Thesis

The role of the Subthalamic Nucleus in facial expression in Parkinson's disease

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Graz, 07.08.2024

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 07.08.2024 *Laura Fölser m.p.*

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Zusammenfassung

Ziele

Die Zielsetzung dieser Arbeit war zunächst die systematische Suche und Zusammenfassung der gegenwärtig verfügbaren Literatur, die sich mit der Hypomimie bei der Parkinson-Krankheit befasst. Im experimentellen Teil galt unser Interesse der Beleuchtung der Auswirkungen der Tiefen Hirnstimulation (THS) des Nucleus Subthalamicus mit und ohne gleichzeitiger Gabe von oraler dopaminerger Medikation auf die Hypomimie, gemessen anhand des MDS-UPDRS-III subitem 19. Weiters waren diese Auswirkungen sowohl auf motorische (MDS-UPDRS-III-Gesamtscore, Axialer Subscore und Appendikularer Subscore) als auch auf nicht-motorische Symptome (Depression, Angst und Apathie) der Parkinson-Krankheit und mögliche Korrelationen von Interesse. Dies soll Hinweise darauf geben, ob die Hypomimie bei Parkinson-Patient/innen eher ein motorisches oder ein nicht-motorisches Symptom ist.

Methoden

Demografische und klinische Daten von 54 Patient/innen mit diagnostizierter Parkinson-Krankheit, die sich zwischen 2016 und 2022 am St. George's University Hospital, London, einer THS des Nucleus Subthalamicus unterzogen, wurden erfasst. Die Parameter *MDS-UPDRS-III subitem 19 (Hypomimie)*, *MDS-UPDRS-III Gesamtscore*, *MDS-UPDRS-III Axialer Score* und *MDS-UPDRS-III Appendikularer Score* wurden vor und nach der Operation, mit und ohne begleitender Gabe oraler dopaminerger Medikation untersucht. Der Parameter *LEDD* (Levodopa-äquivalente Tagesdosis) und Fragebögen für *Angst*, *Depression* und *Apathie* wurden ebenfalls vor und nach der THS untersucht, jedoch nur nach dem Erhalt von oraler dopaminerger Medikation.

Die Mittelwerte der Parameter wurden berechnet und in 3 Vergleichen gegenübergestellt, um folgende Konstellationen zu beurteilen:

1. Effekt der THS ohne Einnahme von oraler dopaminerger Medikation
   (vor THS ohne Medikation vs. nach THS ohne Medikation)

2. Effekt der THS unter Einnahme von oraler dopaminerger Medikation (vor THS mit Medikation vs. nach THS mit Medikation)

3. Effekt von oraler dopaminerger Medikation bei bestehender THS (nach THS ohne Medikation vs. nach THS mit Medikation)

Außerdem wurden mögliche Korrelationen zwischen den Parametern untersucht, um die Hypomimie besser kategorisieren zu können.

Ergebnisse

Es zeigte sich eine signifikante Verbesserung des MDS-UPDRS-III subitem 19 Scores (Hypomimie Score), des MDS-UPDRS-III Gesamtscores, des Axialen Subscores und des Appendikularen Subscores durch die THS ohne zusätzliche orale Medikation (1. Vergleich) und durch orale dopaminerge Medikation nach erfolgter THS (3. Vergleich). Die THS unter zusätzlicher Gabe von oraler dopaminerger Medikation (2. Vergleich) führte nur bei dem MDS-UPDRS-III Gesamtscore, dem Appendikularen Subscore und dem Angst-Score zu einer signifikanten Verbesserung.

Die Hypomimie korrelierte mit dem MDS-UPDRS-III Gesamtscore, dem Appendikularen Subscore und dem Symptom Angst, wobei die Korrelation zwischen der Hypomimie und dem MDS-UPDRS-III Gesamtscore am stärksten war.

Schlussfolgerungen

Die Ergebnisse zeigten, dass sich die Hypomimie bei Parkinson-Krankheit gemessen anhand des MDS-UPDRS-III subitem 19 nach THS des Nucleus Subthalamicus verbesserte. Aufgrund der starken Korrelation des Hypomimie Scores mit dem MDS-UPDRS-III Gesamtscores und des guten Ansprechens auf Levodopa und THS lässt sich argumentieren, dass sich die Hypomimie am besten als motorisches Symptom einordnen lässt. Ein Vergleich der Wirksamkeit von Levodopa und THS zeigte jedoch, dass mit zusätzlicher THS hinsichtlich der Hypomimie nur mehr wenig erreicht werden kann, wenn ein/e Patient/in medikamentös bereits gut eingestellt ist.

Zusammenfassend lässt sich sagen, dass diese Arbeit neue Informationen über Korrelationen von Hypomimie bei Parkinson-Krankheit liefert und zeigt, dass die Hypomimie auf die THS des Nucleus Subthalamicus anspricht.

Abstract

Objective

The objective of this work was to firstly, summarize the present body of knowledge on hypomimia in Parkinson's disease (PD) with a narrative review of the currently available literature. Secondly, it was to investigate the effects of deep brain stimulation (DBS) within the subthalamic nucleus with and without the concurrent administration of oral dopaminergic therapy on hypomimia, measured by the MDS-UPDRS-III subitem 19. A secondary aim is to study these effects on motor (MDS-UPDRS-III total, axial, and appendicular score) and non-motor symptoms (depression, anxiety, and apathy) of Parkinson's disease and to find possible correlations. This should help further categorize hypomimia in PD patients as a motor or a non-motor symptom.

Materials and Methods

Demographic and clinical characteristics of 54 patients diagnosed with Parkinson's disease, who underwent DBS surgery within the subthalamic nucleus between 2016 and 2022 at St. George's University Hospital, London were collected. The parameters *MDS-UPDRS-III subitem 19* (*hypomimia)*, *MDS-UPDRS-III total score*, *MDS-UPDRS-III axial score*, and *MDS-UPDRS-III appendicular score* were documented pre- and post-surgery, with and without dopaminergic therapy. The parameter *LEDD* (levodopa equivalent daily dose) and self-reported questionnaires for *anxiety*, *depression*, and *apathy* were documented pre- and post-surgery, but only after the intake of oral dopaminergic medication.

The mean values of the parameters were calculated and contrasted in 3 comparisons in order to assess the following scenarios:

1. Effect of DBS without oral dopaminergic medication
   (pre DBS off medication vs. post DBS off medication)
2. Effect of DBS with oral dopaminergic medication
   (pre DBS on medication vs. post DBS on medication)
3. Effect of oral dopaminergic medication after DBS-surgery
   (post DBS off medication vs. post DBS on medication)

Secondly, correlations between the parameters were examined in aim to categorize the symptom hypomimia.

Results

We found significant improvement of hypomimia according to the subitem 19 of the MDS-UPDRS-III, the MDS-UPDRS-III total score, the MDS-UPDRS-III axial score, and the MDS-UPDRS-III appendicular score due to DBS without additional oral dopaminergic medication (1. comparison) and due to oral dopaminergic medication after DBS-surgery (3. comparison). DBS with additional oral dopaminergic medication (2nd comparison) only led to significant improvement of the MDS-UPDRS-III total score, the MDS-UPDRS-III appendicular score, and the anxiety score.

Hypomimia showed clear correlations with the MDS-UPDRS-III total score, the MDS-UPDRS-III appendicular score and the symptom anxiety, whereby the correlation between hypomimia and the MDS-UPDRS-III total score was the strongest.

Conclusion

The results showed that hypomimia measured by the MDS-UPDRS-III subitem 19 is STN-DBS responsive. Moreover, we suggest that hypomimia can be best characterized as a motor symptom due to its strong correlation with the MDS-UPDRS-III total score and its improvement after dopaminergic therapy and STN-DBS. However, a comparison of the efficacy of levodopa and DBS shows that little more can be achieved in the context of hypomimia with DBS if a patient is already on optimized dopaminergic medication.

In conclusion, this thesis provides novel information on correlations of hypomimia in PD and shows STN-DBS responsiveness of hypomimia.

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List of Abbreviations

CBS	…… Corticobasal Syndrome
COMT	…… Catechol-O-methyl transferase
DaT SPECT	…… Dopamine transporter single-photon emission computed tomography
DBS	…… Deep brain stimulation
DLB	…… Dementia with Lewy Bodies
DSM-V	…… Diagnostic and Statistical Manual of Mental Disorders
EMG	…… Electromyogram
FDG-PET	…… Fluorodeoxyglucose positron emission tomography
fMRI	…… Functional magnetic resonance imaging
GABA	…… Gamma-Aminobutyric acid
GPi	…… Globus pallidus internus
LCIG	…… Levodopa-carbidopa intestinal gel
L-DOPA	…… Levodopa
LECIG	…… Levodopa-entacapone-carbidopa intestinal gel
LEDD	…… Levodopa equivalent daily dose
MAO-B	…… Monoamine oxidase-B
MDS-UPDRS	…… Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale
MoCA	…… Montreal Cognitive Assessment
MPTP	…… 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	…… Magnetic resonance imaging
MSA	……. Multiple System Atrophy
NMDA	…… N-methyl-D-aspartate-type

NSAID	…… Non-steroidal anti-inflammatory drug
PD	…… Parkinson’s disease
PIGD	…… Postural instability and gait difficulty (type of PD)
PPN	…… Pedunculoptine nucleus
PSP	…… Progressive Supranuclear Palsy
STN	…… Subthalamic Nucleus

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1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder after Alzheimer's disease (1). In PD, neurodegeneration mainly affects dopaminergic neurons and therefore leads to a lack of the neurotransmitter dopamine in the brain. This results in numerous motor and non-motor symptoms. Beside the hallmark features bradykinesia, rigidity, tremor and postural instability, patients also experience hypomimia, a reduction of facial expression, better known as "masked face" (2). Hypomimia can be a great burden not only for the affected patients, but also for their family members and caregivers. It can lead to restrictions in the ability to show emotions or communication in general (3).

Despite its great impact on patients' well-being and quality of life, there are only few studies addressing this problem and there is no specific treatment available to date. Therefore, it is important to better understand the mechanisms behind hypomimia in order to explore avenues for future treatments. In this longitudinal study, we assessed the effect of medication and/or deep brain stimulation within the subthalamic nucleus (STN-DBS) on motor and non-motor scores, with a special focus on hypomimia. DBS is an invasive device-aided therapy, that is widely used to treat PD tremor as well as motor fluctuations and dyskinesias (4). For a better understanding the following pages of introduction contain an overview of Parkinson's disease, deep brain stimulation and the current state of knowledge on hypomimia.

1.1 Parkinson's disease

1.1.1 Definition and epidemiology

In 1817 James Parkinson first described symptoms of a disease that was later named after him in his "An essay on the shaking palsy" (5). Back then he used the term "lessened muscular power" to describe the unusual movements he discovered in 6 cases. Today we know Parkinson's disease (PD) is the second most common neurodegenerative disorder, associated with a spectrum of motor and non-motor

symptoms (1). Clinical features include four cardinal symptoms: bradykinesia (including hypokinesia and akinesia), rigidity, tremor, and postural instability (2).

PD is a progressive disorder with an estimated prevalence of 0.3% in the general population in industrialized countries. This prevalence increases to 1.0% in people of 60 years and older and 3.0% in people of 80 years and older. The median age of occurrence is 60 years with a median duration of 15 years from diagnosis to death (1). Hirsch et al. (6) showed in a systematic review and meta-analysis that the overall incidence rate was 37.55 per 100,000 person-years in females of 40 years and older and 61.21 in males of 40 years and older. In most of the studies, the incidence rates of females peaked between the ages 70 and 79 and rose from 3.26 per 100,000 person-years at an age of 40-49 to 103.48 at the age of 80+. In males the incidence rates increased from 3.57 per 100,000 person-years at the ages of 40-49 up to 258,47 at the age of 80+. In half of the studies the incidence of males even continued to rise after the age of 80 in comparison to females (6). The results of a study by Haaxma et al. (7) also showed gender related differences in symptoms and severity of PD. Women tend to have milder phenotypes of PD, as they present with lower rates of motor impairment and higher tremor rates (67%) in comparison to men (48%). They suggested women have better neuroprotection due to higher striatal dopamine baseline levels because of stronger estrogen-activity (7).

Today there are over 6 million people suffering from PD worldwide. The Global Burden of Disease Study estimates that in 2040 this number will have doubled (8), which underpins the importance of research in this field.

1.1.2 Pathophysiology and risk factors

PD is a neurodegenerative disorder based on the degeneration of dopaminergic neurons within the substantia nigra in the midbrain which is part of the basal ganglia circuitry. The basal ganglia include the caudate nucleus and the lentiform nucleus, consisting of the pallidum/globus pallidus and the putamen. The pallidum and the putamen are located laterally of and separated by the internal capsule from the medial parts: the caudate nucleus, the thalamus, the subthalamic nucleus, and the substantia nigra. However, because of their functional and local connection (they are only incompletely separated by fibers of the internal capsule) putamen and

caudate nucleus are combined under the term striatum. The pallidum can be divided into a medial (internal) and a lateral (external) segment. The subthalamic nucleus and substantia nigra (which consists of the pars reticulata and the pars compacta) are also part of the basal ganglia because of their connections to the caudate nucleus, the putamen, and the pallidum (9).

There are two efferent pathways from the pallidum to the thalamus: the direct and the indirect pathway (see *Figure 1*). The direct pathway gets activated by glutamatergic projections from the sensorimotor cortex and dopaminergic (D1 activation) projections from the substantia nigra pars compacta. This leads to GABA-ergic inhibition of the globus pallidus internus and the substantia nigra pars reticulata, resulting in decreased inhibition of the neurons in the ventrolateral and -anterior nuclei of the thalamus. D1 activation also leads to GABA-ergic inhibition of the substantia nigra pars compacta as negative feedback. The indirect system also gets activated by glutamatergic projections from the sensorimotor complex but inhibited by dopaminergic (D2 inhibition) projections from the substantia nigra pars compacta. Through GABA-ergic projections this leads to reduced inhibition of the globus pallidus externus and thereby to increased inhibition of the subthalamic nucleus. This results in decreased glutamatergic activation of the globus pallidus internus and substantia nigra pars reticulata, which also leads to reduced inhibition of the thalamus similar to the direct pathway. From the thalamus fibers first lead to the premotor cortex and then to the motor cortex through glutamatergic projections. This closes the cortical-striatal-pallidal-thalamic-cortical motor loop (9).

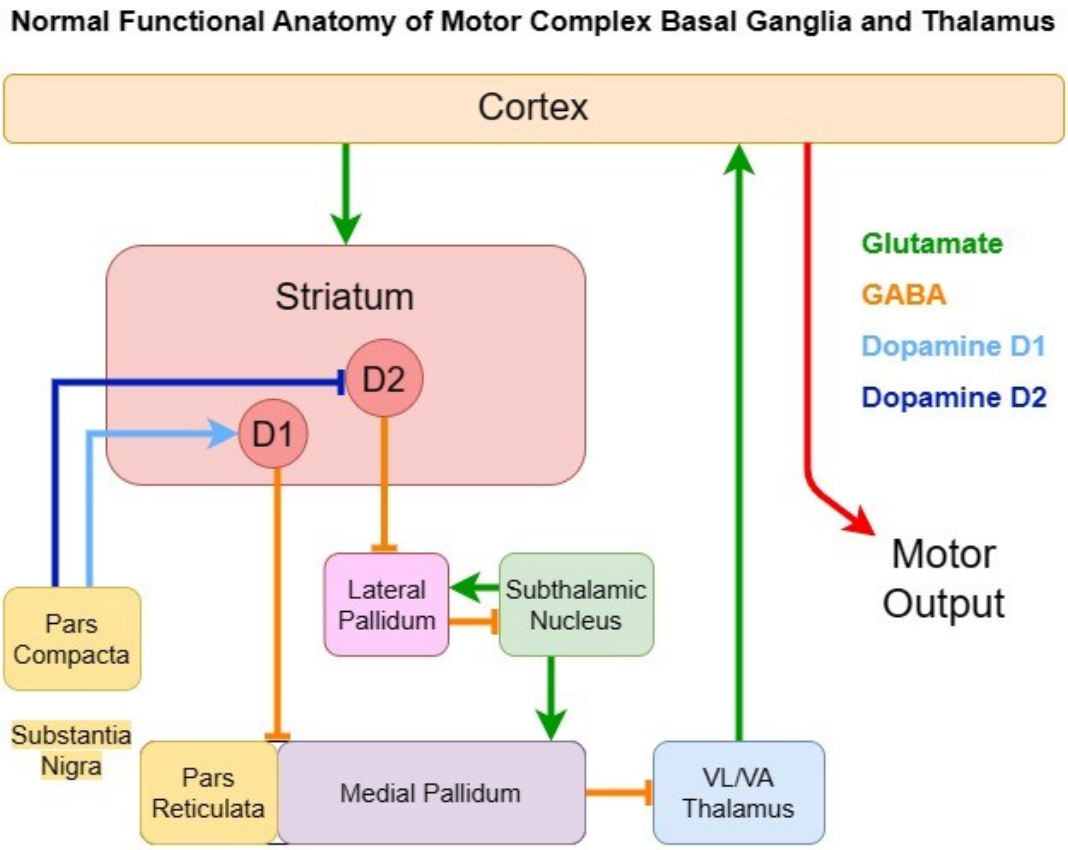

Figure 1: Normal Functional Anatomy of Motor Complex Basal Ganglia and Thalamus - Adapted from Ropper et al. (9)

In comparison to the brain physiology of a healthy subject, the pathophysiology of PD is based on the destruction of dopaminergic neurons and depigmentation in the substantia nigra pars compacta. This leads to impairment of motor functions because of decreased thalamocortical input through reduced activation of the direct pallidothalamic pathway via D1 receptors and reduced inhibition of the indirect pathway via D2 receptors (see *Figure 2*) (9,10).

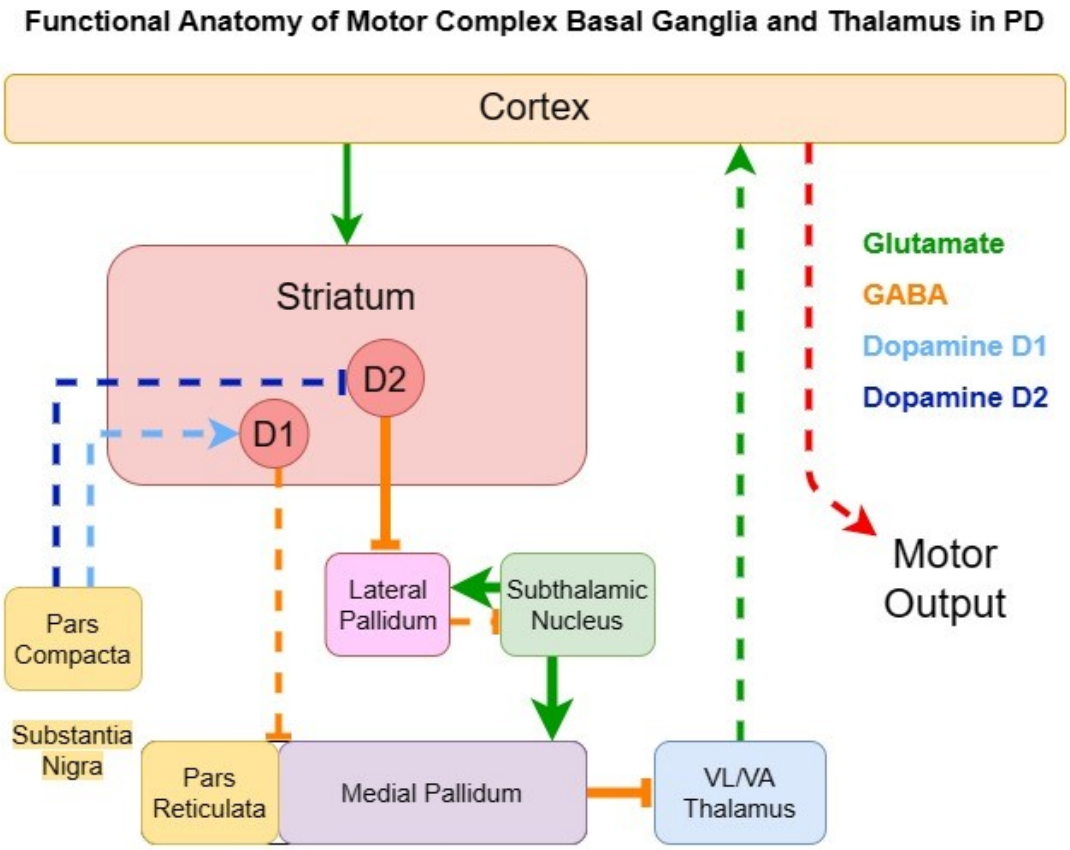

Figure 2: Functional Anatomy of Motor Complex Basal Ganglia and Thalamus in PD - Adapted from Ropper et al. (9)

In dopaminergic neurons of PD patients there is accumulation of misfolded protein that turns into the so called “Lewy bodies”. They mainly consist of alpha-synuclein and ubiquitin and impair normal neuronal function. Additionally, systems that are designed to repair neuronal abnormalities like the ubiquitin-proteasome system become damaged. Another process that could be important in PD is mitochondrial dysfunction and increased oxidative stress (10,11).

In 2003 Braak et al. (12) introduced a staging scheme to classify the degree of pathology based on different pattern of accumulation of alpha-synuclein. There are six stages describing increasing infestation of different brain structures associated with growing severity of PD symptoms. In stages 1 and 2 the lower brainstem and the olfactory system are affected resulting in olfactory deficits. Clinically this represents a prodromal phase of the disease. At the time when motor symptoms of

PD occur, the neuronal loss is amounting to about 60-70% in the substantia nigra (10,12).

Four years later Braak et al. (13) published the “dual-hit hypothesis” to explain the development of PD. He proposed that an unknown, maybe viral pathogen introduces itself to the brain through the olfactory pathway, which correlates with the pathologic presentation of Braak stages 1 and 2. It was also hypothesized that the pathogen may enter the gut through swallowing nasal secretions, thereby accessing the central nervous system and the vagus nerve. Evidence for this hypothesis are Lewy bodies that can be found in intestinal structures and the vagus nerve (13).

Yet, the cause for PD is still unclear in 85% of cases, called “idiopathic”. In 5 to 15% of PD cases other family members are affected too, as a result of several genetic factors, which is known as “hereditary Parkinson’s disease” and indicates family history as a risk factor (10,11). As described in chapter 1.1.1 *Definition and epidemiology*, the study of Hirsch et al. (6) showed that higher age and male gender also represent risk factors for the development of PD.

A review by Ascherio and Schwarzschild (14) compared several studies regarding risk factors and protective factors for developing PD. For example, the consumption of milk and dairy products correlates positively with the risk of developing PD. However, the conclusions of multiple cohort studies are more compatible with the higher PD risk being due to the urate-lowering effect of dairy products. Another association was found between PD and exposure to pesticides. Neurotoxic effects were discovered in a metabolite of MPTP that gets converted into a pro-parkinsonian molecule and has a similar structure to the herbicide paraquat. In France, Parkinson’s disease occurring in farmers has therefore been defined as occupational illness since 2012. Further risk factors that have been identified are methamphetamine-intake, melanoma, and traumatic brain injuries. Protective factors, amongst others, are the consumption of tobacco, coffee/caffeine, and green and black tea. Moreover, physical activity, higher urate levels and the intake of NSAIDs, calcium channel blockers, statins, and flavonoids also showed protective characteristics in multiple studies (14).

1.1.3 Symptoms

Idiopathic Parkinson's disease is a progressive neurological disorder that causes several motor and non-motor symptoms. The four cardinal motor symptoms are bradykinesia (including hypokinesia and akinesia), tremor, rigidity, and postural instability (see *Figure 3*) (2). The clinical presentation of PD can vary markedly, which led to the definition of distinct subgroups: "tremor dominant", "akinetic-rigid", "postural instability and gait difficulty" (PIGD) and "indeterminate" (11,15). This can be useful for prognostic aspects and selection of treatment options. Patients with tremor dominant PD, e.g., show slower disease progression and less disability than patients with PIGD PD (11).

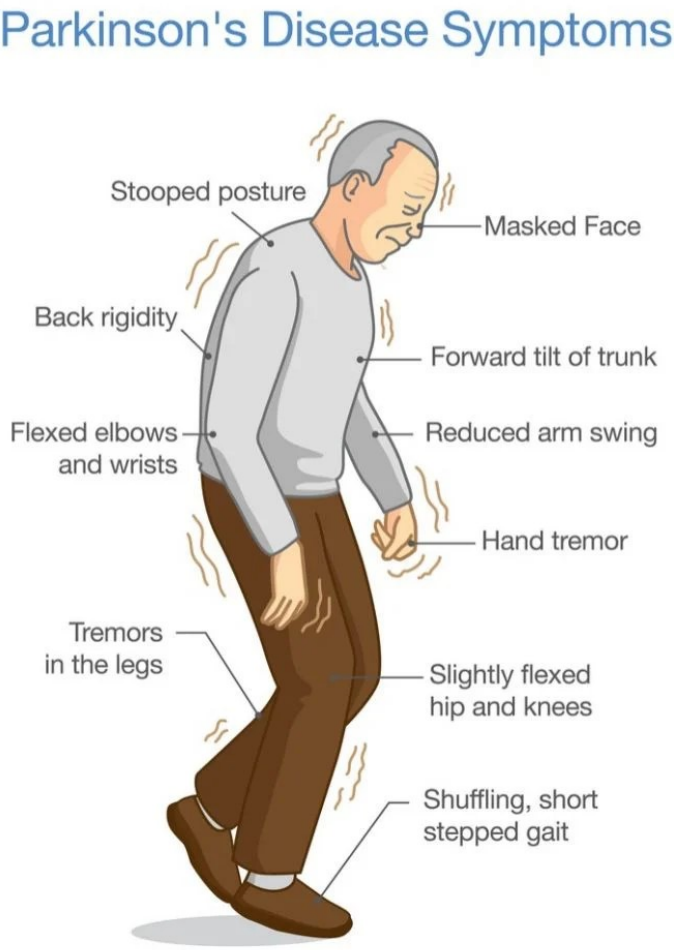

Figure 3. Man with Parkinson's disease (16)

1.1.3.1 Motor symptoms

Motor symptoms can be divided into appendicular motor signs (bradykinesia and rigidity) and axial signs (posture, gait, and balance impairment) (17). The central feature of PD is bradykinesia, which means slowness of voluntary movements. In contrast, hypokinesia and akinesia refer to loss of spontaneous motions and movements that are also delayed in execution with smaller amplitude, for example, micrographia in patients handwriting (18). In the beginning bradykinesia presents as slowness when executing tasks of daily living or impairment of performing precise tasks like buttoning a shirt. As the disease progresses, it manifests clinically in the limbs, such as a noticeable decrease in arm swing during walking. Bradykinesia is the hallmark of PD that correlates best with the severity of dopamine deficiency. To assess bradykinesia the patient performs rapid, repetitive movements, for example, finger taps, foot taps, or alternating hand pronation-supination movement. The examiner first evaluates the change of the tempo of the repetitive movement with regard to the presence of “fatiguing”, and second the change of the amplitude, which characteristically reduces over time (“decrement”) (2).

Another very important symptom is resting tremor. Patients usually present with a unilateral or asymmetric tremor of the upper limb(s) with a frequency of 4 to 6 Hz, which is more prevalent in distal parts of limbs. The hand tremor is the most common presentation, traditionally described as “pill-rolling tremor”, in which the thumb and the index finger touch and perform circular movements. Rest tremor can also occur in the lips, chin, jaw, or legs. In contrast to essential tremor, it rarely affects the head (apart of the chin) and the voice and usually disappears in action and sleep. Some PD patients have a history of essential tremor, years before the occurrence of PD, which is therefore debated as a risk factor (2,10,19).

Rigidity is an increased resistance and stiffness caused by increased muscle tone. Patients with PD typically show “Lead pipe rigidity”, which is characterized by a constant resistance to motion throughout the entire range of movement. The other type of rigidity that might be seen in PD is “Cogwheel rigidity”, which is defined as a resistance that stops and starts as the limb is moved through its range of motion. On clinical examination, rigidity is detected during passive movements of limbs during extension, flexion, and rotation around a joint. Rigidity occurs proximal (neck, hip) and distal (wrists, ankles), can begin unilateral, but will also spread to the

contralateral side during the disease course. It is often accompanied by pain, so if it occurs as early manifestation, it easily gets misdiagnosed as bursitis or arthritis. In the later course of the disease rigidity occurring in neck and torso can lead to postural deformities like anterocollis or scoliosis (2,10). Some patients may also develop a striatal hand or a striatal toe, which was reported in 20% of PD patients (20). Further skeletal abnormalities include flexion of the torso (camptocormia), flexion of the neck, and scoliosis. The Pisa syndrome is also a deformity of the trunk, characterized by a reversible lateral bending of the torso. Rigidity can usually be observed during clinical examination. However, in unclear cases the Froment's maneuver is used. Resistance is increased in passive movements of one limb when the patient performs a voluntary action with the contralateral limb (2,10).

The fourth of the cardinal symptoms of PD is postural instability and it occurs in the later course of the disease. If it appears early on, it is a red flag and may point to another neurodegenerative disorder like PSP (Progressive Supranuclear Palsy) or MSA (Multiple System Atrophy) (2). Williams et al. (21) showed in a retrospective study that the median duration from disease onset to first fall in PD was with 108 months significantly longer than in MSA (42 months) and PSP (47 months). There are other factors that may increase the risk of falls in these patients, for example, other symptoms like orthostatic hypotension, sensory changes due to higher age or comorbidities, and reduced proprioception. Unfortunately, postural instability only shows mild improvement after dopaminergic treatment. It can be tested using the "Pull-Test", where the patient quickly gets pulled back and should not take more than two steps to stabilize again (2).

Another motor abnormality that is known as one of the most disabling characteristics is freezing of gait, the loss of movement, which makes it impossible to take another step and usually lasts up to 10 seconds. It represents an important risk factor for falls and was shown to be more dominant in the PIGD subtype. Freezing occurs mostly in legs during walking but can also affect arms, eyelids, or the patients' speech. There are 5 subtypes: start hesitation (when beginning to walk), turn hesitation, destination hesitation, hesitation in tight quarters, and open space hesitation. Freezing occurring during OFF-state is usually responsive to dopamine therapy (2).

Additional manifestations of PD can be dysarthria, dysphagia and sialorrhea. Another important presentation is reduced facial expression and slowed blinking rate, which will be discussed in more detail in chapter 1.2. *Hypomimia* (2).

Because of a decline of inhibitory mechanisms of the frontal lobe, some patients experience a reappearance of primitive reflexes, like the primitive glabellar reflex, or the palmomental reflex. Another interesting symptom that can occur are mirror movements, which means that voluntary movements on one side trigger unintentional mirrored motions in contralateral muscles (2). In a study by Cochen de Cock et al. (22) PD patients were video monitored during sleep and showed improvement during REM-sleep or REM-sleep behavior disorder of at least one motor symptom. They suggested that this could be due to movements being generated in the motor cortex and lower motor neurons bypassing the extrapyramidal system (22).

1.1.3.2 Non-motor symptoms

Equally important as motor symptoms but commonly underrecognized are non-motor features in PD including cognitive changes, neurobehavioral disorders, autonomic impairment, and sensory and sleep abnormalities. Symptoms like REM-sleeping behavior disorder, hyposmia, and autonomic symptoms can already occur in the prodromal stage of the disease, even years before the onset of motor symptoms. About 90% of PD patients experience non-motor symptoms and they often strongly contribute to the quality of a patient's life and may not respond to dopaminergic therapy. In some cases, dopaminergic treatment can even worsen symptoms like orthostatic hypotension, psychosis, or cause sleep attacks (2,23).

Autonomic symptoms in PD include orthostatic hypotension, which occurs in up to 50% (24), sphincter dysfunction, sweating dysfunction, and erectile dysfunction. Another huge burden to a PD patients' life are neuropsychiatric signs and cognitive decline. The chances to develop dementia are 6 times higher in PD patients according to a prospective study of Aarsland et al. (25). PD patients suffering from dementia are more likely to develop depression, apathy, anxiety, and hallucinations. Some patients also show mood disorders and problems with multitasking and

decision-making or symptoms of compulsive behavior like craving, binge-eating, excessive gambling, or shopping and hypersexuality. REM-sleep behavior disorders occur in one third of PD patients and are considered as prodromal sign. Patients' partners or caregivers would describe patients acting out their dreams, screaming, grabbing, punching, and jumping whilst asleep. Some also experience insomnia or struggle with increased day time sleepiness. Sensory symptoms are also frequent in PD patients, but they are not always diagnosed as such. Olfactory symptoms are present in 90% of PD patients and at first occurrence there is a 10% increased risk of developing PD in the next 2 years. Other sensory abnormalities can be paresthesia, akathisia, and pain (2,10,26).

1.1.4 Diagnosis and classifications

Diagnosis of PD can be difficult in some cases, especially if motor symptoms are not that distinctive yet. Another challenge may also pose delineation from other differential diagnoses, as tremor is also present in other tremor syndromes, such as essential tremor or dystonic tremor, and parkinsonism is also present in other neurodegenerative parkinsonian syndromes, such as MSA, PSP, DLB (Dementia with Lewy Bodies), and CBS (Corticobasal Syndrome). Secondary parkinsonism may occur due to toxins, head trauma, or merely as a side effect of several mostly anti-dopaminergic drugs (2,10).

Today, PD remains a clinical diagnosis. It requires precise history-taking and physical examination. The medical history should include motor and non-motor symptoms, as well as family history, especially first-degree relatives in young-onset PD cases. As patients suffering from PD show clear dopamine responsiveness a Levodopa challenge also helps narrowing down differential diagnoses. To date there are no clinical biomarkers available (10). While structural imaging, ideally cerebral magnetic resonance imaging (MRI), is required for exclusion of differential diagnosis, functional imaging is not routinely used but can be helpful in some cases. The dopamine transporter single-photon emission computed tomography (DaT SPECT) and the fluorodeoxyglucose positron emission tomography (FDG-PET) scan depict accumulation of a radioactive tracer, which binds to dopamine transporters in the basal ganglia. Depending on the method used this can help with

delineation from atypical parkinsonian syndrome or essential tremor. MRI can be useful to exclude inflammatory, vascular, and neoplastic causes and help identify specific pattern of atrophy pointing to specific differential diagnoses (11,23). Historically, only the histopathological presence of Lewy bodies at autopsy is considered as standard criterion for the diagnosis of PD (27). There are, however, diagnostic criteria developed by the “UK Parkinson’s Disease Society Brain Bank” and the “National Institute of Neurological Disorders and Stroke” (2).

Since 2015 the Movement Disorder Society Clinical Diagnostic Criteria for PD are used for clinical research and to guide clinical diagnosis. The criteria are designed to standardize the diagnostic procedure, ensuring it can be replicated in various centers and utilized by clinicians who may not be as experienced in diagnosing Parkinson's disease. Although motor symptoms remain central, there's a growing acknowledgment of non-motor symptoms' significance (28).

Recently, a biological classification for PD (SynNeurGe) was published, integrating pathological α-synuclein presence (Syn), evidence of neurodegeneration (Neur), and pathogenic gene variants (Ge) with clinical features. However, the initial application of these criteria was for the moment exclusively suggested for research (29).

To evaluate the severity of PD there are two widespread scales that can be helpful. The Hoehn and Yahr scale can be used for a rough overview of the progression of the disease based on the degree of disability with a range from zero, which means no signs at all, to 5, which means the patient is wheelchair bound (30). A more precise assessment and the gold standard in clinical assessment is the Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). It is also a commonly used tool in studies to evaluate and compare the progression of PD. It contains 65 questions divided in four sections: mentation, behavior, and mood (I), activities of daily living (II), motor examination (III), and complications of therapy (IV). Each item gets rated from 0 to 4 (0 = normal, 1 = slight, 2 = mild, 3 = former severe and 4 = severe). The first section consists of 13 questions divided into two parts. The first part (mentation, behavior, and mood) is rated by the examiner, the second part is a questionnaire completed by the patient or if not possible by a care giver. The second section includes 13 questions referring

to activities of daily living, which are also completed by the patient. Part III, the motor examination, consists of 33 questions with a total of 18 units, as some refer separately for the right or the left side of the body. It is rated by the examiner, just like the fourth part, which consists of a total of 6 questions and relates to adverse symptoms of the therapy. Facial expression is examined in part 3 (motor examination) as item number 19, which is why the synonym *MDS-UPDRS-III subitem 19* will be used in this thesis. For the interpretation of my results, it is important to know that the facial expression score ranges from 0 to 4, with 0 representing a normal facial expression and 4 representing a complete masked face with lips that are parted most of the time when the mouth is at rest. The MDS-UPDRS-III total score ranges from 0 to 132. The axial score is comprised of the sub-items “gait”, “posture” and “postural” and ranges from 0 to 16. The appendicular score spans from 0 to 48 and assesses rigidity in the four extremities, finger tapping, hand movement, pronation-supination movement, and agility of the legs (31).

1.1.5 Therapy

To date only symptomatic treatments are available in everyday clinical practice based on pharmacological, surgical, and ancillary treatment. Initially, oral dopaminergic therapy is started. As the disease progresses and the therapeutic window of oral therapy becomes smaller and more complex, device assisted therapies may become helpful. Non-pharmacological therapy should be recommended at every stage of the disease (11).

Non-pharmacological therapies include physical exercise and physiotherapy, self-education, support groups, speech training, and nutritional consultation. Especially the importance of regular exercise focused on flexibility, balance, and strength should not be underestimated as it can have a huge impact on joint rigidity and flexed posture (10). In a review by Emig et al. (31) they analyzed 31 studies and reviews about the role of different physical exercises in PD treatment. Whether the exercise was aerobics (32), tango (33) or tai chi (34): independent of the type of exercise, major improvements of PD motor symptoms and non-motor symptoms were shown. Moreover, physical exercise improved disease progression and quality of life in general (31).

Pharmacological therapy for PD motor symptoms is mainly focused on dopamine substitution and the gold standard for PD treatment is levodopa (= L-DOPA). In contrast to dopamine, L-DOPA passes the blood-brain barrier and acts at the level of the substantia nigra pars compacta where it gets converted into dopamine. Levodopa leads to a remarkable improvement of motor symptoms, especially in early disease stages, but can also cause hypotension and nausea. Sometimes polypharmacy is required to lower adverse effects and attain complementary benefits. With the additional administration of a decarboxylase inhibitor (carbidopa, benserazide) dopaminergic side effects can be reduced by reducing conversion to dopamine in the peripheral blood. Further medication classes that are used for PD patients include dopamine agonists (e.g., ropinirole, pramipexole) and monoamine oxidase-B inhibitors (e.g., rasagiline, selegiline). Dopamine agonists directly stimulate the postsynaptic dopamine receptors, while MAO-B inhibitors restrain the metabolism of dopamine. Anticholinergic preparations such as trihexyphenidyl are not used routinely as they can induce a decline in cognitive function. For the treatment of dyskinesias N-methyl-D-aspartate-type (NMDA) glutamate receptor antagonists (amantadine) may be useful (11). Non-motor symptoms may in fact not be levodopa responsive and then need the same therapy as they would without PD as underlying disease (23).

A big problem of long-term oral treatment is that the duration of levodopa effect decreases and disabling side-effects may occur because of non-physiological pulsatile stimulation of dopamine receptors. This can result in motor complications, which can be impairing and difficult to treat. They appear in about 50% of PD patients who received levodopa for over 5 years and in up to 100% of young-onset PD patients. Motor complications include fluctuations, dyskinesias, dystonia, and other involuntary movements, that can occur in ON- and OFF-phases (35,36).

If PD symptoms are no longer controllable with oral dopaminergic therapy, device assisted therapies become necessary. Established treatment options include subcutaneous apomorphine, which has only a short activity span and can be delivered via subcutaneous injection to address acute OFF-episodes, or through continuous infusion to alleviate motor fluctuations (37). Another option is levodopa-carbidopa intestinal gel (LCIG) or the combination therapy of LCIG with entacapone (LECIG). The Catechol-O-methyl transferase (COMT) inhibitor entacapone in

LECIG is commonly added to levodopa therapy to increase half-life. Therefore, lower overall levodopa doses are needed, and potentially harmful metabolites of levodopa can be reduced (38). A newer option which is already in use in some parts of the world and has recently been introduced in Austria is subcutaneous foslevodopa/foscarbidopa (39). Another recent advancement involves the emergence of magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS), a non-invasive treatment primarily evaluated for essential tremor, with trials for Parkinson's disease in early stages. While the primary focus of the technique lies in treating parkinsonian tremor by targeting the thalamus, recent reports have also explored lesioning of the subthalamic nucleus (37).

A more invasive option for PD treatment and an important aspect in this study is deep brain stimulation (DBS) of the subthalamic nucleus or the globus pallidus internus via implanted electrodes. DBS works via several mechanisms with electrical and neurochemical effects locally and network wide. Additionally, it affects synaptic plasticity, modulation of oscillatory activity, neuroprotection, and neurogenesis (4). In chapter 1.2.4.2 *Deep brain stimulation* it will be discussed in more detail (4).

1.2 Hypomimia

1.2.1 Introduction

Communication does not just work through words, but also through non-verbal actions, like gestures and facial expressions. They are essential tools for communication, the basis of social interaction, and have important influence on the quality of life. Hypomimia is an early and very common symptom in PD, also known as “masked face”. Although it occurs in up to 70% of PD patients, it may gets misinterpreted as lack of interest or depression by physicians (3,17). Hypomimia is also associated with the experience of rejection and reduced joy in relationships between PD patients and their partners (40). Moreover, reduced facial muscle control becomes relevant in clinical practice when it results in speaking difficulties, swallowing impairments, and drooling (17,41). Overall, PD patients with hypomimia report worse quality of life compared to PD patients without hypomimia (17).

So even though hypomimia has a huge impact on a patient's well-being there are relatively few studies that deal with the impairment of performing facial expressions in this cohort. In motor examinations it is important to investigate hypomimia independent from limb bradykinesia because there are some pathophysiological differences. In comparison to the limbs, the motor neurons of the face do not receive any reciprocal or recurrent inhibition. Facial muscles do not act on joints and show lower inertia (3). Hypomimia has also no visual feedback or conventional proprioceptive feedback system (42). Moreover, there is a difference between the muscle activation of face and limbs shown in EMG examinations (3). In limb movements a triphasic pattern can be seen, which is absent in facial movements, because they are finer and more complex (3,43). Another major point is that additional factors like rigidity and tremor, that can influence bradykinesia of the limbs, hardly affect the face (3). In the MDS-UPDRS scale, the item "facial expression" gets evaluated in part III "Motor examination" (44). However, there is a lack of objective tools to rate the severity of hypomimia, which makes evaluations more difficult (42).

Hypomimia presents as reduction of spontaneous and voluntary facial expressions (45–50), and abnormal blinking (51,52). It is characterized by wider palpebral fissures, flattened nasolabial folds, less wrinkles on the orbicularis oris, and an involuntarily opened mouth (2). There are different pathophysiological pathways for voluntary (posed) and involuntary (emotional, spontaneous) facial movements. For example, while lesions in cortical motor areas and the pyramidal tract lead to facial paresis of voluntary control, spontaneous movements are not affected because the corticofacial projection from the mesial frontal region is maintained. Disruption of facial involuntary control would result from lesions in the white matter of the frontal lobe, mesial temporal lobe, operculum, insula, striatocapsular territory, or the thalamus (3). Despite their different pathophysiological pathways, there is a correlation between the impairment of emotional and posed grinning of PD patients (47). Spontaneous smiling in PD patients is characterized by reduced frequency of smiling and lower mouth opening (3). In general, they mostly struggle due to impoverished movements and individuation loss (46). Studies investigating the most impaired voluntary facial expression in PD patients resulted in somewhat heterogenous outcomes. Simons et al. (48) suggested PD patients primarily have

problems expressing happiness, surprise, and disgust, while Bandini et al. (53) named anger and disgust as the two most impaired expressions. PD patients also struggle to show pain as facial expression, although they seem to have higher pain sensitivity than control groups. This could lead to poor pain recognition by care givers (50). PD patients also struggle with incongruent expressions, for example, making an angry face while watching humorous videos (48).

Regarding hypomimia of the upper face, blinking is abnormal in voluntary, spontaneous, and reflex blinking. PD patients show normal peak velocity and amplitude in voluntary blinking but the interphase between the closing and opening phase is longer. In contrast, the blinking rate of spontaneous blinking is reduced in most PD patients, as well as the velocity and amplitude of the opening and closing phase (51). Hypomimia, motor scores, and MDS-UPDRS scores correlate with resting blink frequency but not with blink frequency during spontaneous conversations. In some PD patients, however, the spontaneous blinking rate is increased, as a form of dystonia (42). Reflex blinking in PD patients shows enhanced excitability in the closing phase in tests, in which the supraorbital nerve is stimulated (51).

There are different approaches to the treatment of hypomimia. Besides levodopa treatment, which will be described more precisely in chapter 1.2.4 *Levodopa responsiveness*, and STN-DBS, which will be discussed in chapter 1.2.5 *Deep brain stimulation*, hypomimia improves with physiotherapy. It is based on different aspects of facial emotion perception, including not only facial muscle activation, but also emotion recognition tasks, proprioceptive stimulation, emotional evocative exercises, and mimicking facial expressions displayed by a therapist. The explanation why this approach showed better outcome than pure facial muscle exercises could be based on the embodiment theories. These suggest that the same motor circuits are activated by executing and observing the same exercise (54).

Hypomimia occurs mostly bilaterally and Ozekmekçi et al. (55) showed that asymmetric hypomimia (=hemihypomimia) is observed in only 6.4% of PD patients, and in these cases occurs on the more affected side of the body. Due to a suggestion that hemispheric dominance for emotional processing may influence asymmetry in facial expressions, Ricciardi et al. (56) examined possible asymmetry

in voluntary emotion expressivity. They had 20 PD patients portray 6 basic emotions, then produced chimeric faces of each of these, and had volunteers rate them in terms of expressiveness. However, the results did not support the theory of hemispheric dominance after evaluating the two hemifaces in PD patients. As already mentioned in chapter 1.1.3.1 *Motor symptoms* an improvement of PD motor symptoms was shown during REM-sleep and REM-sleep behavior disorders. Facial expressions were also reported to normalize in 47% of the participants during REM-sleep (22).

1.2.2 Correlation with other symptoms

Hypomimia is also known as “facial bradykinesia” and in many books listed as manifestation of bradykinesia, an appendicular motor sign. However, studies that showed associations between hypomimia and facial emotion recognition cast doubt whether it is a pure motor symptom or more likely a complex set of impaired neural, affective, and cognitive mechanisms. Opinions with what kind of symptoms hypomimia correlates best and what other relationships may be observed differ (57).

Generally, many studies agree that hypomimia shows a strong correlation with the severity of motor symptoms and therefore with the MDS-UPDRS-III score, disease progression and longer duration of PD (17,42,46,47,57). Motor symptoms can be divided into appendicular cardinal motor signs (bradykinesia and rigidity) and axial motor signs (gait, posture, and balance disorders). While rigidity and tremor hardly have any effect on the face, Ricciardi et al. (17) showed that there is a strong correlation between hypomimia and axial signs. Cepeda et al. (42) also examined this correlation, but the only significant relationship they found between hypomimia, and motor symptoms is with distal bradykinesia. They showed that hypomimia correlates with timed tests, which are objective measures for bradykinesia. Moreover, they found correlations with rigidity scores, freezing of gait episodes, and the presence of dyskinesias (42).

Correlations were not only examined between hypomimia and motor symptoms, but also non-motor symptoms were investigated. Ricciardi et al. did not find any correlation with depression and anxiety, but showed strong correlations between hypomimia and worsened apathy, a symptom that is associated with lower levels of

striatal dopamine transporters. This was also confirmed in a study by Sampedro et al. (57). They suggested that apathy itself might have an additional effect on hypomimia. The evidence about a relationship between hypomimia and cognitive scores are inconclusive. While Ricciardi et al., Sampedro et al., and Marneweck et al. (46) did not find any correlation to cognitive functions, Cepeda et al. discovered a positive relationship. They discovered that hypomimia correlates with cognitive performance and cognitive decline, while they did not find any correlation with depression scores (42).

Another interesting correlation that will be discussed in the following chapter is the suggestion that hypomimia correlates with the ability to recognize facial expressions of other people (57–60).

1.2.3 Correlation between facial emotion recognition and facial expression

As discussed above, communication does not only happen through words, but also through gestures and facial expressions, and therefore it is important for both sides to infer the emotional state of their conversation partner through their facial expressions. The problem in PD is that patients might not only struggle to show their own emotions, but they can also be impaired recognizing other people's emotions. This problem does not appear to be secondary to depression or visuospatial deficits and it is more prominent in PD patients with apathy and cognitive decline (57). The hallmark of PD is the degeneration of dopaminergic neurons in the ventral striatum, the subthalamic nucleus, and other structures of the basal ganglia. There is a connection from the ventral striatum and subthalamic nucleus to other brain regions that play a role in facial emotion recognition, such as the orbitofrontal cortex and the amygdala (61). A meta-analysis by Gray et al. (61) showed that PD patients struggle more with recognizing negative emotions (anger, disgust, sadness, fear) than positive emotions (happiness, surprise). Interestingly, they found no significant correlation between the impairment of emotion recognition and the severity of motor symptoms, unlike hypomimia, which correlates with higher MDS-UPDRS-III scores (17,42,46,47,57). Moreover, they discovered larger deficits of emotion recognition in patients that underwent STN-DBS. In this cohort, patients showed a greater

impairment recognizing fearful faces post-surgery when compared to pre-surgery (61).

Despite the large number of papers about emotion recognition deficits in PD, only a few specifically investigated the relationship with hypomimia and if they share the same pathophysiological pathway (57–60). Indicative for a correlation between executing and observing facial emotions might be a fMRI study that was performed on healthy subjects and showed largely overlapping patterns of activation during performing and watching facial expressions (62). However, there are two considerations that could limit these findings. Firstly, similar activation patterns do not necessarily prove co-dependance of two different tasks. Secondly, other neuroimaging studies showed that different emotions, whether they are executed or observed, activate different regions of the brain (59,63).

Ricciardi et al. (59) and Marneweck et al. (58) studied PD patients and healthy participants and investigated the correlation of hypomimia and emotion recognition deficits. PD patients performed poorer in both tasks when compared to the control group. They also found a linear correlation between these two activities. Ricciardi et al. showed an impairment in PD patients in all 6 basic emotions: happiness, sadness, anger, disgust, surprise, and fear in both tasks, independent from the type of emotion, and suggested an involvement of an overall unified system rather than the concept of different neural systems for different emotions (59). Moreover, Marneweck et al. showed problems of PD patients recognizing identities from faces. They found a positive correlation of identification of faces and recognition of facial expressions but not with voluntary facial control. However, the results of Bologna et al. (60) differ. They also studied PD patients and healthy controls and their performance on facial control and emotion recognition. The results showed impairment in the expression of all six basic emotions, but only recognition difficulties in the emotions disgust, fear, and sadness. The lack of connection between the kinematic of facial emotion expression and facial emotion recognition, led to their interpretation that there are different pathophysiological pathways in these two abnormalities. They suggested that impairment of performing facial expressions in PD is triggered by impairment of basal ganglia loops and abnormal activation in the frontal lobe, while impaired emotion recognition arises mainly from

involvement of components of the limbic system, including the amygdala and the insula (60).

1.2.4 Treatment options for hypomimia

1.2.4.1 Levodopa treatment

Therapy of hypomimia can be quite challenging. As previously mentioned, L-DOPA is the gold standard of PD therapy and can improve motor symptoms. As hypomimia has strong correlations with PD motor symptoms, Ricciardi et al. (17) dealt with the question of whether hypomimia also responds do levodopa in a study comparing PD patients with hypomimia to PD patients without hypomimia. They found a strong improvement of facial expressivity throughout the whole group, independent of age, gender, and disease duration, which was mainly associated with improvement of axial symptoms. They suggested hypomimia arises due to low dopaminergic levels and is therefore a levodopa responsive symptom (17). In contrast to these results, Marsili et al. (47) did not find any correlations in their cohort. They investigated the frequency of smiling and showed that neither posed smiling nor voluntary smiling significantly improved under levodopa therapy (47).

Considering levodopa responsiveness on blinking in PD patients, Bologna et al. (52) showed, that levodopa stabilizes the spontaneous blinking rate of PD patients. However, it has no effects on reflex blinking and voluntary blinking, but reversed the prolonged inter-phase pause during two blinks that occurred after STN-DBS (52).

1.2.4.2 Deep brain stimulation

Deep brain stimulation is a neurosurgical intervention, used for the treatment of PD symptoms, but also other movement disorders like essential tremor, dystonia and to a lesser extent, neuropsychiatric disorders that are resistant to treatments, such as epilepsy and obsessive-compulsive disorder. Chronic electric stimulation can reduce pharmaco-resistant motor fluctuations, tremor, bradykinesia, and rigidity and shows better results than ablative surgery in terms of general outcome, flexibility, morbidity, and mortality (64). The precise process responsible for the improvement

of motor symptoms is still not fully understood but it has been suggested that DBS works via several mechanisms with electrical and neurochemical effects local and network wide. Additionally, it affects synaptic plasticity, modulation of oscillatory activity, neuroprotection, and neurogenesis. In other words, DBS disconnects input and output signals in the basal ganglia, which prevents abnormal information flow (4,64).

In 1948, Pool was the first to implant deep brain stimulating electrodes in the caudate nucleus of a PD patient with the original intention to treat non-motor symptoms like depression and anorexia (65). The concept of modern deep brain stimulation owes a lot to Benabid et. al. (66), who continued developing it and used the method to improve tremor in PD patients.

Most commonly DBS is used in the subthalamic nucleus (STN-DBS). While it can improve tremor within a few seconds and bradykinesia and rigidity within minutes to hours, axial symptoms may improve after hours to days. Another option for the placement of the electrodes is the globus pallidus internus (GPi-DBS), which is often better tolerated in older patients. DBS of the globus pallidus internus might relief dystonic movements, but there are no major differences in therapeutic efficacy (4). A meta-analysis by Liu et al. (67) showed a slight difference between the locations, as STN-DBS allowed a greater reduction of PD medication, while GPi-DBS improved psychiatric symptoms better. Alternatively, electrodes can be placed within the ventral intermediate nucleus of the thalamus, which reduces PD induced tremor and essential tremor. However, the main targets for DBS remain the STN and the GPi because they do not only improve tremor, but also bradykinesia and rigidity. Currently, potential benefits of placement of electrodes in the pedunculoptine nucleus (PPN-DBS) are being investigated, as it may improve postural instability, gait disorder, freezing of gait, and risk of falls in PD patients, while STN-DBS does not affect these symptoms (64,68).

Firstly, it is important that DBS surgery needs to be performed by specialized centers with experience. Secondly, to carefully select potential patients for DBS to achieve optimal outcome. DBS works best for PD patients that show levodopa responsive motor complications, are younger than 70 years, have a disease duration of over 5 years, and show good cognitive function. It is important to

underline, that not all PD patients would benefit from DBS, because symptoms as freezing of gait and falls usually do not improve after therapy. Moreover, it is reported that some patients develop severe depression and apathy. After all, it is an invasive treatment option with surgical risks and therefore not appropriate for older patients (64,69).

Bologna et al. (52) reported that STN-DBS increases the reduced spontaneous blinking rate of PD patients and the peak velocity and amplitude of voluntary blinking, which probably occurs because of changes of cortico-basal ganglia activity. Moreover, it prolongs the inter-phase pause duration in voluntary blinking, that may indicate adverse effects of STN-DBS on the cranial region. This finding could be also important for gaining a better understanding of the pathophysiology of eyelid opening apraxia, a possible side effect after STN-DBS. Reflex blinking of PD patients showed no changes after STN-DBS (52).

To the best of my knowledge there are no other publications that examine hypomimia responsiveness to STN-DBS yet. As already mentioned, it is reported that axial symptoms like postural instability and freezing of gait are not STN-DBS responsive and based on the suggestion of Ricciardi et al. (17) hypomimia fits best as an axial sign (64). This would be indicative of hypomimia not being STN-DBS responsive. However, Cepeda et al. (42) found strong parallels between hypomimia and distal bradykinesia, and appendicular cardinal motor symptoms (bradykinesia and rigidity) are known to respond well to STN-DBS (64).

2. Methods

2.1 Introduction - Search strategy

A systematic PUBMED search was carried out to provide an overview of the current state of knowledge and the available literature. The search term cited in Table 1 has achieved a total of 90 results (reference date: 01/10/2022). Relevant publications were used for a narrative review of the current state of knowledge in the chapters 1.2.1 *Introduction* and 1.2.2 *Correlation with other symptoms*.

(parkinson's disease[ti] OR "Parkinson Disease"[Mesh]) AND (hypomimia[ti] OR facial emotion[ti] OR face bradykinesia[ti] OR facial bradykinesia[ti] OR facial expression[ti] OR facial expressions[ti] OR facedness[ti] OR facial musculature[ti])
Table 1. PUBMED search term

Studies were considered relevant if they addressed hypomimia in patients with idiopathic Parkinson's disease and were written in English. In addition, the function "similar articles" was used to add papers that were considered relevant.

2.2 Subjects

All consecutive patients scheduled to receive bilateral STN-DBS between 2016 and 2022 at St. George's University Hospital, London were screened and invited to participate in the study.

General Inclusion Criteria:

- Patients with a diagnosis of PD as per MDS criteria, undergoing bilateral STN-DBS as per clinical indication

General Exclusion Criteria:

- Dementia as per DSM-V criteria and MoCA score <26/30
- Severe psychiatric symptoms
- Presence of any other severe neurological or psychiatric disorder
- Conditions that interact with facial movements like a history of Bell's palsy, injections of botulinum toxin or maxillofacial defects

Data collected from 54 patients diagnosed with PD, who underwent STN-DBS surgery, was included in this analysis. Patients' demographic and clinical characteristics were gathered including gender, age, age at onset, disease duration and information on PD medications, which were then converted in total levodopa equivalent daily dose (LEDD) and LEDD dopamine-agonists.

Parameter	Women	Men	Total
Number	38	16	54
Age	59.5 ± 6.1	60.4 ± 6.0	59.8 ± 6.1
Age at onset	48.7 ± 7.1	49.1 ± 6.5	48.8 ± 6.9
Disease duration	11.0 ± 4.5	11.6 ± 5.2	11.2 ± 4.8
LEDD pre DBS	1182 ± 431	1005 ± 330	1131 ± 416
LEDD post DBS	892 ± 413	847 ± 454	879 ± 430

Table 2. Demographic data of subjects

2.3 Outcome Measures

Clinical evaluation included motor and non-motor symptoms using standardized clinical scales and self-administered questionnaires. Motor symptoms and motor complications were assessed using the Movement-Disorder-Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III-IV, which is described in chapter 1.1.4 *Diagnosis and classifications*. Movement disorder specialists assessed hypomimia by digital video recordings by means of the item 19 of the MDS-UPDRS part III.

Non-motor symptoms were assessed using the Hamilton depression rating scale, the Hamilton anxiety rating scale, the Apathy evaluation scale, and the Montreal Cognitive assessment (MoCA).

Patients were evaluated in four different conditions at the following time points:

T0= Baseline, before the surgery

- In OFF medication condition = after a 12-hour overnight medication break ("**Pre DBS OFF MED**")

- In ON medication condition = 60 minutes after their regular first morning dose of levodopa ("**Pre DBS ON MED**")

T1= 12-months after STN-DBS with electrodes switched on to the respective customized setting

- In OFF medication condition = after a 12-hour overnight medication break ("**Post DBS OFF MED**")
- In ON medication condition = 60 minutes after their regular first morning dose of levodopa ("**Post DBS ON MED**")

In this work I refer to a total of 7 parameters:

- MDS-UPDRS-III total score
- MDS-UPDRS-III subitem 19 (facial expression) score
- MDS-UPDRS-III axial score
- MDS-UPDRS-III appendicular score
- Depression
- Anxiety
- Apathy
- LEDD

All parameters were measured in ON MED condition pre and post STN-DBS, whereas only the MDS-UPDRS-III facial expression, total, axial, and appendicular scores were also evaluated in OFF MED condition pre and post STN-DBS. The mean values of the parameters were calculated and contrasted in 3 comparisons:

1. **Pre DBS OFF MED** vs. **Post DBS OFF MED**
2. **Pre DBS ON MED** vs. **Post DBS ON MED**
3. **Post DBS OFF MED** vs. **Post DBS ON MED**

Moreover, the correlations between the parameters were calculated. Correlations between MDS-UPDRS-III facial expression, total, axial, and appendicular scores were examined in all three comparisons, while the parameters *depression*, *anxiety*, *apathy*, and *LEDD* were only evaluated in the second comparison.

2.4 Statistical Analysis

The software SPSS Statistics Version 28 was used for all statistical analysis. Results were considered statistically significant with a p-value of $p \leq 0.05$ (*), very significant with a p-value of $p \leq 0.01$ (**) and highly significant with a p value of $p \leq 0.001$ (***). The Wilcoxon test was used for the mean comparison of the respective absolute values of MDS-UPDRS-III facial expression, total, axial, and appendicular scores in the 3 comparisons described above.

The Spearman test was performed to estimate the strength of the correlation of the parameters in the 3 comparisons using the delta changes of MDS-UPDRS-III facial expression, MDS-UPDRS-III total, MDS-UPDRS-III axial, MDS-UPDRS-III appendicular, anxiety, apathy, depression, and LEDD scores.

The delta changes were calculated as follows:

1. (Pre DBS OFF MED – Post DBS OFF MED) / Pre DBS OFF MED

2. (Pre DBS ON MED – Post DBS ON MED) / Pre DBS ON MED

3. (Post DBS OFF MED – Post DBS ON MED) / Post DBS OFF MED

The main objective is to evaluate the potential impact of STN-DBS with and without medication on hypomimia. Another aim is to study the effects of STN-DBS with and without medication on motor symptoms (MDS-UPDRS-III total, axial, and appendicular score) and the effects of STN-DBS with medication on non-motor symptoms (depression, anxiety, and apathy) and possible correlations.

3. Results

MDS-UPDRS-III subitem 19, total and axial scores are contrasted and interpreted in each of the 3 comparisons described above. The MDS-UPDRS-III facial expression score ranges from 0 to 4, the total score from 0 to 132, the axial score from 0 to 16, and the appendicular score from 0 to 48 (70). All results are significant except of the results of the three parameters *MDS-UPDRS-III facial expression*, *MDS-UPDRS-III axial*, and *depression* in the second comparison "Pre DBS ON MED vs. Post DBS ON MED". Graphic representations for these parameters can be viewed in the appendix.

3.1 DBS improved the MDS-UPDRS-III subitem 19, the total score, the axial score, and the appendicular score in patients that were off medication

3.1.1 DBS improved facial expression in patients off medication

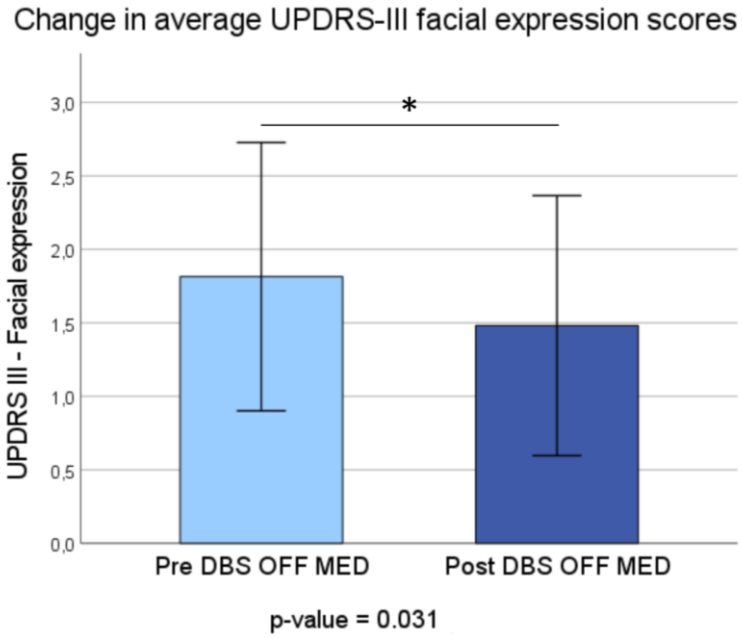

Figure 4. Bar chart: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III facial expression scores

Off medication, the MDS-UPDRS-III subitem 19 score decreased from 1.81 to 1.48 on average due to STN-DBS (p = .031, see *Figure 4*). We therefore found a significant effect of STN-DBS on hypomimia in PD patients that were off medication.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS OFF MED	1.81 ± 0.91	0	4
Post DBS OFF MED	1.48 ± 0.89	0	4

Table 3. Descriptive statistics: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III facial expression scores

3.1.2 DBS improved the MDS-UPDRS-III total score in patients off medication

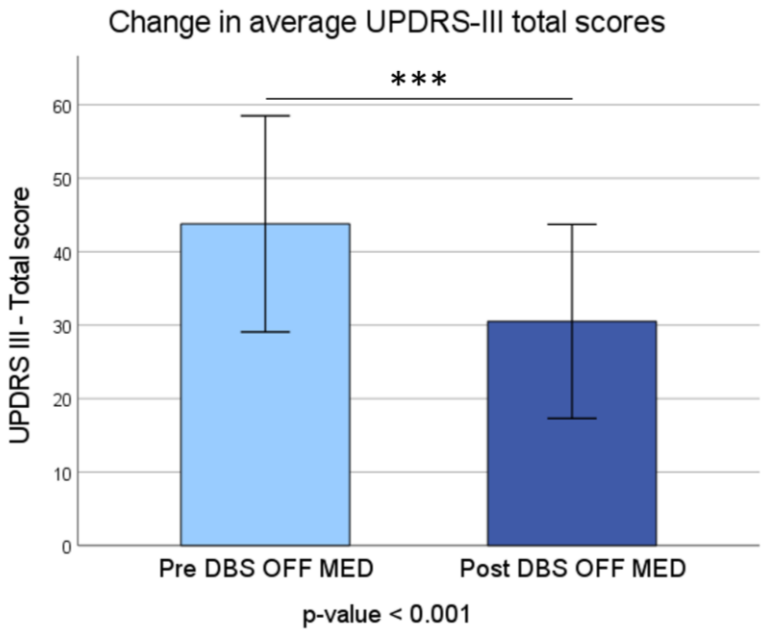

Figure 5. Bar chart: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III total scores

Figure 5 depicts that the MDS-UPDRS-III total score in off medication condition decreased from 43.80 to 30.52 on average due to STN-DBS (p < .001). This shows an improvement of the MDS-UPDRS-III total score in PD patients off medication when DBS was switched on.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS OFF MED	43.80 ± 14.72	17	78
Post DBS OFF MED	30.52 ± 13.21	4	59

Table 4. Descriptive statistics: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III total scores

3.1.3 DBS improved the MDS-UPDRS-III axial score in patients off medication

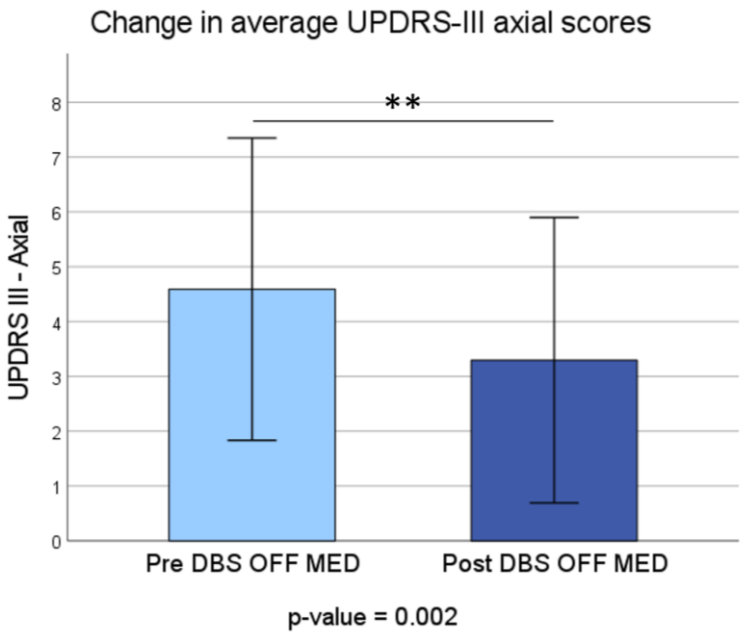

Figure 6. Bar chart: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III axial scores

In patients that were off medication, the axial score decreased from 4.59 to 3.30 due to STN-DBS surgery (p = .002, see *Figure 6*). This shows us a significant improvement of the MDS-UPDRS-III axial score due to STN-DBS in PD patients that were off medication.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS OFF MED	4.59 ± 2.75	0	10
Post DBS OFF MED	3.30 ± 2.60	0	10

Table 5. Descriptive statistic: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III axial scores

3.1.4 DBS improved the MDS-UPDRS-III appendicular score in patients off medication

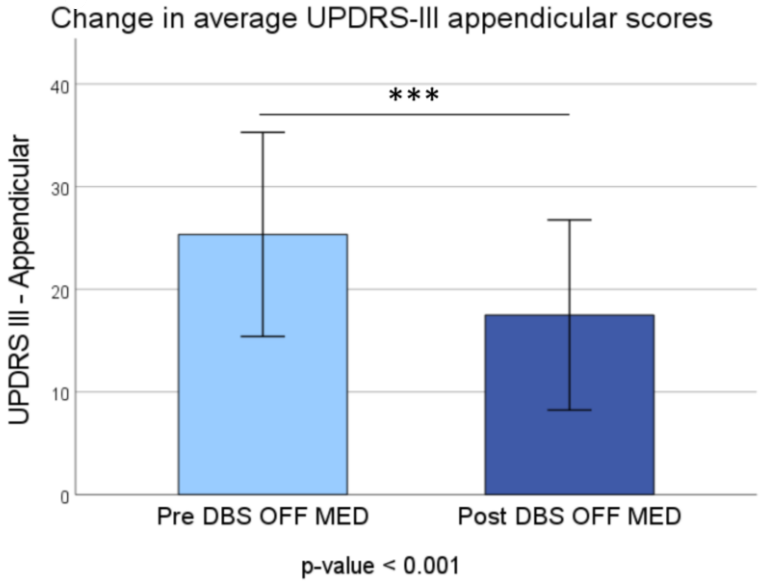

Figure 7. Bar chart: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III appendicular scores

Off medication, the appendicular score decreased from 25.35 to 17.50 on average due to STN-DBS ($p < .001$, see *Figure 7*). This reflects that DBS stimulation did not only lead to an improvement of facial expression, the MDS-UPDRS-III total score, and the MDS-UPDRS-III axial score, but also improved the MDS-UPDRS-III appendicular score in PD patients off medication.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS OFF MED	25.35 ± 9.94	7	47
Post DBS OFF MED	17.50 ± 9.27	2	37

Table 6. Descriptive statistic: Pre DBS OFF MED vs. Post DBS OFF MED – MDS-UPDRS-III appendicular scores

3.1.5 Hypomimia correlated with the MDS-UPDRS-III total score but not with the axial and appendicular scores in patients off medication in the conditions before and after DBS surgery

Correlations between the MDS-UPDRS-III facial expression, total, axial, and appendicular score were analyzed in patients off medication in the conditions before and after DBS surgery.

Hypomimia only correlated with the MDS-UPDRS-III total score ($r = .327$, $p = .021$), but not with the axial and appendicular score in our first comparison. However, the MDS-UPDRS-III axial score ($r = .730$, $p < .001$) and the appendicular score ($r = .535$, $p < .001$) both correlated with the total score, and with each other ($r = .476$, $p < .001$).

3.2 DBS did not significantly affect hypomimia in patients on optimized oral dopaminergic treatment

3.2.1 DBS led to no significant improvement of hypomimia in patients on medication

The result of the MDS-UPDRS-III facial expression sub-score pre DBS ON MED vs. post DBS ON MED was not significant (p= .103, see *Figure 20*, 6. *Appendix*). This means that no effect of DBS stimulation on the facial sub-score could be found when patients were on their optimized oral dopaminergic treatment.

3.2.2 DBS improved the MDS-UPDRS-III total score in patients on medication

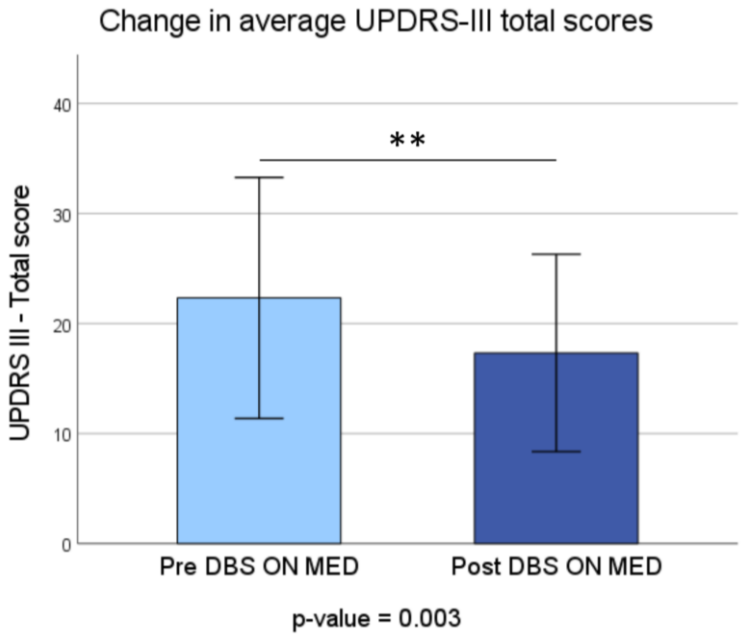

Figure 8. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – MDS-UPDRS-III total scores

On medication, the MDS-UPRDS-III total score decreased from 22.33 to 17.33 on average due to STN-DBS (p = .003, see *Figure 8*). This shows a significant improvement of the MDS-UPDRS-III total score in PD patients that were on oral dopaminergic treatment when DBS was switched on.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS ON MED	22.33 ± 10.95	5	46
Post DBS ON MED	17.33 ± 8.97	3	43

Table 7. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – MDS-UPDRS-III total scores

3.2.3 DBS led to no significant improvement of the MDS-UPDRS-III axial score in patients on medication

The result of the MDS-UPDRS-III axial score pre DBS ON MED vs. post DBS ON MED was not significant (p = .269, see *Figure 21*, 6. *Appendix*). Therefore, no additional effect of STN-DBS on the axial score could be found when patients were on medication.

3.2.4 DBS improved the MDS-UPDRS-III appendicular score in patients on medication

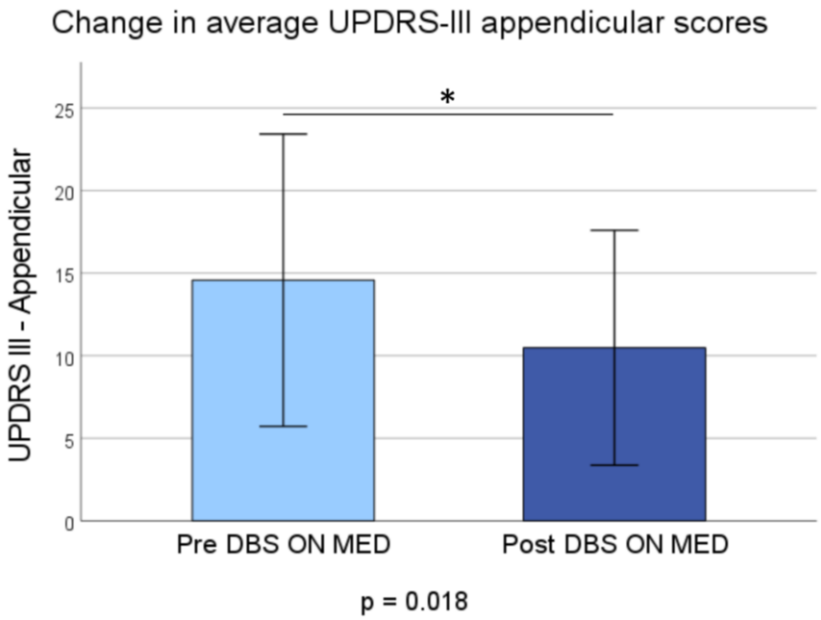

Figure 9. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – MDS-UPDRS-III appendicular scores

In patients that were on medication, the appendicular score decreased from 14.57 to 10.48 due to STN-DBS surgery (p = .018, see *Figure 9*). This shows us a significant improvement of the MDS-UPDRS-III appendicular score due to STN-DBS in PD patients that received their optimized oral dopaminergic medication.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS ON MED	14.57 ± 8.85	3	38
Post DBS ON MED	10.48 ± 7.11	0	28

Table 8. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – MDS-UPDRS-III appendicular scores

3.2.5 DBS improved anxiety in patients on medication

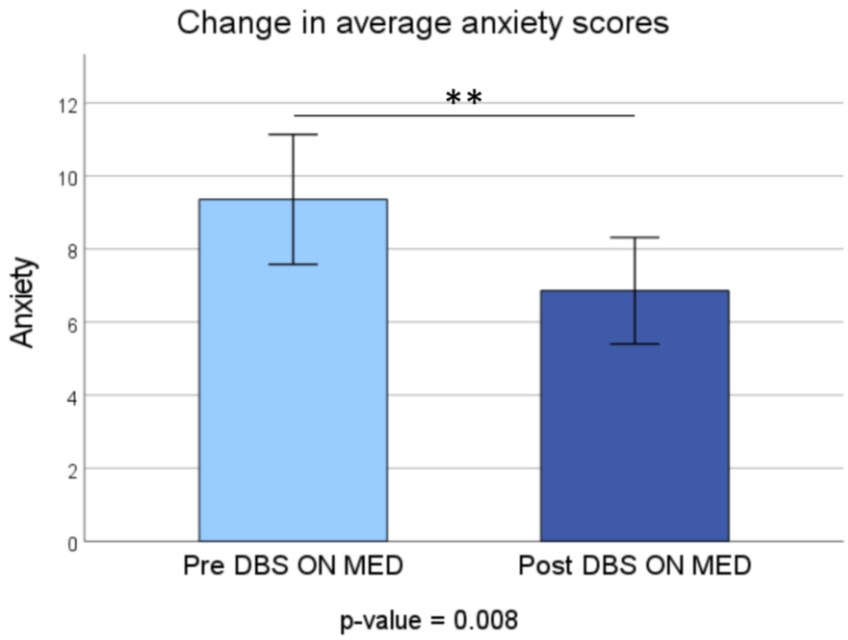

Figure 10. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – Anxiety scores

On medication, the Hamilton anxiety score decreased from 9.65 to 6.77 on average due to STN-DBS (p > .001, see *Figure 10*). This reflects that STN-DBS led to a significant reduction of anxiety in PD patients when they were on oral dopaminergic medication.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS ON MED	9.65 ± 6.42	0	23
Post DBS ON MED	6.77 ± 5.07	0	21

Table 9. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – Anxiety scores

3.2.6 DBS led to no significant improvement of depression in patients on medication

The result of the Hamilton depression score pre DBS ON MED vs. post DBS ON MED was not significant (p = .208, see *Figure 22*, 6. *Appendix*). This means that no effect of DBS stimulation on depression could be found when patients were on optimized oral dopaminergic treatment.

3.2.7 DBS led to an increase of the apathy score in patients on medication

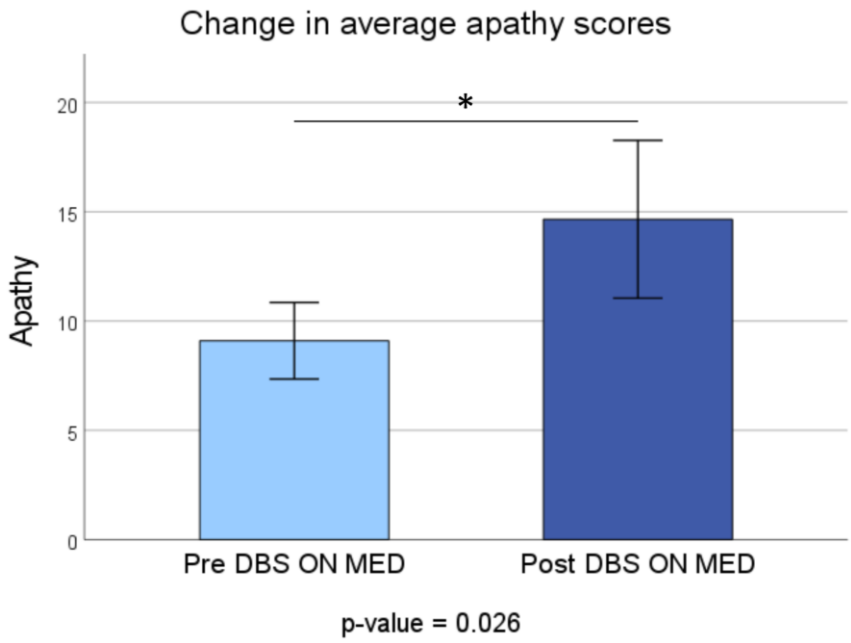

Figure 11. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – Apathy scores

On medication, the apathy score increased from 9.30 to 14.37 on average due to STN-DBS (p = .026, see *Figure 11*). Therefore, PD patients on medication seem to experience worse apathy post-surgery on average.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS ON MED	9.30 ± 6.23	0	27
Post DBS ON MED	14.37 ± 12.74	0	49

Table 10. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – Apathy scores

3.2.8 Overall LEDD was reduced after DBS surgery

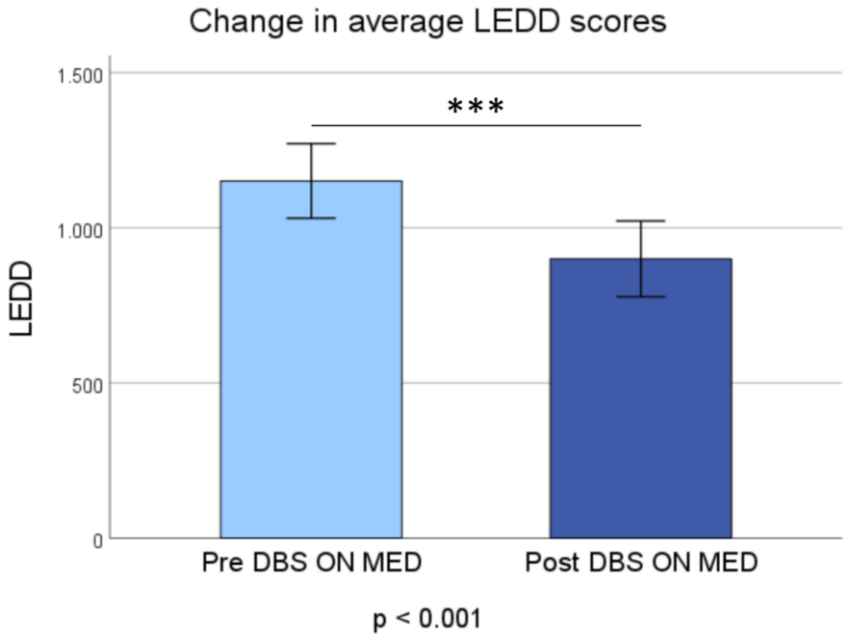

Figure 12. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – LEDD scores in mg

After STN-DBS the levodopa equivalent daily dose decreased from 1131 mg to 879 mg on average (p < .001, see *Figure 12*). That means STN-DBS had a significant influence on the required dose of oral dopaminergic medication. This is very important and well described in the literature and may lead to less dopaminergic side effects.

Parameter	Mean ± SD (mg)	Minimum (mg)	Maximum (mg)
Pre DBS ON MED	1131 ± 416	200	2468
Post DBS ON MED	879 ± 431	40	2000

Table 11. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – Total LEDD scores

3.2.9 Hypomimia correlated with the MDS-UPDRS-III total score, MDS-UPDRS-III appendicular score and anxiety in patients on medication in the conditions before and after DBS surgery

Correlations between MDS-UPDRS-III subitem 19, total score, axial score, appendicular score, depression, apathy, anxiety, and LEDD score were examined in patients on medication in the conditions before and after DBS-surgery.

The facial expression score correlated with the MDS-UPDRS-III total score in the second comparison (r = .495, p = .007, see *Figure 13*). This means that patients with worse hypomimia also tend to suffer from higher MDS-UPDRS-III total scores.

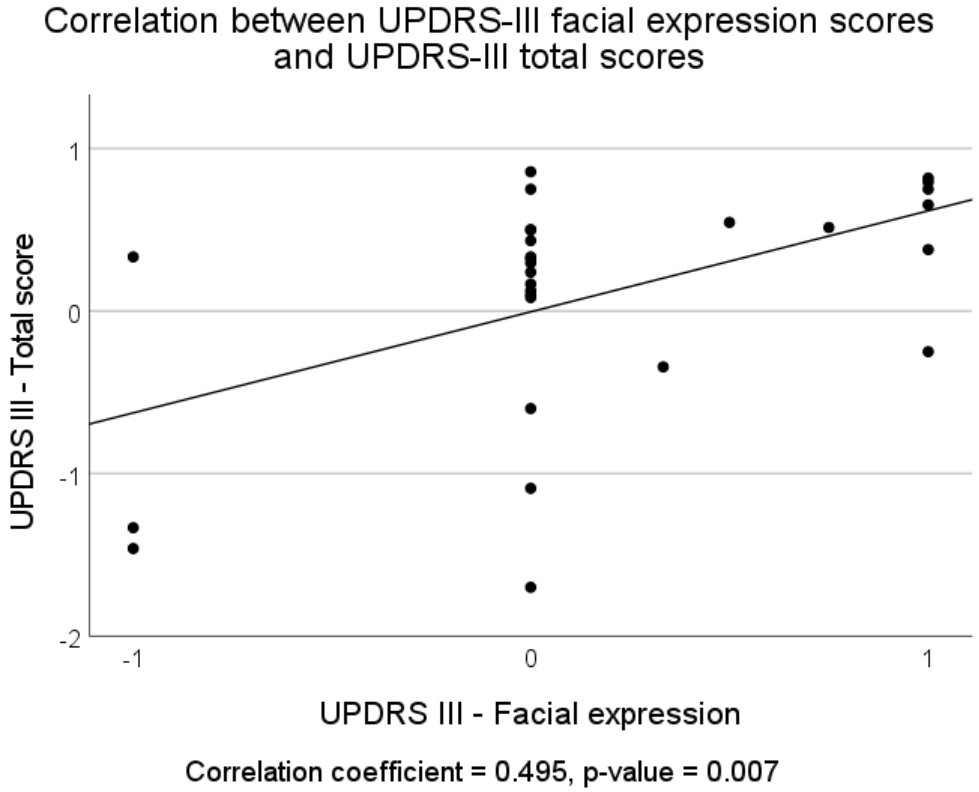

Figure 13. Scatterplot: Pre DBS ON MED vs. Post DBS ON MED – Correlation between MDS-UPDRS-III facial expression scores and MDS-UPDRS-III total scores

Moreover, facial expression correlated with the MDS-UPDRS-III appendicular score in our second comparison (r = .465, p = .013, see *Figure 14*). This shows that PD patients with worse hypomimia also seem to experience worse appendicular cardinal motor symptoms like bradykinesia and rigidity.

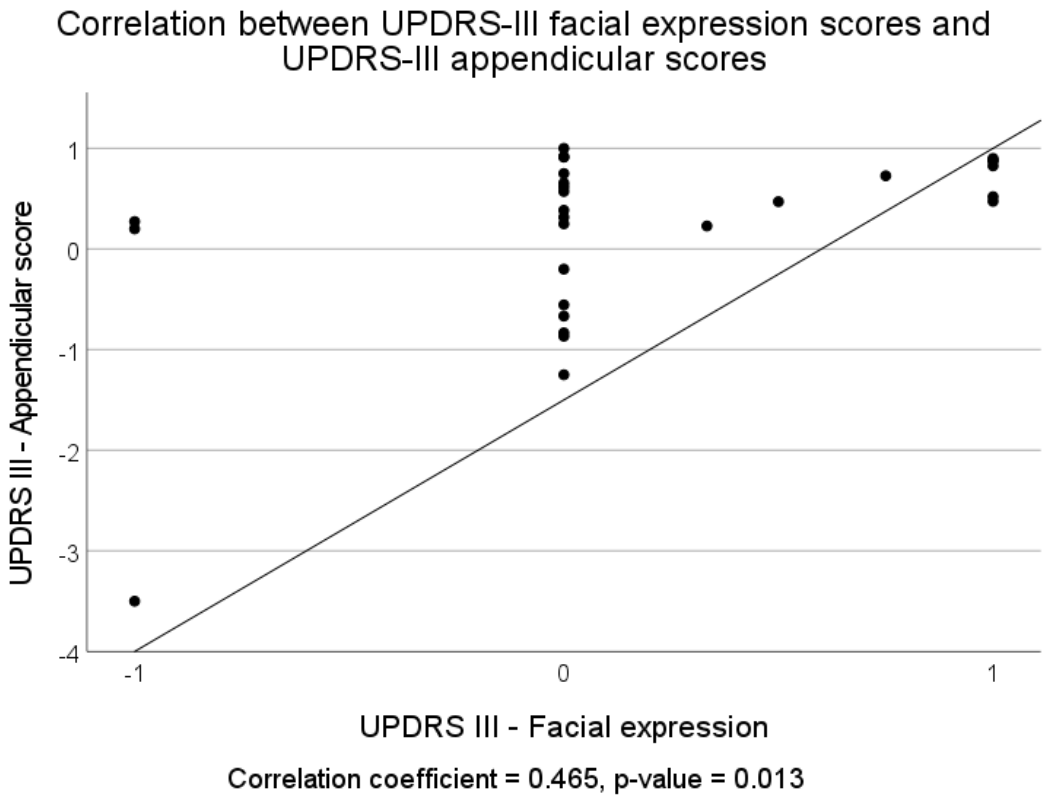

Figure 14. Scatterplot: Pre DBS ON MED vs. Post DBS ON MED – Correlation between MDS-UPDRS-III facial expression scores and MDS-UPDRS-III appendicular scores

It was also interesting that facial expression correlated with anxiety in the second comparison (r = .444, p = .034, see *Figure 15*). This means that PD patients with worse hypomimia also suffer from worse anxiety.

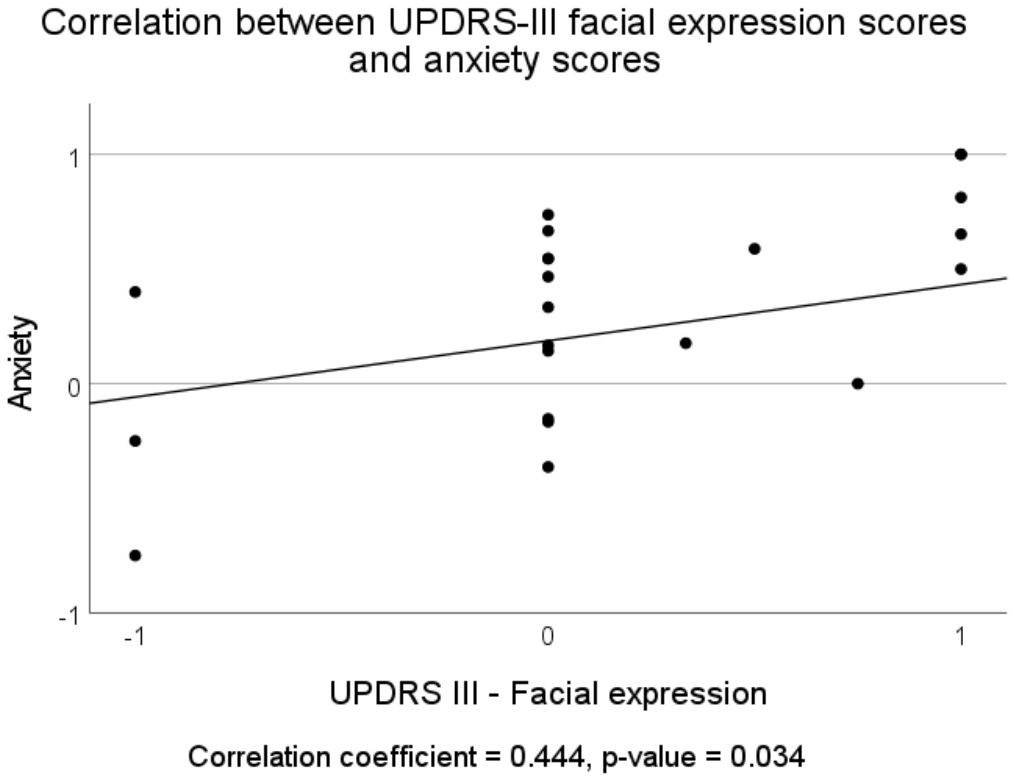

Figure 15. Scatterplot: Pre DBS ON MED vs. Post DBS ON MED – Correlation between MDS-UPDRS-III facial expression scores and anxiety scores

Further correlations were found between the MDS-UPDRS-III total and axial score (r = .630, p < .001), between the MDS-UPDRS-III appendicular score and apathy (r = - .335, p = .021), and between depression and anxiety (r = .830, p < .001). The parameter LEDD showed no correlations with any of the parameters assessed.

3.3 Dopaminergic oral medication improved the MDS-UPDRS-III subitem 19, the total score, the axial score, and the appendicular score in patients post DBS surgery

3.3.1 Medication improved hypomimia in patients after DBS surgery

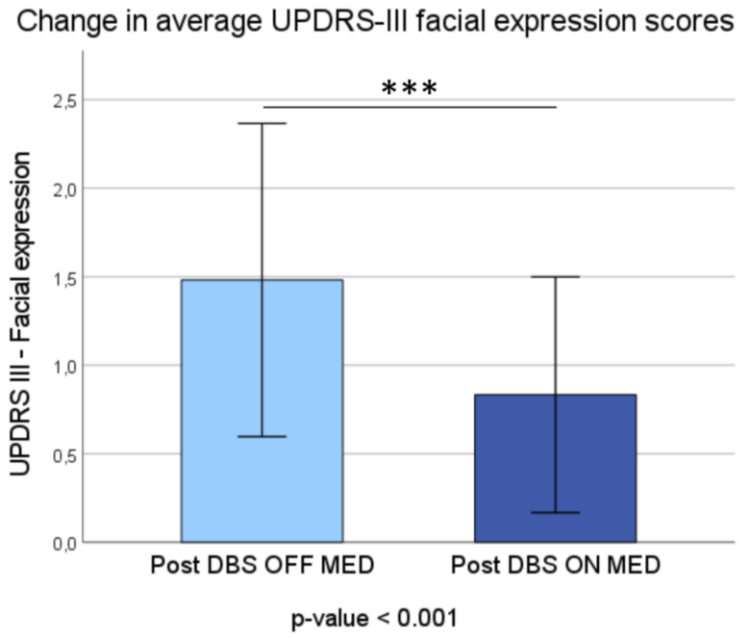

Figure 16. Bar chart: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III facial expression scores

Post STN-DBS surgery, the MDS-UPDRS-III subitem 19 score decreased from 1.48 to 0.83 on average when comparing patients in the off-medication and on-medication conditions ($p < .001$, see *Figure 16*). This shows a significant improvement of facial expression in PD patients post-surgery after receiving medication.

Parameter	Mean ± SD	Minimum	Maximum
Post DBS OFF MED	1.48 ± 0.89	0	4
Post DBS ON MED	0.83 ± 0.67	0	2

Table 12. Descriptive statistics: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III facial expression scores

3.3.2 Medication improved the MDS-UPDRS-III total score in patients after DBS surgery

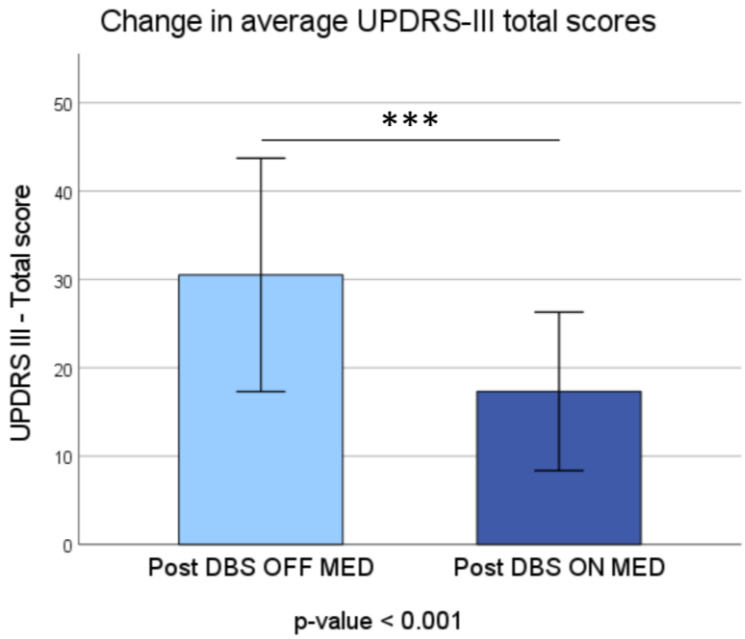

Figure 17. Bar chart: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III total scores

Post STN-DBS surgery, when comparing patients in the off-medication and on-medication conditions, the MDS-UPDRS-III total score decreased from 30.52 to 17.33 on average ($p < .001$, see *Figure 17*). This reflects that medication led to an important improvement of the MDS-UPDRS-III total score in PD patients after DBS surgery.

Parameter	Mean ± SD	Minimum	Maximum
Post DBS OFF MED	30.52 ± 13.21	4	59
Post DBS ON MED	17.33 ± 8.97	3	43

Table 13. Descriptive statistics: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III total scores

3.3.3 Medication improved the MDS-UPDRS-III axial score in patients after DBS surgery

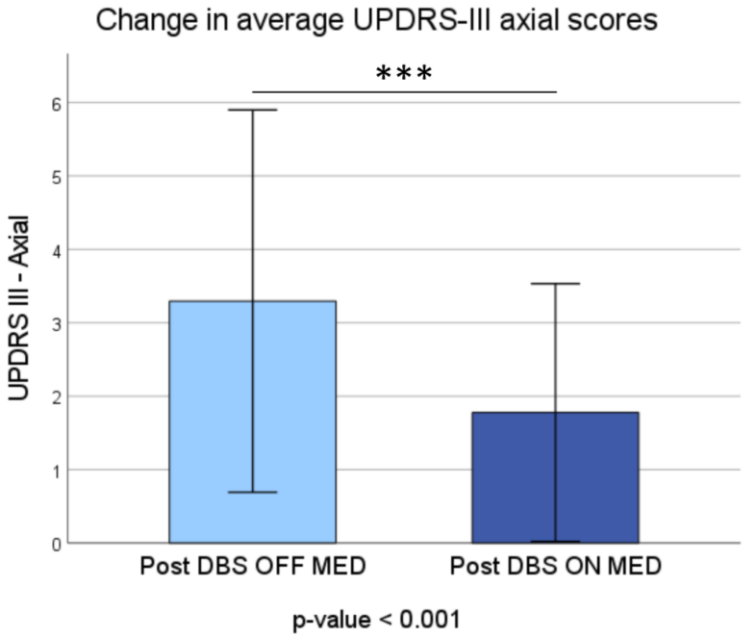

Figure 18. Bar chart: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III axial scores

Post STN-DBS surgery, the axial score decreased from 3.30 to 1.78 on average when comparing patients in the off-medication and on-medication conditions ($p < .001$, see *Figure 18*). Medication therefore improved not only facial expression and the MDS-UPDRS-III total score, but also improved axial score in PD patients post-surgery.

Parameter	Mean ± SD	Minimum	Maximum
Post DBS OFF MED	3.30 ± 2.60	0	10
Post DBS ON MED	1.78 ± 1.76	0	7

Table 14. Descriptive statistics: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III axial scores

3.3.4 Medication improved the MDS-UPDRS-III appendicular score in patients post DBS surgery

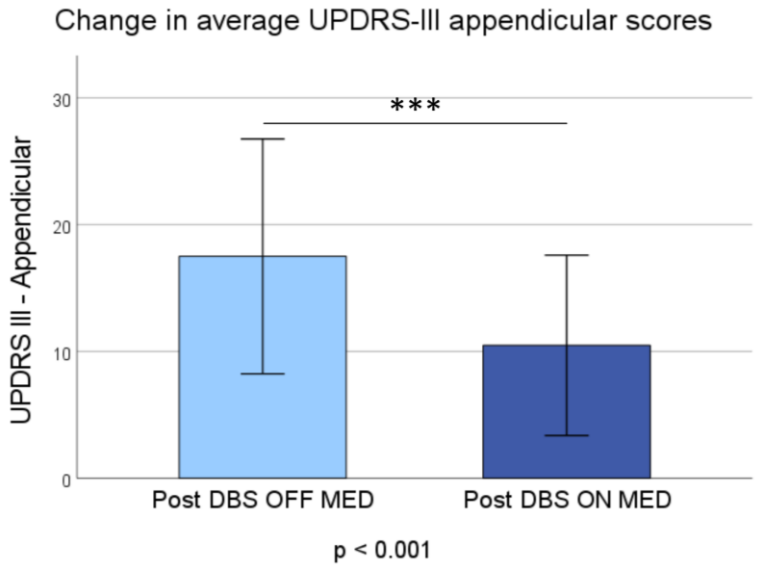

Figure 19. Bar chart: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III appendicular scores

Post STN-DBS surgery, when comparing the medication off and on condition, the MDS-UPDRS-III appendicular score decreased from 17.50 to 10.48 on average due to medication ($p < .001$, see *Figure 19*). This reflects that optimal oral dopaminergic medication led to an important improvement of the MDS-UPDRS-III appendicular score in PD patients after DBS surgery.

Parameter	Mean ± SD	Minimum	Maximum
Post DBS OFF MED	17.50 ± 9.27	2	37
Post DBS ON MED	10.48 ± 7.11	0	28

Table 15. Descriptive statistics: Post DBS OFF MED vs. Post DBS ON MED – MDS-UPDRS-III appendicular scores

3.3.5 Hypomimia in patients post DBS surgery in the conditions on and off medication correlated with the MDS-UPDRS-III appendicular score

Correlations between MDS-UPDRS-III facial expression, total, axial, and appendicular scores were examined in patients post DBS surgery in the conditions on and off medication.

The MDS-UPDRS-III appendicular score was the only parameter that correlated with hypomimia, but it showed a negative correlation ($r = -.368$, $p = .025$). Moreover, the MDS-UPDRS-III total and axial scores correlated ($r = .474$, $p = .002$), as well as the MDS-UPDRS-III total and appendicular scores ($r = -.844$, $p < .001$).

In summary our results show that STN-DBS led to an improvement of hypomimia, the MDS-UPDRS-III total score and the axial score in patients that were off medication. However, in patients that were already on oral dopaminergic medication STN-DBS only slightly improved the MDS-UPDRS-III total score and axial score. We noticed that the biggest changes of the parameters happened in the last comparison, when patients post DBS surgery received their optimal oral dopaminergic treatment.

4. Discussion

The aim of this thesis was to provide an overview of the current state of knowledge on hypomimia in patients with PD and to investigate if hypomimia shows STN-DBS-responsiveness. Moreover, we aimed to examine possible correlations with motor and non-motor symptoms. This was done to further categorize hypomimia as doing so may eventually lead to better treatment strategies. STN-DBS is a neurosurgical intervention that is used for the treatment of motor symptoms in Parkinson's disease like tremor, rigidity, bradykinesia, and axial symptoms (4). There is a significant body of evidence pointing to STN-DBS-responsiveness of hypomimia due to data showing a relationship between hypomimia and motor symptoms, as well as a levodopa-responsiveness of hypomimia (17,42).

This study is especially important as to date there is still a lack of information on hypomimia in PD, despite it representing a huge burden for PD patients and their partners and care givers in everyday life (3). Patients experiencing hypomimia suffer from a diminished ability to express emotions and therefore are hampered in their ability to communicate (40). Diagnosis can be especially challenging, as hypomimia may initially be misinterpreted as depression or lack of interest. But also, therapy may be quite difficult, as there are heterogenous results found in the literature as to how exactly this symptom is best categorized and therefore treated (3). That is because existing studies still do not agree on whether hypomimia is best categorized as a motor symptom (with the further subdivision into appendicular and axial symptom) or non-motor symptom (17,42,46,47,57). It is evident that more research is needed in the field, as it may help improve the lives of many people affected by this disease, especially as numbers of those affected are predicted to double by 2040 (8).

In our study we examined the relationship between hypomimia, assessed by movement disorder specialists, using the MDS-UPDRS-III subitem 19 (facial expression), and the MDS-UPDRS-III total score, the MDS-UPDRS-III axial score, the MDS-UPDRS-III appendicular score, anxiety, depression, apathy, and LEDD. We found weak evidence linking hypomimia to axial symptoms and only controversial associations with appendicular symptoms. However, there was a strong correlation between hypomimia and the MDS-UPDRS-III total score and we

discovered a relationship between hypomimia and anxiety, where patients with more severe hypomimia showed higher anxiety scores. We did not find a significant association to apathy and depression. Based on the result in our cohort, we suggest that hypomimia is best characterized as a motor symptom, as we found stronger correlations with the MDS-UPDRS-III total score than with emotional parameters such as apathy, anxiety, and depression.

This would suggest that hypomimia could be treated in the same way as other motor symptoms in PD. Previous data investigated treatment options of hypomimia such as levodopa (17,52) and physiotherapy (54), which both showed good results. But in the course of the disease levodopa has its limitations due to development of fluctuations and disabling side-effects (35,36). At this point, device-aided therapies can be useful, one of them being deep brain stimulation. This poses the question if STN-DBS also affects hypomimia. To the best of our knowledge there are no publications existing that examined hypomimia responsiveness to STN-DBS and based on the results of previous studies, we have not been able to determine if hypomimia responds to STN-DBS. Following the suggestion by Ricciardi et al. (17) hypomimia fits best as an axial sign and it is reported that axial symptoms (postural instability, freezing of gait) are not STN-DBS responsive (64). By contrast, Cepeda et al. (42) found strong parallels between hypomimia and distal bradykinesia, and appendicular cardinal motor symptoms such as bradykinesia and rigidity are known to respond well to STN-DBS (64).

In our first comparison we contrasted the average changes of the parameters hypomimia, MDS-UPDRS-III total, MDS-UPDRS-III axial, and MDS-UPDRS-III appendicular scores in PD patients that were off medication before and after STN-DBS surgery in order to investigate the effect of the stimulation itself. We found a significant improvement of all four parameters.

Comparing the average scores of patients that were on optimized oral dopaminergic medication before and after they received STN-DBS surgery we found that only the result of the MDS-UPDRS-III total score and appendicular score showed significant improvement. However, during STN-DBS only, the MDS-UPDRS-III total score was much higher (30.52) than the average score in patients that only received oral dopaminergic therapy (22.33). This implies that when comparing the therapeutic

outcomes of oral dopaminergic medication alone to those of STN-DBS alone, oral medication yields greater results in terms of the MDS-UPDRS-III total score. It is important to note that there was no further improvement of hypomimia in PD patients that were on optimized oral dopaminergic medication through STN-DBS surgery.

The hypomimia score, the MDS-UPDRS-III total score, the MDS-UPDRS-III axial score, and the MDS-UPDRS-III appendicular score improved significantly in patients post-surgery after they received their oral dopaminergic therapy.

We also investigated the effect of STN-DBS on the non-motor symptoms *anxiety*, *depression*, and *apathy* in PD patients that were on medication. The anxiety score improved due to STN-DBS, whereas the depression score showed no significant result. Of note, there was a worsening of the apathy score due to STN-DBS. This phenomenon is already known and has been investigated in a Meta-Analysis by Zhang et al. (69). They analyzed apathy in patients after STN-DBS and GPi-DBS, and the result showed that STN-DBS worsened the state of apathy, while GPi-DBS did not lead to any significant change in the apathy score.

This study has certain limitations. Firstly, the study population consisted of only 54 PD patients, of whom only 16 were male. Secondly, while movement disorder specialists rated facial expression via video rating, there was no objective method with which to quantify facial expression. Thirdly, the patients were examined in the morning before their first dose of levodopa, whereby residual levodopa may still have been present in the body due to the intake of prolonged-release formulations.

In conclusion, this thesis provides novel information on the effects of medication and STN-DBS on hypomimia in PD and helps characterize hypomimia more as a motor symptom. However, we still do not know exactly which symptom hypomimia is most concordant with. Our findings suggest that it does not qualify as an axial motor sign. Furthermore, the association between hypomimia and appendicular cardinal motor signs (bradykinesia and rigidity) also lacked clear correlations. Future studies should try to classify hypomimia even better by looking for correlations with other PD symptoms and including larger study populations. Since OFF-periods in Parkinson's disease are a key indication for the use of STN-DBS, future studies should also focus on the reduction of OFF-periods through STN-DBS. This could be an

important step towards finding a better targeted therapy for hypomimia in Parkinson's patients and therefore improving patients’ quality of life.

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6. Appendix

In the second comparison *Pre DBS ON MED vs. Post DBS ON MED* the results of the parameters *MDS-UPDRS-III facial expression*, *MDS-UPDRS-III axial* and *depression* are not significant and can be viewed below.

6.1 DBS led to no significant improvement of hypomimia in patients on medication

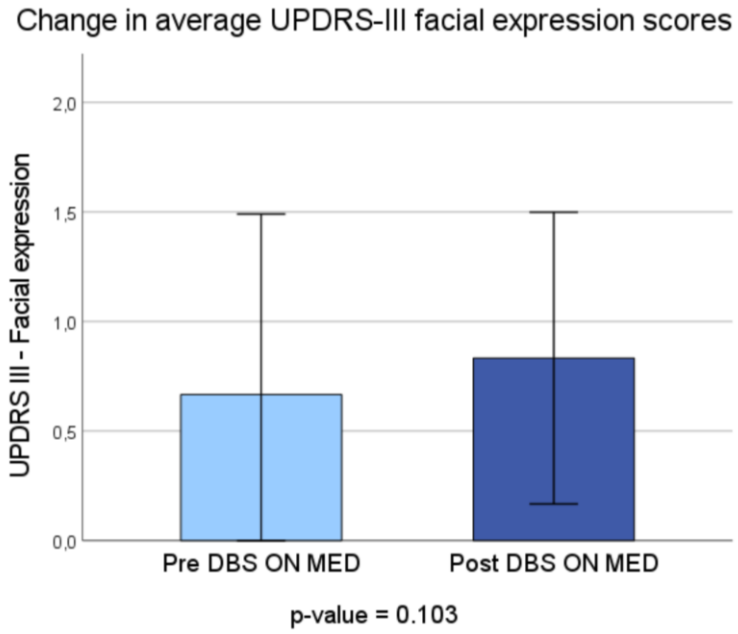

Figure 20. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – UPDRS-III facial expression scores

We did not find a significant effect of DBS stimulation in PD patients that were on optimal oral dopaminergic medication (p = .103, see *Figure 20*). This means that there is no evidence that hypomimia can be treated with STN-DBS in Parkinson's patients receiving oral dopaminergic treatment.

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS ON MED	0.67 ± 0.82	0	4
Post DBS ON MED	0.83 ± 0.67	0	2

Table 16. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – MDS-UPDRS-III facial expression scores

6.2 DBS led to no significant improvement of the axial score in patients that were on oral dopaminergic medication

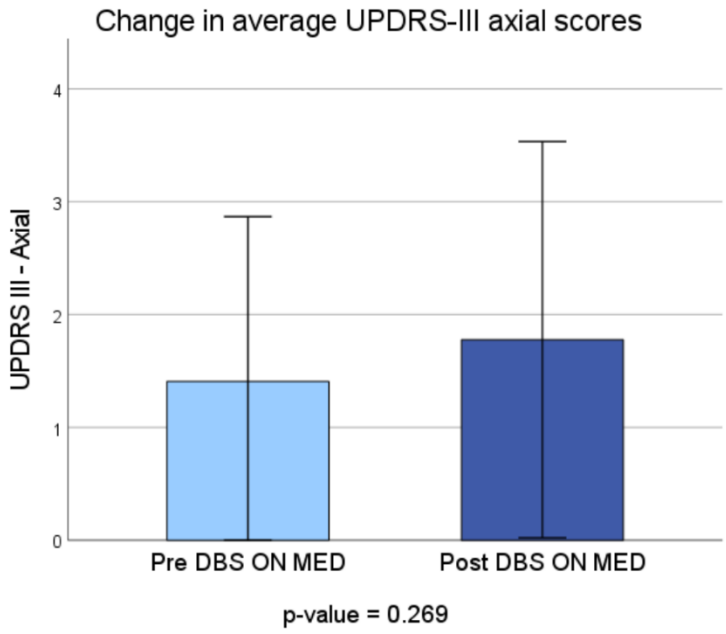

Figure 21. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – MDS-UPDRS-III axial scores

DBS did not lead to a significant improvement of the axial score in PD patients that were on medication (p = .269, see *Figure 21*).

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS ON MED	1.41 ± 1.46	0	7
Post DBS ON MED ON STIM	1.78 ± 1.76	0	7

Table 17. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – MDS-UPDRS-III axial scores

6.3 DBS led to no significant improvement of depression in patients on medication

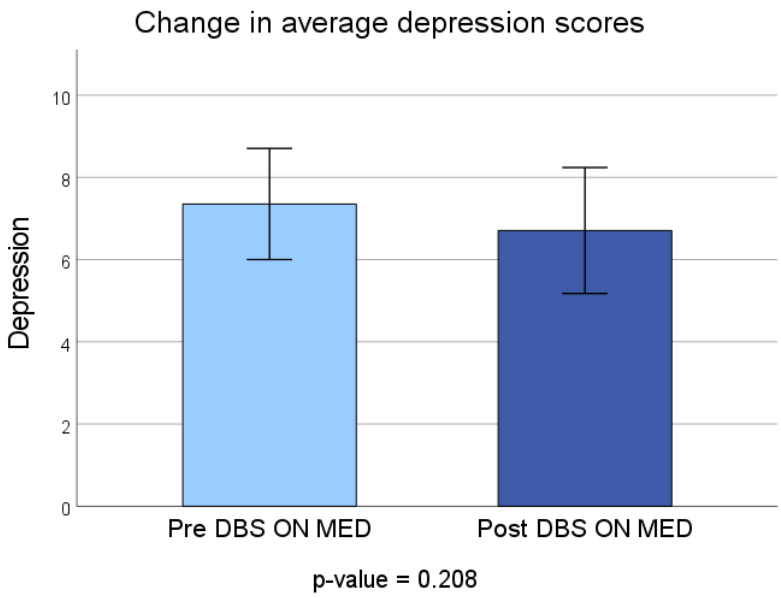

Figure 22. Bar chart: Pre DBS ON MED vs. Post DBS ON MED – Depression scores

We did not find a significant improvement of depression in PD patients that were on oral dopaminergic treatment due to DBS-surgery (p = .208, see *Figure 22*).

Parameter	Mean ± SD	Minimum	Maximum
Pre DBS ON MED	7.39 ± 4.57	0	18
Post DBS ON MED	6.76 ± 5.16	0	22

Table 18. Descriptive statistics: Pre DBS ON MED vs. Post DBS ON MED – Depression scores