± 12.3, preoperative off medication 42.3 ± 15.2, postoperative on medication/off stimulation 41.4 ± 13.2, and postoperative on medication/on stimulation 16.1 ± 9.4; preoperative on medication vs postoperative on medication/on stimulation, $p = 0.006$), while the levodopa-equivalent daily dose was reduced (mean preoperative 957 ± 440 mg vs postoperative 313 ± 189 mg, $p < 0.001$). The SBR did not differ significantly before and 1 year after DBS, regardless of PD subtype. Preoperative DAT availability was not related to the change in UPDRS III score, but the change in DAT availability was significantly correlated with the change in UPDRS III score (contralateral head of the caudate VOI, $p = 0.014$; contralateral putamen VOI, $p = 0.018$).

CONCLUSIONS Overall, DAT availability did not change significantly after 1 year of STN-DBS. However, on an individual basis, the improvement in UPDRS III score was associated with an increase in DAT availability, whereas DAT availability before STN-DBS surgery did not predict the clinical outcome. Whether a subtype-specific pattern of preoperative DAT availability can become a reliable predictor of successful STN-DBS must be evaluated in larger study cohorts.

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KEYWORDS Parkinson's disease; deep brain stimulation; dopamine transporter; SPECT; functional neurosurgery

In Parkinson's disease (PD), the degeneration of dopaminergic neurons in the substantia nigra is causative for the development of motor symptoms. Dopamine deficiency in the substantia nigra leads to less excitement of the striatum, which in turn causes increased excitation of the subthalamic nucleus (STN) and the pars interna of the globus pallidus. These effects result in thalamic inhibition and thus lower thalamocortical activity, leading to parkinsonian symptoms such as akinesia and rigidity.[1,2]

The stereotactic treatment of movement disorders expe-

ABBREVIATIONS DAT = dopamine transporter; DBS = deep brain stimulation; D2R = dopamine D2 receptor; LEDD = levodopa-equivalent daily dose; PD = Parkinson's disease; SBR = specific binding ratio; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale; VOI = volume of interest; [^{123}I]FP-CIT = [I-123] *N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane.

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rienced a renaissance in functional neurosurgery with the application of deep brain stimulation (DBS). The success of this therapy has brought functional neurosurgical therapy into the focus of interest for those patients who will benefit from DBS. Initially, stereotactic functional neurosurgery was used to lesion subcortical structures, including the STN and the globus pallidus, for the treatment of PD.[3,4] Bilateral simultaneous stimulation is currently the most reliable and best-in-class neurosurgical method in terms of positive effects on motor symptoms, such as akinesia, tremor, and rigidity. This therapy is suitable for patients with bilateral symptoms as well as for patients with purely asymmetrical symptom manifestation.[5] Although DBS may reduce the dose of levodopa and other antiparkinsonian drugs, DBS is not a cure, as it only treats symptoms. Based on current knowledge, functional stereotaxy is justified only in PD and not in atypical neurodegenerative parkinsonian syndromes, although DBS is a reliable and reproducible method.[5,6]

While DBS is widely accepted as the surgical therapy for the improvement of motor symptoms, the selection of candidates who will benefit from DBS remains challenging. The potential outcome of DBS therapy can be predicted by the responsiveness of motor symptoms to dopaminergic medication.[7] Imaging methods that are capable of visualizing and quantifying nigrostriatal dopaminergic transmission might also provide important additional information on the outcome and the individual clinical course after DBS surgery.[8] Thus, SPECT using dopamine transporter (DAT)–specific radiotracers such as [I-123] *N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([^{123}I]FP-CIT; also known as [^{123}I]Ioflupane) helps to support the clinical diagnosis of PD, although it cannot primarily be seen as a diagnostic study.[9]

The measurement of the availability of presynaptic DAT allows quantitative assessment of the integrity and function of the nigrostriatal dopaminergic system before DBS surgery as well as monitoring of the course during DBS treatment.[8] However, the mechanism of how DBS works is not yet well understood. In a pilot study in patients with advanced PD, we were able to demonstrate that striatal [^{123}I]FP-CIT binding did not change between the scan prior to STN-DBS surgery and the 1-year follow-up investigation, while [^{123}I]iodobenzamide binding as a marker of postsynaptic dopamine D2 receptor (D2R) availability increased up to 16%.[10] These data suggest that clinical improvement and reduction of dopaminergic drugs in patients with advanced PD undergoing bilateral STN-DBS are paralleled by stable DAT and recovery of striatal D2R availability within a 12-month period after surgery. To explore the utility of DAT imaging for the selection of appropriate candidates for functional neurosurgery, or for DBS in particular, a recent SPECT study applying [^{123}I]FP-CIT to assess DAT availability and SPECT revealed that the specific binding ratio (SBR) in the striatum positively correlated with Unified Parkinson's Disease Rating Scale (UPDRS) motor score (UPDRS III) improvement after levodopa challenge before surgery and with the reduction of the levodopa-equivalent daily dose (LEDD) after surgery.[7] These data suggest that DAT SPECT may be useful in STN-DBS candidate selection and in the identification of the therapeutic mechanism of STN-DBS in patients with advanced PD and motor symptom fluctuations. However, to translate these findings into clinical routine, further replication is needed by enlarging the study samples and by following up the individual course of DAT availability and motor improvement.

Here, we aim to contribute to a better understanding by 1) determining changes in DAT availability after DBS and 2) assessing whether the clinical outcome (motor symptoms assessed by UPDRS III and LEDD reduction) is predictable prior to the DBS procedure by DAT availability.

Methods

Study Participants

The study was approved by the local ethics committee, and written informed consent was obtained from every patient. We included 27 PD patients (mean age [± SD] 62.7 ± 8.9 years, mean duration of disease 13.0 ± 4.9 years) who subsequently underwent STN-DBS (Table 1). All three subtypes of PD were represented: tremor-dominant PD (n = 3; mean age 55.7 ± 14.5 years, duration of disease 13.3 ± 7.8 years), akinetic-rigid PD (n = 11; mean age 64.6 ± 8.7 years, mean duration of disease 12.8 ± 6.2 years), and equivalence-type PD (n = 13; mean age 62.7 ± 7.5 years, mean duration of disease 13.0 ± 3.1 years). The mean LEDD was 957 ± 440 mg preoperatively and 313 ± 189 mg postoperatively.[11]

Preoperative assessments consisted of structural MRI and neurological, cognitive, neuropsychological, and levodopa response testing. UPDRS III was used to assess motor symptoms preoperatively under medication (preoperative on) and with antiparkinsonian medication discontinued for 12 hours preoperatively (overnight withdrawal, preoperative off) and 12 months postoperatively under medication with the stimulator turned on (postoperative on/on) and off (postoperative on/off). For the planning procedure of STN-DBS, MRI with maximum resolution and a small slice thickness (1 mm) was used. Contrast-enhanced 3D T1-weighted MRI (Intera, Philips) was used to provide spatial orientation and depict the medium-contrasted and potentially compromised blood vessels. In the same session, supplemental T2-weighted 1.5T MRI (Intera) was used to map the actual target structure, the STN, and adjacent anatomical structures, such as the striatum. Both image modalities were then merged layer by layer. Stereotaxy was performed using a rigid stereotactic frame ZD (Zamorano-Dujovny, ZD, Stryker) or an individualized microTargeting Platform (FHC).

In all PD cases, bilateral electrode insertion (model 3389, Medtronic) was performed via a frontal drill hole. Four multichannel microelectrodes with 5 trajectories were applied. The exact target was identified by the best response to stimulation via macroelectrodes. Technical devices were as described.[12,13] The connection of the permanent electrode with a pectorally placed pulse generator was made using extension electrodes and was performed in the same operation.

SPECT Imaging

Before STN-DBS, SPECT imaging applying [^{123}I]FP-CIT was performed in each patient. Additionally, SPECT

TABLE 1. Epidemiological data and results of preoperative and 1-year postoperative UPDRS III scores and LEDD

	PD Subtype			
	All	Tremor-Dominant	Akinetic-Rigid	Equivalence
No. of patients	27	3	11	13
Female	10	0	3	7
Male	17	3	8	6
Mean age, yrs	62.7 ± 8.9	55.7 ± 14.5	64.6 ± 8.7	62.7 ± 7.5
Mean duration of disease, yrs	13.0 ± 4.9	13.3 ± 7.8	12.8 ± 6.2	13.0 ± 3.1
Mean UPDRS III score*				
Preop on	25.6 ± 12.3	42.0 ± 13.5	22.0 ± 9.5	24.9 ± 12.1
Preop off	42.3 ± 15.2	70.0 ± 26.9	39.1 ± 13.0	40.2 ± 10.4
Postop on/on	16.1 ± 9.4	16.0 ± 6.1	18.3 ± 12.9	14.4 ± 7.5
Postop on/off	41.4 ± 13.2	44.3 ± 21.5	38.5 ± 8.5	42.5 ± 14.1
Mean LEDD, mg				
Preop	957 ± 440	506 ± 39	1150 ± 491	920 ± 343
Postop	313 ± 189	350 ± 141	398 ± 223	230 ± 138

Mean values are presented as the mean ± SD.
* Off = off medication; on = on medication; on/off = on medication/off stimulation; on/on = on medication/on stimulation.

imaging was repeated after 1 year of STN-DBS. The scanning procedure was performed using a standardized protocol with SPECT data acquisition 3 hours after intravenous application of approximately 185 MBq [^{123}I]FP-CIT by applying a brain-dedicated camera system (Ceraspect, Digital Scintigraphics Inc.; spatial resolution 7–8 mm full width at half maximum). Imaging data were acquired in a 128 × 128 × 64 matrix within 120 projections (3 parallel-hole ^{123}I-dedicated collimators, 360° rotation, 15 sec/projection, 30-minute scanning time). Sixty-four transaxial slices were reconstructed applying filtered back projection (Butterworth filter, 9th order, cutoff = 0.45 Nyquist frequency). Attenuation correction was performed using Chang's first-order method ($\mu = 0.12\ cm^{-1}$).[14–16]

Imaging Data Processing and Analysis

Individual preoperative MRI data sets were spatially reoriented according to the anterior commissure–posterior commissure onto a standard brain data set using the image processing software PMOD (version 3.5, PMOD Technologies LLC). The individual SPECT images were manually reoriented to the individual preoperative MRI. For analysis, the hemispheres from several patients were switched to standardize ipsilateral and contralateral structures according to the more affected body side. Volumes of interest (VOIs) for the head of the caudate nucleus and the putamen were hand drawn on both hemispheres on 5 consecutive transversal slices of the reoriented individual MRI data sets (PMOD 3.5) and transferred to coregistered SPECT imaging data (Fig. 1).

The SBR was calculated based on the tracer uptake in the striatal VOIs (specific binding of the radioligand) and the tracer uptake in the occipital VOI (nonspecific binding; reference region). It was defined as the ratio of mean count concentration in the striatum (specific binding) to the occipital cortex as a reference region (unspecific binding) (Fig. 1).[2]

Statistical Analysis

All data were tested for normal distribution (Shapiro-Wilk test). Differences in pre- and postoperative conditions were calculated using paired t-tests (normal distribution) or Wilcoxon tests (non-normal distribution). Group differences between PD types were assessed by ANOVA (normal distribution) or Kruskal-Wallis and Mann-Whitney U-tests (non-normal distribution). Correlation analyses were evaluated with Pearson's correlation. Results were considered as statistically significant at $p < 0.05$. For all statistical analyses, IBM SPSS for Windows version 24.0 (IBM Corp.) was used.

Results

Clinical Outcome

After STN-DBS, the UPDRS III score significantly decreased on medication from pre- to postoperatively (preoperative on 25.6 ± 12.3 vs postoperative on/on 16.1 ± 9.4,

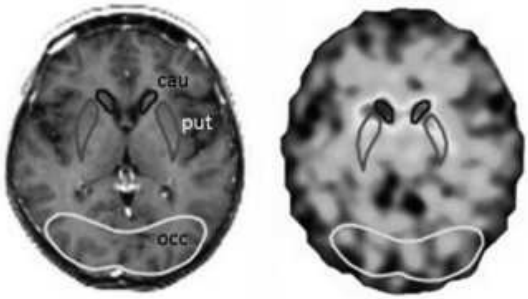

FIG. 1. Axial MR (**left**) and SPECT (**right**) images showing the caudate nucleus (cau), putamen (put), and occipital cortex (occ; reference region) VOIs.

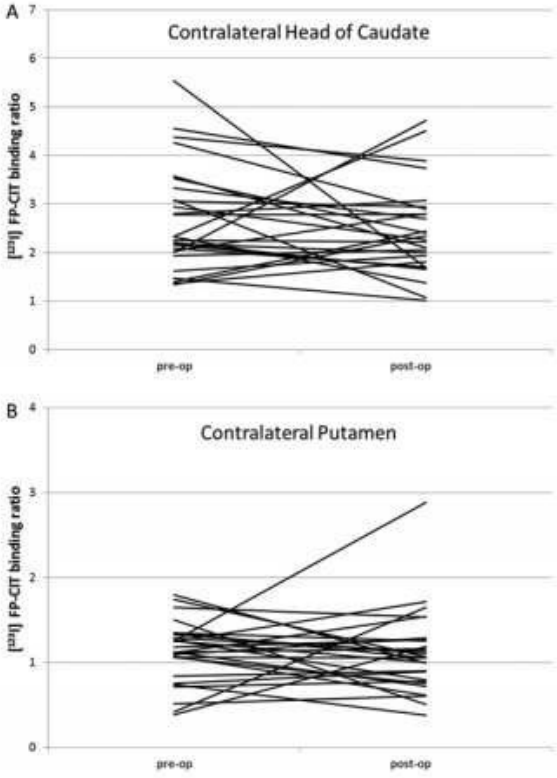

FIG. 2. Line graphs showing individual DAT availability in the contralateral caudate nucleus (**A**) and contralateral putamen (**B**) before and 12 months after STN stimulation.

p = 0.006), while the preoperative off score was 42.3 ± 15.2 and the postoperative on/off score was 41.4 ± 13.2 (Table 1). Also, there was a highly significant decline in LEDD after STN-DBS from 957 ± 440 mg preoperatively to 313 ± 189 mg postoperatively (p < 0.001).

DAT Availability Before and 1 Year After STN-DBS

Overall, there was no significant difference in DAT availability before and 1 year after DBS in any VOI (Figs. 2 and 3).

Correlation of DAT With Epidemiological Data and Clinical Outcome

Individual DAT availability preoperatively correlated negatively with age (contralateral caudate preoperatively R = −0.57, p = 0.002; ipsilateral caudate preoperatively R = −0.68, p < 0.001; contralateral putamen preoperatively R = −0.61, p = 0.001; ipsilateral putamen preoperatively R = −0.62, p = 0.001), with the duration of disease (contralateral caudate preoperatively R = −0.52, p = 0.006; ipsilateral caudate preoperatively R = −0.53, p = 0.005; contralateral putamen preoperatively R = −0.52, p = 0.007; ipsilateral putamen preoperatively R = −0.37, p = 0.059), and with the change in DAT availability (contralateral caudate R = −0.69, p < 0.001; contralateral putamen R = −0.52, p = 0.005) (Fig. 4). Additionally, the disease duration correlated positively with the change in DAT availability (contralateral caudate R = 0.39, p = 0.05; contralateral putamen R = 0.46, p = 0.017).

There was a significant negative correlation between the change in DAT availability in the contralateral caudate and the change in the UPDRS III score (i.e., an increase in DAT availability correlates with a reduction of UPDRS III R = −0.55, p = 0.014; contralateral putamen R = −0.54, p = 0.018) (Fig. 5). No correlation between preoperative DAT availability and the reduction of the UPDRS III score was found. The change in DAT availability did not correlate with the reduction of LEDD. There was also no correlation between the change in UPDRS III and the change in LEDD.

Discussion

The primary goal of this study was to investigate whether motor improvement following STN-DBS was associated with changes of nigrostriatal dopaminergic transmission (i.e., of the presynaptic DAT availability within the 1-year postoperative assessment). We found that after STN-DBS, the change in DAT availability was positively associated with the individual improvement in UPDRS III score, while on a group level no statistically significant difference in DAT availability after 1 year of DBS of the STN was registered. These findings indicate that the individual course of motor symptoms after STN-DBS depends on the individual DAT availability and function. However, based on our current data, we were not able to predict clinical outcome based on the individual preoperative DAT availability.

Changes in DAT Availability After STN-DBS Over the 1-Year Follow-Up

Whether the overall changes in DAT availability after STN-DBS over the 1-year follow-up are in line with a further deterioration of dopaminergic nerve cell loss of the substantia nigra or whether there is a halt of decline remains an open issue. Previous studies have described further deterioration 1 year after DBS.[8,17] Lokkegaard et al. examined PD patients in a similar setting with [^{123}I] FP-CIT SPECT imaging before and 1 year after DBS and showed an annual reduction in DAT availability of 7.7% after surgery, which is similar to the decline in DAT availability that was found in patients with advanced PD who did not undergo DBS.[8] Here, we found similar results, with a reduction of 9.3% in the contralateral caudate.[10]

Studies using [^{11}C]raclopride PET to assess D2R in DBS patients revealed that dopamine levels were not significantly different postoperatively with the stimulation turned on or with the stimulation turned off. These findings indicate that the modulation of phasic dopaminergic activity does not seem to play a crucial role for the STN-DBS mechanisms of action in PD. Whether the findings of unchanged DAT availability 1 year after DBS compared with the baseline scan and the positive association between DAT availability and UPDRS III score during the course reflect tonically preserved or increased function of dopaminergic neurons is hypothetical and should

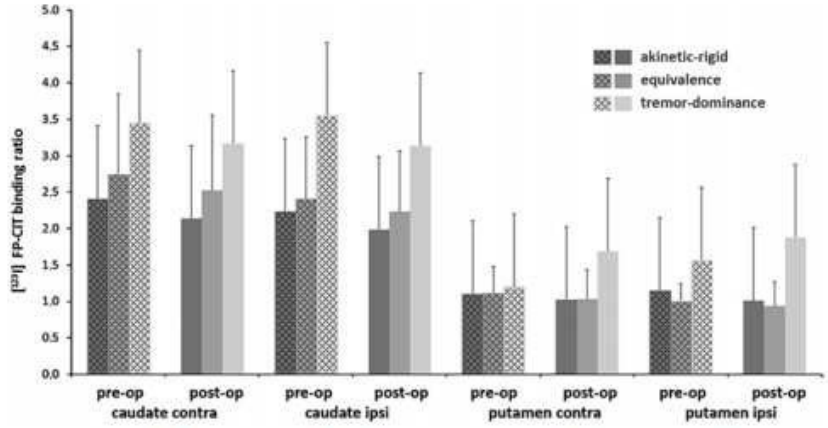

FIG. 3. Bar graph showing the PD subtype–specific DAT availability in the caudate nucleus and putamen before and 12 months after STN stimulation. *Bars* represent the means and *error bars* the SDs. contra = contralateral; ipsi = ipsilateral.

be explored by additional longitudinal [^{11}C]raclopride PET studies.[18,19]

Factors of the Individual Course of Disease and DAT Availability

Although DAT availability remained largely unchanged in the entire STN-DBS cohort, there were, on the other hand, high interindividual differences in DAT binding values over the follow-up time of 1 year, which is in good concordance with previous findings.[4,20] In our study, this variability was independent from the PD subtype. However, with regard to the small number of patients in each subgroup, a larger study cohort is required for subtype-specific correlative analyses.

We found that disease duration correlated positively with the change in DAT availability (i.e., the longer the patients have had PD, the greater was the rise in DAT availability after DBS). This supports our finding that lower DAT availability preoperatively was associated with increasing DAT availability postoperatively. Furthermore, Hanna et al. recently published a study comparing motor improvement and LEDD reduction after STN-DBS among patients younger than and older than 70 years.[21] They asserted that the reduction in motor symptoms was almost equal between both groups, and they even found a larger decline in LEDD in the elderly patients.[9]

Although it is under debate why PD patients experience a benefit from DBS, our study also sees a clinical improvement since we found a significant reduction of the UPDRS III scores on medication as well as a reduction of antiparkinsonian medication. This is in concordance with recent multicenter trials.[22,23] As there was no correlation between preoperative DAT availability and the change in UPDRS III score or LEDD, the clinical outcome was not predictable by DAT availability before the operation. Lokkegaard and colleagues described a very similar finding in which the change in DAT was not correlated with baseline DAT.[8] Nevertheless, low DAT availability preoperatively correlated with an increase in DAT after DBS. Furthermore, the increase in DAT availability postoperatively was correlated with a reduction in the UPDRS III score, indicating that low preoperative DAT availability was associated with a rise in central dopaminergic transmission and thus with a better outcome. In contrast to our findings, Nakajima et al. reported a better outcome, that is, a stronger improvement in UPDRS III score in patients with higher DAT availability preoperatively.[7] Whether low preoperative DAT availability is a predictor of the positive effect of STN-DBS and should therefore be considered as a parameter in patient selection needs to be further investigated.

Implications and Pathophysiological Aspects of the Study Findings

Our data suggest that STN-DBS has an effect on DAT availability and hence on dopaminergic neurotransmission in some patients, as well as that functional DAT regulation is still working even in very progressed states of nigrostriatal dopaminergic nerve cell degeneration. Our finding, that an increase in DAT availability is associated with a better outcome, is an important aspect in the consideration of how DBS works.

Different hypotheses explaining a neuroprotective effect of DBS have been postulated. For instance, STN-DBS led to increased dopaminergic cell survival in primates. This has been attributed to decreased glutamatergic excitotoxicity resulting from a stimulated STN.[24,25] Additionally, the signaling of brain-derived neurotrophic factor, known to be a neuroprotective growth factor, is increased by STN-DBS.[26]

Also, modification of other neurotransmission systems such as GABA and glutamate transmission should be considered to contribute to the effect of DBS.[27] For example, Yamawaki et al. showed that glutamatergic synaptic plasticity under STN-DBS is dependent on a dopaminergic state in rats.[28]

Limitations

An observation period of 1 year seems to be short for a

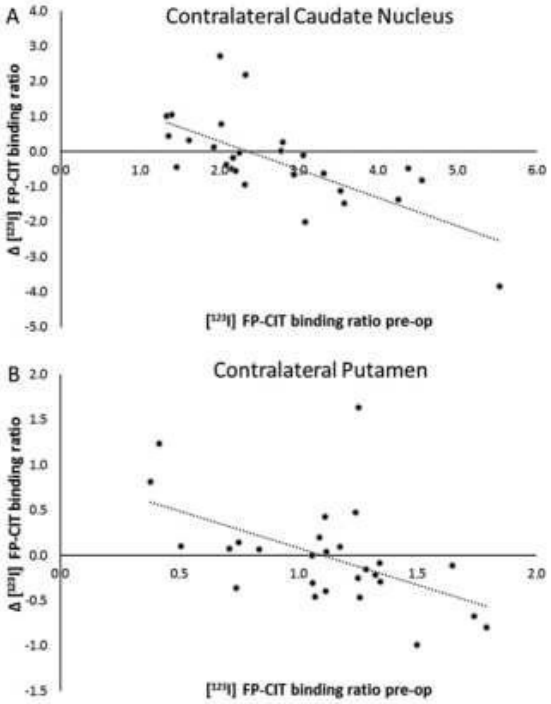

FIG. 4. Scatterplots showing the change in individual DAT availability in the contralateral caudate nucleus (**A**) and contralateral putamen (**B**) in relation to DAT before stimulation.

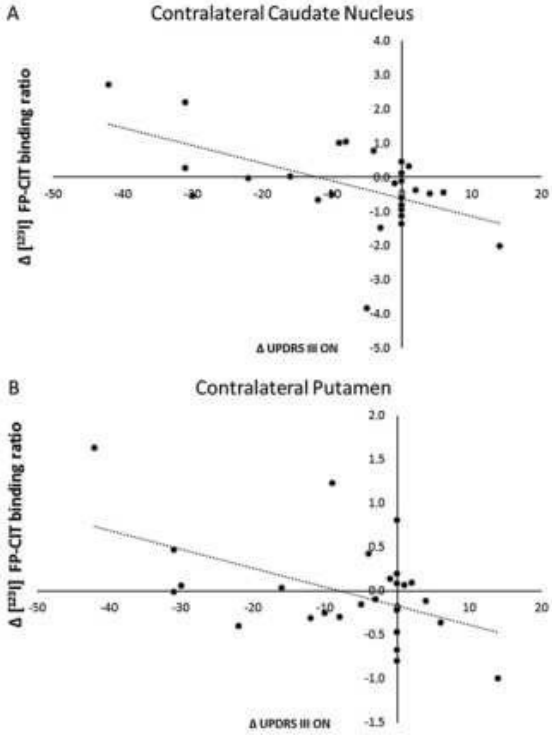

FIG. 5. Scatterplots showing the change in DAT availability in the contralateral caudate nucleus (**A**) and contralateral putamen (**B**) in relation to change in on-medication UPDRS III score.

chronic condition like PD. For further studies, repeating a DAT scan after a longer period could be advisable. Furthermore, the current observational study as a clinical extension study of our previous work did not include an evaluation with postoperative assessment during simulation on/medication off based on the treatment protocol.[10] The study protocol rather reflects the clinical situation with continued low-dose levodopa accompanying STN-DBS and avoiding patient discomfort. Further experimental assessment including a simulation on/medication off design will be done in similar studies with prospective designs in the future. Also, a direct comparison with a control group of patients with advanced PD not undergoing STN-DBS would be interesting. We did not investigate if the exact electrode position within STN plays a role for the change in DAT availability or the clinical outcome. Koivu et al. suggested several differences in clinical outcome depending on electrode position, as it has been seen together with changes in DAT availability by one recent study.[29,30] This remains a topic of further investigation.

Additionally, VOI analysis as a method to analyze DAT availability should be discussed, especially because the overall target-to-background ratio was quite low.

Our results could be biased by pharmacological effects of antiparkinsonian medication on [^{123}I]FP-CIT SPECT imaging. Although there is no evidence that levodopa and dopamine agonists influence brain imaging, long-term pharmacological effects cannot be ruled out.[25,31,32]

Conclusions

In accordance with our own previous findings, DAT availability was stable 1 year after STN-DBS.[10] However, DAT availability before surgery did not predict the clinical outcome after this follow-up period under STN-DBS, although on an individual level an increase in dopaminergic transmission after STN-DBS was associated with a better outcome in UPDRS III motor scores. These findings indicate that this change in DAT availability plays a significant role in how DBS works. Future studies are needed to evaluate whether preoperative DAT SPECT can become a reliable predictor for successful DBS.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Winkler, Löser, Hesse. Acquisition of data: Winkler, Löser, Luthardt, Rullmann, Weise, Meixensberger, Hesse. Analysis and interpretation of data: Winkler, Löser, Luthardt, Rullmann, Hesse. Drafting the article: Winkler, Löser, Luthardt, Rullmann, Hesse. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Winkler. Statistical analysis: Löser, Luthardt, Rullmann. Administrative/technical/material support: Winkler, Luthardt, Rullmann. Study supervision: Winkler, Sabri, Meixensberger, Hesse.

Supplemental Information

Previous Presentations

Parts of this work were presented at the 2nd International Conference on Deep Brain Stimulation, Düsseldorf, Germany, March 16, 2016, and at the 54th Annual Conference of the German Society of Nuclear Medicine, Dresden, Germany, April 22, 2016.

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3 Summary of Work

A dissertation submitted in fulfilment of the requirements for the doctor medicinae (Dr. med.) to the Faculty of Medicine, Leipzig University, Germany

Striatal dopamine transporter availability and individual clinical course within the 1-year follow-up of deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease

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Carried out at:
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Supervisors:
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02/2021

3.1 Background

Parkinson's disease (PD) is pathophysiologically characterized by the degeneration of dopaminergic neurons in the substantia nigra (SN) which causes motor symptoms. Following the basal ganglia circuit dopamine depletion in the SN leads to a decreased activation of the striatum. Hence, the globus pallidus internus (GPi) and the subthalamic nucleus (STN) experience an increased activation (Figure 1). All in all, these effects generate thalamic inhibition and reduced thalamocortical activity both of which are held responsible for the development of parkinsonian symptoms like bradykinesia and rigidity.[57]

Deep brain stimulation (DBS) in terms of bilateral simultaneous stimulation of the STN is an effective and reliable surgical treatment for PD, especially for motor symptoms. It has been proven to improve the patients' quality of life and to reduce the dose of antiparkinsonian medication.[14,91,91] Although DBS has been shown to be safe and clinically beneficial the mechanism by which it works and the selection of adequate patients remain a topic of active debate.

Dopamine transporter (DAT) SPECT as a radiotracer-based imaging method which makes the depiction of the presynaptic dopamine transporters possible and might therefore as a marker of the integrity of the nigrostriatal dopaminergic system reveal further information on the course of disease and the outcome of patients after DBS and might even be relevant for selecting patients preoperatively.

Data regarding the relation between DAT availability and the beneficial therapeutic effect of DBS are sparse.

Thus, the intention of our study was to investigate whether DAT availability changes after DBS and whether a prediction of the clinical outcome regarding motor symptoms is possible on the basis of DAT availability.

3.2 DAT availability changes after STN-DBS

We did not find a statistically significant change in DAT availability after one year in the overall group. However, we found a non-significant reduction of 9.3% in the contralateral caudate which is comparable to previous studies showing a further decline in DAT availability which has even been described to be similar to the decline in patients treated conservatively, only.[30,31,47] Anyway, in contrast to the overall stable DAT availability we registered high inter-individual differences which has also been reported in previous studies.[51,56] In our cohort these differences were not attributed to the different PD subtypes.

Our study showed a negative correlation between DAT availability and the age of patients as well as the duration of disease. Also, a positive correlation between the duration of disease and the change in DAT was found, i.e. the increase in DAT availability was higher the longer the patients have been diagnosed with PD. We also found an association between lower DAT availability preoperative (pre-op) and increasing DAT availability postoperative (post-op). In concordance to the subsequent assumption that elderly patients benefit from DBS also, a recent study comparing the long-term clinical outcome after STN-DBS in patients over and under the age of 70 years reported a similar improvement of motor symptoms in both groups and an even higher reduction of the L-dopa equivalent daily dose (LEDD) in the elderly group.[27]

All in all, although we could not establish a significant change in DAT availability, pre-op DAT availability as well as the age and the duration of disease seem to have an individual impact on how DAT availability develops after STN-DBS.

3.3 Pre-op DAT availability predicts the clinical outcome

Like different multicenter trials we also found a significant clinical improvement with a reduction of the Unified Parkinson's Disease Rating Scale (UPDRS III) in the "on"-state and LEDD.[14,59,91,93] Pre-op DAT availability did not correlate with any of these changes, i.e. the clinical outcome was not predictable by the assessment of pre-op DAT availability. However, there was a correlation between low DAT pre-op and rising DAT post-op which in turn was correlated with a decline in the UPDRS III. These findings indicate STN-DBS might cause an increase in dopaminergic transmission leading to a better outcome. In opposition to this a better outcome was described to be associated with higher baseline DAT by Nakajima et al.[55] To sum up, to date it is unclear if pre-op DAT can predict the clinical outcome and thus can be relevant for patient selection.

3.4 DBS has a neuroprotective effect

The aspect that we found an increase in DAT to be correlated with a better outcome seems to be important for the understanding of how DBS works. Therefore, DBS seems to have an impact on dopaminergic metabolism and transmission which could

be referred to long-term effects, such as synaptic network plasticity and neuroprotection. In concordance to this hypothesis of neuroprotection, in primates studies have found that STN-DBS caused increased dopaminergic cell survival. [7,90] Moreover, STN-DBS has been shown to increase the neuroprotective growth factor brain derived neurotrophic factor.[79]

3.5 Limitations and future direction

Of course, our observation period of one year is short since PD is known to be a chronic, long-lasting condition. Therefore, a second DAT scan in a long-term follow-up may further help to disentangle different aspects on the functioning of DBS.
Furthermore, the long-term disease course of patients treated conservatively only compared to patients who underwent STN-DBS would be interesting.
The exact electrode position within STN-DBS seems to be important for the clinical outcome.[41] It remains a topic of further investigation if electrode position has an impact on dopaminergic transmission and thus on DAT availability, too.

3.6 Conclusion

Our study showed that STN-DBS did not lead to a significant change in DAT availability after one year. Baseline DAT availability did not predict the clinical outcome statistically. Nonetheless, an increase of DAT availability post-op was associated with a better outcome. Altogether, these results suggest that a change in dopaminergic transmission is relevant for the mechanism of action of STN-DBS. Further investigation is necessary to assess if pre-op DAT availability can be reliably used as a predictor for successful DBS.

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5 Attachments

5.1 Index of Abbreviations

contra	Contralateral
DAT	Dopamine transporter
DATSCAN	Dopamine transporter scan
DBS	Deep Brain Stimulation
FDG	F-Fluordesoxyglucose
FPCIT	N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane
GABA	Gamma-aminobutyric acid
GPe	Globus pallidus externus
GPi	Globus pallidus internus
GPi-DBS	Deep Brain Stimulation of the Globus pallidus internus
ipsi	Ipsilateral
LEDD	L-dopa equivalent daily dose
MAO-B	Monoaminoxidase-B
MIBG	Metaiodobenzylguanidine
MRI	Magnetic Resonance Imaging
PD	Parkinson’s Disease
PET	Positron Emission Tomography
Post-op	Postoperative
Pre-op	Preoperative
SBR	Specific-to-unspecific binding ratio
SN	Substantia nigra
SNc	Substantia nigra, pars compacta
SNr	Substantia nigra, pars reticulata
SPECT	Single Photon Emission Computed Tomography
STN	Subthalamic nucleus
STN-DBS	Deep Brain Stimulation of the subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
VOI	Volume of interest
y	years

5.2 List of figures

5.3 Academic Contribution

Academic contribution of Julia Löser for the publication: “Striatal dopamine transporter availability and individual clinical course within one-year follow-up of deep brain stimulation of the subthalamic nucleus in patients with Parkinson’s disease”.

Authors: **Julia Löser**, Julia Luthardt, Michael Rullmann, David Weise, Osama Sabri, Jürgen Meixensberger, Swen Hesse, Dirk Winkler

Conception and design of study: **JLö**, JLu, MR, OS, JM, SH, DWe
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Analysis and/or interpretation of data: **JLö**, JLu, MR, SH, DWi
Drafting of the publication manuscript: **JLö**, JLu, MR, SH, DWi
Approval of the version of the manuscript to be published: **JLö**, JLu, MR, DWe, OS, JM, SH, DWi

We herein confirm that the above-mentioned tasks have been performed by JLö. Moreover, all other people involved have been stated correctly.

Signatures

Leipzig, 30. 03. 2021

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5.4 Declaration of the independent writing of this thesis

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

17.05.2021 .....

Datum

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Unterschrift

5.5 Declaration of Submission

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Einreichungserklärung

Die von
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vorgelegte Dissertation wurde betreut von

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