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‘Mechanisms of Body Mass Gain in Parkinson’s Disease Patients after Deep Brain Stimulation of the Subthalamic Nucleus’

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Declaration of Authorship

I hereby formally declare that this dissertation is my own original work. This thesis has not previously been accepted in substance for any degree and is not being concurrently with the application for any degree. Furthermore, I confirm that I have clearly referenced all sources (either from a printed source, the Internet, or any other source) used in this work in accordance with departmental requirements. All references and verbatim extracts have been quoted, and all sources of information, including graphs and datasets, have been specifically acknowledged.

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‘Lust und Liebe sind die Fittiche zu großen Taten‘

(Lust and love are the wings to great deeds)

– Johann Wolfgang von Goethe

Abstract

Neurological disorders are an increasing global burden and therefore one of the major health challenges in the 21st century. Most of the neurological brain diseases are network or circuit disorders in which a particular dysfunction within a circuitry causes the development and expression of functional impairments in individual patients. Parkinson's disease (PD) is thereby the fastest growing neurological disorder worldwide. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a well-established therapy in advanced PD for managing severe motor complications. Despite the well-established evidence that DBS is an effective treatment option for PD, many challenges remain, both in the short and long term. Interestingly, a dysfunctional information flow of cortico-striatal networks has been proposed to be involved in the pathogenesis of both, overweight and obesity, and PD. In this context, an increase in body mass was thereby observed in the majority of patients with PD that underwent STN DBS. Apart from metabolic changes such as alterations in energy expenditure, an abnormal modulation of the mesolimbic system accounted for changes in motivated behavior, food intake, and body mass. However, the exact extent and time course, as well as the underlying pathophysiological mechanisms of this body mass gain, remain unclear.

Therefore, in a series of experiments, I aimed to investigate the mechanisms of body mass gain as side effect of DBS treatment in PD patients. Initially, a systematic review and meta-analysis aimed to clarify the extent and time course of body mass gain according to STN DBS. Second, the next study aimed to determine the influence of STN DBS on clinical symptoms, body mass, BMI, body composition, and behavior related to food intake and reward sensitivity. The third study with DBS-treated PD patients under both conditions – active stimulation and inactivated stimulation – was used to determine the acute modulatory effects of STN DBS on the motivational attraction of food cues as well as the exact role of STN DBS in cognitive functions and eating behavior in patients with PD. I used an fMRI paradigm to investigate alterations in brain substrates of hedonic hunger and associated changes in cognitive control of eating behavior due to the modulatory effects of DBS on cortical-subcortical imbalances.

First of all, significant improvements in motor symptoms were observed after STN DBS. However, all three studies confirmed a significant postoperative body mass and BMI gain. The body mass gain occurred thereby rapidly and sustained in most of all patients. It is thereby mainly accompanied by an increase in fat mass (FM), with the upper parts of the body particularly affected. Moreover, patients were normal weight, overweight, and obese prior to the surgery, which confirms the observation that an increase in body mass is not necessarily associated with malnutrition and underweight. Postoperative body mass gain was thereby determined by a regional effect of stimulation on adjacent structures that are involved in the central regulation of reward and energy balance. Activation patterns within associative and

limbic parts of the STN correlated with divergent amounts of body mass gain. Accordingly, the increase in FM was associated with stimulation of the limbic subdivision of the STN. In addition, changes in the behavioral inhibition system were found as a result of high-frequency stimulation. Finally, STN DBS increased the salience of food cues, especially for sweet foods, while at the same time leading to declined activations in reward areas.

To summarize, our results clearly demonstrate a massive body mass gain after STN DBS and indicate the first predictive factors of body mass gain. The findings suggest a potential imbalance in both top-down and bottom-up processing of appetitive food cues, which may reflect a lack of control over the desire to eat, altered sensitivity to food reward cues, and changes in eating behavior, including higher food intake and increased appetite. Our findings emphasize the metabolic relevance of high-frequency stimulation of subcortical areas, because primarily FM gain as a side effect was observed, which can lead to metabolic repercussions and negative health effects.

In conclusion, this thesis presents novel insights into the underlying pathophysiological mechanisms that link STN DBS with body mass gain and, in consequence, associated negative health effects in PD patients, thereby underlining the need to develop tailored therapies in neuromodulation to pave the way for personalized medicine.

Zusammenfassung

Neurologische Erkrankungen und hier insbesondere die Erkrankungen des zentralen Nervensystems stellen aufgrund der wachsenden Anzahl an Patienten eine der globalen gesundheitswirtschaftlichen Herausforderungen des 21. Jahrhunderts dar. Viele dieser Erkrankungen sind neurodegenerativ und gehen mit einer Störung von neuronalen Netzwerken einher. Der Morbus Parkinson ist die weltweit am schnellsten wachsende neurodegenerative Erkrankung. Die tiefe Hirnstimulation (Deep Brain Stimulation, DBS) des Nucleus subthalamicus (STN) ist ein etabliertes Therapieverfahren bei fortgeschrittenem Morbus Parkinson, wenn zum Beispiel medikamentöse Therapieoptionen ausgeschöpft sind. Trotz der Evidenz, dass die DBS eine wirksame Behandlungsoption bei Morbus Parkinson ist, bleiben sowohl kurz- als auch langfristig viele Herausforderungen bestehen. Interessanterweise wurde ein gestörter Informationsfluss von kortiko-striatalen Netzwerken bei der Pathogenese sowohl von Übergewicht und Adipositas als auch von Morbus Parkinson beschrieben. In diesem Zusammenhang kann bei der Mehrzahl der Patienten mit Morbus Parkinson, die im STN stimuliert wurden, eine Zunahme des Körpergewichts beobachtet werden. Neben metabolischen Veränderungen wie beispielsweise Veränderungen des Energieverbrauchs, wurde eine abnorme Modulation des mesolimbischen Systems für Veränderungen von motiviertem Verhalten, der Nahrungsaufnahme und des Körpergewichts postuliert. Das genaue Ausmaß und der zeitliche Verlauf der Gewichtszunahme sowie die zugrunde liegenden pathophysiologischen Mechanismen dieser behandlungsassoziierten Nebenwirkung ist bislang nur in Ansätzen verstanden.

Ziel der vorliegenden Arbeit ist es, zunächst das Ausmaß und den zeitlichen Verlauf der Gewichtszunahme nach STN DBS mittels einer systematischen Übersichtsarbeit zu untersuchen. Als nächstes soll der Einfluss der DBS auf die klinische Symptomatik, das Körpergewicht, den BMI, die Körperzusammensetzung sowie das Verhalten im Zusammenhang mit der Nahrungsaufnahme und der Belohnungssensitivität betrachtet werden. In einer weiteren Untersuchung bei der Patienten mit Morbus Parkinson unter zwei verschiedenen Konditionen, aktiver und inaktivierter Stimulation, mittels Magnetresonanz-tomografie gemessen wurden, sollen die akuten neuromodulatorischen Effekte der STN DBS auf die Motivation und kognitiven Funktionen bezüglich des Essverhalten untersucht werden.

Durch die DBS konnte eine eindeutige Verbesserung der motorischen Symptomatik bei Patienten mit Morbus Parkinson erreicht werden. Weiter konnten alle drei Studien auf eine signifikante postoperative Zunahme des Körpergewichts und des BMI hinweisen. Die Zunahme des Körpergewichts trat dabei bei der Mehrheit der Patienten rasch auf und stabilisierte sich anschließend. Sie geht dabei hauptsächlich mit einer Zunahme von Fettmasse einher, bei der vor allem der abdominale Bereich des Körpers betroffen ist. Zudem

waren die Patienten vor der Operation normalgewichtig, übergewichtig oder adipös, was die Beobachtung bestätigt, dass die Zunahme des Körpergewichts nicht als Normalisierung von krankheitsbedingtem Untergewicht gesehen werden kann. Die postoperative Zunahme des Körpergewichts wurde dabei durch einen regionalen Effekt der Stimulation auf benachbarte Strukturen determiniert, die an der zentralen Regulation von Energiehaushalt und Belohnung beteiligt sind. Aktivierungsmuster innerhalb der assoziativen und limbischen Teile des STN korrelierten dabei mit unterschiedlichen Relationen in der Zunahme des Körpergewichts. Entsprechend war die Zunahme der Fettmasse mit der Stimulation des limbischen Teils des STN assoziiert. Darüber hinaus wurden Verhaltensveränderungen im inhibitorischen System bei den Patienten gefunden. Die DBS führte schließlich zu Veränderungen der Salienz von Nahrungsstimuli, insbesondere bei süßen Nahrungsmitteln, während sie gleichzeitig zu verminderten Aktivierungen in belohnungsassoziierten Arealen des Hirns assoziiert war.

Zusammenfassend lässt sich sagen, dass die Ergebnisse der Dissertation eindeutig eine massive Zunahme des Körpergewichts nach STN DBS hinweisen und neue prädiktive Faktoren der zugrundeliegenden pathophysiologischen Mechanismen aufzeigen. Die Ergebnisse deuten auf ein potenzielles Ungleichgewicht sowohl bei der Top-Down- als auch bei der Bottom-Up-Verarbeitung von appetitiven Nahrungsstimuli hin, was einem Mangel an Kontrolle über das Bedürfnis zu Essen, Veränderungen in der Sensitivität gegenüber nahrungsbedingten Belohnungssignalen sowie Veränderungen im Essverhalten, einschließlich einer höheren Nahrungsaufnahme widerspiegeln. Diese stimulationsinduzierten Plastizitätsveränderungen tragen zur klinischen Manifestation der Zunahme des Körpergewichts bei. Unsere Ergebnisse unterstreichen die metabolische Relevanz der Hochfrequenzstimulation subkortikaler Areale, da primär die Zunahme von viszeralem Fett, als Nebenwirkung dieser Therapie, zu metabolischen Veränderungen und damit einhergehend zu negativen gesundheitlichen Auswirkungen führen kann.

Abschließend ist festzuhalten, dass die vorliegende Arbeit eine enge Interaktion zwischen STN DBS und Zunahme des Körpergewichts demonstriert, wobei neue Einsichten in die zugrundeliegenden pathophysiologischen Mechanismen durch die DBS des STN im Zusammenhang mit der Zunahme des Körpergewichts und den damit verbundenen negativen gesundheitlichen Auswirkungen bei Patienten mit Morbus Parkinson beleuchtet werden konnten. Die Ergebnisse unterstreichen die damit einhergehende Notwendigkeit der Entwicklung personalisierten und individualisierten Therapieansätzen in der Neuromodulation, um die Nebenwirkungen der DBS zu minimieren.

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Abbreviations

AC	Anterior cingulate cortex
BAS	Behavioral activation system
BIS	Behavioral inhibition system
BMI	Body Mass Index
CBBM	Center of Brain, Behavior, and Metabolism
COMT	Catechol-O-methyltransferase
cZi	Caudal zona incerta
DA	Dopamine
DAN	Dorsolateral attention network
DBS	Deep brain stimulation
DMN	Default mode network
DRT	Dopamine replacement therapy
EEG	Electroencephalography
EPI	Echoplanar Image
ET	Essential tremor
FC	Functional connectivity
FFM	Fat-free mass
FM	Fat mass
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
GPe	Globus pallidus externus
GPi	Globus pallidus internus
H-CON	Healthy control subjects
HC-NS	High-caloric non-sweet foods
HC-S	High-caloric sweet foods
ICD	Impulsive control disorder

LC	Low-caloric foods
LEDD	Levodopa equivalent dose
LI	Lateralization index
LID	Levodopa-induced dyskinesia
MDS-UPDRS	Unified Parkinson's disease rating scale
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
NAcc	Nucleus Accumbens
NPY	Neuropeptide Y
OFC	Orbitofrontal cortex
OFF	Deactivated stimulation
ON	Activated stimulation and medication intake
PD	Parkinson's disease
PD-CON	Parkinson's disease control group
PD-DBS	Parkinson's disease group with deep brain stimulation
PET	Positron emission tomography
PPN	Pedunculopontine nucleus
Put	Putamen
ROI	Region of interest
RRC	ROI-to-ROI analysis
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SMN	Sensory-motor network
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SNS	Sympathetic nervous system
SPECT	Single -photon emission computed tomography
STN	Subthalamic nucleus
VAS	Visual-analog scale

VIM	Ventral intermediate thalamic nucleus
VN	Extrastriate visual network
VTA	Volume of tissue activated

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1 Introduction

1.1 General Outline of the Thesis

Neurological disorders are an increasing global burden and therefore one of the major health challenges in the 21st century. After Alzheimer's disease, Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide [1]. Although PD is incurable, highly efficient symptomatic treatment options are available including dopamine replacement therapy and deep brain stimulation (DBS). Over the last 30 years, DBS of the subthalamic nucleus (STN) has become a neurosurgical standard method to treat therapy-resistant tremor or motor complications in advanced disease stages [2–4]. Apart from its therapeutic benefits, negative side effects, such as changes in metabolism, endocrine signaling, and eating behavior have been observed [5–9]. These stimulation-induced side effects are frequently accompanied by a rapid and undesirable postoperative increase in body mass, which frequently causes metabolic repercussions and adverse health implications [5–25].

This body mass gain can be understood as an imbalance between energy intake and energy expenditure, ultimately resulting in overweight and obesity in many patients [26–28]. Body mass gain can thereby be determined by low levels of physical activity, by reward-related overconsumption of highly palatable and energy-dense foods that goes beyond homeostatic needs [29], or a combination of both. In this context, it has been suggested that the dysfunctional processing within cortico-striatal networks may be involved in the pathogenesis of overweight and obesity [29]. In line with that, functional magnetic resonance imaging (fMRI) studies showed clear differences between lean and obese subjects in regard to food image processing [30]. For instance, obese individuals revealed decreased activation of the reward circuitry during food reward receipt accompanied by increased activation during food anticipation [31]. Obesity may therefore be considered as a food addiction disorder involving the same neurocircuitry that regulates food intake and metabolism and that is also affected in other brain disorders, such as obsessive-compulsive disorder or PD [29,32].

Besides the role of the limbic cortico-basal ganglia loop as a key regulator of processing of reward-related features of food cues, postoperative body mass changes may be linked to an influence on hypothalamic neurons that regulate homeostatic and metabolic functions [29].

For these reasons, the investigation of body mass alterations in basal ganglia disorders has attracted much attention in the neuroscientific community, although only a few studies have been conducted so far, reporting varying degrees of body mass gain in patients with PD and other movement disorders (dystonia, essential tremor) after DBS [30]. However, many of these studies were observational studies, and for most of them, a control group was missing. Despite these limitations, different associations were identified including improvement in resting tremor

and dyskinesias [31,32], changes in energy expenditure due to motor improvements [6,16], alterations in the hypothalamic regulation [5,6,33], changes in eating behavior and food intake [7,32,34–38], alterations in dopamine signaling [39], perturbations of homeostatic control [30,39], and the electrode position within the STN [10,40,41].

Nevertheless, it is currently still unclear which factors causally drive this body mass gain. The present PhD thesis thus aims to explain the underlying mechanisms of postoperative body mass gain especially in the context of brain-periphery crosstalk. In view of the paucity of treatment recommendations to prevent this body mass gain and its metabolic consequences, it is important to gain a better understanding of the underlying pathophysiological mechanisms that drive changes in appetite, food intake, motivational reward processing, and, in relation to these, metabolic alterations that contribute to their breakdown in body mass gain and changes in body composition [30,39,42]. Moreover, the interaction between central and peripheral systems caused by DBS in context of body mass gain remained largely unanswered.

Here, I applied three approaches to investigate the mechanisms of body mass gain in PD patients after STN DBS. First, I performed a systematic review and meta-analysis in previously published studies in order to investigate the extent and time course of body mass gain after STN DBS. Second, using a prospective and longitudinal study design, I examined causal interactions of STN DBS and body mass gain and its changes in body composition due to metabolic, neurocognitive, and neuronal plasticity mechanisms (Study 1). Third, I used fMRI to identify DBS-related disruptions of brain circuits involved in cue-elicited reward-seeking behaviors and attentional control resulting in an alteration of, leading to changes in eating habits and increased food intake (Study 2).

1.2 Parkinson's Disease

Movement disorders are often variable and complex in their clinical presentation. Two main forms can be distinguished: hypokinetic conditions are associated with a reduction in voluntary movements, whereas hyperkinetic conditions are presented with an excess of involuntary movements [43]. Both, hypo- and hyperkinetic forms are extrapyramidal disorders that mainly affect the basal ganglia and the corresponding cortex. Among movement disorders, PD is the prototype and most common form of a hypokinetic condition. PD was described very early on with first evidence in Galen's writings, the Bible, and in paintings, even long before the famous '*An Essay on the Shaking Palsy*' by James Parkinson in the early 19th century [44]. The 'official' history therefore begins in 1817 with the first extensive contributions of James Parkinson [44].

PD is characterized by a continuous disease progression due to progressive neurodegeneration. The pathological hallmark of PD is the progressive accumulation of α-synuclein pathology throughout the brain, leading to the formation of Lewy bodies as well as a predominant death of dopaminergic neurons in the substantia nigra pars compacta (SNc) [45]. Before the patients are diagnosed with PD, the classical cardinal motor signs in most patients are preceded by a variable prodromal phase. This phase is often characterized by mostly unspecific non-motor and first mild motor symptoms [46]. The cardinal signs, resting tremor, bradykinesia, muscular rigidity, and postural instability occur due to progressive deficiency of the neurotransmitter dopamine (DA). Other motor dysfunctions include difficulties in initiating and executing voluntary movements as well as impaired execution of movement sequences [45]. The broad spectrum of non-motor dysfunctions affects several neuronal systems, and almost 90 % of PD patients experience them during the course of the disease. Such non-motor symptoms involve multiple domains, including mild cognitive impairment or dementia, sleep-wake cycle dysregulation, mood and affective disorders (depression, apathy, anxiety, impulsive control disorders), hyposmia, autonomic dysfunction (constipation, orthostatic hypotension, urinary dysfunction, sexual dysfunction, somnolence), dysfunction of color vision, sensory symptoms, as well as pain [46–48]. Although altered body mass and BMI are risk factors for PD, they may also arise as non-motor side effects of PD therapies [39,42,67,68,69,70-73].

PD is clinically defined by the presence of bradykinesia with at least one other cardinal motor feature, such as resting tremor, or rigidity [45,47]. The motor signs start unilaterally and remain asymmetrical throughout the disease. The major signs of PD and symptoms that affect activities of daily living, can be captured with the MDS-UPDRS, the Unified Parkinson's disease rating scale, which is the most commonly used scale to assess motor and non-motor disability associated with PD [47,73]. Imaging is an important tool for the differential diagnosis and in particular nuclear imaging of the presynaptic dopaminergic neurotransmission with

Positron emission tomography (PET) or single-photon emission computed tomography (SPECT) typically reveals an impaired dopaminergic uptake in the striatum [45].

Medical treatment comprises the administration of Anti-parkinsonian medications including the DA precursor levodopa as the most efficient drug with the lowest number of adverse effects but also other dopaminergic and non-dopaminergic agents. Surgical methods, i.e. DBS, have revolutionized the treatment of PD in patients with treatment resistant tremor and insufficient motor responses in later stages of the disease, such as wearing off (worsening of motor symptoms before the next dose of levodopa; especially in the morning), motor fluctuations (referring to a decline in the usual benefits of levodopa treatment), nocturnal akinesia, and levodopa-induced dyskinesias.

1.2.1 Epidemiology

Among all neurological disorders, PD has been the fastest growing disease in recent decades [49,50]. The global burden of PD has more than doubled between 1990 and 2015, from initially 3 million up to 6.2 million affected individuals worldwide, which in turn increases also the amounts of costs for treatment. This exponential increase will continue in the future, as the world's population is aging and the incidence of PD increases with age [50]. First estimates therefore predict the future growth of up to 14.2 million cases in 2040 [50]. The age of onset is usually between 50 and 70 years, however, the disease may start under the age of 40 years, which is referred to as early-onset PD and accounts for 3-5 % of all PD cases [47]. Most PD cases appear as 'idiopathic', which means that the disease have an unknown cause. A monogenic cause, however, can be identified in up to 10%, a of patients [51,52].

The incidence of PD is linked to protective and risk factors. For example, smoking is associated with a reduced risk of developing PD [50,53]. Potential risk factors are age, as the most important one, pollutants, such as pesticides, industrial chemicals, or metals [49], but also body mass and dietary intake increase the likelihood for PD [39]. BMI and triceps skinfold thickness are positively associated with an increased risk of PD [71,72], although a recent meta-analysis does not confirm this notion and revealed no significant association between higher BMI and increased PD risk [73,74]. Moreover, the prevalence is not normally distributed between the two sexes as PD is 1.5 to 2 times as common in men than in women [47,49]. Potential contributors to the problem are, for instance, female sex hormones, which can lead to gender-specific differences in exposure to environmental risk factors [47].

In Germany, the estimated prevalence of PD is at least 180,000 –220,000 patients [54] which corresponds to a point prevalence of ~0.2 to 0.25%. Europe is severely affected by demographic aging due to low birth rates and higher life expectancy [303] and as early as 2018, 19 % of the European population was aged 65 and above [303]. In conclusion, it can be

said that this transition into an older population structure will increase the risk of PD in Europe and respectively, in Germany.

1.2.2 Pathophysiology

1.2.2.1 Neuropathology

The neuropathological features of PD include two main pathologies: (i) loss of dopaminergic neurons and in connection with this the depigmentation of the SNc [45] as well as (ii) the intracellular formation of Lewy bodies in the SNc and other brain regions [47,48]. Lewy bodies are aggregates containing abnormally folded α-synuclein and ubiquitin [45]. The enteric and parasympathetic neuronal tissues are the structures that are believed to be earliest affected by α-synucleinopathy. Braak has postulated that PD is caused by a pathogen that enters the body via the nasal cavity and finally reaches the intestine, where it triggers the Lewy body pathology. Furthermore, it has been described that the spread of α-synuclein pathology enters the brain in the caudal brainstem and from spreads out there by a cell-to-cell prion-like transmission [55]. In line with this, α-synuclein pathology initially occurs in monoaminergic and cholinergic neurons of the lower brain stem and in neurons of the olfactory system. In later stages of the disease, it is also found in limbic and neocortical brain areas [56,57]. Due to the caudo-rostral gradient, neuronal loss in the early stages of the disease is usually limited to the lower brainstem and the SNc, but as the disease progresses, neuronal loss expands and affects both hemispheres and the cortex has been found [58]. In addition, dopamine turnover and DA synthesis rate are increased in early disease stages as a compensatory mechanism [59]. This suggests that the degeneration of dopaminergic neurons begins early before the onset of motor signs in PD and therefore, as mentioned above, led to a long prodromal phase in PD [47]. Motor symptoms therefore only occur when about 60-70% of the dopaminergic neurons in the SNc have already degenerated [60].

1.2.2.2 Motor circuit pathophysiology

The selective loss of dopamine-containing neurons leads to an impairment of motor control in patients with PD. Dopaminergic denervation affects the processing of motor-related activity in the basal ganglia, where anatomically distinct circuits interact to enable goal-directed behavior and control of actions [47,61]. To date, four distinct circuits have been identified that influence motor and oculomotor, limbic (emotional regulation), and prefrontal-associative (executive) functions. These circuits are connected by cortical areas and corresponding areas of the basal ganglia and thalamus [61].

The projections of the motor-related cortico-basal ganglia circuit origins at the primary motor cortex, the premotor cortex, the cingulate cortex, and the supplementary motor area and terminate at the dendritic sites of the striatal medium spiny neurons [47]. The striatum is

thereby the main input station from the cortex and projects directly to the globus pallidus internus (GPi; direct pathway) or via the indirect pathway to the globus pallidus externus (GPe), which sends projections to the subthalamic nucleus (STN). The STN projects to the GPi or the substantia nigra pars reticulata (SNr), both of which are the main output nuclei within this network with projections to the ventrolateral thalamus and brainstem. The thalamus then projects then back to the cortex. The striatal projections on GPi or GPe thus form different loops: the 'direct' and the 'indirect' pathway [45,47]. The direct pathway is a monosynaptic connection between striatal, medium-spiny neurons expressing dopamine D1 receptors, and GABAergic neurons in the GPi and SNr. The function of the direct pathway is to elicit neuronal activity that ultimately leads to the initiation of movements [45,47]. In contrast, the indirect pathway originates from medium-spiny neurons in the striatum that express dopamine D2 receptors, and projects to the GPe and subsequently to the STN. The pathway finally enters the GPi via the increased excitatory activity of STN as a glutamatergic relay. Increased GPi activation enhances the inhibitory tone of the GPi-thalamic connection resulting in an inhibition of motor-related neuronal signals and reshaping of ongoing motor programs and, thus extending the time for action selection for the most appropriate response at cortical level. Both, the direct and indirect pathways are regulated by the striatal dopaminergic tone derived from SNc neurons. Dopamine deficiency in the nigrostriatal pathway acts via opposing effects: the D1-mediated effect of the direct pathway is reduced, whereas the D2-mediated activity of the indirect pathway is collectively increased, leading to a greatly increased firing rate of GABAergic output neurons, resulting in an over-inhibition of thalamocortical projections as well as brainstem areas [45,47]. The third pathway is the so called 'hyperdirect' pathway as a monosynaptic link from the prefrontal and motor cortex to the STN via a glutamatergic connection. Its activation leads to a rapidly acting increased activity of GPi and SNr neurons [45,47]. The hyperdirect pathway is thus embedded in such a way that it allows any ongoing motor activity to stop completely [47] and prevents premature responses by reinforcing the activity of the indirect pathway, thereby interrupting the function of the basal ganglia [47].

However, hypokinetic movement disorders cannot be fully explained by the firing rate model due to multiple other interactions. For example, abnormal neural synchronization, changed informational processing, and altered cortico-subcortical coupling are additional causal mechanisms [47]. The Parkinsonian state is in parallel characterized by enhanced beta-band (~ 20 Hz) activity of the basal ganglia, as well as changes in cerebellar activity, and basal ganglia-cerebellar interactions [47]. In line with that, recent research has challenged the traditional concept of a pure basal ganglia disorder by demonstrating direct anatomical connections between basal ganglia and cerebellum in animals [62,63] and humans [64]. The transneuronal transport of rabies viruses showed disynaptic pathways between the dentate nucleus and the striatum [63], as well as between the STN and the cerebellar cortex [62] in

brains of Macaque monkeys. The connections are dense and affect both, the motor and non-motor domains of the basal ganglia and the corresponding regions in the cerebellum. Recently, the presence of connections between the STN and the cerebellar cortex in humans was confirmed using diffusion-tensor imaging [64,65]. Connections were also found between the dentate nucleus and both, the substantia nigra and pallidum, highlighting that reciprocal connections exist between the two circuits and that the cerebellar output may have a direct influence on the functions and operations of the basal ganglia [66].

1.2.3 Treatment of Parkinson's Disease

1.2.3.1 Pharmacological treatment

The development and introduction of levodopa, as a precursor of dopamine, in the 1960s revolutionized the treatment of PD [48]. Pharmacological replacement therapy via a systemic administration of the DA precursor levodopa is nowadays the gold standard in PD treatment [74]. Compared to other Anti-parkinsonian drugs, levodopa offers the greatest symptomatic benefit with the fewest number of side effects [1][1].

DA agonists act at postsynaptic striatal dopamine receptors, mainly at D1 and D2 receptors [75]. DA agonists can thereby bypass the need for metabolic conversion, storage, and release of dopamine at the level of the degenerated nigrostriatal nerve terminals [75], acting thereby directly at the dopaminergic synapse. DA agonists have the advantage of longer half-life times then levodopa. In addition, they are less likely to induce dopaminergic motor complications [1,75] (Fig. 1).

Pharmacological strategies for reducing the time during which medication has a suboptimal efficacy ('OFF' time) include increasing the dosage of dopaminergic medication, fractioning of levodopa dosages in smaller and more frequent applications, or adding catechol-O-methyltransferase (COMT) enzyme inhibitors and/or monoamine oxidase type B inhibitors [1] to inhibit the metabolism of dopamine and thereby to prolong its effect. [1,45,47,48]. The pharmacological treatment of PD also includes non-dopaminergic strategies, e.g. NMDA antagonists like amantadine. Several other neurotransmitter systems have been implicated in PD and could therefore be a target for treatment, for example, noradrenergic, or serotonergic pathways [47].

Although pharmacological treatment leads to a substantial improvement in motor function and non-motor signs, its use is, however, frequently associated with side effects. First, dopamine replacement therapy (DRT) involves both, pre- and postsynaptic mechanisms that can lead to maladaptive neuronal responses that cause drug-induced side effects. For instance, chronic

[1] The first ~5 years of dopaminergic treatment are referred to as the 'honeymoon phase', where the treatment is most effective and causes only minimal side effects [47].

DRT is associated with motor complications, such as motor fluctuations, dyskinesias, and freezing of gait caused by maladaptation of the dopaminergic system. Moreover, DA agonists have a wide range of side effects due to central and peripheral DA stimulation [77]. Autonomic peripheral signs are for instance nausea and vomiting, dizziness, bradycardia, and postural hypotension [77]. In addition, dopamine dysregulation syndrome, punding, psychosis, and excessive stimulation of the brain reward system have been reported [1,45,47,48]. Furthermore, DA agonists can induce neuropsychiatric side effects. Most frequently reported psychological side effects are impulsive and compulsive behaviors like pathological gambling, hypersexuality, compulsive eating and shopping [78]. Pathological gambling and hypersexuality tend to be more frequent in men, whereas compulsive overeating and shopping tend to be more frequent in women [78]. Furthermore, several symptoms do not respond to DRT, such as postural instability and cognitive impairment [1].

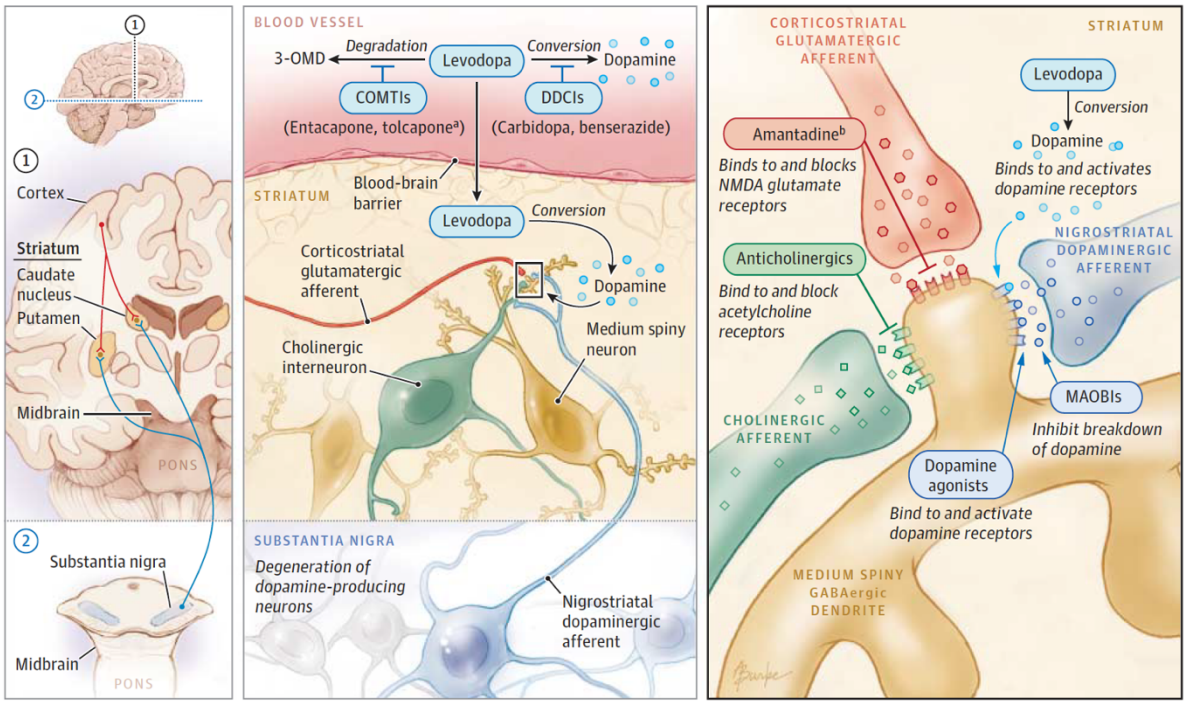

Figure 1. Schematic illustration of neuronal pathways affected in Parkinson's disease and the sites of action of medications for the treatment of motor symptoms from Connolly & Lang (2014). Abbreviations: Dopamine decarboxylase inhibitors (DDCIs), catechol-O-methyltransferase inhibitors (COMTIs), monoamine oxidase type B inhibitors (MAOBIs), NMDA indicates N-methyl-D-aspartate.

Furthermore, the variability in gastrointestinal absorption, transport across the blood-brain barrier, and the short half-life of levodopa lead to a discontinuous drug delivery, which tends to cause motor fluctuations in more advanced disease stages. Although there are novel and innovative forms of levodopa administration through a continuous intestinal infusion of levodopa gel, the side effects still remain [1,45,47,48]. Moreover, the beneficial effects of DRT decrease over time due to progressive neurodegeneration [1].

1.2.3.2 Physical therapy

Exercise-based training and physical therapy exerts positive effects on postural instability, immobility, gait disturbance, and falls [77], but also on speech [45,47,77]. It also modifies the progression of long term motor symptoms and has a positive effect on the physical functioning of PD patients. Furthermore, non-motor symptoms have considerable negative effects on mobility and activities of daily living as well as on quality of life. Recent evidence has shown positive effects of physical training and exercise, such as aerobics, on non-motor symptoms, quality of life, and exercise compliance [77]. In conclusion, physical therapy and exercise-based interventions represent a meaningful complementary therapeutic option that has the potential to increase motor function and effectiveness of pharmacological treatment, and in turn delays disease progression [77].

1.2.3.3 Surgical treatment

In the early 1950s, the first surgical procedures for PD were published, which involved basal ganglia lesioning [78]. Ablative surgeries, mainly pallidotomy and thalamotomy, have been used for the treatment of tremor [48]. Pallidotomy led to a remarkable improvement in motor function and levodopa-induced dyskinesias [79]. In the course of the following decades, pioneering advances in stereotactic techniques have transformed target localization from ablative procedures to methods of reversible stimulation [48,78]. These techniques were gradually refined and ultimately led to the possibility of targeting subcortical regions with millimeter precision [78]. The hour of birth for DBS originated in the discovery of the technique, where electrical stimulation was used for the identification of the correct position of coagulant electrodes for lesional functional neurosurgery in patients with PD and dyskinesias [80].The pioneers of high-frequency stimulation were Delgado (1952), Bekthereva (1963), Sem-Jacobsen (1965), as well as Cooper in 1978 [80]. After decades of lesional functional neurosurgery and first observations on electrical stimulation of deep brain nuclei, the modern area of DBS began in the late 1980s. Benabid was the first scientist who published an article about successful treatment of a drug-resistant tremor patient with chronic high-frequency stimulation in the ventral intermediate thalamic nucleus (VIM) [3,78,81]. With the development of implantable pulse generators, the ultimate replacement of thalamotomy in tremor patients began. These generators were capable of delivering chronic high-frequency stimulation and had the advantage of adjusting the exact location and dose of stimulation to maximize the therapeutic response and minimize therapeutic side effects [3]. At the same time, Pollak's group started to stimulate a new target in patients with PD: the subthalamic nucleus (STN) [80]. The idea of chronic application of electrical current to the brain in order to treat movement disorders has been innovated since then [78].

Therefore, DBS is based on the finding that electrical high-frequency stimulation (100-200 Hz) can mimic the effect of a lesion without destroying brain tissue [47]. Since this therapy option is reversible, safe, and adaptable, it has become the predominant surgical procedure in the treatment of movement disorders, although it remains a symptomatic therapy and does not change the underlying pathophysiology [78,80]. Today, DBS has become a well-established and routine therapy to improve motor function and quality of life in patients with various movement disorders, with PD being by far the most common indication [3].

1.2.3.4 Deep brain stimulation in movement disorders

High-frequency stimulation of the STN has been shown to be very effective for tremor, bradykinesia, and rigidity with minimal stimulation-evoked side effects [3,78]. Moreover, the GPi as a target for DBS has been explored for in dystonia and PD. In PD, both targets lead to beneficial improvements in motor control and quality of life, but the STN appears to have a greater impact during OFF periods [3]. STN DBS is thus the optimal target region for PD treatment, because it reduces MDS UPDRS II scores (activities of daily living), MDS UPDRS-III scores (motor impairment) on average by 50-60 % compared to OFF medication states before the implantation [45,47]. In contrast, STN DBS is associated with slightly more adverse side effects on cognition and mood than GPi stimulation [78]. Furthermore, this treatment target allows the reduction in medication to a greater extent [3].

To give a short overview, the DBS system consists of one electrode (= lead) per hemisphere, which is placed into a specific target region in the brain (Fig. 2). The leads are connected via an extension cable to a pulse generator, which is implanted in the area of the pectoral wall and less often in the abdominal wall under the skin [82]. The leads vary in the number of contacts and can occur as ring electrodes or segmented leads [83]. There are many parameters that influence the potential outcome of DBS: The electrical field can be generated in the monopolar (contact anode, pulse generator cathode, spherical shape around the end of the electrode) or bipolar mode (one contact anode, another contact cathode, smaller ellipsoid shape). Bipolar stimulation leads to reduced stimulation-induced side effects due to the more focused electrical field [84,85]. Another possibility to modify the electrical stimulation field is current steering, where the current can be shaped and directed by using segmented electrodes [86]. In addition to the stimulation field, the choice of contacts, the parameters of the electric field (pulse width, amplitude, and frequency) influence the DBS outcome [78,84–86].

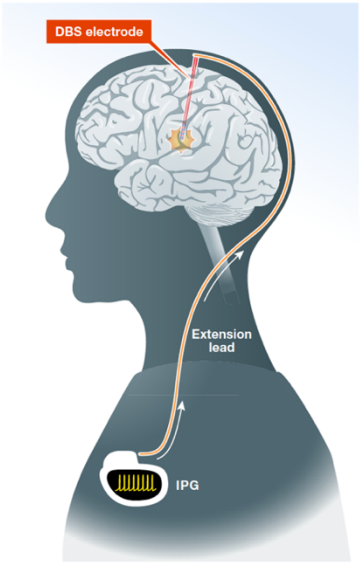

Figure 2. DBS system used for clinical applications from Jakoks *et al.* (2019). IPG indicates an implanted pulse generator.

PD is increasingly being treated with DBS because abnormal motor patterns improve [87,88] (Fig. 3). There is strong evidence that under certain circumstances DBS therapy achieves a better result than the best medical treatment under the pre-requisite of an optimized candidate selection [78]. First, the main indications for DBS in PD are motor fluctuations, unpredictable off times, debilitating drug-induced dyskinesias, and medication-refractory tremor, as well as factors that are important considerations for DBS surgery, particularly the risk of cognitive decline after DBS surgery, which can lead to suboptimal clinical responses [78,89,90,91]. Neuropsychological and neuropsychiatric comorbidities are additional indications. It has been estimated that about 30% of DBS treatment failures are related to incorrectly selected patients. Therefore, several critical factors are required when deciding on a DBS candidacy: age, disease duration, levodopa responsiveness[2] as well as other comorbidities [78]. Recent findings from the EARLYSTIM study [78,94] have shown that a younger age leads to more robust effects of motor improvement, quality of life, and fewer side effects [78].Therefore, the selection of potential candidates with sufficient consideration of outcome predictors is a complex process that requires an interdisciplinary team of experienced neurosurgeons and trained neurologists adaptation [78].

[2] Levodopa responsiveness is defined as the extent of motor benefit that is usually achieved with the levodopa challenge test by providing a single dose of levodopa. Motor improvements are assessed using the MDS-UPDRS-III score. The response to levodopa is indicated by the decrease in MDS-UPDRS-III scores. In addition, tolerability (time course of the response, type and distribution of dyskinesias, psychological effects, and motor deterioration) is also assessed [92,93].

But how effective is DBS? Some researchers postulate the DBS treatment as a 'second honeymoon phase' in PD treatment [94]. DBS has been shown to control motor symptoms for a longer period of time than pharmacological treatment alone, it significantly increases the number of hours within the 'ON' state (period of time with sufficient effect on motor impairments of the medication), it leads to a reduction in medication and thus reduces the risk of medication-induced side effects and involuntary movements (LIDs; levodopa-induced dyskinesia) [3,78,94]. Furthermore, DBS reduces falls and is also beneficial for the treatment of insomnia and pain. Furthermore, DBS improves the daily living skills (feeding, dressing, getting up from a chair, or walking) and consequently improves the patient's quality of life [3,78]. However, the effects on non-motor symptoms are highly variable, including gait and postural instabilities, speech, sleep, and cognition [78,82]. Most of these beneficial effects and functional improvements have been shown to be stable for up to five years [2,3,95], although deterioration in akinesia, speech, freezing of gait, postural stability, and cognitive functions have been observed between the first and fifth year [2,3,95].

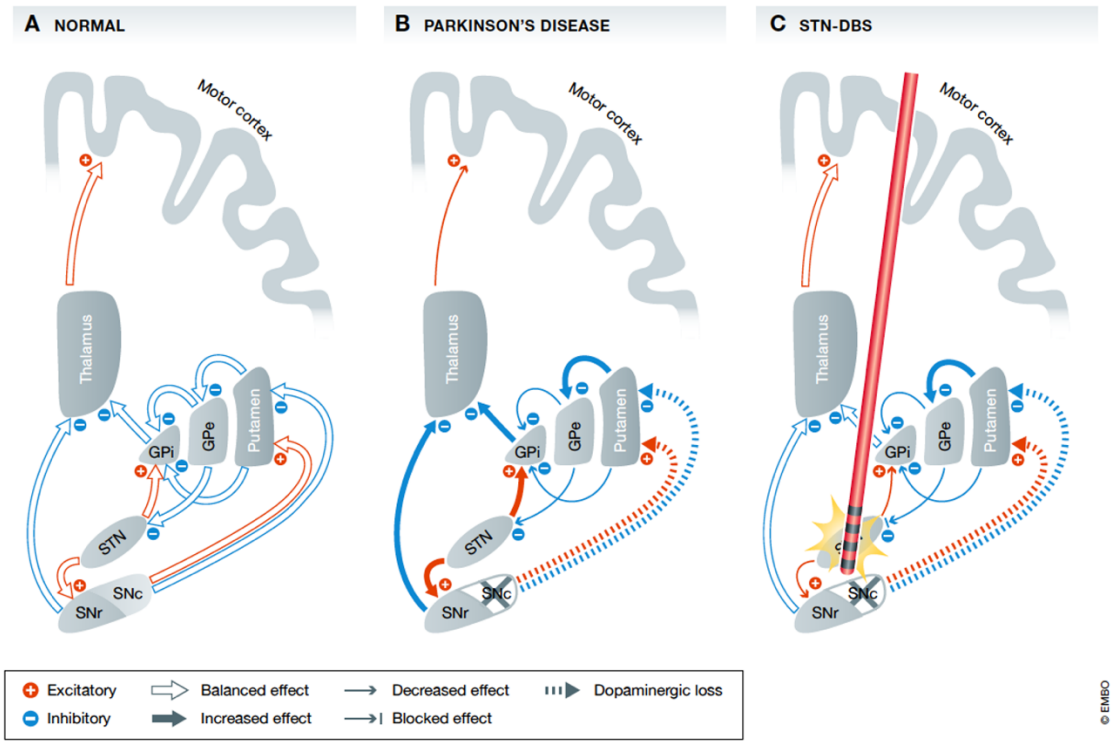

Figure 3. Effects of Parkinson's disease and DBS on basal ganglia networks by Jakoks *et al.* (2019). Abbreviations: GPi, internal globus pallidus; GPe, external globus pallidus; STN, subthalamic nucleus; SNr, substantia nigra pars reticulata; Snc, substantia nigra pars compacta.

1.2.3.5 Targets of deep brain stimulation in Parkinson's disease

As previously mentioned, different target regions can be modulated in PD. The GPi and the STN as the key motor relay structures are the most common targets for PD treatment [47,94]. The STN, which is also recognized as corpus Luysii, is a 3 x 5 x 12 mm lens-shaped nucleus

located at the diencephalon-mesencephalic junction [40] (Fig. 4A-B) and acts as an important relay station of the direct pathway to control thalamocortical excitability [61]. The STN, like other basal ganglia nuclei, can be divided into a sensorimotor, associative, and limbic subdivision, based on its connections to specific functionally segregated regions of the striatum, pallidum, and cortex [40,61]. The STN and the internal basal ganglia circuitry with its connections form multiple functionally segregated neural circuits to select between competing 'goals', 'actions', and 'movements' [61]. Moreover, the basal ganglia are also involved in decision-making, whereas phasic dopamine signals in the ventral striatum supports reward-associated learning, thereby triggering 'go' signals (via D_1 receptors within the direct basal ganglia pathway) for reward seeking-oriented behavior, and avoidance of harmful actions by directing 'no-go' signals through D_2-receptor-mediated actions within the indirect basal ganglia pathway [100,101]. Therefore, PD patients with levodopa treatment present specific deficits in the learning-induced association of negative outcomes due to pharmacological dopamine overstimulation [61]. However, this gives the STN a complementary role in decision-making by providing an adaptive 'hold-on' signal in case of conflicting decisions. The STN 'no-go' signal inhibits automatic responses towards stimuli, allowing additional time for the central processing of goal-directed behaviors [61] (Fig. 4C-D). As a result, high-frequency stimulation of the STN eliminates the subthalamic 'no-go' signal to facilitate movements, while thereby potentially leading to cognitive or affective disinhibition, depending on the exact electrode position and the corresponding stimulated circuit [61]. Therefore, STN neurostimulation is a complex therapy, whose success depends on the selection of suitable candidates, optimal placement, and proper postoperative adjustment of stimulation parameters and Anti-parkinsonian medication [61].

However, VIM can be targeted to treat the tremor-dominant PD subtype. Stimulation of the zona incerta can also be used for tremor suppression [81]. Another target for PD treatment is the pedunculopontine nucleus (PPN) due to its reported efficacy on freezing of gait and postural instability in smaller case series [96].

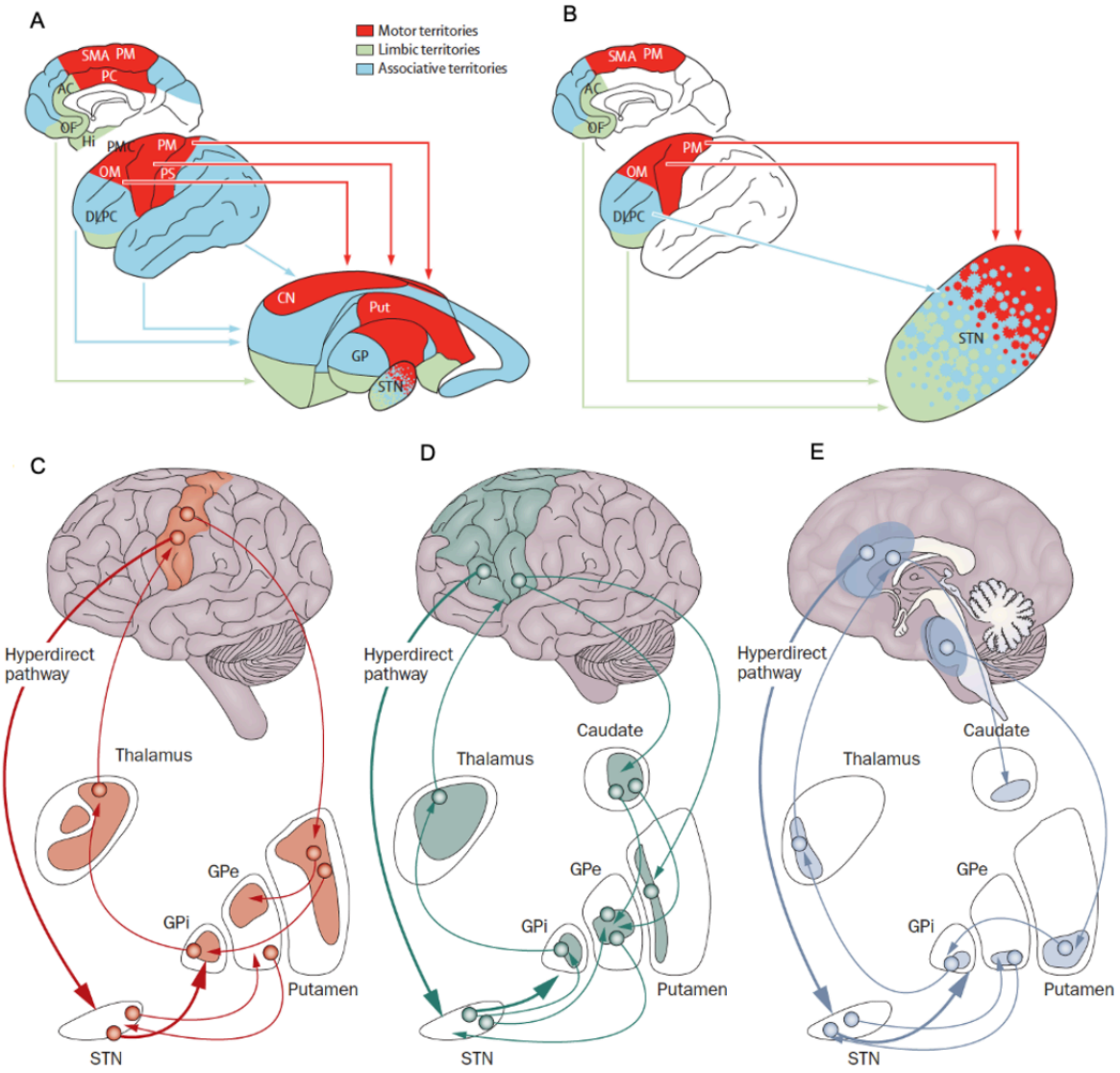

Figure 4. Structure of the STN, forming anatomically and functionally segregated neuronal circuits of the basal ganglia with thalamic nuclei and frontal cortical areas by Castrioto *et al.* (2014) and Volkmann *et al.* (2010). Abbreviations: GPi, internal globus pallidus; GPe, external globus pallidus; STN, subthalamic nucleus; SMA, supplementary motor area; PM, primary motor cortex; PC, posterior cingulate; AC, anterior cingulate; OF, orbitofrontal cortex; HI, hippocampus; DLPC, dorsolateral prefrontal cortex; OM, oculomotor field; PMC, premotor cortex; PS, primary sensory cortex; CN, caudate nucleus; Put, putamen.

Excursus

As already mentioned, the STN plays a major role in reward processing and behavioral response control which goes beyond its motor function within the basal ganglia circuitry [8,96]. Numerous animal studies demonstrated that the STN is involved in motivation for food [8]. For instance, the STN increases its firing rate during food reward anticipation and food delivery in monkeys [97,98], while in rats, lesions of the STN led to an increase in motivation for stimuli that are associated with food in a variety of behavioral experiments and decreased the motivation for artificial rewards [99]. Evidence from human studies found in patients with STN

lesions or tumors increased appetite and hyperphagia, arguing for the participation of the STN in control of food intake in humans [67]. Accordingly, active stimulation of the STN potentially leads to food craving, binge eating, and in consequence, body mass gain [8].
Recent evidence confirmed thereby that high-frequency stimulation or lesioning of the STN led to impairments in the ability to appropriately inhibit responses in rats and in humans [100,101]. Subthalamotomy or STN DBS is associated with behavioral and neuropsychiatric conditions, such as impulsive control disorders that reflect deficits in inhibitory control, such as binge eating [100,101]. Similarly, STN DBS impairs the capacity to withhold responses to no-go trials in a conditioned go/no-go paradigm [102,103].
In line, more medially located electrodes within the STN are associated with greater body mass gain [8,31,40,41,104], caused by a stimulatory effect of DBS on fiber bundles projecting from or to the hypothalamus [21,69], or by directly current diffusion to the hypothalamic nuclei, thereby causing disruptions in the global function of the hypothalamus involving regulation of eating behavior and metabolism [69].

1.2.3.6 Mode of action of the DBS

The classical assumption of the DBS effect is the ‘inhibition hypothesis‘. This hypothesis is based on the classical rate model and postulates that the overactive firing rate of STN and GPi is blocked by DBS [94,105,106]. This hypothesis has advanced, and the mechanisms of actions are more complex. The mode of action goes beyond the classical rate model and additionally includes jamming, bursting, disruption of pathological firing pattern, molecular mechanisms of action [94,105–107] (Fig. 5A), as well as actions at the synaptic level such as synaptic inhibition and synaptic depression [94]. At the molecular and cellular level, DBS activates neurons and astrocytes, which leads to a modulation of the neuronal firing rate and neurovascular coupling, regulation of cerebral blood flow as well as changes in neuro- and gliotransmitter release [94,105,106].

Further, DBS acts locally and at the systemic level by stimulating both afferent and efferent axons and subsequently increasing the downstream neurotransmitter release [105] (Fig. 5B). In rats, putaminal GABA levels are increased by high-frequency stimulation compared to control animals. The increased DBS-related GABA release in the internal pallidum and the unchanged levels of glutamate were previously confirmed in humans undergoing GPi DBS [108].

On an oscillatory level, DBS induces jamming, a regular time-locked discharge that prevents the neurons from returning to pathological spontaneous baseline activity. Also, abnormal bursting oscillatory discharge patterns observed in PD are normalized by DBS. In PD, a pathological oscillatory activity of the beta-band between the cerebellum, basal ganglia, and cortex was found. DBS disrupts and suppresses these excessive beta oscillations, which corresponds to an improvement of bradykinesia and rigidity [105]. On a neural systems level, DBS has both excitatory and inhibitory effects [94,105,106]. Many neuroimaging studies have shown that the benefits of DBS are caused by regional changes in neuronal activity within the motor network. For instance, the acute effect of DBS in resting motor circuitry increase the functional connectivity from the cerebellum to the putamen, from PFC to the cerebellum, as well as from the cerebellum to the SMA [66]. Therefore, the cumulative effects of DBS at molecular, cellular, and network levels produce observable clinical effects in PD [106].

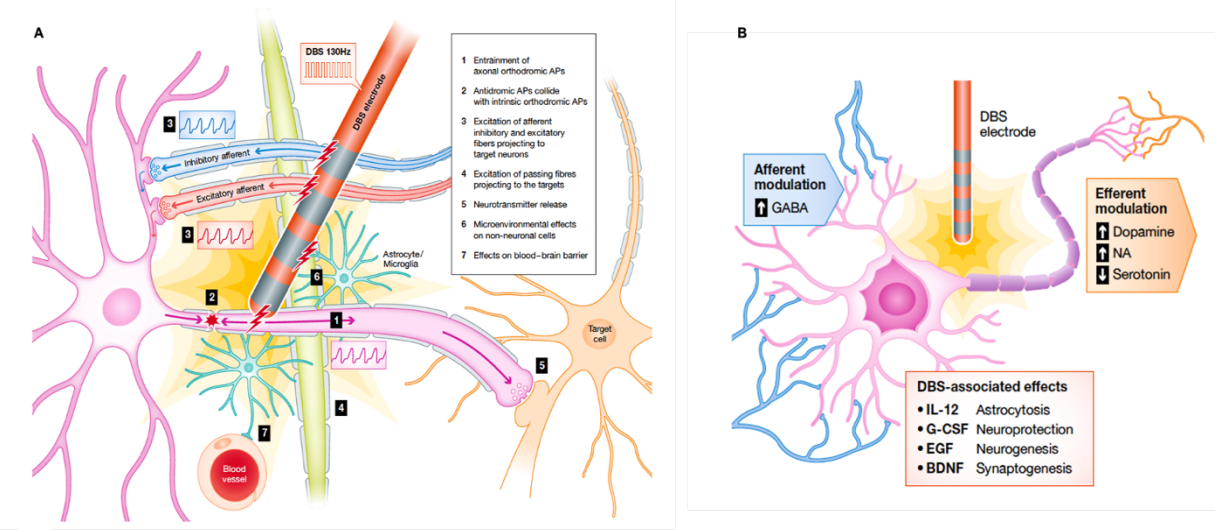

Figure 5. Electrical effects of DBS and effects of DBS at the molecular level by Jakobs *et al.* (2019).

1.2.3.7 Short and long term side effects of DBS

Adverse events and side effects can be categorized into surgical or non-surgical, hardware-related, or electrical stimulation-induced side effects [78]. Furthermore, although the surgical complications are small, but still three times as high as the complications of best medical treatment, it has potential risks like any other surgery: wound infections, bleedings (hemorrhage) with associated seizures, neurological impairment, lead misplacements, as well as confusion after surgery [109], which accounts for a morbidity rate of 1-3% [47]. Moreover, the comparison of the adverse effects of STN vs. GPi stimulation, although there were no major differences in surgical and hardware-related complications, the effects on cognition, mood, and gait are highly variable [78]. For instance, STN DBS may worsen cognition and behavior more strongly compared to GPi stimulation, although motor outcomes were

equivalent [3]. Besides surgical complications, short term and long term side effects also include hardware- and stimulation-related side effects. Short term side effects include, for instance, often speech problems, reduced verbal fluency, tingling sensation of pins or needles, dizziness, involuntary muscle contractions (dystonic movements), fatigue, unresponsiveness to dopaminergic medication, as well as problems with balance (increased sway) and coordination, but also unresponsiveness symptoms such as freezing of gait and axial symptoms [78,109–111]. Long term side effects include loss of battery strength, breakage of electrodes or leads, worsening of depression and apathy, impulsive and compulsive behavioral disorders such as hypersexuality, gambling, compulsive buying, excessive eating behavior [78,109,110], as well as metabolic alterations [30].

1.2.4 Metabolic changes after DBS

Metabolic interruptions include thereby changes in energy expenditure through improvement of tremor, rigidity and dyskinesias, increased physical activity and sleep alterations after STN DBS [9,16,30,39]. Furthermore, endocrine alterations and perturbations in hypothalamic metabolic regulation [5,6,33] were found influencing postoperative body mass and body composition [30]. For instance, changes in the limbic cortico-basal ganglia loop and direct effects of high-frequency stimulation of the STN on adjacent structures by current diffusion, lead to disruptions in the regulation of energy balance, eating behavior, and food intake [29,30,39].

It is striking that the increase in body mass has consistently been reported as a side effect of DBS, which -– at least partially – counteracts the positive effects of motor improvement following STN DBS. Body mass gain can thereby be considered as a communication disorder between the central and peripheral nervous system, caused by a dysfunctional information flow of different brain circuits that are involved in metabolic regulation and reward processing [112]. The mechanisms that regulate energy metabolism and food intake and their influences and alterations in PD are discussed in the following section.

1.3 Energy Metabolism

In order to understand body mass alterations in PD comprehensively, concepts of energy homeostasis have to be considered.

1.3.1 Energy homeostasis in humans

Energy homeostasis is determined by both energy intake and energy expenditure. To maintain energy homeostasis and thus, constant body mass, energy expenditure and energy intake must be kept in balance. Total energy expenditure can be thereby divided into resting energy expenditure, thermic effects of food, and activity-related energy expenditure [113]. Resting energy expenditure typically accounts for 60-70% of daily energy expenditure and is defined as the amount of energy that is essential to sustain life [113]. It is remarkable that the brain account for only 2% of the total human body mass, but is responsible for 20% of an individual's resting energy expenditure [114,115]. Moreover, neurodegenerative disorders are also characterized by profound changes in brain metabolism, which are believe to initiate and promote disorders such as AD, PD, or amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) [114,115].

The thermic effect of food is defined as increase in resting energy expenditure due to food intake, digestion, absorption, metabolism, and storage of energy [42,113,116] and accounts for up to 10% of total energy expenditure. The most variable form of total energy expenditure is activity-related energy expenditure and is determined by daily activities such as walking to work, home cleaning, dancing, or shopping [113] and can thus be modulated by lifestyle. Obesity and the pathological increase in fat storage can therefore be simplified and physically constituted according to the law of thermodynamics if the energy intake exceeds the energy consumption over a certain period of time, and thus there is a positive energy balance [39]. Nowadays, energy imbalances are often caused by the 'obesogenic' environment in the Western communities, which means, for instance, high availability of tasty and energy-dense foods as well as the presence of powerful food cues combined with a low level of physical activity due to motorization [39].

If, for example, the energy balance of a person was only 100 kcal a day – contained in, e.g. 20 g of chocolate or 14 g of butter – above his balanced energy homeostasis of energy intake and consumption, this would result in an annual energy surplus of 36500 kcal. Assuming that 1 kg body fat corresponds to an energy equivalent of 7000 kcal, this 'energy surplus' would result in a body mass gain of 5 kg per year, which easily lead to overweight and obesity. This example shows that the homeostasis of body mass is integrated by complex and closely coordinated principles. The following section focusses on the concept of energy intake.

1.3.2 Energy intake and its regulation

Unbalanced energy homeostasis would lead to either an increase or decrease in body mass and thus body fat mass [39,67]. The 'classical' concept of 'satiety' and 'feeding' centers as anatomically separate brain regions has recently been replaced by a more complex network of interconnected neurons with homeostatic and non-homeostatic (often referred as hedonic) circuitries [42,69]. Both circuitries receive and integrate central orexigenic (appetite-stimulating) and anorexigenic signals (appetite loss), peripheral signals, and of course, signals from nutrients *per se* [67,69]. The main homeostatic center in the brain is the hypothalamus, which is involved in feeding behavior by balancing appetite-enhancing and satiety-regulating hormones within different hypothalamic nuclei [39,67,117]. An imbalance of these opposing signals, for instance, leptin, ghrelin[3], gut peptides, glucose, or insulin levels, and fatty acids [69], determines the amount of food intake, food ingestion, and consequently body mass [39,67,69]. However, many people eat not only because of homeostatic but also due to non-homeostatic signals, such as in a social context or for pleasure. With regard to the hedonic system, sensory information are integrated to control the food reward system [69,119,120]. The hedonic circuitry is composed of several different hotspots, including the mesolimbic dopaminergic system, the dorsal striatum, the insula, the anterior cingulate cortex, and the orbitofrontal cortex [69,119–126]. Previous research has unraveled the neurocircuits that underlie food decisions and the circuits underlying valence coding. For instance, the choice of food is mainly dependent on taste, and the amygdala is recognized to evaluate and initiate the balancing of cues such as the encoding of palatability [127,128]. Given the central location of the amygdala within a dense neuronal network that transmits food- and feeding-relevant information into valence patterns, it directly influences the willingness to eat. These valence patterns are stored in the amygdala as hedonic drive signals, which is implied as incentive learning through taste experience and works together with memory and reward systems [127–129]. Moreover, the Nucleus Accumbens (NAcc), as well as the ventral tegmental area, are crucial brain structures for hedonic food intake. Increased motivation and preference for certain rewards are directly driven by cholinergic and glutamatergic input from the dorsolateral tegmentum to the NAcc, caused by increased dopamine release [127,128]. The ventral tegmental area is also involved in working memory processes for decision-making as well as determines the salience of cues, which in turn is important for learning [127–130]. Food choices are thereby guided by certain brain networks, for instance, the salience network, which is directly associated with reward. It is composed of, for instance, the insula, the anterior

[3] For instance, leptin, as an adipokine produced by adipose tissue, thereby reflecting an organisms energy storage, produces anorexigenic effects leading to satiety and an interruption of food intake [67,69,118]. In contrast, ghrelin, as a peptide synthesized by the gastric mucosa during fasting, promotes feeding behavior as well as the secretion of growth hormones, which could lead to body mass gain [39,67,69].

cingulate cortex, the amygdala or ventral striatum, and is recognized to be able to identify biologically and cognitively relevant cues for controlling a variety of complex brain functions, such as flexibility in behavior, self-awareness, and eating behavior [121–126,129,131–134]. An important mediator for these processes is dopamine.

Moreover, food intake is also affected by DA. It affects food intake thereby in both systems: it directly modulates the hypothalamic regulation of the homeostatic system as well as the hedonic regulation of eating [39]. With regard to the hedonic system, exposure to food-related cues or to the food itself leads to activation of the mesolimbic dopaminergic system, as mentioned above. It is striking that dopamine depletion within the NAcc does not lead to a reduction in the hedonic response to pleasurable food, which suggests that dopamine is not required for the 'liking' of certain types of food [39]. Instead, dopamine influences motivational processes of food intake, which are also referred to as 'wanting' or 'incentive salience' of a pleasant food reward [39,119,120]. Accordingly, rising synaptic dopamine levels in rodents led to increased motivation for high efforts, measured by running activity or lever pressing, to obtain tasty food [39,135]. In contrast, rodents with dopamine deficiency showed stable or even slightly increased food intake when tasty food could be acquired without much effort [39,136]. Therefore, dopamine D2 receptors are mainly involved in eating behavior by modulating the motivation to eat, and the reward properties of food [39,67].

Since dopaminergic effect alters the motivation to eat, dopaminergic pathways are also involved in eating disorders. For example, the restoration of dopamine in the dorsal striatum has restored the food intake of rodents that would otherwise die of starvation [39,137]. Therefore, regulated dopamine release in the dorsal striatum seems to be important for the normal eating behavior of rodents [138] and humans [139]. Obese individuals have low dopamine synthesis capacity in the dorsal striatum, as well as low availability of D2 receptors, which led to overeating compared to healthy control subjects [140]. Moreover, pharmacological treatment with dopamine agonists in PD could lead to compulsive eating, which is considered an impulsive control disorder, and consequently, to an increase in body mass [39]. This effect seems to be mediated by D3 receptors in the mesolimbic dopaminergic pathways, especially in the NAcc and ventral striatum [39]. In contrast, elevated dopamine levels in rodents and humans could lead to inhibition of food intake [138]. For instance, the use of dopamine transporter inhibitors or amphetamines reduced food intake in healthy subjects [141]. Furthermore, PD patients under methylphenidate treatment showed a loss of body mass [139]. In line with this, dopamine inhibits food intake by tonic inhibition of orexin-producing neurons in the lateral hypothalamus [39].

In conclusion, dopaminergic actions have opposite effects on eating behavior. Excessive dopaminergic states lead to inhibition of food intake, but can also lead to binge and nocturnal

eating behavior due to increased motivational states, leading to an urge to eat. Hypodopaminergic states, on the other hand, lead to the retention of taste and preference for food-related cues, which leads to a hyperphagic state of snack eating. Both conditions influence body mass [39,67].

The serotonergic and noradrenergic systems also have the potential to change body mass, as both systems are interconnected with the hypothalamus and thus, may therefore influence the homeostatic regulation of energy intake [39,67]. Serotonin is recognized to play a role in eating behavior, mood, depression, and sleep [39,67]. Furthermore, the precursor of serotonin is the essential amino acid tryptophan, which is known to be present in dietary carbohydrates [39]. The neurodegeneration of the serotonergic system could thus play a role in the preference for sweets and chocolate in PD [8,104,142–145], which could act as a compensatory mechanism as high carbohydrate levels increase brain dopamine and serotonin levels and thus mood [67]. In addition, a positive correlation between BMI and the availability of serotonin transporters has been described, indicating increased serotonin transporter binding in PD patients who experienced body mass gain [67,146]. Moreover, both serotonergic neurons and the noradrenergic locus coeruleus express orexin receptors and have dense orexin fiber projections. For instance, the degeneration of the locus coeruleus in rodents leads to body mass loss, which could be reversed by STN DBS. This finding suggests that body mass alterations in PD could be explained by the interaction of the STN, locus coeruleus, and hypothalamus [39,147].

1.3.3 Body mass and its determinants in Parkinson's disease

Longitudinal observations described variations in body mass already in the pre-motor state of PD [38], at the time of diagnosis, and during the subsequent years of disease [39,67]. Since the very first publications of James Parkinson in 1817 [39], PD has been repeatedly reported to cause unintended body mass loss and a lower BMI than in the general population, especially in advanced stages of PD, which is often correlated with disease severity and disease duration [39,67,69]. The body mass loss is thereby associated with low body fat mass in PD patients [5,6,9,11,13,16,19,33,149]. The predictors for this body mass loss are numerous and complex. For instance, it has been suggested that the role of dopamine in the hedonic regulation of eating behavior and the knowledge of dopaminergic dysfunction in PD by producing anorexigenic signals in the hypothalamus should be considered as crucial for body mass loss in PD [69]. Moreover, numerous endocrine alterations have been described in PD, for instance decreased orexin- and melanin concentrations, disturbed glucose levels, disruptions in melatonin, insulin resistance, and changes in bone metabolism, whereby some of them could determine body mass and body mass fluctuations [67,69]. Likewise, this phenomenon can also be determined by dopaminergic treatment [69]. Furthermore, it is believed that a reduced

calorie intake caused by motor impairments, such as impaired hand coordination due to tremor and rigidity, as well as due to gastrointestinal problems, such as dysphagia and reduced bowel motility, leads to energy imbalances and thus to a body mass loss in patients with PD [39,67,69]. Several studies have revealed an increased energy expenditure in PD, caused by disease severity, motor impairments, and motor complications resulting in body mass loss [150–153]. In addition, many non-motor characteristics play a role in determining body mass in PD, such as severe constipation, impairments in olfaction and taste, apathy, fatigue, and changes in motivation and mood [67].

Despite of body mass loss, body mass gain and an increase in BMI due to dopaminergic dysfunction in PD have also been described [67]. It has been shown that this increase in body mass in PD patients can lead to the development of 'sarcopenic obesity' with excessive accumulation of adipose tissue and depletion of lean body mass [67]. Higher food intake, dopamine-replacement therapy, reduction of energy expenditure, changes in sleep patterns, and disturbed central regulatory metabolic mechanisms are possible mechanisms contributing to body mass gain [39,67,69]. Nevertheless, STN DBS seems to also play an important role in body mass gain in PD patients [6,8,12,13,16,31–34,41].

Body mass gain following DBS of the subthalamic nucleus in Parkinson's disease

Several pathophysiological mechanisms that drive body mass gain after STN DBS have been postulated, for instance, improvements in motor signs [31,32], changes in energy metabolism and energy expenditure [6,16,18,154] such as reduced free-living energy expenditure [9], reduction of both lipid and protein oxidation, increased glucose oxidation [33], reduced growth hormone secretion resulting in decreased lipolysis [67,155], and increased concentrations of the orexigenic neuropeptide Y [5,6,11,13,156], increased fat mass and disruptions in its hormone secretion [11] (Fig. 6), as well as a decrease in Anti-parkinsonian medication [6,79,157]. At the first glance, unexpected increase in both, leptin and ghrelin concentrations [13] have also been found. In addition, dopaminergic dysregulation of the non-homeostatic control of eating behavior may contribute to body mass gain after STN DBS [7,32,34–38]. Although dopaminergic treatment is generally reduced after STN DBS, eating disorders are reported as side effects, which may be caused by abnormalities in dopaminergic signaling, similar to alterations that have been described in impulsive control disorders [39,67,69]. A PET study revealed changes in brain metabolism in areas of the brain that are important for feeding, such as the orbitofrontal and anterior cingulate cortices [158], indicating that hedonic dysregulation is involved in the pathogenesis of body mass gain after STN DBS.

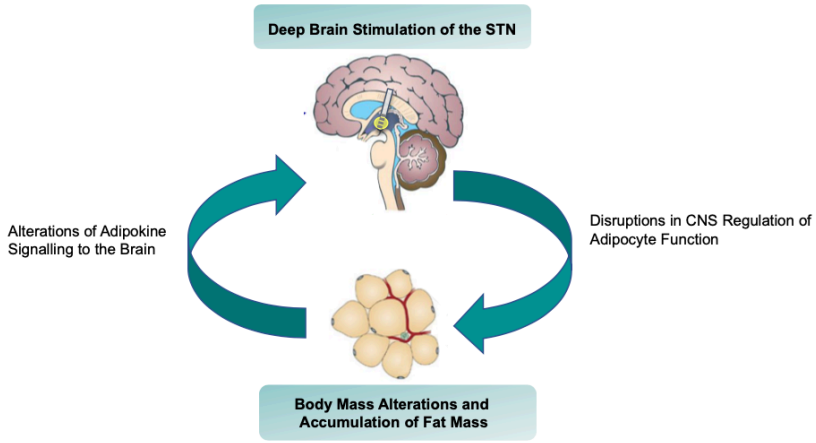

Figure 6. Schematic representation of brain-peripheral crosstalk caused by STN DBS. Abbreviations: CNS, central nervous system.

However, the effect of body mass gain after DBS is not limited to patients with PD and to STN as a stimulation target. An increase in body mass after surgery was also observed for other movement disorders, including dystonia and essential tremor (ET) [14,23,159]. Furthermore, body mass gain has been reported in patients with PD treated with GPi DBS or unilateral pallidotomy [14,79,160–162]. Interestingly, VIM DBS did not lead to any change in body mass in patients with ET, but it did lead to a significant increase in body mass in patients with PD [23,163]. However, body mass gain was higher in patients with bilateral STN DBS compared to unilateral STN stimulation or bilateral GPi DBS in PD [12,14,161]. These results taken together suggest that DBS may have a general effect on physiological mechanisms of body mass homeostasis. To what extent the improvement of the underlying movement disorder is related to changes in body mass is still unclear. The target-dependent extent of the change in body mass may indicate the involvement of various mechanisms that go beyond the mere normalization of abnormal movement patterns.

The pathophysiological mechanisms responsible for fluctuations in body mass therefore remain – at least partially – unexplained and probably seemed to be multifactorial, with homeostatic and non-homeostatic mechanisms contributing to this.

1.4 Research Question and Hypotheses

The present PhD thesis focuses on body mass gain following STN DBS in patients with PD. Despite evidence for an association between STN DBS to body mass gain, only a few studies investigated this association, and none of them addressed the extent and time course of body mass gain after STN DBS, neither systematically, nor in a prospective or longitudinal study design with control groups, nor in connection with brain-periphery crosstalk. In a series of experiments described in this thesis, I aimed to address questions regarding body mass gain as a side effect of DBS treatment in PD patients.

First of all, a systematic review and meta-analysis of the extent and time course of body mass gain after STN DBS will clarify (i) the magnitude of the relationship between STN DBS and body mass gain, (ii) the extent of body mass and BMI gain, and (iii) the time course of the assumed body mass and BMI gain. We hypothesized that STN DBS is associated with a body mass gain, that goes far beyond the normalization of body mass in PD patients who normally lose body mass during the course of disease progression.

Secondly, several hypotheses have been put forward to explain body mass gain after STN DBS in PD patients, including central and peripheral mechanisms. However, none of them investigated body mass gain from a prospective and longitudinal perspective in the same subgroup of PD patients, testing thereby multiple mechanisms simultaneously. Study 1 thus aimed to determine the influence of STN DBS on clinical symptoms, body mass, BMI, body composition, and behavior in the context of food intake and reward sensitivity. The following hypotheses were assessed:

Hypothesis I: STN DBS is associated with changes in body mass, body mass index, and body composition compared to PD patients under pharmacological treatment and healthy controls.

Hypothesis II: STN DBS is associated with an improvement in motor symptoms and eating motor skills, and leads to a reduction in Anti-parkinsonian medication compared to PD patients under pharmacological treatment and healthy controls.

Hypothesis III: PD is associated with changes in body mass in adulthood, while STN DBS modulates the direction of body mass development as compared to PD patients under pharmacological treatment and healthy controls.

Hypothesis IV: In PD patients, electrode position is associated with improvements in motor symptoms and alterations in body mass, BMI, and body composition.

Hypothesis V: STN DBS is associated with changes in hedonic eating, inhibition of eating behavior, and food intake as compared to PD patients under pharmacological treatment and healthy controls.

Finally, only a few studies investigated the effect of STN DBS on reward processing, on motivational changes towards food and its relation to body mass gain. It is reasonable to expect that both motivation and control are likely to be altered by the fact that STN DBS determines food intake, appetite, and body mass control. In Study 2, PD patients with STN DBS were therefore tested under both, active DBS and inactivated DBS, conditions. To the best of our knowledge, this is the first study to investigate the acute modulatory effects of STN DBS on the motivational attraction of food cues as well as the precise role of STN DBS in cognitive functions and eating behavior in patients with PD. Our aim is to investigate changes in the brain substrates of hedonic hunger and related changes in cognitive control of eating behavior due to DBS, which leads to changes in cortical-subcortical imbalance and brain responses to food cues. I aimed to assess the following hypotheses:

Hypothesis I: PD patients with STN DBS will show increased reactivity to images of sweet foods and a higher preference for high-calorie food images under active stimulation compared to inactivated stimulation and compared to healthy control subjects due to dopamine replacement therapy and STN DBS.

Hypothesis II: Changes in functional connectivity are observed in the salience and reward circuitry due to active stimulation and in comparison to healthy control subjects. These alterations in the reactivity towards food cues in pre-defined brain circuits are associated with body mass changes after STN DBS.

Hypothesis III: The electrode position is correlated with changes in motor symptoms and alterations in body mass.

2 Methods

This PD project was carried out at the Center of Brain, Behavior, and Metabolism (CBBM) as a collaborative project between the Department of Neurology and the Department of Internal Medicine at the University Hospital of Lübeck.

2.1 Systematic Review and Meta-Analysis

This systematic review [30] investigated the effects of STN DBS on extent and time course of body mass changes in patients with PD. A computerized search identified relevant articles using a priori defined inclusion and exclusion criteria.

Search strategy

The review focuses on original studies that investigated body mass gain in patients with PD after STN DBS, taking into account the PRISMA recommendations. A computerized search of all STN DBS studies in PD was conducted in MEDLINE, Cochrane Library, Clinical Trials, and Livivio, which included the following search terms (last search on 11 November 2017): (((Parkinson) OR (Parkinson´s disease) OR (PD)) AND (((weight) OR (body mass) AND ((change) OR (gain) OR (increase))) AND ((STN DBS) OR (Subthalamic nucleus deep brain stimulation) OR (deep brain stimulation) OR (DBS) OR (GPi deep brain stimulation) OR (globus pallidus deep brain stimulation) OR (pallidal deep brain stimulation))). The search was based on articles published between 1984 and 2017 and was limited to English and German publications, but not on the age and gender of the subjects or the origin of publication.

Study selection and data collection

All abstracts and articles of the computerized search were independently reviewed for potential relevance by two investigators (JS, BW). All disagreements were resolved by further consideration of a third investigator (NB) and by consensus.
The following studies were excluded: reviews, letters, commentaries, abstracts, posters, case reports, correspondences to articles, and duplicate citations of publications in various search portals. Furthermore, animal studies, studies including DBS of the GPi, the ventral intermediate thalamic nucleus (VIM), or the caudal zona incerta (cZi), studies with alternative surgical methods (e.g. pallidotomy), articles on non-body mass-related outcomes, studies evaluating body mass gain in another disease, and studies aimed at other research questions were not considered.

The included studies had to contain at least one of the following outcomes: absolute body mass before and after STN DBS or body mass changes, absolute body mass index (BMI) before and after STN DBS, or body mass changes. Normal weight (BMI: 18.5-24.9 kg/m^2),

overweight (BMI: 25.0-29.9 kg/m^2), and obesity (BMI: ≥30.0 kg/m^2) were defined according to the WHO definition. In addition, the UPDRS-III and IV scores (Unified Parkinson's Disease Rating Scale, see Chapter 2.2.2), as well as levodopa equivalent doses (LEDD; see Chapter 2.2.2), were examined to show the effectiveness of DBS treatment. Moreover, sufficiently specified numerical baseline and follow-up outcome data for body mass, BMI, UPDRS-III, UPDRS-IV, and LEDD were required as well as data on standard deviations (SD) or standard errors of the mean.

2.1.1 Statistics of Systematic Review and Meta-Analysis

Results are given as mean ± SD. The data was analyzed and displayed using Excel Version 2016 (Microsoft, Redmond, WA), SPSS Statistics 22.0 (SPSS Inc., Chicago IL), and GraphPad Prism Version 7.03 (GraphPad Software, La Jolla CA) for Windows®. The paired Student's t-test was used to test for changes in body mass, BMI, UPDRS-III and IV, and LEDD. The effect size of body mass and BMI changes were described by Cohen's d. Variables that are associated with changes in the main dependent variables (i.e. body mass, BMI) were analyzed using the Pearson correlation. Missing result data and SDs were calculated. All results were considered statistically significant at the 5% level.

2.2 Study 1 – Longitudinal Evaluation of Metabolic Profile After Deep Subthalamic Nucleus DBS in Patients with Parkinson's Disease

2.2.1 Characteristics of the study population

Subjects

Three groups were included in this study: PD patients undergoing STN DBS (PD-DBS), PD patients with best medical treatment as a disease control group (PD-CON), and healthy control subjects (H-CON).

Thirty-two unrelated patients with PD (mean age of onset: 47.2 ± 8.9 years, mean age: 57.3 ± 8.0 years) were included. All patients fulfilled the diagnostic criteria of the Movement Disorder Society [73]. Eight of them had a positive family history with at least one first or second-degree relative also affected by PD. Fourteen patients underwent DBS surgery (mean age of onset: 45.7 ± 9.5 years, mean age at DBS: 56.6 ± 8.4 years; Group: PD-DBS), and 18 patients were assessed under the best medical treatment (mean age of onset: 48.4 ± 8.1 years, mean age at baseline: 57.9 ± 7.9 years; Group: PD-CON).

All DBS surgeries were performed at the University Hospital Schleswig-Holstein, Campus Lübeck by the same highly experienced neurosurgeons (D. Rasche, MD and Prof. Dr. V. Tronnier). The DBS-treated patients were operated on both sides, and the electrode model 3389 (Medtronic, Minneapolis, MN, USA) was implanted bilaterally. The patients were provided

with the Medtronic Activa RC pulse generator (rechargeable, n=12; Medtronic) and PC (non-rechargeable, n=2). The extension cables connecting the electrodes and the pulse generator had a length of 60 cm. The total weight of the DBS system was 48g (RC) and 75g[4] (PC), respectively.

The H-CON group consisted of 25 neurologically healthy control subjects (mean age at baseline: 59.4 ± 8.0 years). Three of them had a positive family history for movement disorders.

The groups were matched for age, gender, body mass, and BMI.

At baseline, demographics, socioeconomic status, and education were assessed through an interview.

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a screening tool for mild cognitive impairment and/or dementia in PD. The MoCA evaluates seven cognitive domains on a single page. The domains are: visuospatial/executive functions, naming (animals), verbal memory registration and learning, attention, abstraction, 5-minute delayed verbal memory, and orientation. The total score ranges from 0 to 30 points. The cut-off value for mild cognitive impairment is < 26 [164–166].

Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory [167] is a scale for assessing the dominance of a person's right or left hand. The self-reporting inventory consists of 10 items (i.e. activities such as writing) and a lateralization index was calculated. The lateralization index (LI) can range from -1 (extremely left-handed) to 1 (extremely right-handed).

General study design

This study was conducted in the Department of Neurology (Head: Prof. Thomas Münte, MD) and the Department of Internal Medicine I (Head: Prof. Hendrik Lehnert, MD (until 2019), Prof. Jens Marquardt, MD (since 2019)), and Institute of Endocrinology and Diabetes (Head: Prof. Sebastian Schmid, MD, and Prof. Jens Mittag, PhD.) of the University Hospital Lübeck. The experiments were performed at the Metabolic Core Unit (Head: Prof. Sebastian Schmid, MD), the Siemens Skyra 3T MR scanner[5] (CBBM), and the Philips Achieva 1.5T MR scanner of the Department of Neuroradiology (Head: Prof. Peter Schramm, MD)[6].

[4] The weight of the DBS device was ignored in body mass analysis.
[5] PD-CON and H-CON.
[6] PD-DBS.

The design of this observational, prospective, and longitudinal case-control study is shown in Figure 7. All participants gave their informed written consent prior to the inclusion and had the opportunity to withdraw their consent at any time without declaration of reasons. Detailed information and written material were provided at least 24 hours prior to inclusion. The project was approved by the Ethics Committee of the University of Lübeck (AZ17-198 (GRK1957); Appendix A) and was conducted in accordance with the Helsinki Declaration. All participants received an expenses allowance of a total of 250€ (50€ for T_0, T_{6M}, and T_{12M}, 25€ for T_{3M}, and an additional 50€ for completion of all four appointments). All participants fulfilled the complete inclusion and exclusion criteria.

Randomization of patients with PD was not applicable as DBS was individually indicated by the responsible neurologist. The PD patients were measured in the best possible condition:

- T_0: best medical treatment (PD-CON, PD-DBS; Med 'ON')
- T_{3M}, T_{6M}, T_{12M}: best medical treatment (PD-CON; Med 'ON') or best medical treatment and active DBS (PD-DBS; Med 'ON', Stim 'ON').

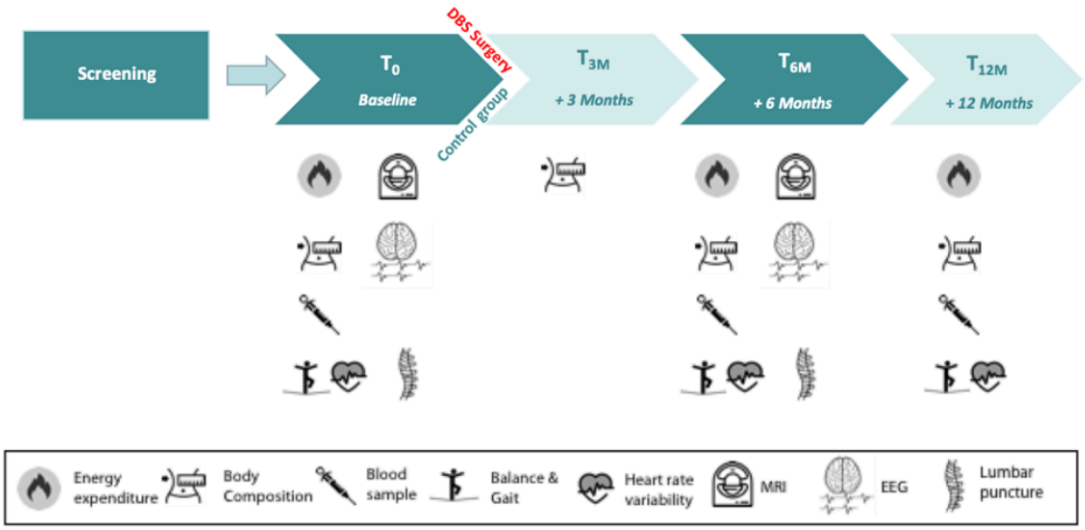

Figure 7. Overview of the study design. Prior to the study, all subjects underwent a preclinical assessment to rule out concurrent neurological, psychiatric, and metabolic disorders. All subjects were measured prior to DBS surgery, as well as 3 (T_{3M}), 6 (T_{6M}), and 12 months (T_{12M}) after DBS surgery.

Participants were studied at four different time points within 12 months (Fig. 7):

- T_0: 2 weeks[7] prior to DBS surgery (PD-DBS) or at baseline (PD-CON, H-CON)
- T_{3M}: 12 weeks after DBS surgery (PD-DBS) or after T_0 (PD-CON, H-CON)
- T_{6M}: 24 weeks after DBS surgery (PD-DBS) or after T_0 (PD-CON, H-CON)

[7] The assessment was performed before the preoperative adjustment of stable PD medication in most patients. The adjustment was part of the periprocedural program.

- T_{12M}: 48 weeks after DBS surgery (PD-DBS) or after T_0 (PD-CON, H-CON)[8]

Before T_0, T_{6M}, and T_{12M}, the participants were asked to complete a 7-day physical activity and sleep quality measurement using wrist-accelerometry recordings (Motionwatch 8, CamNtech; Cambridge, UK)[9]. On each test day, the subjects arrived at 8 a.m. in the morning. They were instructed to fast overnight and drink only water in the morning. All PD patients took their medication as prescribed during the measurement days. In the morning of T_0, T_{6M} and T_{12M}, a clinical examination and an interview on health and medical history were conducted. A device for measuring the activity of the sympathetic nervous system (SNS)[10] (Actiheart®, CamNTech, Cambridge, UK) was then attached to the chest, recording physical activity, heart rate, and Inter-Beat-Interval. Afterwards, resting energy expenditure[10] [168] was assessed using an indirect calorimetry device (Vmax 29, CareFusion, San Diego, California, USA) with a ventilated hood system over a period of 30 minutes. VO_2, VCO_2, and ventilation were measured [169,170]. Subsequently, the body composition was measured using an air-displacement plethysmograph (Bod Pod(R), COSMED, Rome, Italy; Chapter 2.2.3), and blood samples were taken. Afterwards, the participants received a standardized breakfast. Immediately before and after breakfast, a computerized wanting-liking food preference test was performed on the subjects (Chapter 2.2.6). After breakfast and now – under non-fasting conditions – a computerized analysis of balance and gait performance[10] was performed using the wearable APDM's Mobility Lab System™ (Mobility Lab, APDM Inc., Portland, OR), which consists of six wireless, body-worn motion sensors. Movement-related energy expenditure[10] was then determined using a portable chest-worn indirect calorimeter device (METAMAX 3B, Cortex Biophysics, Leipzig, Germany) to measure VO_2, VCO_2, and ventilation over a period of 11 minutes. Afterwards, the participants received a standardized lunch and had a subsequent break of 60 minutes in which they could rest and fill out questionnaires.[11] After the break, fMRI and electroencephalography[12] (EEG) measurements were performed. Following the EEG, the subjects underwent a so-called 'Cookie Test' to measure the individual food preference of different types of sweet food (Chapter 2.2.6). All meals served, i.e. breakfast and lunch, were individually calculated by multiplying the individuals resting energy expenditure by 1.3 and precisely weighing and preparing them. At the end of each measurement day, the amount of meals[13] that has been left over was also weighed. If the subjects additionally gave their written informed consent, a lumbar puncture was finally performed at the Outpatient Clinic of the

[8] The time range of measurements varied in a frame of ± 4 weeks for time points T_{3M} to T_{12M}.
[9] This measurements are part of doctoral thesis of Laura Lokowandt (Inaugural dissertation, Medical Section, Department of Neurology, University of Lübeck).
[10] These measurements are part of doctoral thesis of Laura Lokowandt (Inaugural dissertation, Medical Section, Department of Neurology, University of Lübeck).
[11] Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, Beck's Depression Inventory, Power of Food Scale, as well as Eating Disorder Examination- Questionnaire are not part of the present thesis.
[12] Analysis of serum, fMRI and EEG are not part of the present thesis.
[13] Analysis of meals are not part of the present thesis.

Department of Neurology. The same protocol was used for T_0 and T_{6M}. At T_{3M}, only the body composition was assessed (Fig. 7). At T_{12M}, a shortened protocol was done excluding all tests after the balance and gait analysis.

The primary outcome parameter of the present study was the change in body composition with the following secondary outcomes:

- Motor function and medication
- Neuropsychological behavioral parameters
- Heart rate variability
- Resting and activity-related energy expenditure
- Balance and gait parameters
- Neural activity toward food cues measured by EEG and fMRI

2.2.2 Assessment of the clinical status

The motor symptoms of PD were assessed by an experienced neurologist (N. Brüggemann, MD, H. Hanssen, MD, V. Tadic, MD) using the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr Scale [73]. Eating behavior-related impairment of motor function was measured with a self-rating visual-analog scale.

Unified Parkinson's Disease Rating Scale

The Unified Parkinson's Disease Rating Scale developed by the Movement Disorder Society (MDS-UPDRS) [73] was used to assess non-motor and motor symptoms of PD. This comprehensive scale is composed of four different sections: Parts I and II: Non-Motor and Motor Experiences of Daily Living; Part III: Motor Examination; and Part IV: Motor Complications. Part I and II consists of 13 items, Part II of 18 items, and Part IV of 6 items. The items were scored using a 5-point numerical rating scale (0 = normal, 1 = slight, 2 = mild, 3 = moderate, 4 and 5 = severe). The total score of Part I is 68, for Part II is 52, for Part III is 132, and for Part IV is 24. A higher score corresponded to a more severe PD symptomatology [171–173]. The MDS-UPDRS-IV, which indicates motor complications due to Anti-parkinsonian medical treatment, and total MDS-UPDRS including Part IV could only be calculated for PD patients.

Hoehn and Yahr Scale

The Hoehn and Yahr scale [174] was used to assess the stage of PD and the level of disability independent of the MDS-UPDRS. The scale is composed of 6 stages, ranging from no signs of disease (Stage 0) to the need for a wheelchair or being bedridden unless assisted Stage 5).

Motor skills for eating behavior

The motor functions specific to eating behavior were assessed with the help of a self-developed visual analog scale (VAS) as a 100-mm scale, ranging from ‘not at all’ to ‘extremely’ and includes 3 items: swallowing, eating procedure, and use of cutlery. The higher the value, the higher the motor impairment when eating (Appendix B.1).

Anti-parkinsonian Medication

The LEDD was calculated to estimate the equivalent amount of the total individual Anti-parkinsonian drugs in milligram of levodopa. Published conversion factors were used for the different types of medication [175].

2.2.3 Assessment of the nutritional profile

Body mass and body composition

Body height was measured with a wall-mounted stadiometer (Harpender Pocket Stadiometer, Lancing, UK) [176] under standardized conditions [177].

The body composition was assessed with an air-displacement plethysmography system (Bod Pod(R), COSMED, Rome, Italy). After a calibration process[14], participants were seated in the closed Bod Pod chamber twice in a row for 60 seconds while wearing underwear or swimwear and a bathing cap. The body volume was indirectly measured within the chamber by determining the volume of air displaced inside the closed chamber caused by the volume of air displacement of the seated participant in the closed capsule. Age, gender, and height were manually entered into the Bod Pod software system. The thoracic gas volume was adjusted to predict the volume in order to correct the volume of air contained in the lungs during the measurement procedure [178]. The total fat mass (FM) and the total fat-free mass (FFM) were calculated from measured body mass and body volume using an age- and ethnicity-dependent algorithm [178,179]. The body mass was determined with high accuracy during the measurement process using an electronic scale connected to an air-displacement plethysmography system (Bod Pod(R), COSMED, Rome, Italy)[15].

[14] First of 3 steps (calibration → warming-up and auto-run → manual volume calibration). The thermal conditions within the laboratory remained constant.

[15] All applied algorithms for calculation follow Boyle’s law, which states that a constant temperature, a constant volume, and a constant pressure are inversely related to each other [178,179].

Body Mass Index and body circumferences

The BMI is defined as the weight of a person in kilograms (kg) divided by the square of the height of the person in meters (m).

The body circumferences were measured with an inelastic tape in centimeter (cm) at three sites: waist, hip, and neck. All measurements were carried out three times, and then the mean value was calculated for each site. For the waist circumference, the tape was passed around the body between the iliac crest and the costal margin of the lower limb [177]. The cut-off values for central adiposity are ≥ 94 cm for males and ≥ 80 for females [176,177]. To assess the hip circumference, the tape was passed around the participant and positioned at the widest part over the buttocks and was measured horizontally at the level of the greatest lateral extension [177,180,181]. Participants were asked to relax before the measurement and not to contract their gluteal muscles [176]. The waist-to-hip ratio was calculated by dividing the waist circumference (cm) by the hip circumference (cm) with cut-off values of ≥ 0.90 for males and ≥ 0.80 for females. Neck circumference was measured while the participants were asked to look forward and relax the neck muscles [182,183,184].

Development of body mass over the course of the disease

In a retrospective interview, the individual body mass development as an adult between the 18th year of life and today was examined. In addition, PD patients were asked to describe the development of their body mass over the course of the disease. Required were the lowest and highest body mass in adulthood, body mass at PD diagnosis for PD patients, and body mass ten years ago for controls. This interview consisted therefore of the following questions: 'What was your lowest body mass as an adult and at what age?' and 'What was your highest body mass as an adult and at what age?'. For PD patients, we asked 'When were you diagnosed with PD, and what was your approximated body mass at that time?' For healthy control subjects, we used the question 'Can you please describe the development of your body mass as an adult?'.

2.2.4 Laboratory examination

Metabolomic profile and hormones in the blood[16]

Blood samples for the analysis of metabolic markers and food-related hormones were taken under fasting conditions. at the time points T_0, T_{6M}, and T_{12M}. An intravenous cannula was inserted into a vein of the elbow and blood was withdrawn using 2 serum tubes (S-Monovette® 4.9 ml; Servoprax, Wesel, Germany), 2 whole blood EDTA tubes (S-Monovette® 2.7 ml; Servoprax, Wesel, Germany), 2 plasma tubes (S-Monovette® 2,7 ml; Servoprax, Wesel,

[16] The analysis of hormones is not part of the thesis.

Germany), and 1 Paxgene™ tube (BD Biosciences, New Jersey, USA). A total, of ~35 ml of blood was taken.

The plasma glucose concentrations were immediately after blood sampling with the glucose oxidase method using EKF-Diagnostics Biosen C-Line (EKF Biosen C-Line glucose analyzer, EKF Diagnostic GmbH, Barleben, Germany). The plasma of the remaining blood was immediately centrifuged at 4°C at 4000 rpm for 10 minutes (Labofuge 400R, Heraeus Instruments, Hanau), while the serum remained at room temperature for 30 minutes and was then centrifuged. After centrifugation, some of the supernatants were pipetted and aliquoted and frozen at -80°C until analysis. For analysis of the cell blood count, samples were prepared for analysis in the LADR Laboratory (Geesthacht, Germany). The Paxgene tube was stored at room temperature until the end of the measuring day and then frozen at -20°C for two days and then at -80°C until analysis.

2.2.5 Locating the active contact sites and estimating the volume of tissue activated

The next section explains how DBS leads were localized in the patient's brain.

Visualization of electrodes

The PD-DBS group underwent postoperative MR imaging or high-resolution CT imaging on a clinical scanner within 5 days after surgery. DBS electrodes were localized with the LEAD DBS Toolbox version 2.2.3 (http://www.lead-dbs.org; [83]) within MATLAB 2019 (The MathWorks, USA) for DBS lead visualization.

First, preoperative MR- or CT- images were co-registered with the LEAD DBS toolbox using SPM12 and Advanced Normalization Tools [185]. The results of the co-registration were then checked visually. Normalization to the MNI space was also performed within the toolbox by using Advanced Normalization Tools, a visual inspection was performed after application, followed by a brainshift correction as the electrodes caused nonlinear deformations of the brain [83]. The brainshift algorithm within LEAD DBS uses a threefold linear registration and was followed by a visual check. The electrode localization was divided into two steps: automated pre-localization and manual localization. Automated lead pre-localization on MR images was performed with the TRAC/CORE algorithm [186] and on CT images with the PaCER toolbox [304]. The electrode trajectories were then manually adjusted so that they optimally matched the visible artifacts in the postoperative image if automatic localization did not match the MR or CT artefact.

Estimation of the volume of tissue activated

DBS parameters were mapped into the standardized patient space using the subcortical electrophysiological approach. The parameters were determined individually for each patient

(selection of stimulation contacts, bipolar vs. monopolar, amplitude, pulse width, and frequency) and the volume of tissue activated (VTA) as an approximation of the DBS-activated tissue was modelled using the Dembek 2017 Atlas within the toolbox [83,186].

2.2.6 Assessment of non-homeostatic regulation of food intake

Assessment of behavioral inhibition and behavioral activation systems

The sensitivity levels of the behavioral inhibition and behavioral activation systems were measured using the Behavioral Inhibition and Behavioral Activation Systems questionnaire (BIS/BAS; Appendix B.4). The BIS/BAS scales include a self-assessment measure of avoidance and approach tendencies that includes 20 items consisting of a 7-item BIS scale and a 13-item BAS scale [187]. The BIS system is sensitive to aversive, punitive, or novel stimuli, and the BAS system is sensitive to appetizing and rewarding stimuli. The questionnaire uses a score with a 4-point scale (1=not at all true, 2=somewhat not true, 3=somewhat true, 4=all true). Items 2 and 22 were swapped for analysis.

Assessment of hunger and stress levels using visual-analog scales

A 100 -mm VAS was applied at seven different time points, over the study day at T_0 and T_{6M}, to assess hunger and stress levels: before and after breakfast, before and after lunch, before MRI measurement, as well as before and after EEG (Appendix B.2 and B.3). At T_{12M}, VAS was only assessed before and after the breakfast. The VAS consisted of two questionnaires with 38 items and was anchored from ‘not at all’ to ‘extremely’. Higher values indicated higher stress and hunger levels. The analysis was performed four times (before and after breakfast, before and after the EEG) using two distinct approaches:

I) Analysis of the desire to eat (in general, sweet foods, savory foods)
II) Analysis of items related to the regulation of food intake (hunger, satiety, appetite, thirst)

Neurocognitive assessment of hedonic hunger

The assessment of hedonic appetite control, food reward sensitivity, and food preference was performed using a computer-based ‘wanting-liking’ task. The hedonic appetite comprises both a pleasure component (‘liking’) and a motivational component (‘wanting’) [119,120]. The tests were performed with MATLAB 2019 (The MathWorks, USA) on a 17" laptop with Windows 10 as the operating system. Forty-two photographs of various food items were visually presented on the screen, which differed in terms of calorie content (low vs. high) and taste (sweet vs. savory). Three categories could be distinguished: high-caloric non-sweet food images (HC-NS), high-caloric sweet food images (HC-S), and low-caloric food images (LC). The subjective preference for the different food items was assessed by rating each image in relation to the

general liking ('How much do you like this food?') on a scale of 1 ('not at all') to 5 ('very much'). The current 'wanting' was assessed in the same way with the question 'How much do you want this food right now?' (Fig. 8). In both tests, the respective ratings were entered directly into the actual image mask via the keyboard. The images were presented in a randomized order, including the initial image. The first question was balanced across all subjects. The order of the initial question ('wanting' first or 'liking' first) remained the same for each individual subject over all measurements. The participants were instructed to reply as accurately and as quickly as possible. The analysis was performed by calculating the difference between the two sessions for each category: wanting HC-NS, wanting HC-S, wanting LC, liking HC-NS, liking HC-S, and liking LC [119,120,188].

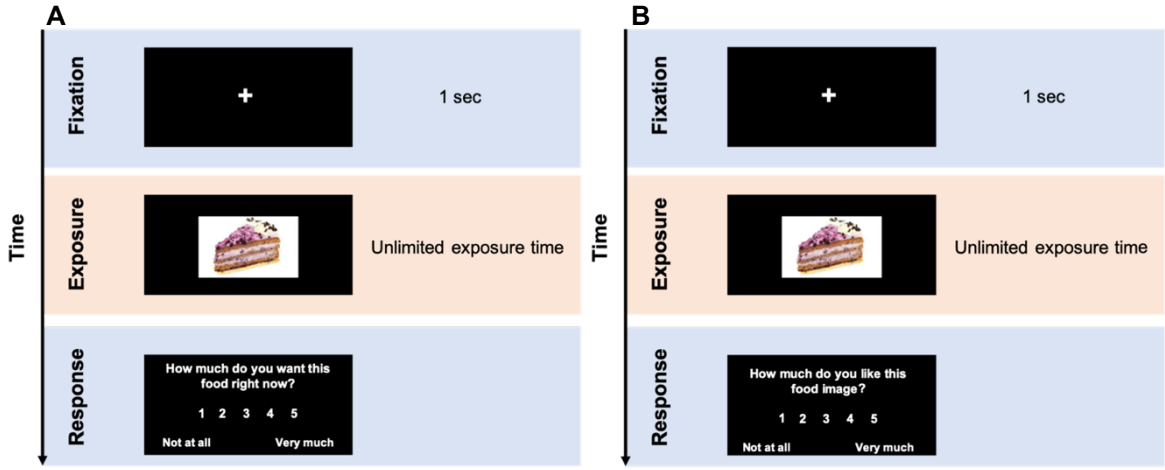

Figure 8. Experimental design of the wanting-liking task. (A) In the 'wanting' condition, the fixation cross was followed by food images in a randomized order, and participants were asked to answer the question about the wanting condition. (B) In the 'liking' condition, the same procedure was performed, with the exception of the initial question.

Assessment of snacking behavior

The self-developed 'Cookie-Test' at the end of the measurement day consisted of high-fat, sweet cookies (Griesson American Chocolate Cookies Minis, Griesson - de Beukelaer GmbH & Co. KG, Polch, Germany; Griesson Chocolate Cookies Minis, Griesson - de Beukelaer GmbH & Co. KG, Polch, Germany) and sweet, low-fat food (grapes), as well as water and apple spritzer. In total, 50 g of American chocolate cookies with a total of 251 kcal, 50 g of chocolate cookies minis with 241 kcal, 200 g grapes with 134 kcal, as well as 500 ml apple spritzer with 130 kcal, were provided. The total amount of served energy was 756 kcal. The amount of energy that have been consumed was calculated for each category.

2.2.7 Statistics of Study 1

The results are given as mean value ± SD. The software used for analysis was Excel Version 2016 (Microsoft, Redmond, WA), SPSS Statistics 25.0 (SPSS Inc, Chicago, IL), and GraphPad Prism version 8.0 for Windows® (GraphPad Software, La Jolla, CA) The distribution of gender between groups was calculated using the χ^2 test. A one-way ANOVA was used to test for differences between the metric data. The paired students t-test was used to test for changes in the parameters between the time points. The calculation of the normal distribution for each variable was performed using the Kolmogorov-Smirnov test. If the data were not normally distributed at baseline (T_0), normalization with the logarithmic transformation (natural logarithm; z-transformation) was performed to achieve a normal distribution of data. The analyses of the data over time were based on a mixed general linear model (GLM)[17] due to individual missing data points, including the main factors 'Group' (PD-DBS vs. PD-CON vs. H-CON), and 'Time point' (for repeated measurements during the experiment: T_0, T_{3M}, T_{6M}, T_{12M}). The GLM included Bonferroni Post-hoc tests for the main factors. For comparisons of changes within a group over time, GLM was calculated with Bonferroni Post-hoc tests for each group individually and separately using an in-house MATLAB script to correct for multiple testing. In all analyses, a p-value <0.05 was considered significant.

The correlation analysis of VTA and primary outcome parameters (DBS-related body mass change and change in BMI, FM, UPDRS) was performed with the LEAD Group [83]. Active contacts were visualized to illustrate the individual placement of the electrodes.

[17] RmANOVA was used for LEDD, lifetime-related body mass development, and VAS.

2.3 Study 2 – Effects of Subthalamic Nucleus DBS on Body Mass-Related Effects on Neuronal Circuitries

2.3.1 Subjects and study design

Forty-three patients diagnosed with idiopathic PD, according to the clinical diagnostic criteria of the Movement Disorder Society [73] with STN DBS, and 19 healthy control subjects[18] (mean age: 65.8 ± 7.1 years; H-CON) were recruited.

The PD patients[19] (age at onset: 50.2 ± 9 years, mean age at the examination: 61.4 ± 9 years) received DBS 3 to 78 months prior to inclusion in the study (mean time: 24 ± 8 months). Eleven had a positive family history with movement disorders. All patients continued to take their dopaminergic medication throughout the study (Med ON).

Patients and healthy control subjects were matched for age and gender. The handedness was assessed using the Edinburgh Handedness scale [167]. Cognitive function was tested using MoCA [165,166].

Stereotactic bilateral DBS electrode implantation was performed at the University Hospital in Lübeck, Hannover, and Magdeburg. STN DBS was maintained without interruption. All patients had MR-approved neurostimulators (Medtronic® Activa series PC or RC). To investigate the DBS-related effects on food image processing, the patients were measured under two conditions: (i) with active stimulation (ON) and (ii) while stimulation was switched off (OFF). Patients with pocket adapters, a previous history of pulse generators other than Activa PC or RC, and patients with impedances of single contacts > 2,000 Ohm in the monopolar stimulation mode or < 250 Ohm in the bipolar mode, and with an uncontrolled resting tremor in the OFF mode were excluded. Both MRI sessions were performed on the same day with a break of one hour between sessions. The order (ON first vs. OFF first) was counterbalanced across all subjects. For safety reasons, an MRI session lasted a maximum of 30 minutes. Since only active bipolar stimulation is allowed during MRI, the stimulation mode and parameters were changed to bipolar in patients with monopolar stimulation and adjusted with the aim to sufficiently control the motor symptoms. The adjustment was done with a maximum time interval to the start of the first MRI session. Immediately before an MRI session, the patients were neurologically examined by a specialist for movement disorders, according to the MDS-UPDRS. The examinations were videotaped and subsequently rated by another movement disorder specialist (Prof. A. Münchau, MD), blinded for the stimulation mode. For rigidity, the ratings from the onsite examiner were used. After both MRI sessions, the stimulation

[18] Among the healthy control subjects, 47% were female. MR measurements of the present study were performed by Henrike Hanßen (PD patients and healthy control subjects) and by the author of the present PhD thesis (healthy control subjects). The subsequent analyses were performed by Julia Steinhardt.

[19] Among the PD patients, 18% females were included.

parameters were adjusted to the initial settings, and treatment impedances were tested. The neurological examination was repeated to confirm that patients had returned to their initial clinical state.

The study was approved by the local ethics committee of the University of Lübeck, Germany (AZ15-212), and all participants gave their written consent prior to their inclusion. The study was conducted in accordance with the Helsinki Declaration.

MR data acquisition at 1.5T MR scanner

During both sessions, echoplanar images (EPI) for task-related fMRI (110 volumes, 38 slices, TR=3000 ms, TE=50 ms, slice thickness=3 mm, flip angle=90°, slice spacing=3 mm, and FOV=80 x 80 mm^2) were acquired on a Philips Achieva 1.5T (The Netherlands, 8-channel head coil). Furthermore, a 3D MPRAGE sequence was acquired during the first session using the following parameters: 180 slices, TR=7.3 ms, TE=3.3 ms, slice thickness=1 mm, flip angle=8°, slice spacing=1 mm, and FOV=256 x 256 mm^2. The head of the subject was fixed during the entire measurement to avoid head movements.

Experimental Design

Prior to the start of the task experiment, the participants were familiarized with the task and had a five-minute resting-state fMRI measurement with closed eyes (Fig. 9).
The food cue- viewing task was presented as an event -related- design with three types of pictures, corresponding to the respective task condition: (i) sweet food images (high-calorie), (ii) salty food images (high-calorie), and (iii) neutral images. The images were taken from a freely available image set developed by Blechert *et al.* (2014) for investigating eating behavior and appetite [189]. The stimulus set included 120 colored food images (sweet and salty; i.e. chocolate cake, burger) and 60 non-food images (neutral images, i.e. car, flowers). All images had the same resolution and color depth (600~ 450 pixels, 96 dpi, 24 bpp) and were presented on a neutral gray background (RGB 180, 180, 180). The experiment consisted of five runs, each lasting for 3.8 minutes and comprising 36 events per run: 12 images with sweet foods, 12 images with salty foods, and 12 neutral images. The stimuli were presented for 2 s, with an interstimulus interval varying randomly between 4 s and 8 s in a pseudo-randomized order, so that not more than three stimuli from the same category were presented consecutively. Before and after each block, a blank screen with a white fixation cross in the middle was shown for 14 seconds. Presentation software (version 19.2, www.neurobs.com) was used for stimulus presentation and were displayed using a projector that illuminated a rear projection screen at the end of the scanner. Participants viewed the stimuli through an adjustable mirror attached to the head coil and were instructed to look at the center of the image or the fixation cross that would appear between stimulus presentations. In addition, both body mass pre-before surgery

as well as the actual body mass were retrospectively requested on the day of measurement for further analysis and correlation analysis of the body mass change with VTA.

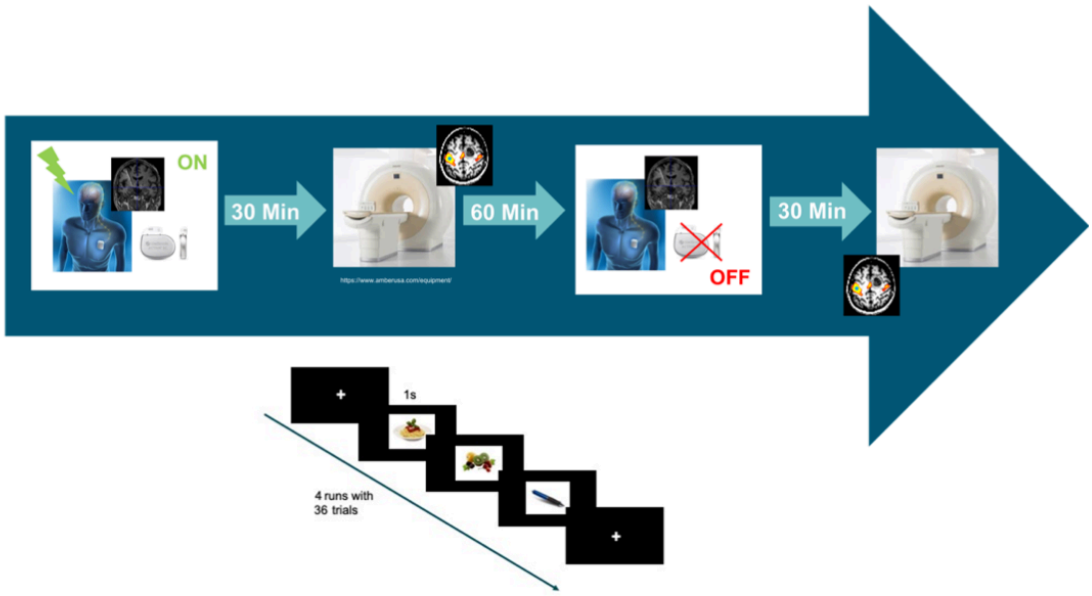

Figure 9. fMRI paradigm. Patients were scanned for 30 minutes during active stimulation, followed by a 60 minutes break. After the break, the stimulator was switched off and the patients were again scanned for 30 minutes. The order of stimulation modes was counterbalanced across all subjects.

2.3.2 Data Preprocessing

The data were preprocessed and analyzed using the CONN Toolbox Version 18a [190], which runs in MATLAB (MathWorks, Natick, MA, USA; Version 19) using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK). The preprocessing was performed using the standard pipeline MNI152 and parameters. Preprocessing steps included realignment, unwarping, and slice-time correction. All structural and functional images were segmented in gray matter, white matter, and cerebrospinal fluid, normalized to Montreal Neurological Institute (MNI) space, and then smoothed with a Gaussian kernel (Full-Width Half-Max = 6 mm). CONN has an implemented component-based noise correction method to reduce physiological and additional noise. Nuisance variables including realignment parameters and parameters are derived from the principle components of white matter and CSF. Nuisance parameters were removed prior to seed-based connectivity analysis using principal component analysis of the multivariate BOLD signal within each of these masks obtained from the segmented T1-weighted MPRAGE scans. The BOLD data was bandpass -filtered (0.008–0.09 Hz) to reduce low-frequency drift and noise effects.

2.3.3 Visualization of electrodes and estimation of the volume of tissue activated

A detailed explanation of the VTA procedure can be found in the previous Section 2.2.5.

2.3.4 Statistics of Study 2

The data were analyzed using whole-brain analysis, seed-based correlation analysis, and region of interest (ROI) analysis. For the whole brain approach, a GLM model for each participant with food condition regressors was performed (images of sweet foods, images of salty foods, neutral images). These models were convolved with the canonical hemodynamic response function and used to generate certain contrast images that compare our task conditions (i.e. food vs. non-food). In the group level analysis, we used a 2 x 3 factorial design with the factors 'Group' (2 levels; stimulation ON vs. OFF; ON vs. H-CON; OFF vs. H-CON) and 'Condition' (3 levels; 3 image categories). The main effects of 'Group' and 'Condition' were analyzed to confirm whether differences in brain activation within a group of PD patients exists between active vs. inactive stimulation as well as between PD patients and healthy control subjects. Further effects were assessed by calculating interaction effects between groups and conditions. The thresholds were set at an FDR-corrected level of $p<0.05$.

The next step was a seed-based correlation analysis. First-level (single-subject) contrasts images were estimated for each of the scans for the following main effects of interest: sweet > salty foods, sweet foods > neutral images, salty > sweet foods, salty > neutral images, neutral > sweet foods, and neutral > salty foods in SPM12. The changes in brain activation between sessions were calculated by generating the following contrasts: PD ON (sweet > salty foods) > PD OFF (sweet > salty foods), PD ON (sweet > salty foods) > H-CON (sweet > salty foods), PD ON (sweet foods > neutral images) > PD OFF (sweet foods > neutral images), PD ON (sweet foods > neutral images) > H-CON (sweet foods > neutral images), PD ON (salty > sweet foods) > PD OFF (salty > sweet foods), PD ON (salty > sweet foods) > H-CON (salty > sweet foods), PD ON (salty foods > neutral images) > PD OFF (salty foods > neutral images), PD ON (salty foods > neutral images) > H-CON (salty foods > neutral images), PD ON (neutral > sweet foods) > PD OFF (neutral > sweet foods), PD ON (neutral > sweet foods) > H-CON (neutral > sweet foods), PD ON (neutral > salty foods) > PD OFF (neutral > salty foods), PD ON (neutral > salty foods) > H-CON (neutral > salty foods), PD OFF (sweet > salty foods) > H-CON (sweet > salty foods), PD OFF (sweet foods > neutral images) > H-CON (sweet foods > neutral images), PD OFF (salty > sweet foods) > H-CON (salty > sweet foods), PD OFF (salty foods > neutral images) > H-CON (salty foods > neutral images), PD OFF (neutral > sweet foods) > H-CON (neutral > sweet foods), and PD OFF (neutral > salty foods) > H-CON (neutral > salty foods). We generated seed-to-voxel connectivity maps for each individual session for different brain networks. The salience network was then used for further analysis [121,123,126,134,191]. The seeds are provided in the CONN software [190]. Connectivity first-level correlation maps were generated in the CONN toolbox by extracting the mean BOLD time course from each seed ROI and calculating correlation coefficients with the BOLD time course of each voxel throughout the entire brain. The resulting coefficients were converted to

normally distributed scores using Fisher's transformation to generate maps of voxel-wise functional connectivity for each seed ROI for each subject. The value of each voxel throughout the entire brain represents the relative degree of functional connectivity with each seed [190]. These maps were then used for second-level analysis of relative functional connectivity, using a two-sided independent t -test to investigate differences in seed-to-voxel connectivity between groups. Participant motion were included as within-subject first-level covariates. Group-level effects were considered significant if they exceeded a peak amplitude of $t > 3.09$, and a family wise- error -corrected cluster extent threshold of $p \leq 0.05$.

The last step was a calculation of ROIs, which were selected according to the literature. We focused on the structures being involved in the processing of food cues [127–129,192,193]: orbitofrontal cortex (OFC), lateral occipital cortex, insula, NAcc, striatum, amygdala, brainstem, and hippocampus. The purpose of this ROI-based analysis was to determine the impact of active stimulation on functional connectivity changes between the central structures of eating behavior and food intake in comparison to age-matched healthy controls. The same statistical procedure as above was applied.

3 Results

The first section describes the results for the systematic review of the magnitude of the relationship of body mass gain and STN DBS, as well as the extent and time course of this body mass gain [30]. The next section presents the results of Study 1 as a prospective and longitudinal study on alterations in the nutritional and metabolic profile of patients with PD treated with STN DBS compared to PD patients under best medical treatment and to healthy control subjects. In the last section, the results of Study 2 are presented, which examined the acute effect of STN DBS on the motivational attraction of food cues in PD patients.

3.1 Systematic Review and Meta-Analysis

Study selection and characteristics

The literature search identified 206 potentially relevant articles, of which 154 studies were evaluated for a more detailed analysis (Fig. 10). After the selection process, 54 studies [2,5,6,8–11,13–25,33,36,39–41,67,79,95–98,110,147,149,156–163,194–203] fulfilled the inclusion criteria described above. For the analysis, 38 studies could be included, of which 18 (47%) were prospective case studies, 12 (32%) were prospective case-control studies, 4 (11%) were retrospective case studies, 2 (5%) were retrospective case-control studies, 1 (2.5%) was a cross-sectional, and 1 (2.5%) was a retrospective survey study. In total, the 38 selected studies included 979 patients with PD and STN DBS and 287 controls, consisting of non-stimulated patients with PD under best medical treatment (N=186) and healthy controls (N=101).

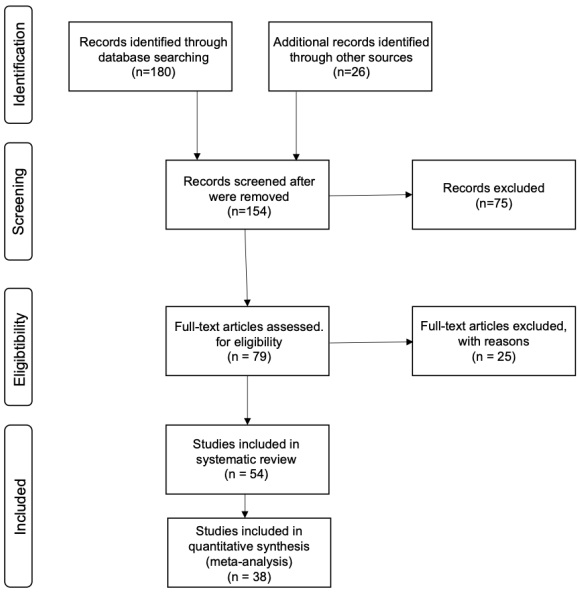

Figure 10. A systematic overview and meta-analysis PRISMA flowchart.

Patient characteristics

Demographic information on subjects were provided in Appendix C. The sample sizes of the study ranged from 7 to 57 subjects (mean±SD: 25.8 ± 11.6; N = 979) with a follow-up time between 1 to 60 months after DBS implantation (mean±SD: 17.8 ± 15.2 months). Average age across all studies was 59.0 ± 7.5 years (range: 54.9 - 66.0; N = 833), mean disease duration prior to surgery 12.4 ± 4.0 years (range: 8.5 - 15.7; N = 680). There was no specification of the ethnicity of the subjects in the studies.

Changes in body mass

The analysis showed a significant increase in body mass in 21/21 studies (100 %) with complete data sets at the latest time point of follow-up [5–22,24,25]. For these 21 studies, the overall pooled mean body mass gain was +5.7 kg (baseline body mass: 73.3 kg; range of body mass gain: 1.3 - 11.1; N = 446; $p < 0.0001$; Fig. 11) with a corresponding effect size of d = 0.64 (Fig. 12). To minimize a potential bias, a secondary analysis was performed for different postoperative time points 3, 6, 12 months, and greater than 12 months of follow-up.

The mean body mass gain 3 months after surgery was +3.3 kg (baseline body mass: 73.7 kg; range of body mass gain: 1.1 - 5.9; N = 190; $p < 0.001$) with a corresponding effect size of d = 0.66. The average change in body mass from baseline to 6 months following DBS was +3.9 kg (baseline body mass, 75.0 kg; range of body mass gain: 2.6 - 5.5; N = 127; $p < 0.001$; d = 0.22). After 12 months of follow-up, the body mass increased by +6.4 kg (baseline body mass: 71.4 kg; range of body mass: 2.9 - 11.1; N = 241; $p < 0.0001$; d = 0.72). After more than 12 months follow-up, the body mass gain remained stable at +6.1 kg (baseline body mass: 69.2 kg; range of body mass gain: 4.9 - 8.1; N = 66; p = 0.003; d = 1.02).

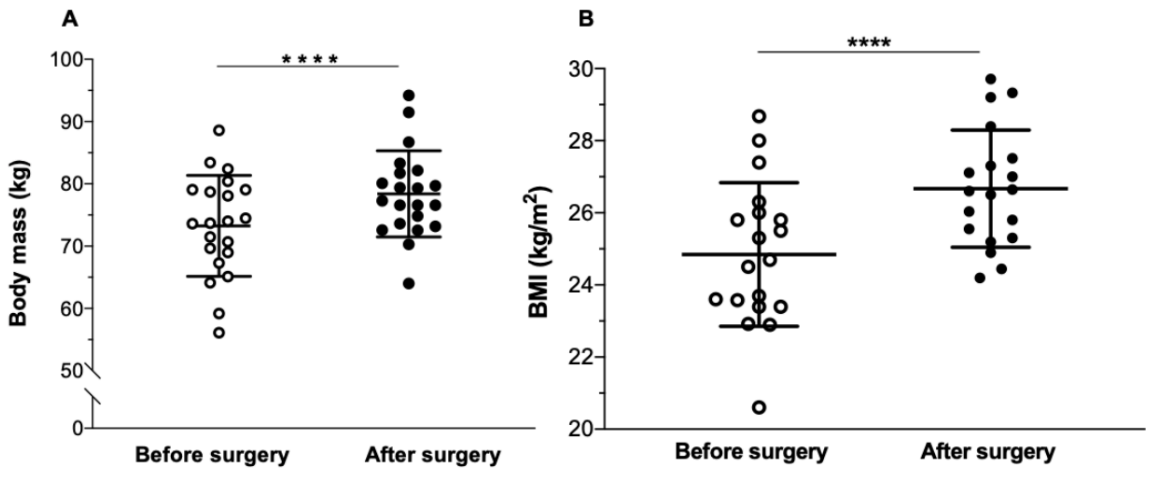

Figure 11. Changes in body mass and BMI in the study population. (A) Mean body mass change over all studies as a comparison between body mass before surgery and at longest follow-up (N = 446, ****$p < 0.0001$). (B) Mean change in BMI over all studies as a comparison between body mass before surgery and at longest follow-up (N = 512, ****$p < 0.0001$). Open circles: before surgery; closed circles: after surgery. The values are represented

as mean values and 95% confidence intervals indicated by solid lines. The dots represent individual values of subjects.

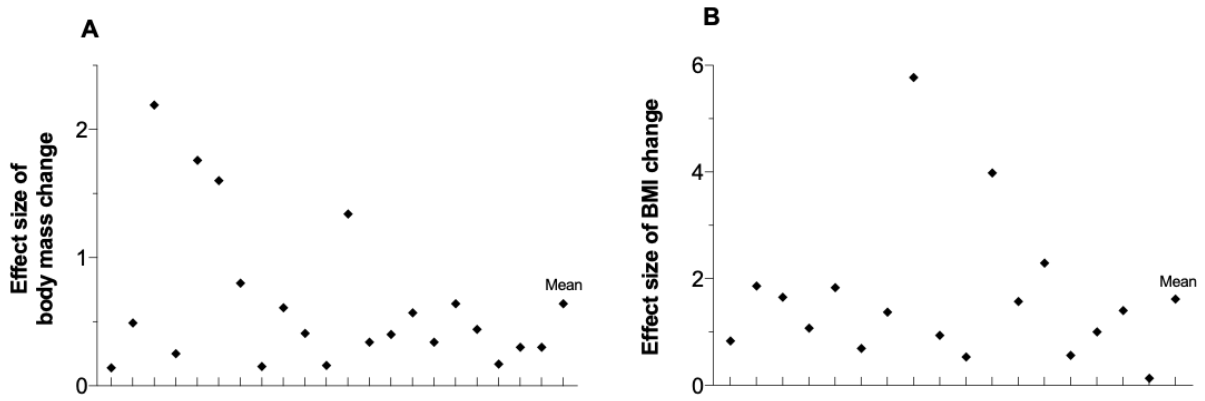

Figure 12. Effect sizes of the available studies. Effect sizes of DBS-related body mass (A) and BMI (B) changes.

Changes in BMI

Nineteen studies (N = 512) were available for the evaluation of the BMI. All studies showed an increase in BMI at the latest follow-up [5,6,8–11,13,16,18,19,21,25,153,162,198,199,203, 204]. The overall pooled mean increase in BMI was +1.8 kg/m^2 (baseline BMI: 24.8 kg/m^2; range of BMI gain: 0.4 - 3.2; $p < 0.0001$; Fig. 11) with a mean effect size of d = 1.61 (Fig. 12) for the latest follow-up.

We also evaluated the time course of BMI gain and found an increase of +1.0 kg/m^2 already 3 months after DBS (baseline BMI: 25.1 kg/m^2; range of BMI gain: +0.1 - 1.3; N = 185; $p = 0.0042$; d = 1.08; Fig. 13). Here, the number of patients with overweight increased from 46% to 71%. The change in mean BMI from baseline to 6 months was +1.6 kg/m^2 (baseline BMI: 25.1 kg/m^2; range of BMI gain: 0.8 - 2.0; N = 236; $p = 0.0004$; d=0.87) with an increase in the proportion of patients with overweight from 55% to 77%. At 12 months of follow-up, the BMI increased by +2.1 kg/m^2 (baseline BMI: 24.5 kg/m^2; range of BMI gain: 0.4 - 4.7; N = 199; $p < 0.0001$; d = 2.14). As a result, the proportion of patients with overweight increased from 52% at baseline to 88%. At a postoperative interval of more than 12 months of stimulation, the BMI increased by +2.0 kg/m^2 (baseline BMI: 23.9 kg/m^2; range of BMI gain: 0.9 - 2.9; N = 103, $p = 0.0031$; d = 1.65) in comparison to the preoperative BMI. In this subgroup, 100% had a normal body mass before surgery, of which 44% developed overweight.

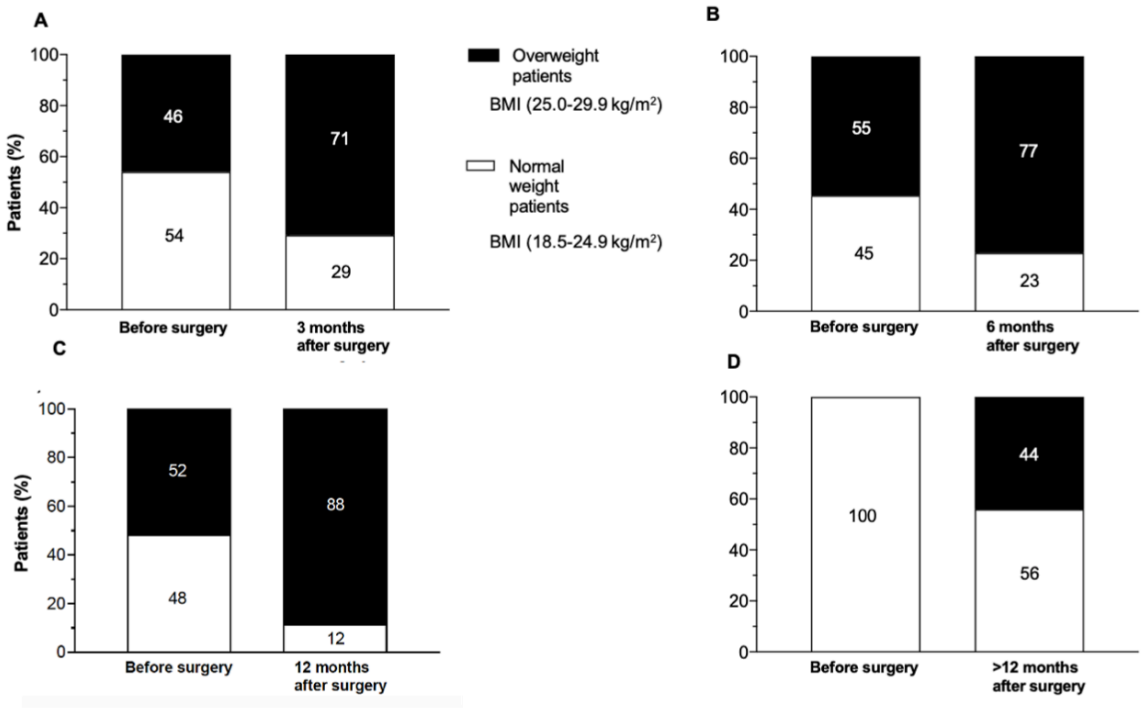

Figure 13. Distribution of nutritional status as assessed by BMI in the study population. BMI - normal weight (18.5-24.9 kg/m^2), - overweight (25.0-29.9 kg/m^2). (A) 3 months after surgery (B) 6 months after surgery (C) 12 months after surgery (D) More than 12 months after surgery. The proportion of patients with normal weight is shown in white and the proportion of patients with overweight is shown in black in all bars.

Effects of STN DBS on motor function

In the 25 studies (N = 696) with complete UPDRS-III datasets [6,10,11,13,16–20,22,24,33,95,96,149,156–158,161,162,162,195,196,200,202], the total mean UPDRS-III in the DBS ON state decreased from 34.7 (range: 6.4 - 67.6) at baseline to 16.7 at the latest follow-up (range: 5.0 - 39.3; $p < 0.0001$; Fig.14A). Similarly, DBS led to an improvement in the mean dyskinesia score [10,16–18,95,158,162,195,196] in the UPDRS-IV from 4.9 at baseline (range: 1.4 - 11.0) to 1.9 (range: 0.1 - 2.6; N = 252; $p = 0.0014$; Fig. 14B) postoperatively.

Change in levodopa-equivalent doses

In 24 studies [5,6,8–11,13,16–20,24,33,95,149,156–158,162,195,196,200] (N = 652), the overall pooled mean LEDD decreased from 1141 mg/day at baseline (range: 831 - 1507) by 44 % to 644 mg/day at the latest available follow-up (range: 402 - 1149 mg/day; N = 652; $p < 0.0001$; Fig. 14C).

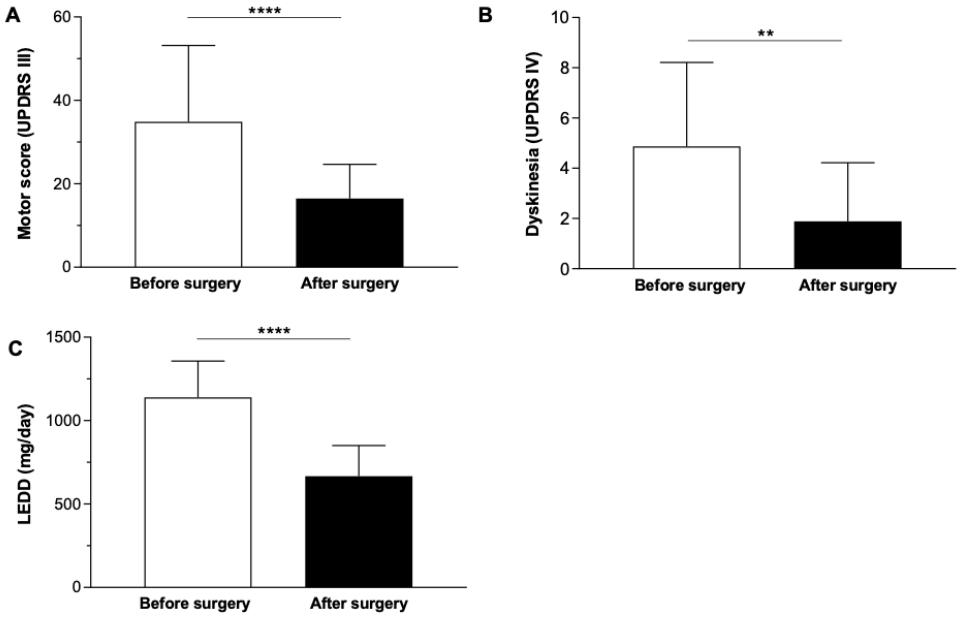

Figure 14. Changes of motor scores and LEDD. (A) UPDRS-III (****p<0.001), (B) dyskinesias (**p = 0.001), and (C) LEDD (****p < 0.001). Before surgery, white bars; after surgery, black bars. Values are mean values±SD.

Predictors of body mass gain after STN DBS

To assess predictive factors of body mass gain after surgery, we performed a correlation analysis of the following variables: delta body mass, delta BMI, delta LEDD, delta UPDRS-III, delta UPDRS-IV, disease duration, age, as well as body mass preoperatively. The change in body mass was correlated with age (r = -0.4239, p = 0.031; Fig. 15A). Mean change in BMI was positively correlated with the mean change in LEDD (r = 0.440, p = 0.0231; Fig. 15B), and in UPDRS-III scores if ‘on levodopa’ (r = 0.502, p = 0.010; Fig. 15C). The postoperative mean change of LEDD was correlated with the disease duration (r = -0.399, p = 0.022; Fig. 15D).

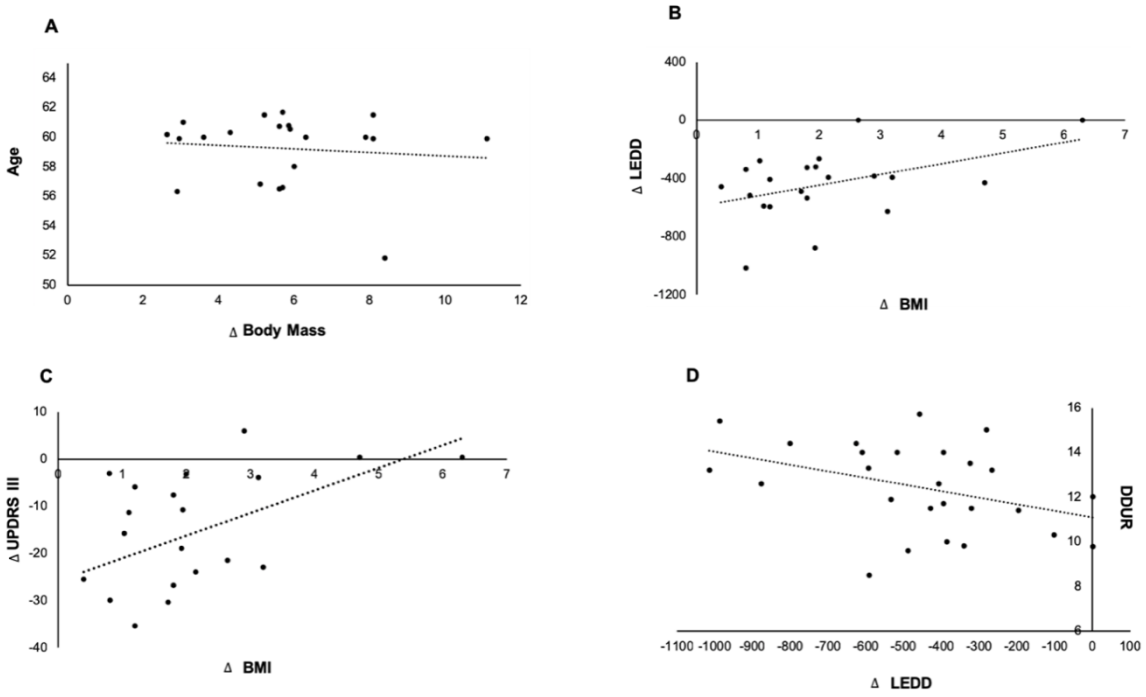

Figure 15. Predictive factors of body mass and BMI gain after STN DBS in patients with PD. (A) Correlation of postoperative changes in body mass and age. (B) Correlation of the mean change in BMI and the mean change in LEDD. (C) Correlation of the mean change in BMI and the mean change in UPDRS-III. (D) Correlation of the mean change in LEDD and disease duration. All values are mean differences between pre- and postoperative values.

3.2 Study 1 – Longitudinal Evaluation of Metabolic Profile After Subthalamic Nucleus DBS in Patients with Parkinson's Disease

3.2.1 Characteristics of the study population

Subjects

Three different study groups were included in this study: PD patients undergoing STN DBS (PD-DBS), matched PD patients with best medical treatment as a disease control group (PD-CON), and healthy control subjects (H-CON; Table 1). There were no dropouts in the PD-DBS group. Seventeen out of 19 patients with PD (13 men and 4 women) and 21 of 25 healthy controls (11 men and 10 women) completed the entire study[20].

Table 1. Demographic parameters of participants in Study 1 at baseline.

Baseline (T_0)	PD-DBS	PD-CON	H-CON	p
Age (years)	56.6±8.4	57.9±7.9	59.4±8.0	0.590
Body mass (kg)	81.4±17.5	81.8±14.0	77.3±11.7	0.526
BMI (kg/m^2)	26.7±4.3	26.3±4.2	25.6±3.3	0.682
Gender (male/female)	8/6	13/5	12/13	0.267
Age of disease onset (years)	45.7±9.5	48.4±7.9	n.a.	0.941
Disease duration (years)	9.8±4.6	9.8±4.9	n.a.	0.991
Handedness (Score)	0.7±0.5	0.7±0.5	0.9±0.3	0.229
Education (years)	14.6±2.9	15.9±3.2	15.3±2.9	0.702
MoCA (Score)	25.6±1.7	28.9±1.3	28.0±1.6	0.118
MDS-UPDRS-Total ON (Score)	56.5±16.3	46.8±18.4	4.5±3.1*	**<0.001**
MDS-UPDRS-I ON (Score)	9.6±5.8	10.3±6.1	2.7±2.5*	**<0.001**
MDS-UPDRS-II ON (Score)	13.4±7.8	9.7±6.2	0.5±0.9*	**<0.001**
MDS-UPDRS-III ON (Score)	32.0±8.1	25.2±8.4†	1.8±1.7*	**<0.001**
MDS-UPDRS-IV ON (Score)	6.1±4.6	2.1±2.4*	n.a.	**<0.001**
Hoehn & Yahr Stage (ON)	2.0±0.3	2.0±0.5	n.a.	0.622
L-Dopa equivalent dose (mg/day)	833±491	796±513	n.a.	0.838

[20] Data log for Study 1 was March, 2020.

Baseline (T_0)	PD-DBS	PD-CON	H-CON	p
Fasting Glucose Levels (mg/dl)	93.6±7.2	94.8±14.6	89.2±13.3	0.243

Notes. Results are expressed as mean values±SD. Hoehn & Yahr stage is represented as median values±SD. *ANOVA revealed differences between the PD patients from both groups and healthy control subjects. † ANOVA revealed difference between PD-DBS and PD-CON. PD-DBS, patients with PD that underwent DBS surgery; PD-CON, patients with PD under best medical treatment; H-CON, healthy control subjects. MoCA, Montreal Cognitive Assessment; MDS-UPDRS, Movement Disorder Society – Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent dose.

3.2.2 Effects of deep brain stimulation of the subthalamic nucleus on nutritional profile

Changes in body mass

Results of body mass analysis revealed effect for time point ($p = 0.027$; $F = 3.191$; Fig. 16), a trend for group ($p = 0.061$; $F = 2.835$), as well as a time x group interaction (all $p \leq 0.001$; $F=7.509$). As additional finding, body mass varied between PD-DBS and PD-CON ($p = 0.026$; CI: 0.510, 10.636) and showed a trend for differences between PD-DBS and H-CON ($p = 0.050$; CI: -0.281, 8.80).

Baseline

At T_0, body mass was 81.4±17.5 kg in PD-DBS, 81.8±14.0 kg in PD-CON, and 77.3±11.7 kg in H-CON ($p = 0.526$; Table 1).

Follow-up time points

Three months after stimulation, body mass increased by +2.8 kg (baseline body mass: 79.4 kg; N = 12; range of body mass gain, -0.6 to 9.3; $p < 0.001$) in PD-DBS. The mean change in body mass after a stimulation duration of 6 months was +3.4 kg (baseline body mass: 79.5 kg; N = 12; range of body mass gain, -8.2 to 11.2; $p = 0.025$). At the last follow-up, the overall mean body mass increased in comparison to baseline by +5.4 kg (baseline body mass: 77.1 kg; N = 9; range of body mass gain, -3.9 to 16.0; $p = 0.018$).

At T_{3M} in the PD-CON group, overall mean body mass decreased by -1.1 kg (baseline body mass: 83.2 kg; N = 14; $p = 0.004$). For later follow-ups, overall pooled mean body mass remained stable (T_{6M}: 81.3±11.3 kg (baseline body mass: 82.0 kg; N = 14; $p = 0.125$); T_{12M}: 81.3±12.3 kg (baseline body mass: 81.7 kg; N = 13; $p = 0.135$)).

For H-CON, the overall mean body mass remained stable at T_{3M} (77.3±12.1 kg; baseline body mass: 77.5 kg; N = 24; $p = 0.312$), T_{6M} (76.9±11.5 kg; baseline body mass: 76.8 kg; N = 24; $p = 0.455$), as well as at T_{12M} (78.3±11.5 kg; baseline body mass: 78.3 kg; N = 21; $p = 0.488$).

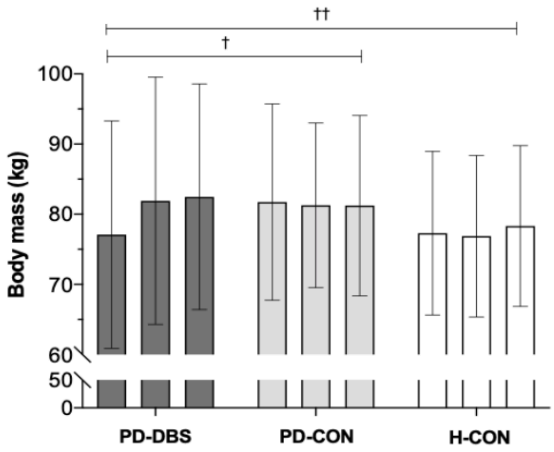

Figure 16. Body mass changes in the study population. Mean body mass change over time as comparison between groups and time points: body mass pre-surgery (first bar per group), body mass at 6 months after surgery or baseline measurement (T_{6M}; second bar per group) and at 12 months after surgery or baseline measurement (T_{12M}; third bar per group). PD-DBS, patients with STN DBS (dark gray bars); PD-CON, PD patients under best medical treatment (light gray bars); H-CON, healthy control subjects (white bars). Values are shown as mean values. † PD-DBS vs. PD-CON, p≤0.05; †† PD-DBS vs. H-CON, p≤0.05.

Changes in BMI

Results of BMI analysis revealed main effects for group and time point (all $p \leq 0.050$; all $F \geq 2.829$), as well as a time x group interaction ($p = 0.023$; $F = 2.651$). Moreover, difference between PD-DBS and PD-CON reached the level of significance ($p = 0.052$; CI: -0.011, 3.220), and a difference between PD-DBS and H-CON ($p = 0.003$; CI: 0.534, 3.436) was found.

Baseline

At T_0, BMI was not significant different between the groups ($p = 0.682$; Table 1; Fig. 17A).

Follow-up time points

At T_{3M}, the mean BMI increased by +1.0 kg/m^2 to 27.3 kg/m^2 (baseline BMI: 26.3 kg/m^2; N = 12; range BMI gain, -1.5 to +2.7; $p = 0.007$). Six months after DBS device implantation, BMI increased by +1.10 kg/m^2 compared to baseline (baseline BMI: 26.3 kg/m^2; N = 12; range BMI gain, -2.3 to +3.3; $p = 0.021$; Fig. 17B) to 27.4 kg/m^2. The portion of patients with normal weight decreased from initially 36 % to 25 % ($p = 0.048$) and the portion of patients with overweight increased from 43 % to 58 % ($p = 0.044$), whereas the portion of patients with obesity was slightly reduced by 4 % ($p = 0.366$) at T_{6M}. At T_{12M}, the overall BMI increased by +1.8 kg/m^2 compared to baseline (baseline BMI: 26.0 kg/m^2; N = 9; range BMI gain, -1.3 to +5.7; $p = 0.022$; Fig. 17C), whereby the portion of patients with overweight remained stable at 44 % ($p = 0.111$). The portion of patients with normal weight remained stable at 22 % ($p = 0.311$), whereas the share of patients with obesity increased to 34 % ($p = 0.050$). In

PD-CON, at T_{3M} BMI remained stable at 26.4±3.9 kg/m^2 (baseline BMI: 26.7 kg/m^2; N = 14; p=0.365). BMI further persists stable at T_{6M} (26.1±3.8 kg/m^2; N = 14, p = 0.135) and T_{12M} (26.0±3.8 kg/m^2; N = 13; p = 0.110). In H-CON, the BMI remained stable over the study period (T_{3M}: 25.7±3.2 kg/m^2 (N = 24; p = 0.273); T_{6M}: 25.5±3.2 kg/m^2 (N = 24; p = 0.449); T_{12M}: 25.9±3.0 kg/m^2 (N = 23; p = 0.486)).

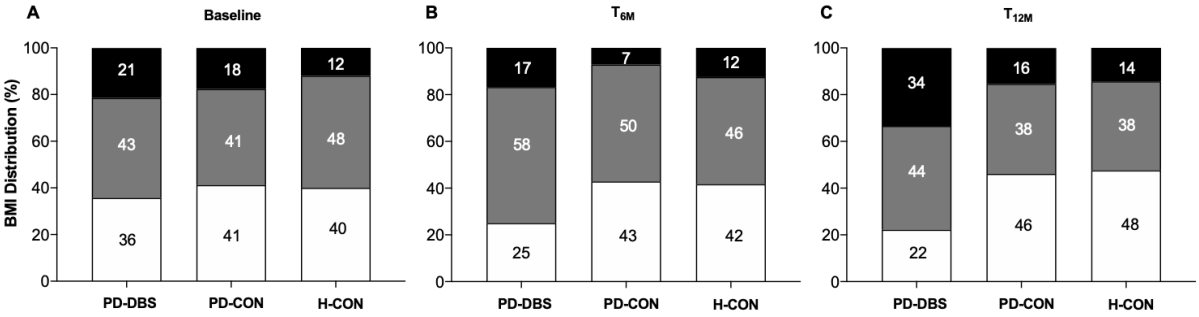

Figure 17. Body mass index changes in the study population. Mean BMI change over time as comparison between groups and time points. White bars indicate normal weight (BMI: 18.5-24.9 kg/m^2), dark gray bars indicate overweight (BMI: 25.0-29.9 kg/m^2), and black bars indicate obesity (BMI≥ 30.0 kg/m^2) at baseline (A), 6 months after stimulation or baseline measurement (T_{6M}; B), and 12 months after stimulation or baseline measurement (T_{12M}; C). PD-DBS, PD patients with STN DBS; PD-CON, PD patients under best medical treatment; H-CON, healthy control subjects.

Changes in body composition

Results of FM analysis revealed a main effect for group ($p < 0.002$; $F > 6.621$), but no effect for time point ($p = 0.941$; $F = 0.132$). However, a time x group interaction ($p < 0.001$; $F = 6.854$) was found. FM was higher in PD-DBS compared to PD-CON ($p = 0.009$) and H-CON ($p = 0.003$). Results of FFM analysis revealed an effect for group ($p < 0.001$; $F > 6.846$), but no differences over time and no time x group interaction (all $p \geq 0.823$). There were differences between PD-DBS and PD-CON ($p = 0.009$) and between PD-CON and H-CON ($p = 0.003$).

Baseline

At T_0, FM was 31.8±12.7 % (range: 7.8 to 47.9; Fig. 18A) and FFM 68.2±12.7 % (range: 35.3 to 74.7; Fig. 18A) in PD-DBS. In PD-CON, average FM and FFM were 29.5±9.9 % (range: 8.4 % to 46.5 %) and 70.5±9.9 % (range: 53.5 % to 91.6 %), respectively. In H-CON, average FM was 34.2±8.5 % (range: 19.7 % to 49.1 %) and FFM was 65.8±8.5 % (range: 50.9 % to 80.3 %). Therefore, no significant differences at baseline between the groups has been observed ($p = 0.357$).

Follow-up time points

In PD-DBS, FM increased at T_{3M} to 35.2 % (range FM changes: -3.4 % to +10.5 %; N = 12; p = 0.053). In accordance, FFM decreased to 64.8 % (range FFM change: -30.0 % to +3.4 %).

At T_{6M}, FM stabilized at 35.6 % (range FM:17.5 % to 51.5 %; N = 12; p = 0.379; Fig. 18B). FFM also stabilized at 64.4 % (range FFM: 48.5 % to 82.5 %). At T_{12M}, FM decreased to 34.7 % (range FM: 18.3 % to 52.2 %; N = 9; p = 0.011; Fig. 18C) and FFM increased to 65.3 % (range FFM: 47.8 % to 81.7 %).

In PD-CON, FM decreased at T_{3M} by 2.4% (range FM: 5.0 to 46.0; N = 14; p = 0.002) compared to T_0 and remained then stable at 29.1±10.8 % (range FM: 6.1 to 45.3; N = 14; p = 0.365) at T_{6M}, as well as at T_{12M} at 29.0±9.8 % (range FM: 9.5 to 45.3; N = 13; p = 0.386). For H-CON, there were no changes in FM over time (T_{3M}: 33.5±7.7 % (range FM: 19.8 to 48.0; N = 24; p = 0.355); T_{6M}: 33.4±8.2 % (range FM: 16.4 to 47.6; N = 24; p = 0.234); T_{12M}: 34.6±8.0 % (range FM: 19.7 to 50.1; N = 21; p = 0.247)).

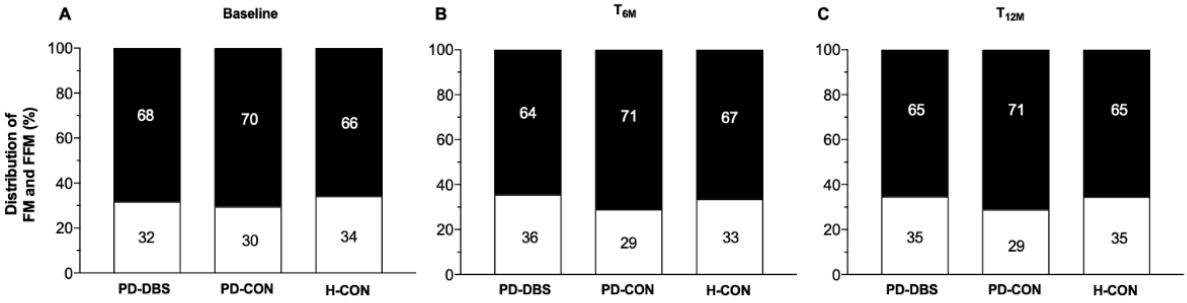

Figure 18. Changes in FM and FFM in the study population. Mean change in FM (white bars) and FFM (black bars) over time as comparison between groups and time points. (A) Change in FM and FFM at baseline, (B) 6 months after stimulation or baseline measurement (T_{6M}), and (C) 12 months after stimulation or baseline measurement (T_{12M}). T_{3M} is not shown in the figure. PD-DBS, patients with STN DBS; PD-CON, PD patients under best medical treatment; H-CON, healthy control subjects.

Changes in body circumferences

Results of waist circumference analysis revealed a main effect for group (p < 0.029; F > 3.617; Fig. 19), but no differences over time and no time x group interaction (all p ≥ 0.879). Waist circumference was higher in PD-DBS compared to PD-CON (p < 0.001; CI: 3.201, 12.781) and H-CON (p = 0.001; CI: 2.275, 10.964).

Results for hip circumference analysis revealed no main effects for group, time point, as well as no time x group interaction (all p ≥ 0.532).

Waist-to-hip ratio revealed a trend for group (p = 0.088; F = 2.571), but no differences over time and no time x group interaction (all p ≥ 0.365). A trend for differences between PD-DBS and H-CON (p = 0.098; CI: -0.029, 0.560) was found.

Results for neck circumference analysis revealed a main effect for group (p < 0.007; F > 5.034), but no differences over time and no time x group interaction (all p ≥ 0.617). Neck circumference was higher in PD-DBS compared to PD-CON (p = 0.022) and H-CON (p = 0.040).

Baseline

At T_0, neck circumferences were 38.6±4.8 cm in PD-DBS, 39.0±2.9 cm in PD-CON, and 37.8±3.6 cm in H-CON (p = 0.619). Waist circumference were 93.5±12.0 cm in PD-DBS, 91.5±11.9 cm in PD-CON, and 89.4±12.1 cm in H-CON (p = 0.599). Hip circumference were 105.0±11.5 cm in PD-DBS, 105.2±23.1 cm in PD-CON, and 105.7±5.2 cm in H-CON (p = 0.372). Waist-to-hip ratio were 0.89±0.1 in PD-DBS, 0.86±0.1 in PD-CON, and 0.84±0.1 in H-CON (p = 0.320).

Follow-up time points

At T_{3M}, waist circumference increased by +4.08 cm (range: 72.0 to 127.0; p = 0.004), hip circumference by +2.04 cm (range: 89.0 to 124.0; p = 0.042), and neck circumference by +1.57 cm (range: 34.0 to 46.5; p = 0.043) compared to baseline in PD-DBS. The waist-to-hip ratio remained stable at 0.91±0.1 (range: 0.8 to 1.0; p = 0.413). At T_{6M}, waist circumference increased by +2.5 cm (range: 72.0 to 127.0; p = 0.004; Fig. 19A) and hip circumference by +3.84 cm (range: 89.0 to 124.0; p = 0.042; Fig. 19B),whereas waist-to-hip ratio remained stable at 0.91±0.1 (range: 0.8 to 1.0; p = 0.413; Fig. 19C), and neck circumference increased by +1.11 cm (range: 34.00 to 46.50; p = 0.043; Fig. 19D) compared to baseline. At T_{12M}, waist circumference decreased to 94.8±11.8 cm compared to baseline (range: 72.00 to 127.00; p = 0.023; Fig. 19A), whereas hip circumference (p = 0.361; Fig. 19B) and waist-to-hip ratio remained stable (range: 0.8 to 1.0; p = 0.180; Fig. 19C). Neck circumference increased further to 40.2±3.9 cm (range: 34.0 to 46.5; p = 0.039; Fig. 19D).

In PD-CON, at T_{3M} waist circumference (92.8±10.8 cm; range: 72.0 to 108.5; p = 0.463), hip circumference (103.9±5.8 cm; range: 92.0 to 112.0; p = 0.223), waist-to-hip ratio (0.89±0.1; range: 0.7 to 1.0; p = 0.174), and neck circumference (39.7±2.9 cm; range: 34.0 to 45.0; p = 0.236) remained stable. All circumferences persists further stable at T_{6M} (waist: 91.7±10.6 cm (range: 72.0 to 108.5; p = 0.466), hip: 103.8±6.0 cm (range: 92.0 to 112.0; p = 0.221), and neck: 39.3±2.6 cm (range: 34.0 to 45.0; p = 0.132), waist-to-hip ratio: 0.88±0.1 (range: 0.7 to 1.0; p = 0.172); Fig 19. A-D) and at T_{12M} (waist: 91.3±12.1 cm (range: 72.0 to 108.5; p = 0.366), hip: 104.3±4.7 cm (range: 92.0 to 112.0; p = 0.179), waist-to-hip ratio: 0.88±0.1 (range: 0.7 to 1.0; p = 0168; Fig. 19A-C). Only neck circumference increased at T_{12M} compared to T_0 to 39.8±2.8 cm (range: 34.0 to 45.0; p = 0.018; Fig. 19D).

In H-CON, all circumferences remained stable at T_{3M} (waist: 90.1±12.9 cm (range: 70.5 to 111.0; p = 0.350), hip: 105.7±4.7 cm (range: 97.0 to 114.0; p = 0.401), waist-to-hip ratio: 0.85±0.1 (range: 0.7 to 1.0; p = 0.238), and neck: 37.8±4.0 cm (range: 32.5 to 45.5; p = 0.273), T_{6M} (waist: 89.2±11.6 cm (range: 70.5 to 111.0; p = 0.457), hip: 103.8±4.7 cm (range: 97.0 to 114.0; p = 0.052), neck: 37.8±3.4 cm (range: 32.5 to 45.5; p = 0.500), waist-to-hip ratio: 0.86±0.1 (range: 0.7 to 1.0; p = 0.039; Fig. 19A-D), as well as at T_{12M} (waist: 89.6±12.7 cm

(range: 70.5 to 111.0; p = 0.065), hip: 104.7±5.8 cm (range: 97.0 to 114.0; p = 0.081), neck: 38.2±3.8 cm (range: 32.5 to 45.5; p = 0.379), waist-to-hip ratio: 0.85±0.1 (range: 0.7 to 1.0; p = 0.487; Fig. 19A-D).

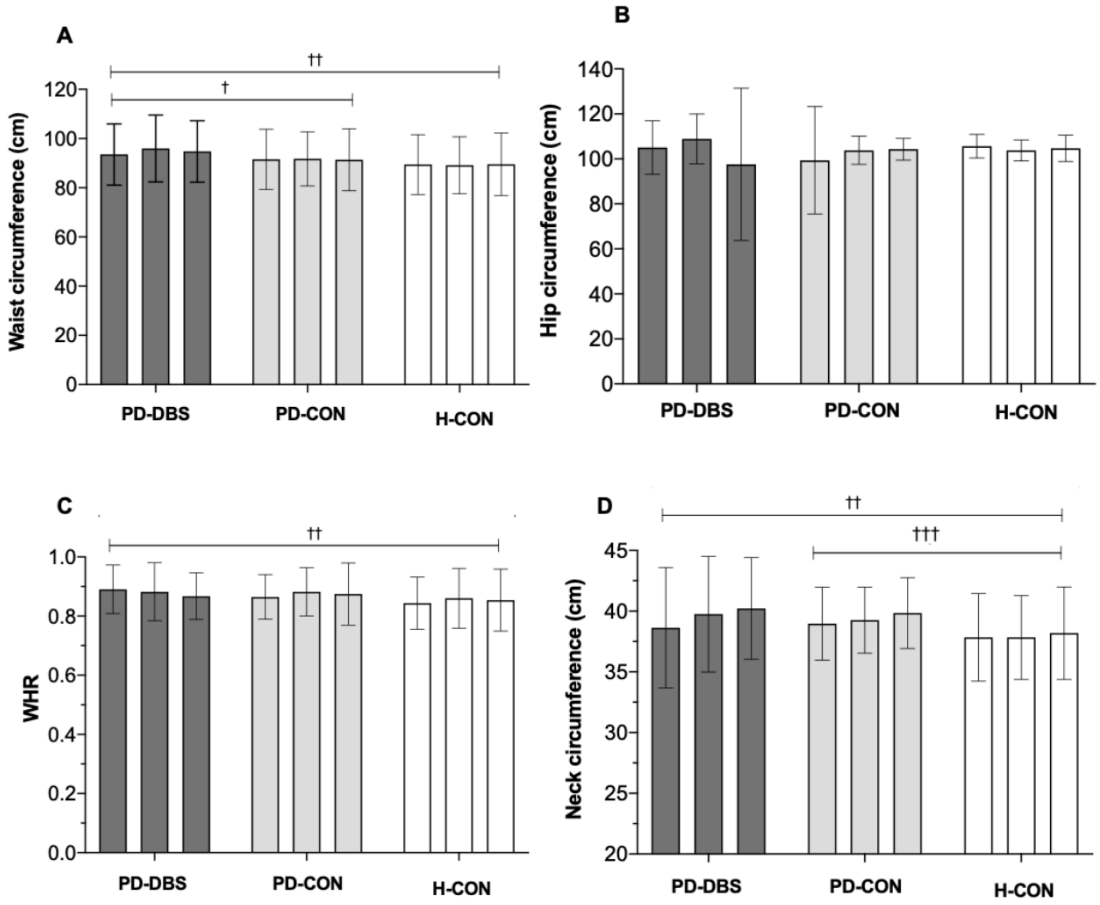

Figure 19. Change in body circumferences over time. Mean change in circumferences over time as comparison between groups and time points: pre-surgery (first bar per group), at 6 months (T_{6M}; second bar per group), and at 12 months (T_{12M}; third bar per group). (A) Change in waist circumference, (B) change in hip circumference, (C) change in waist-to-hip-ratio (WHR); and (D) change in neck circumference. PD-DBS, PD patients with STN DBS (dark gray bars), PD-CON, PD patients under best medical treatment (light gray bars); H-CON, healthy control subjects (white bars). Values are shown as mean values±SD.† PD-DBS vs. PD-CON, p≤0.05; †† PD-DBS vs. H-CON, p≤0.05; ††† PD-CON vs. H-CON, p≤0.05.

Body mass development over the entire course of the disease

Results of analysis of lowest body mass in adulthood revealed main effects for body mass and group (all $p \leq 0.007$; all $F \geq 5.545$; Fig. 20+21). Lowest body mass was higher in PD-DBS (72.6±13.5 kg) than PD-CON (66.7±10.3 kg; $p < 0.005$) and H-CON (65.6±11.0 kg; $p = 0.053$). Results of highest body mass in adulthood analysis revealed a main effect for body mass ($p < 0.001$; $F = 28.383$; Fig. 20+21), but no effect for group ($p = 0.222$), indicating no differences between the groups (PD-DBS: 90.4±17.4 kg; PD-CON: 86.6±12.8, H-CON: 84.0±12.4 kg; all $p \geq 0.123$).

Analysis of results of body mass at PD diagnosis revealed effects for body mass and group (all $p \leq 0.049$; all $F \geq 4.284$; Fig. 20+21). Moreover, body mass at PD diagnosis varied between PD-DBS and PD-CON ($p = 0.049$). PD-DBS group showed thereby a higher body mass at diagnosis (82.8±13.5 kg) as compared to PD-CON group (77.4±11.4 kg; $p = 0.049$) Analysis of BMI at diagnosis revealed main effects for body mass and group (all $p \leq 0.035$; $F \geq 4.970$; Fig. 20+21). Again, differences of BMI at diagnosis between PD-DBS and PD-CON ($p = 0.024$) were found and reflected in a trend for higher BMI at diagnosis (27.3±4.4 kg/m^2) in PD-DBS as compared to PD-CON group (24.9±3.5 kg/m^2; $p = 0.056$).

Results of percent change in body mass from the highest body mass in adulthood compared to body mass at T_0 analysis revealed no main effects for body mass and group (all $p \geq 0.166$; all $F \leq 1.866$; Fig. 20+21).

Finally, analysis of results of percent change in body mass from diagnosis to T_0, no effects for body mass and group ($p \geq 0.357$; $F \leq 0.883$; Fig. 20+21) were present.

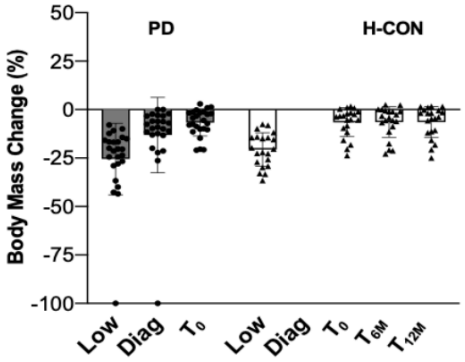

Figure 20. Body mass change in percent normalized to the highest body mass in adulthood. PD-DBS and PD-CON group are illustrated as pooled group (dark gray bars), whereas H-CON group are shown in white bars. Values are shown as mean values±SD. Circles indicate individual values for PD patients, triangles indicate individual values for healthy control subjects.

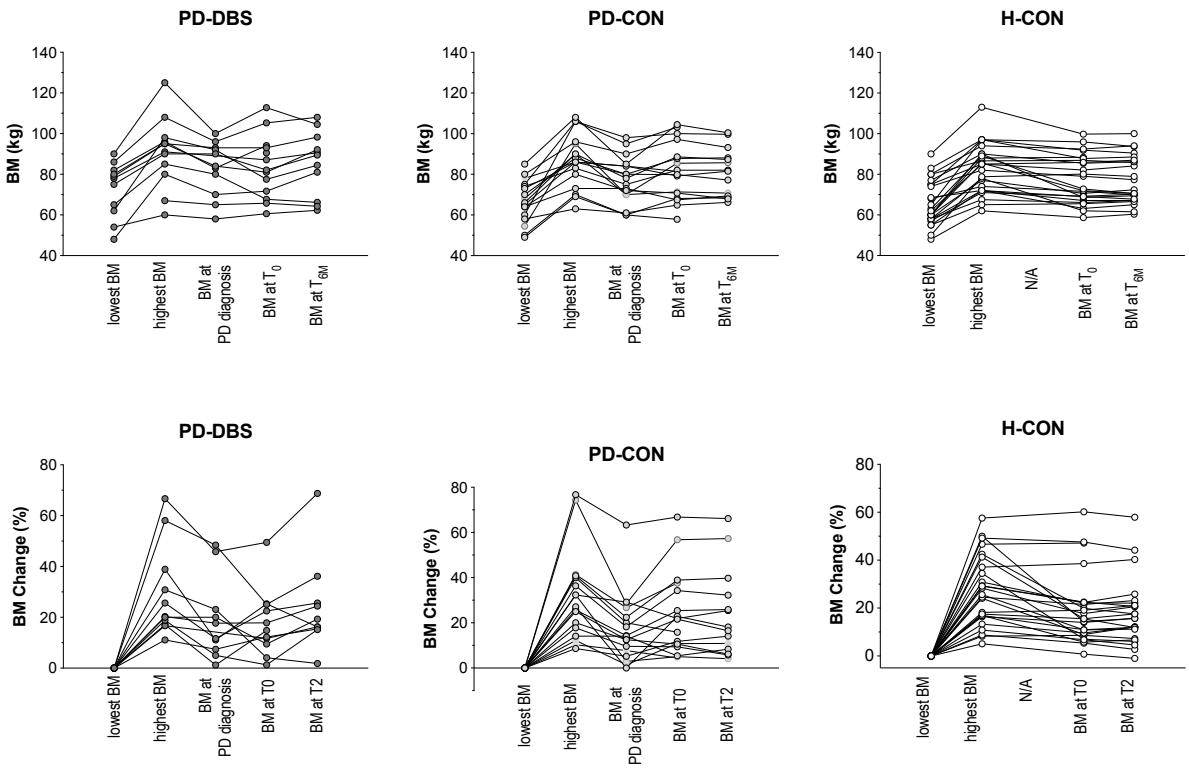

Figure 21. Body mass changes in adulthood over time for all groups. Upper row shows lowest and highest body mass in adulthood, body mass at PD diagnosis, body mass at baseline (T_0) and body mass at T_{6M} in all groups. The lower row shows percent change in body mass, with lowest body mass as initial point for change. PD-DBS, patients with STN DBS; PD-CON (dark gray dots) , PD patients under best medical treatment (light gray dots); H-CON, healthy control subjects (white dots). Lines indicate single subjects.

3.2.3 Clinical effects of deep brain stimulation of the subthalamic nucleus in PD patients

Improvements in motor function after STN DBS

MDS-UPDRS-I revealed differences in the main factor group ($p < 0.001$;$F > 41.631$; Fig. 22A), but no differences over time and time x group interaction (all $p \geq 0.873$). PD-DBS and H-CON as well as PD-CON and H-CON showed differences in this score (all $p \leq 0.001$). For PD-DBS, there were no changes over time in motor activities of daily living (T_0: 9.4±5.8; T_{6M}: 8.7±4.3, $p=0.194$; T_{12M}: 10.4±5, $p = 0.358$). In PD-CON, the score decreased from initially 10.3±6.0 at T_0 to 8.0±4.8 at T_{6M} ($p = 0.051$) and remained stable with 7.9±3.8 at T_{12M} ($p = 0.490$). In H-CON, the score remained stable over time (T_0: 2.7±2.5; T_{6M}: 2.6±2.2, $p = 0.335$; T_{12M}: 1.8±1.9, $p = 0.156$).

MDS-UPDRS-II revealed again differences for the main factor group ($p < 0.001$; $F = 85.546$ Fig. 22B), but no differences over time and no time x group interaction (all $p \geq 0.702$). Differences in scores were found between PD-DBS and PD-CON, PD-DBS and H-CON, as well as between PD-CON and H-CON (all $p \leq 0.005$). There were no changes in MDS-UPDRS-

II in PD-DBS over time (T_0: 13.4±7.8; T_{6M}: 11.5±7.5, p = 0.369; T_{12M}: 13.0±5.4, p = 0.286). The same results were found in PD-CON (T_0: 9.7±6.2; T_{6M}: 8.0±5.9, p=0.313; T_{12M}: 8.5±6.6, p = 0.334) and in H-CON (T_0: 0.5±0.9; T_{6M}: 0.4±0.9; p=0.209; T_{12M}: 0.2±0.4, p = 0.289).

Chronic effect of stimulation led to a significant improvement in MDS-UPDRS-III showing differences for group, and time point (all $p \leq 0.001$; all $F \geq 6.065$; Fig. 22C), as well as time x group interaction ($p < 0.001$). Differences in MDS-UPDRS-III were found between PD-DBS and PD-CON, PD-DBS and H-CON, as well as between PD-CON and H-CON (all $p \leq 0.001$). Moreover, differences were found between baseline and T_{6M}, as well as between baseline and T_{12M} (all $p < 0.001$). For PD-DBS, MDS-UPDRS-III by 59.4±2.6% at T_{6M} (p = 0.001), and remained stable at T_{12M} (p = 0.247). In PD-CON, the MDS-UPDRS-III decreased from 23.24±8.4 at T_0 to 19.6±9.1 at T_{6M} (p = 0.034) and remained stable at 21.9±11.0 at T_{12M} (p = 0.212). In H-CON, the score remained stable over time at T_0 (1.8±1.7) and T_{6M} (1.4±1.6; p = 0.158), and slightly increased to 2.4±1.8 (p = 0.048) at T_{12M}.

Analysis of MDS-UPDRS-IV revealed differences in the main factor group ($p < 0.01$;$F > 6.002$; Fig. 22D), but no differences over time ($p > 0.221$), and a trend for a time x group interaction (p = 0.096). PD-DBS and PD-CON showed differences in MDS-UPDRS-IV (p = 0.017). For PD-DBS, the motor complications decreased from 6.1±4.6 at T_0 to 3.3±2.9 at T_{6M} (p=0.041) and remained stable at 3.3±3.5 after 12 months of stimulation (p = 0.455). In the PD-CON group, the score for motor complications first remained unchanged (T_0: 2.11±2.4; T_{6M}: 2.16±1.9; p = 0.442) and increased then at T_{12M} to 3.3±3.3 (p = 0.002).

The total MDS-UPDRS revealed significant effect for time point ($p < 0.016$; $F > 4.529$; Fig. 22E), a trend for group (p = 0.099), but no time x group interaction (p=0.842). Time points T_0 and T_{6M} differed significantly (p = 0.023), whereas T_0 and T_{12M} revealed only a trend to differ (p = 0.091). For the PD-DBS group, the total MDS-UPDRS score decreased from 56.5±16.3 at baseline to 41.8±14.1 at T_{6M} (p = 0.037) and remained then stable at 42.2±17.6 at T_{12M} (p = 0.351). In the PD-CON group, the total MDS-UPDRS score decreased from 46.0±18.4 at baseline to 34.6±19.3 at T_{6M} (p = 0.015) and remained then stable at 38.5±19.4 (p = 0.113).

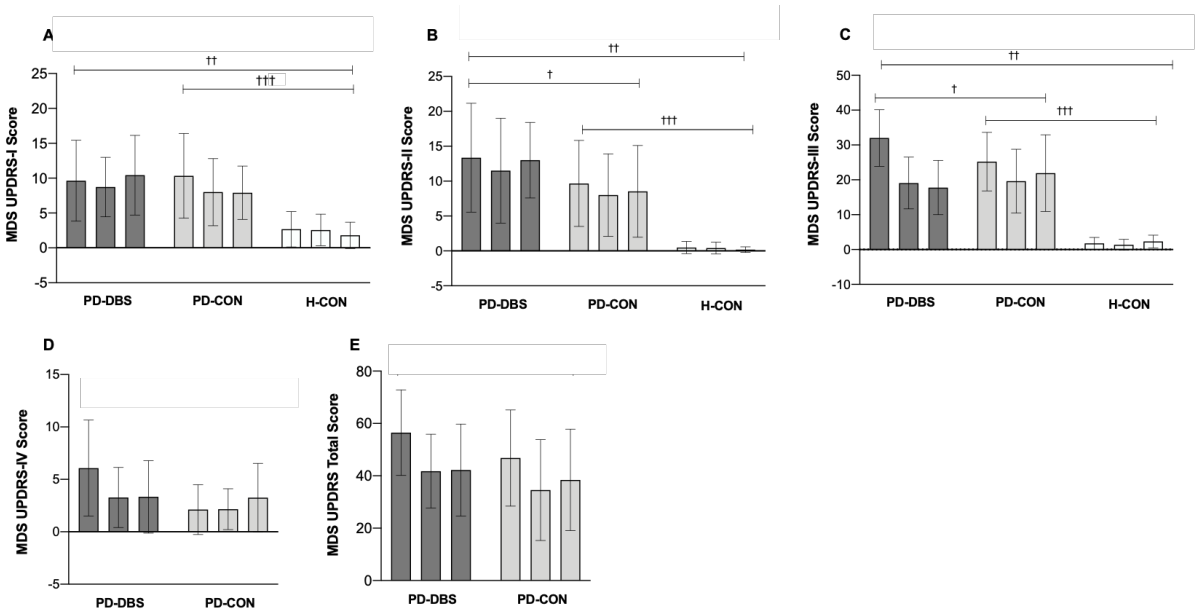

Figure 22. Changes in Unified Parkinson's Disease Rating Scale. Mean change in MDS-UPDRS scores over time as comparison between groups and time points: baseline (T_0, first bar per group), after 6 months (T_{6M}; second bar per group) and after 12 months (T_{12M}; third bar per group). PD-DBS, patients with STN DBS (dark gray bars); PD-CON, PD patients under best medical treatment (light gray bars); H-CON, healthy control subjects (white bars). (A) Non-motor activities of daily living, (B) Motor activities of daily living, (C) Motor symptoms, (D) Motor complications, and (E) MDS-UPDRS total score. Values are shown as mean values±SD. † PD-DBS vs. PD-CON, p≤0.05; †† PD-DBS vs. H-CON, p≤0.05; ††† PD-CON vs. H-CON, p≤0.05.

Effects of STN DBS on motor skills for eating behavior

The *Swallow Subscale* showed a main effect for group ($p < 0.001$; $F > 16.447$; Fig. 23A), but no differences over time and no time × group interaction (all $p \geq 0.135$). Differences in *the swallow subscale* were found between PD-DBS and H-CON as well as between PD-CON and H-CON (all $p < 0.001$). In PD-DBS, swallowing improved after 6 months of stimulation ($p = 0.023$), and then worsened at T_{12M} ($p = 0.037$). In PD-CON group, swallowing deteriorated between baseline and T_{6M} ($p = 0.039$) and remained stable afterwards ($p = 0.090$). The swallow subscale remained stable over time for H-CON (all $p \geq 0.384$).

Problems with the eating procedure showed a main effect for group ($p < 0.001$; $F > 24.487$; Fig. 23B), no effect over time ($p = 0.196$), no time x group interaction effect ($p = 0.013$). PD-DBS and H-CON, as well as PD-CON and H-CON, showed differences in this score (all $p \leq 0.001$). PD patients under chronic stimulation showed a stable score at baseline and at T_{6M} ($p = 0.122$), but then an increase in eating problems at T_{12M} ($p = 0.047$). The score remained stable in the PD-CON group (all $p \geq 0.101$), as well as in the H-CON group (all $p \geq 0.369$).

The *Cutlery Use* subscale showed a main effect for group ($p < 0.001$; $F > 36.108$; Fig. 23C), but no differences over time and no time x group interaction (all $p \geq 0.448$). Differences in this

score were found between PD-DBS and H-CON as well as between PD-CON and H-CON (all $p \leq 0.001$). For the PD-DBS group, no differences in this score were found over time (all $p \geq 0.121$). Similar results were found in PD-CON (all $p \geq 0.069$) and in H-CON (all $p \geq 0.225$).

The total score of impairments of the eating motor skills again showed a main effect for group ($p < 0.001$; $F > 26.411$; Fig. 23D), but no differences over time and no time × group interaction (all $p \geq 0.605$). Differences in the total score were found between PD-DBS and H-CON as well as between PD-CON and H-CON (all $p \leq 0.001$). For PD-DBS, the overall score decreased from initially 49.4 ± 64.1 at baseline to 28.1 ± 35.5 at T_{6M} ($p = 0.024$) and then increased to 67.9 ± 79.7 at T_{12M} ($p = 0.020$). The PD-CON and the H-CON remained stable over time (all $p \geq 0.062$).

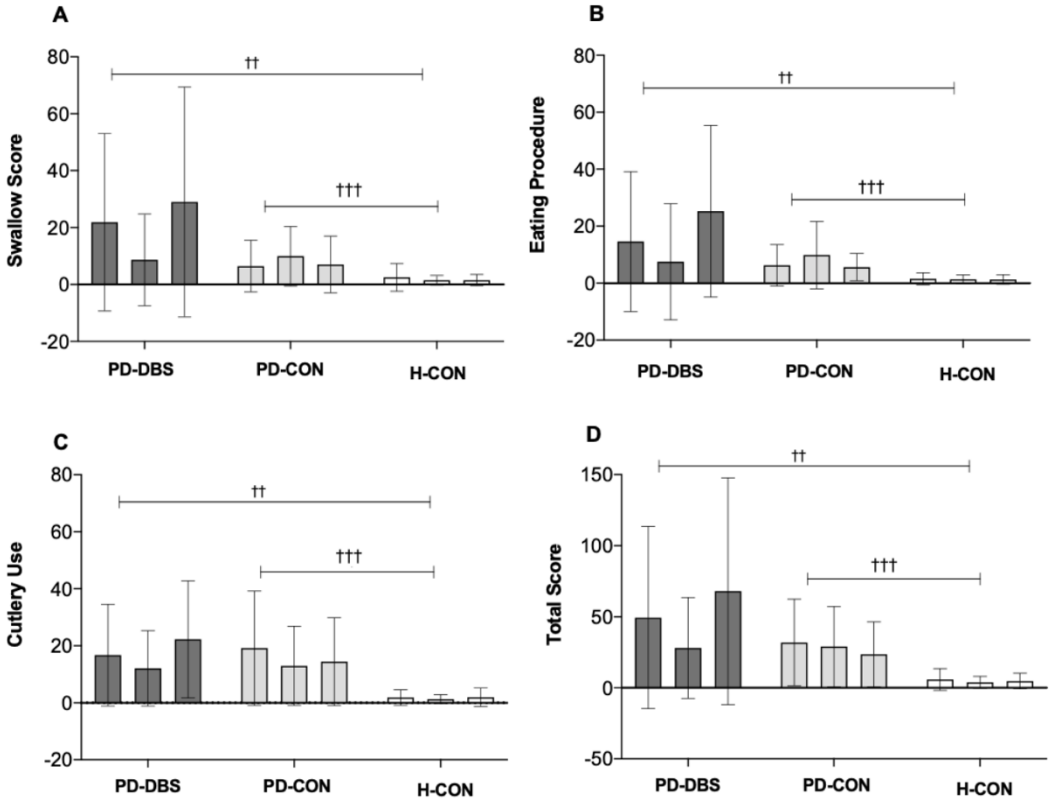

Figure 23. Motor skills for eating behavior. Mean change over time as comparison between groups and time points: baseline (T_0, first bar per group), after 6 months (T_{6M}; second bar per group) and after 12 months (T_{12M}; third bar per group). PD-DBS, patients with STN DBS (dark gray bars), PD-CON, PD patients under best medical treatment (light gray bars); H-CON, healthy control subjects (white bars). (A) Swallow score, (B) Eating procedure score, (C) Cutlery use score, and (D) total score. Values are shown as mean values±SD. †† PD-DBS vs. H-CON, p≤0.05; ††† PD-CON vs. H-CON, p≤0.05.

Changes in Anti-parkinsonian medication

LEDD revealed an effect for doses ($p < 0.001$; $F = 192.416$; Fig. 24), but no effects for group, time point, as well as no time x group interaction (all $p \geq 0.122$). For PD-DBS, LEDD decreased from 833±491 mg/day at baseline by 45% to 462±435 mg/day at T_{6M} ($p = 0.021$), and remained stable at 498±291 mg/day after 12 months of stimulation ($p = 0.061$). For PD-CON, LEDD remained stable over time (T_0: 796±513 mg/day; T_{6M}: 765±475 mg/day, $p = 0.606$; T_{12M}: 687±432 mg/day, $p = 0.123$).

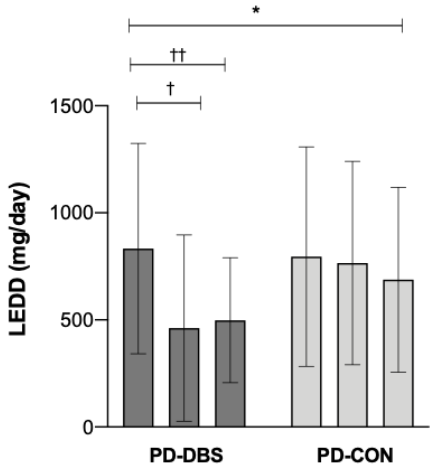

Figure 24. Change in LEDD over time. Mean change in LEDD over time as comparison between groups and time points: pre-surgery (first bar per group), at 6 months after surgery or baseline measurement (T_{6M}; second bar per group), and at 12 months (T_{12M}; third bar per group). PD-DBS, patients with STN DBS (dark gray bars); PD-CON, PD patients under best medical treatment (light gray bars). Values are shown as mean values±SD. † T_0 vs. T_{6M}, $p \leq 0.05$; †† T_0 vs. T_{12M}, $p \leq 0.05$.

3.2.4 Effects of electrode localization on body mass changes in Parkinson's disease

Visualization of electrodes

The localizations of electrodes for all PD patients in Study 1 (PD-DBS) are shown in Figure 25. Coordinates of electrode positions can be seen in Appendix D.

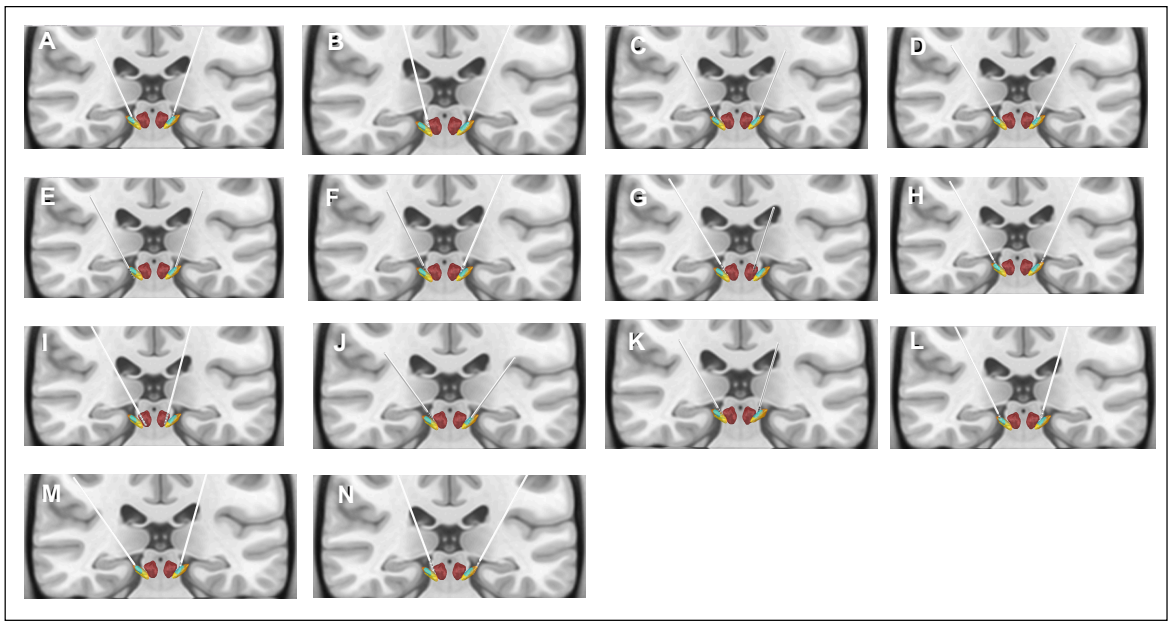

Figure 25. Target report. The sensorimotor part of the STN is shown in orange, the limbic STN in yellow, the associative STN in blue, and the red nucleus is shown in red (for illustration). The leads and subcortical regions are illustrated within the distal atlas. A-N) showing distance from lead contact center to its closest STN voxel for each individual subject of PD-DBS (N=14). The localization of the lead contacts was suboptimal for subject 7 (G) and subject 9 (I). These subjects were therefore excluded from further correlation analysis of individual VTA intersection and body mass, BMI, and FM changes after 6 months of stimulation.

Relationship of STN activation with metabolic and clinical outcomes

The first step was to assess the relationship between body mass change as a comparison between T_0 and T_{6M} and activation patterns within the STN. Here, the analysis of VTA did not show a significant correlation between STN_{Total} ($p = 0.455$; Fig. 26A), STN_{Motor} ($p = 0.130$; Fig. 26B), and $STN_{Associative}$ ($p = 0.479$; Fig. 26D) and body mass changes. However, there was a trend for a significant positive correlation of activation in STN_{Limbic} ($p = 0.094$; $r = 0.44$; Fig. 26C) and body mass change.

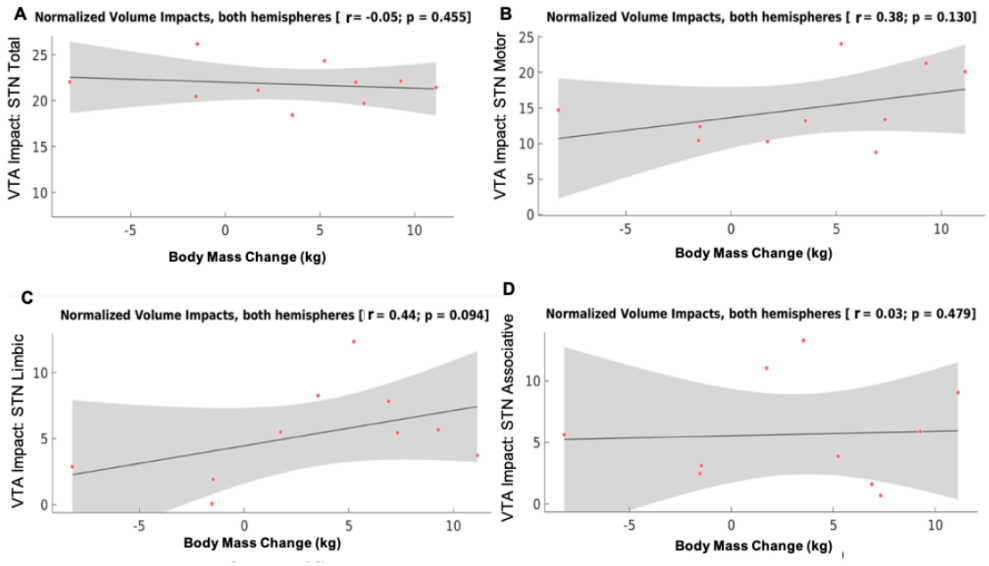

Figure 26. Correlation analysis of VTA intersection and body mass difference. VTA intersection with total STN (A), motor part of STN (B), and associative part of STN (D) does not explain body mass change after 6 months of stimulation. (C) The VTA intersection with the limbic part of STN shows a moderate correlation and a trend with body mass change after 6 months of stimulation (r = 0.44; p = 0.094).

Since the body mass index is a more sensitive marker of metabolic changes, the relationship was assessed between change in BMI as a comparison between T_0 and T_{6M} with activation patterns within the STN. There was no correlation for BMI and STN_{Total} (p = 0.468; Fig. 27A), STN_{Motor} (p = 0.187; Fig. 27B), or $STN_{Associative}$ (p = 0.488; Fig. 27D). However, there was again a trend for a significant positive correlation between change in BMI and activation in STN_{Limbic} (p = 0.073; r = 0.50; Fig. 27C).

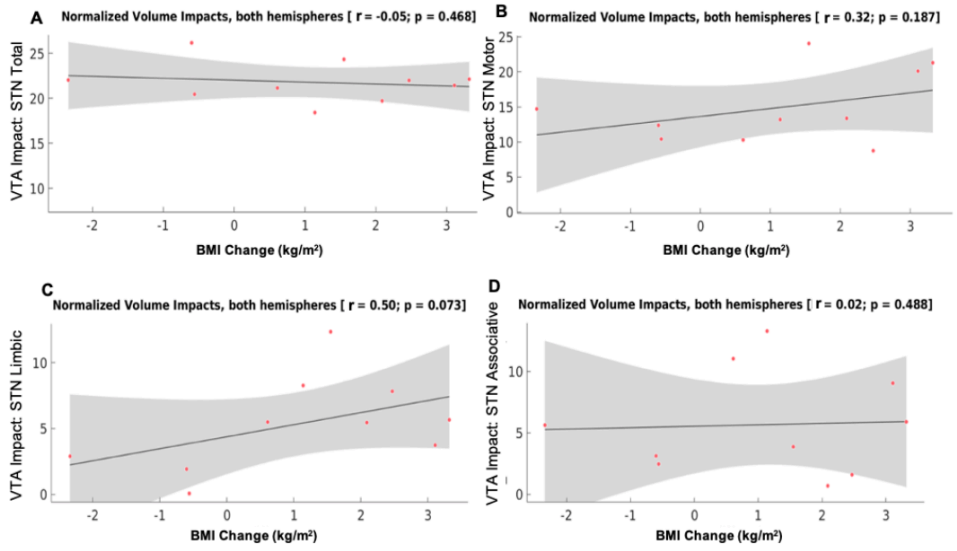

Figure 27. Correlation analysis of VTA intersection and BMI difference. The VTA intersection, with total STN (A), motor part of STN (B), and associative part of STN (D) does not explain the change in BMI after 6 months of stimulation. (C) The VTA intersection with the limbic part of the STN shows a moderate correlation and a trend with BMI change after 6 months of stimulation (r = 0.50; p = 0.073).

Although some patients did not gain body mass and consequently BMI, all patients changed their body composition towards a higher FM amount (see Section 3.2.2). Therefore, correlation analysis of activation patterns within the STN and the change in FM was performed as a comparison between T_0 and T_{6M}. The results showed no correlation for the activation in STN_{Total} ($p = 0.490$; Fig. 28A), STN_{Motor} ($p = 0.209$; Fig. 28B), or $STN_{Associative}$ ($p = 0.221$; Fig. 28D) with changes in FM. However, a positive correlation between change in FM and co-stimulation of the limbic part of the STN ($p = 0.035$; $r = 0.59$; Fig. 28C) was found.

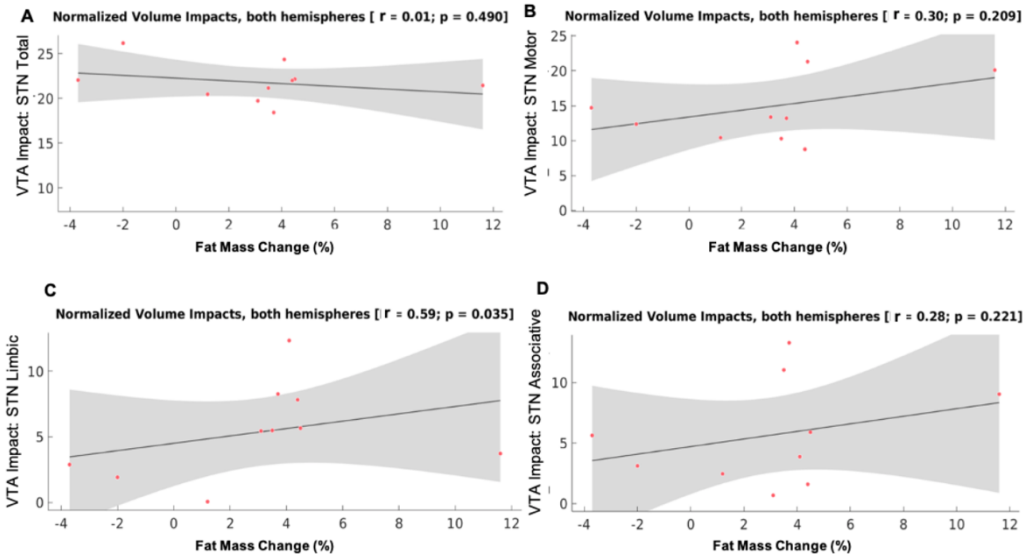

Figure 28. Correlation analysis of the VTA intersection and the difference in FM. VTA intersection with total STN (A), motor part of STN (B), and associative part STN (C) does not explain the change in FM after 6 months of stimulation. (C) VTA intersection with the limbic part of STN shows a moderate correlation and a significant effect with a change in FM after 6 months of stimulation ($r = 0.59$; $p = 0.035$).

The last step was to assess improvement in clinical outcome parameter due to stimulation. Here, the improvement of the MDS-UPDRS-III score as comparison between T_0 and T_{6M} was positively correlated with the activation within the motor part of the STN ($p = 0.051$; $r = 0.58$; Fig. 29B). In contrast, changes in clinical motor signs did not correlate with VTA in STN_{Total} ($p = 0.131$; Fig. 29A), STN_{Limbic} ($p = 0.211$; Fig. 29C) or $STN_{Associative}$ ($p = 0.367$; Fig. 29D).

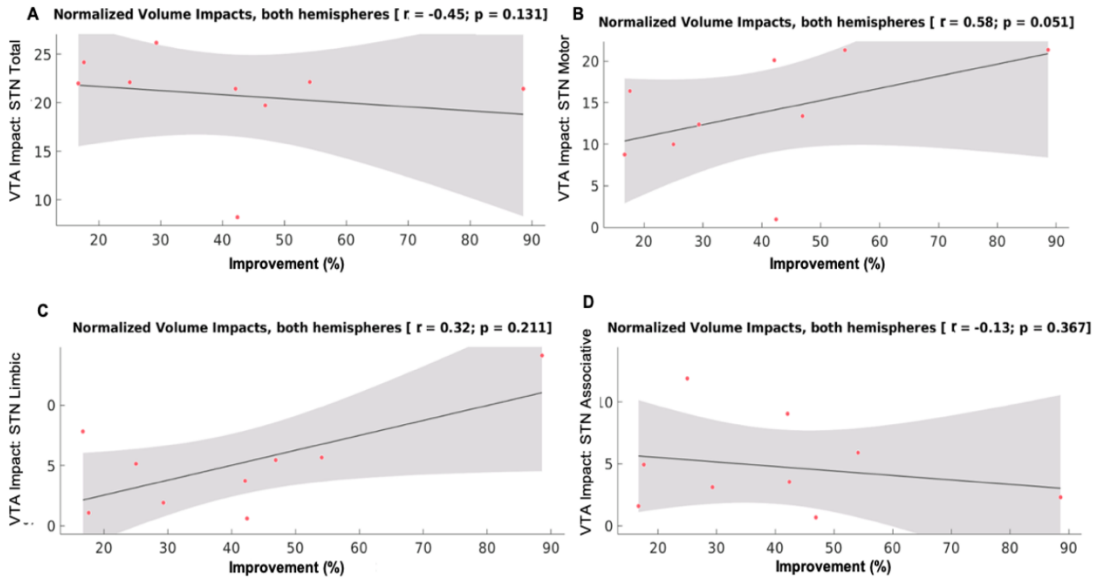

Figure 29. Correlation analysis of VTA intersection and MDS-UPDRS-III improvement. VTA intersection with total STN (A), limbic part of the STN (C), and associative part of the STN (D) is not related to the improvement of motor signs after 6 months of stimulation. (B) The VTA intersection within the motor STN explains the improvement in motor signs (p = 0.051; r = 0.58).

3.2.5 Effects of deep brain stimulation of the subthalamic nucleus on the regulation of non-homeostatic food intake

Changes in behavioral inhibition and behavioral activation systems

The results of the *BAS total score* showed no main effects for group, time point, as well as no time x group interaction (all p ≥ 0.266; Fig. 30A).

The results of the *BAS Drive sub-score* analysis revealed no main effects for group, time point, as well as no time x group interaction (all p ≥ 0.259; Fig. 30B).

The results of the *BAS Fun Seeking sub-score* analysis showed an effect for group (p < 0.049; F ≥ 5234.505; Fig. 30C), but no changes over time and no time x group interaction were found (all p ≥ 0.689). The *BAS Fun Seeking sub-score* was higher in H-CON compared to PD-CON (p = 0.047).

The results of the *BAS Reward Responsiveness sub-score* analysis showed no main effects for group, time point, as well as no time x group interaction (all p ≥ 0.234; Fig. 30D). *BAS Reward Responsiveness sub-score* was higher in H-CON compared to PD-CON (p = 0.064).

The results of the *BIS total score* analysis showed no effects for group, time point, as well as no time x group interaction (all p ≥ 0.387; Fig. 30E).

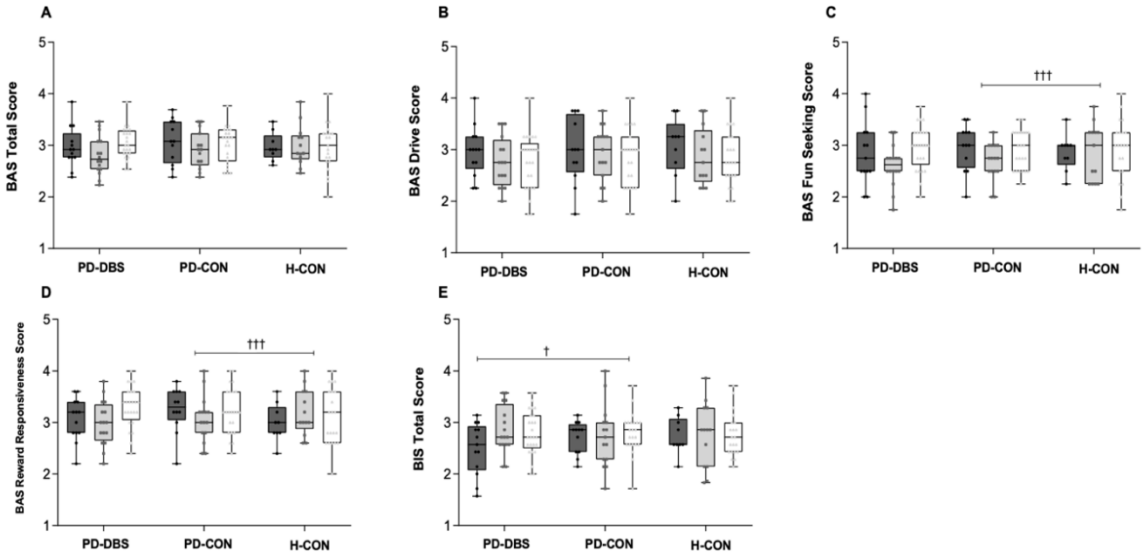

Figure 30. Assessment of behavioral inhibition and activation systems. Mean change in scores over time as a comparison between groups and time points: pre-surgery (first bar per group), at 6 months (T_{6M}; second bar per group), and at 12 months (T_{12M}; third bar per group). PD-DBS, patients with STN DBS (dark gray bars); PD-CON, PD patients under best medical treatment (light gray bars); H-CON represents healthy control subjects (white bars). (A) Change in the BAS total score, (B) change in the BAS Drive score, (C) change in the BAS Fun Seeking score, (D) change in BAS Reward Responsiveness score, and (E) change in the BIS total score. Values are displayed as a boxplot with minimal and maximal values as whiskers. The dots represent individual values of subjects. † PD-DBS vs. PD-CON, $p \leq 0.05$; ††† PD-CON vs. H-CON, $p \leq 0.05$.

Changes in hunger and stress levels

The results of the first analysis of desire to eat as a comparison before and after the breakfast showed effects for desire to eat in the general eating item ($p < 0.001$; $F = 97.239$; Fig. 31A,) as well as a time x item x group interaction ($p = 0.046$; $F = 2.592$). Moreover, the results for the analysis of the sweet foods item and savory foods item showed effects for desire to eat (all $p \leq 0.001$; all $F \geq 37.364$; Fig. 31 B-C). However, there were no effects over time and no time x group interactions (all $p \geq 0.133$). Repeated analysis of desire to eat as a comparison before and after EEG measurement showed no significant effects for desire to eat and time point of the general eating item (all $p \geq 0.226$; $F \leq 1.578$; Fig. 31D). For the sweet foods item, as well as for the savory foods item, there were no significant effects for feelings of hunger, time point, as well as no time x group interaction (all $p \geq 0.099$; Fig. 31E-F). In general, neither at T_0 nor T_{6M}, the groups showed no differences in the desire to eat.

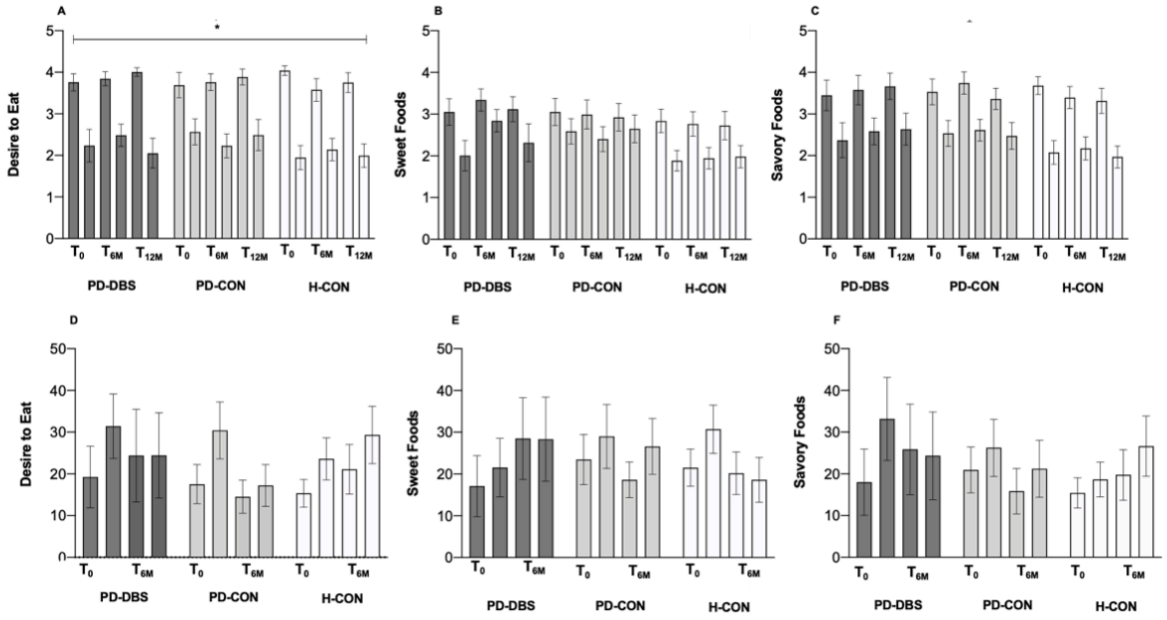

Figure 31. Illustration of the desire to eat. Mean change in scores over time as a comparison between groups and time points: pre-surgery (T_0), at 6 months (T_{6M}), and at 12 months (T_{12M}). PD-DBS, patients with STN DBS (dark gray bars); PD-CON, PD patients under best medical treatment (light gray bars); H-CON represents healthy control subjects (white bars). (A-C)): As comparison before (always the first bar) and after the breakfast (always the second bar) for time points T_0, T_{6M}, and T_{12M}. (D-F)): As comparison before (always the first bar) and after the EEG measurement (always the second bar) for time points T_0 and T_{6M}. Values are given as mean values±SD.

The results of the analysis of the regulation of food intake showed in the comparison before and after the breakfast effects in feelings of hunger ($p < 0.001$; $F = 79.440$; Fig. 32A), in feelings of satiety ($p < 0.001$; $F = 71.991$; Fig. 32B), in feelings of appetite ($p < 0.001$; $F = 46.698$; Fig. 32C), as well as for thirstiness ($p < 0.001$; $F = 104.399$; Fig. 32D). There were no changes over time as well as no time x group interactions (all $p \geq 0.110$). These results led to the conclusion that the regulation of food intake in the morning was not significantly different between the groups at T_0 and T_{6M} in comparison before and after the breakfast. The results of the repeated analysis showed as a comparison before and after EEG measurement an effect in the feelings of hunger ($p = 0.001$; $F = 79.440$; Fig. 32E), as well as in time point ($p = 0.029$; $F = 5.225$), and a significant time x group interaction ($p = 0.012$; $F = 5.128$). Furthermore, results showed significant effects in the feelings of satiety ($p < 0.001$; $F = 21.078$; Fig. 32F), in feelings of appetite ($p < 0.001$; $F = 19.223$; Fig. 32G), and feelings of thirst ($p = 0.006$; $F = 8.773$; Fig. 32H), but no effects over time and no time x group interactions (all $p \geq 0.096$).

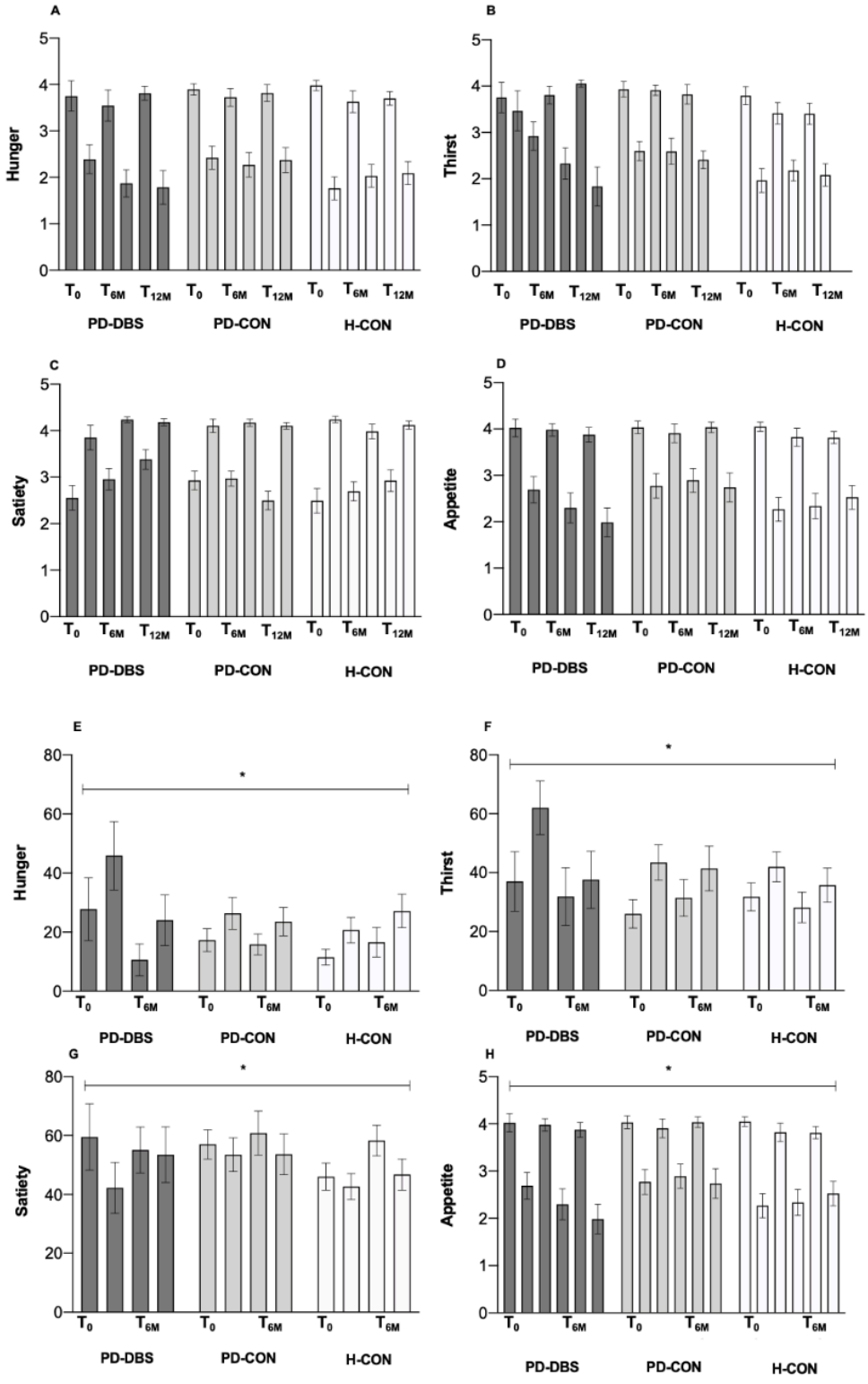

Figure 32. Illustration of the regulation of food intake. Mean change in scores over time as a comparison between groups and time points: pre-surgery (T_0), at 6 months (T_{6M}), and at 12 months (T_{12M}). PD-DBS, patients with STN DBS (dark gray bars); PD-CON, PD patients under best medical treatment (light gray bars); H-CON represents healthy control subjects (white bars). (A-D): As comparison before (always the first bar) and after the breakfast (always the second bar) for time points T_0, T_{6M}, and T_{12M}. (E-H): As comparison before (always the first bar) and after the EEG measurement (always the second bar) for time points T_0 and T_{6M}. Values are shown as mean values±SD.

Changes in motivation and pleasure for food cues

The results of the analysis for a change in the wanting for high-calorie sweet foods as a comparison before and after breakfast showed no effects for wanting and for group (all $p \geq 0.261$), as well as no time x group interaction ($p = 0.229$).

The results of the analysis of a change in wanting for high-calorie non-sweet foods showed no effects for wanting and for group ($p \geq 0.670$), as well as no time x group interaction ($p = 0.858$).

The analysis of a change in wanting for low-calorie foods showed an effect for group ($p = 0.017$; $F = 4.192$), but not for wanting ($p = 0.248$) and also no time x group interaction ($p = 0.685$). Wanting for low-calorie foods increased over time in PD-DBS compared to H-CON ($p = 0.015$; CI: 0.070, 0.859).

Results for a change in liking for high-calorie sweet foods showed no effects for liking and group (all $p \geq 0.303$), as well as no time x group interaction ($p = 0.238$).

The analysis of change in liking for high-calorie non-sweet foods showed no effects for liking and for group (all $p \geq 0.266$; all $F \leq 1.247$), as well as no time x group interaction ($p = 0.231$). The change in the linking of high-calorie non-sweet foods increased in the PD-DBS group over time ($p = 0.036$; $F = 3.799$) as a difference between time points T_{6M} and T_{12M} ($p = 0.048$) [21].

The results of the analysis of a change in liking for low-calorie foods as a comparison before and after the breakfast showed significant effects for liking for and for group (all $p \leq 0.001$; $F \geq 11.123$), as well as a time x group interaction ($p = 0.033$; $F = 2.723$).

Alterations in the regulation of snacking behavior

At baseline, the results for the analysis of total calories consumed showed an effect for total calories ($p = 0.049$; $F = 3.196$) between the groups. However, this effect was no longer present in T_{6M} ($p = 0.513$; $F = 0.676$).

The results of the analysis of the consumed amount of sweet chocolate cookies showed no differences between the group's at baseline ($p = 0.211$; $F = 1.603$) as well as at T_{6M} ($p = 0.476$; $F = 0.754$).

Results of the analysis of the amount eaten of high-fat sweet cookies revealed no differences between the groups in terms of the number of calories consumed at baseline ($p = 0.395$; $F = 0.944$) as well as at T_{6M} ($p = 0.345$; $F = 1.088$).

The amount of healthy sweet foods consumed showed differences at baseline ($p = 0.010$; $F = 5.078$) with a higher intake in PD-DBS compared to H-CON at baseline ($p = 0.012$), but

[21] Bonferroni-Holm corrected significance equals p=0.016.

not at T_{6M} ($p = 0.935$; $F = 0.076$).

The results of the analysis of the number of calories consumed with apple spritzer showed a trend at baseline for a group difference ($p = 0.051$; $F = 3.145$) and a significant group difference at T_{6M} ($p = 0.005$; $F = 6.002$), again with higher intake for PD-DBS compared to H-CON, both, at baseline ($p = 0.016$) and at T_{6M} ($p = 0.005$).

Results of the analysis of non-carbonated water and carbonated water showed no differences between the groups in the number of calories consumed at baseline (all $p \geq 0.235$; all $F \leq 1.490$) and also at T_{6M} (all $p \geq 0.554$; all $F \leq 0.589$).

3.3 Study 2 – Effects of Subthalamic Nucleus DBS on Body Mass-Related Effects on Neuronal Circuitries

Subjects

Forty-three patients diagnosed with idiopathic PD, according to the clinical diagnostic criteria of the Movement Disorder Society [73], and nineteen healthy control subjects, were recruited. Demographic data are listed in table 2.

Table 2. Demographic data and clinical variables of the study population.

	PD Patients	Healthy Control Subjects	p-value
Sample size	21	19	0.081
Age (years)	63.9±9.1	65.8±7.1	0.460
Disease duration (years)	12.2±4.4	n.a.	n.a.
MoCA (Score)	24.6±3.2	27.4±2.2	**0.003**
Hoehn and Yahr	2.5±0.69	n.a.	n.a.
Months since DBS surgery	23.9±16.5	n.a.	n.a.
LEDD (mg)	647±374	n.a.	n.a.
MDS-UPDRS-III DBS and Med ON (Score)	40.9±14.7	n.a.	n.a.
Handedness (Score)	0.8±0.4	0.9±0.3	0.640
Body mass (kg)	81.78±16.1†	80.45±17.1	0.410
Current flow chronic DBS* (mA)	2.6±0.65	n.a.	n.a.
Current flow MRI DBS** (mA)	2.6±0.59	n.a.	n.a.

Notes. The data are shown as mean values ±SD. LEDD, levodopa equivalent dosage, n.a., not applicable; * current flow for chronic DBS, ** current flow for MRI-compatible settings in the bipolar mode. † Pre-surgery-assessed body mass.

Clinical and metabolic effects of STN DBS

The MRI procedure was safe in all patients regardless of the stimulation mode and no side effects were observed during the execution of the MR scanning. After both MRI sessions, no changes were observed in the clinical response to DBS and in the assessment of treatment impedances and current flow. The bilateral STN DBS led to a mean improvement of 22.6 ± 15.5 % of the overall MDS-UPDRS-III score (DBS ON/Med ON vs. DBS OFF/Med ON). Moreover, chronic stimulation of the STN led to a mean increase in body mass of +3.88 kg (range of body mass gain: -9 to +10; N = 17; p = 0.012).

Whole-brain analysis

To test the first hypothesis, which states that the processing of food vs. non-food cues will lead to increased neural activity in brain areas relevant for regulation of food intake during active DBS, a whole -brain approach was used to compare PD patients during active and inactive stimulation with healthy controls.

Whole brain GLM revealed a main effect of DBS in the left lingual gyrus, right cuneus, right middle cingulate gyrus and the central operculum bilaterally (cluster level, uncorrected, $p \leq 0.001$) in the comparison between active DBS versus inactivated DBS. An interaction was found for food images during active DBS in the left lingual gyrus and the superior parietal lobe bilaterally (FWE, $p \leq 0.001$) compared to the inactivated mode. With DBS being switched off, food images were thereby associated with a BOLD response in the left lingual gyrus (FWE, $p \leq 0.001$). In contrast, processing of non-food images showed an increased BOLD response in the left superior parietal lobe (FWE, $p \leq 0.001$) during active stimulation and in the left superior occipital gyrus (FWE, $p \leq 0.001$) during inactivated DBS. In the next step, the comparison between PD patients with inactivated stimulation and healthy control subjects showed a main effect of group in left cuneus, left lingual gyrus, bilateral inferior occipital gyrus, bilateral superior parietal lobe, as well as in left middle temporal gyrus (cluster level, uncorrected, $p \leq 0.001$). Within this comparison, the main effect of condition, meaning food versus non-food, showed a significant effect in the left fusiform gyrus (cluster level, uncorrected, $p \leq 0.001$). Furthermore, the comparison of PD patients under active stimulation with healthy control subjects showed a main effect of group in left lingual gyrus, right inferior occipital gyrus, right postcentral gyrus, right posterior cingulate gyrus, as well as in right superior parietal lobe (cluster level, uncorrected, $p \leq 0.001$). In addition, a main effect of condition within this comparison was found in the right inferior occipital gyrus (cluster level, uncorrected, $p \leq 0.001$), as well as an interaction effect between group and condition was present in the left middle cingulate gyrus and left middle temporal gyrus (cluster level, uncorrected, $p \leq 0.001$).

In the next step, the ROI-based approach was used because of the strong a priori hypothesis of the effects of brain regions involved in motivational processing of food cues [127,128,192,204]. The ROI-based analysis showed significant changes in brain activity in brain areas that are important for controlling food intake and attention: the prefrontal cortex, amygdala, insula, and thalamus ($p \leq 0.001$). In addition, brain activity in motor areas showed significant DBS-related differences in the putamen and SMA ($p \leq 0.001$), whereas activity in putamen was decreased and activity in SMA was increased.

Up to this point, the results showed enhanced processing of food cues in brain areas that are important for encoding of complex images, personal experience, attention, long term memory,

and emotional processing [205–207] during active stimulation. The next step was to test the hypothesis that active stimulation leads to increased reactivity towards high-calorie sweet foods compared to high-calorie salty foods and neutral images and that functional connectivity changes are observed in the salience and reward circuitry.

Seed-based correlation analysis

To assess the specific actions of DBS, a seed -based correlation analysis (ROI-to-ROI (RRC)) was performed to identify PD trait-related (PD vs. control) and DBS-related (DBS ON vs. OFF) activity and connectivity patterns. Moreover, the modulating effect of STN DBS on the stimulus category (sweet food images, salty food images, neutral images) on the time course and functional connectivity of 6 brain networks was examined. Based on their involvement in the pathophysiology of PD and motivated food intake, the following networks were selected: default-mode network (DMN), sensory-motor network (SMN), dorsolateral attention network (DAN), extrastriate visual network, temporal visual association network (VN), and salience network. The functional connectivity analysis (RRC) exclusively revealed significant alterations in the salience network ($p_{FDR\ corr} \leq 0.05$). Within the salience network, seed-based correlation showed increased functional connectivity between the insula and bilateral SMG in PD patients during active stimulation in comparison to inactivated stimulation for sweet foods compared to neutral images ($p_{FDR\ corr} \leq 0.05$; Fig. 33).

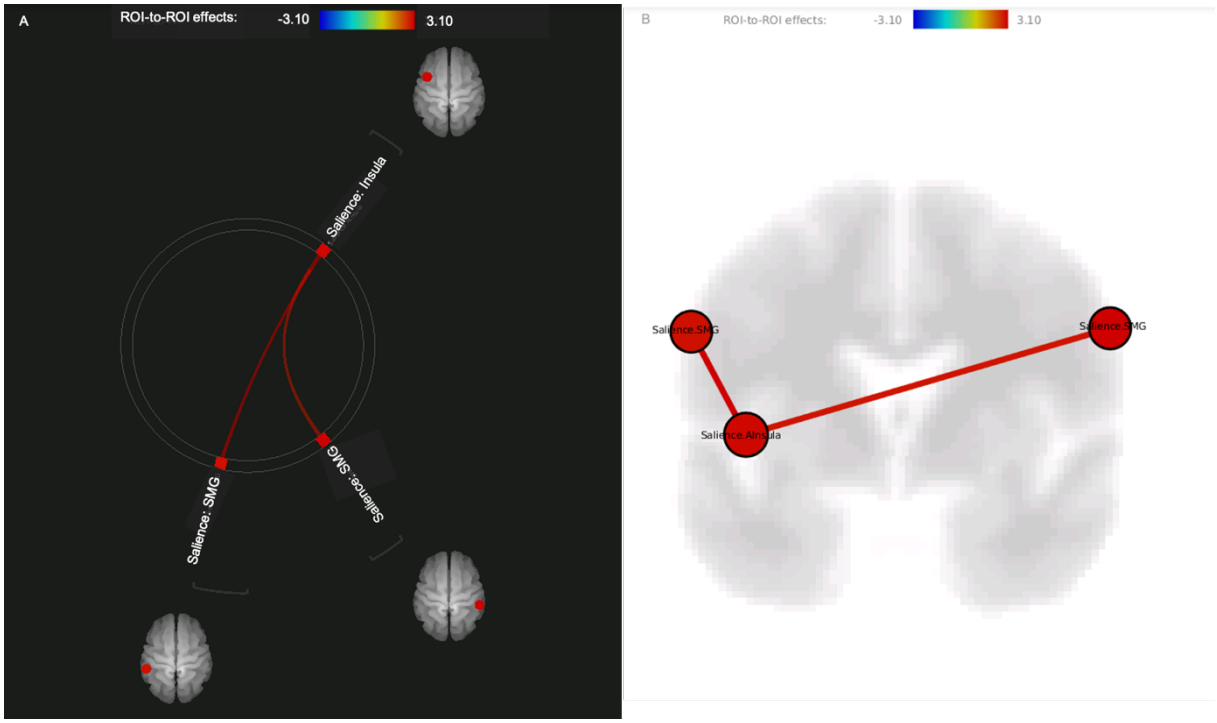

Figure 33. ROI-to-ROI correlation analysis of the salience network as a measure of functional connectivity. Active stimulation leads to alterations in the salience network during sweet food cue processing in contrast to neutral cues. Processing of sweet food cues are mediated by insula-SMG connectivity (p FDR-corr<0.05) shown in (A) ring connectome and (B) in coronal view.

For the processing of salty images, increased FC between Insula and left SMG ($p_{FDR\ corr} \leq 0.05$) was observed in the comparison between stimulation ON vs. OFF. To assess the effect of dopaminergic medication, PD patients with inactivated stimulation (Med ON, DBS OFF) were compared with controls. Here, a decreased FC between the insula and the right SMG was observed in the PD patients for the contrast food vs. neutral images ($p_{FDR\ corr} \leq 0.05$), as well as for sweet foods vs. neutral images ($p_{FDR\ corr} \leq 0.05$).

Next, FC changes in the reward network were assessed to identify neural correlates for changes in food-related motivational behavior. For the comparison of food vs. non-food images in DBS ON vs. OFF, a decreased FC was found for left putamen, right lateral occipital cortex, left amygdala, right lateral occipital cortex, bilateral lateral occipital cortex, bilateral insula, as well as left hippocampus, and left insula ($p_{FDR\ corr} \leq 0.05$). The same comparison (ON vs. OFF) for sweet foods vs. neutral images showed a decreased FC between the left NAcc, the right lateral occipital cortex, the right lateral occipital cortex, the bilateral insula, the right lateral occipital cortex, and the bilateral OFC ($p_{FDR\ corr} \leq 0.05$). For salty foods vs. neutral images, decreased FC was found between right lateral occipital cortex, bilateral NAcc, left putamen, and left insula in the ON condition compared to OFF ($p_{FDR\ corr} \leq 0.05$).

In the comparison DBS ON vs. controls, decreased FC between right lateral occipital cortex and left orbitofrontal cortex for the comparison of salty foods vs. neutral images ($p_{FDR\ corr} \leq 0.05$) was found.

Visualization of electrodes and estimation of the volume of tissue activated

The localizations for all PD patients in Study 2 are shown as a group image in Figure 34.

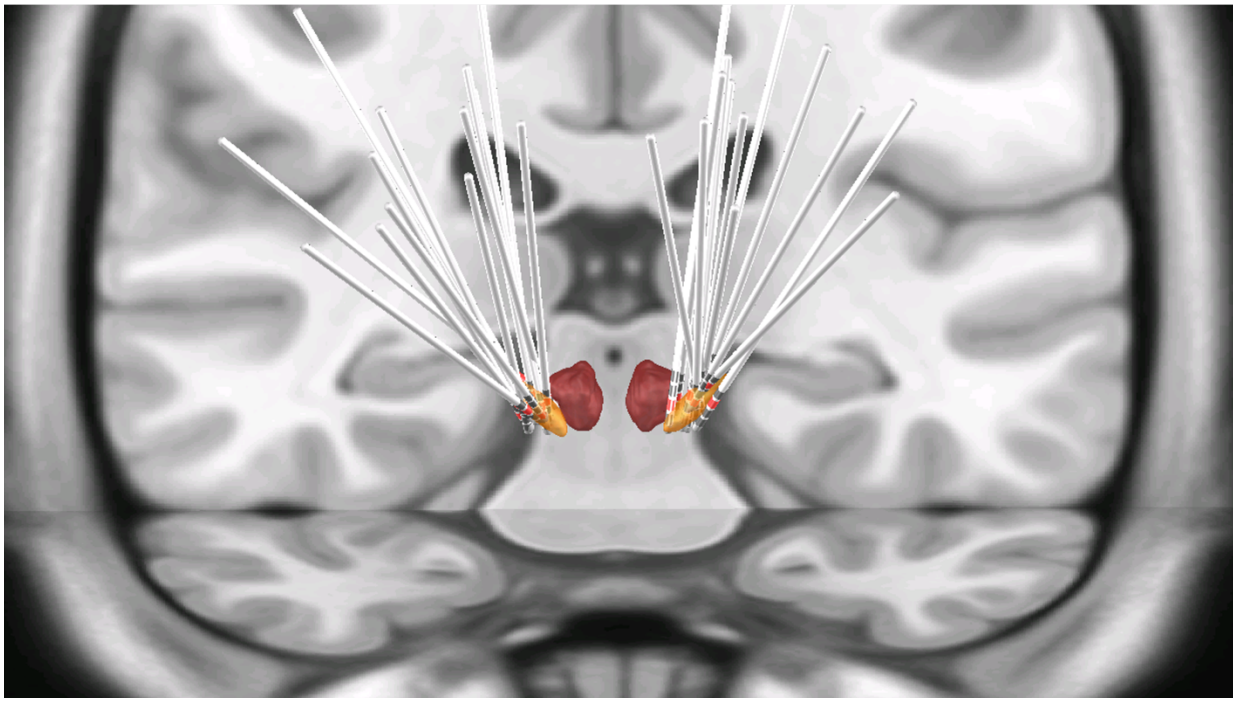

Figure 34. Target report of group electrode localization (N=13). The sensorimotor part of the STN is shown in orange, and the red nucleus are shown in red (for illustration purposes only). The leads and subcortical regions are shown in the distal atlas.

Relationship of STN activation with clinical and metabolic outcomes

Changes of MDS-UPDRS-III scores did not show a correlation of action in STN_{Total} (p = 0.501; Fig. 35A), STN_{Motor} (p = 0.197; Fig. 35B), STN_{Limbic} (p = 0.124; Fig. 35C), as well as $STN_{Associative}$ (p = 0.431; Fig. 35D), with stimulation parameters of chronic DBS.

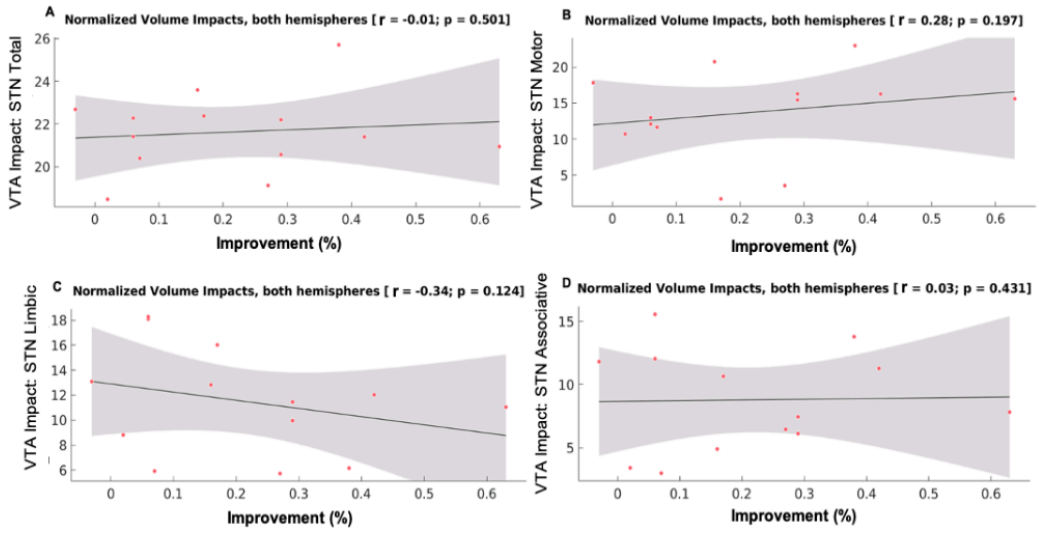

Figure 35. Correlation analysis of VTA intersection of chronic stimulation parameters and MDS-UPDRS-III improvement. No significant correlation was found between (A) VTA intersection with STN overall, (B) VTA

intersection with the motor part of STN, (C) VTA intersection with the limbic part of STN as well as (D) VTA intersection with the associative part of STN.

The next step was the assessment of the association between pre-postoperative body mass change with STN activation. Here, analysis of VTA revealed a correlation with $STN_{Associative}$ ($p = 0.037$; $r = -0.54$; Fig. 36D), but not with STN_{Total} ($p = 0.077$; Fig. 36A), STN_{Motor} ($p = 0.317$; Fig. 36B) and STN_{Limbic} ($p = 0.106$; Fig. 36C).

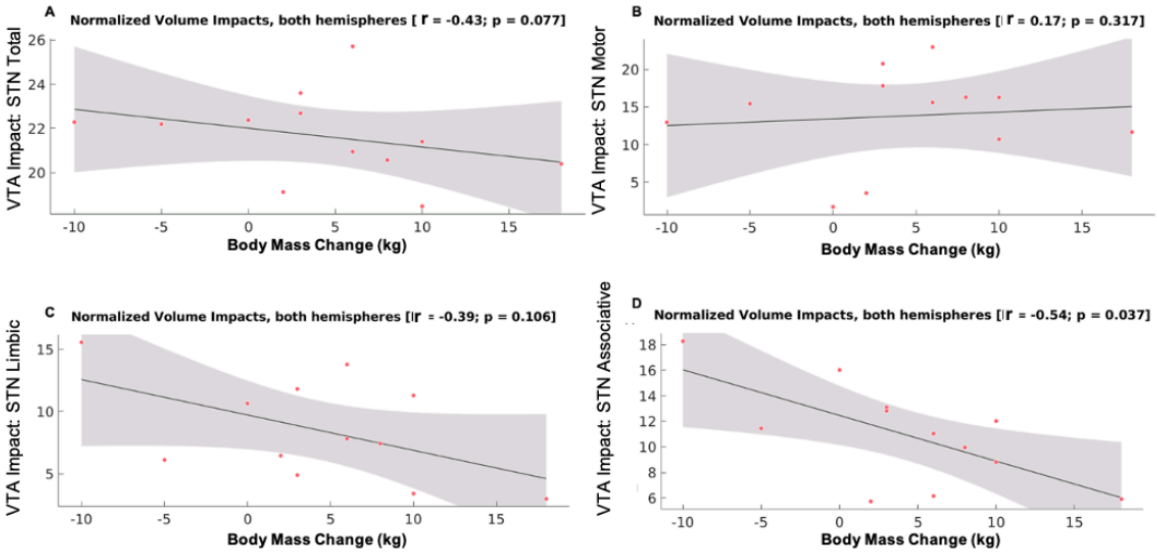

Figure 36. Correlation analysis of VTA intersection of chronic stimulation parameters and body mass change. No significant correlation was found between VTA intersection and (A) STN in total, (B) the motor part of STN, C) and the limbic part of STN. (D) Positive association between the associative part of STN and body mass change ($p = 0.037$; $r = -0.54$).

3.4 Summarized Effects of Body Mass Gain after Deep Brain Stimulation of the Subthalamic Nucleus

The systematic review and meta-analysis revealed that all but one study [198] reported body mass gain after DBS with no study reporting body mass loss. Thus, there is strong and consistent evidence for body mass gain after STN DBS affecting the majority of patients. Furthermore, the maximum body mass gain across studies was 5.9 kg after one month [15] and 11.1 kg one year after DBS [6]. Consistent with the literature, we found a maximum postoperative body mass gain of 9 kg after 3 months of stimulation, 11 kg after 6 months of stimulation, and 16 kg after 12 months of stimulation in Study 1. Our findings are in accordance with the meta-analysis and exceed these results. In Study 2, we found also a variation in body mass, ranging from a body mass loss of 10 kg up to a body mass gain of 18 kg for an average stimulation duration of 24 months. (Fig. 37).

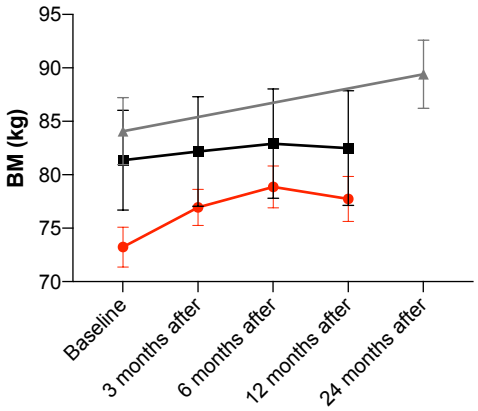

Figure 37. Comparison of results between systematic review, Study 1, and Study 2 of the present thesis. Red line indicate findings from systematic review and meta-analysis. Black line indicate findings from Study 1. Gray line indicate findings from Study 2. BM indicate mean body mass. Values are shown as mean vaules±SD.

4 Discussion

The present PhD thesis focused on the underlying pathophysiological mechanisms of body mass gain after STN DBS in PD, which not only contribute to a better understanding of DBS-related changes in neural networks and metabolism, but also provide an avenue for gaining insights into the underlying disease and mode of action of DBS.

Three independent studies in medicated PD patients in whom STN DBS was previously established were used in a question-specified model to unravel metabolic and neural connectivity changes as a result of DBS. In a first study, a systematic meta-analysis showed strong and consistent evidence for body mass gain after STN DBS, affecting the vast majority of patients (Chapter 3.1). In this connection, the second study using a clinical-experimental approach (Chapter 3.2) was able to show various changes not only in body mass and BMI, but also in body composition and hedonic eating behavior in the short and long term after DBS surgery. In the third study (Chapter 3.3), the acute effects of STN DBS led to various changes in network connectivity that drive attention, salience, reward seeking, and food intake. STN DBS appears to facilitate the craving for sweet foods and has an influence on behavior. All of these interactions add to existing evidence of body mass gain as a side effect of STN DBS [30].

The present thesis additionally corroborates several previous studies that show changes in body mass and reward-dependent brain circuits due to high-frequency stimulation. The present work may help to better understand the extent of interactions between the brain and the periphery, especially FM as peripheral organ, as a result of STN DBS. Finally, the results suggest a direct interaction between high-frequency stimulation, lead localization, and metabolic alterations of the body in a patient-specific way. These findings challenge the concept of personalized medicine to prevent negative health implications of treatment-specific side effects.

4.1 Alterations in Nutritional and Metabolic Profile after DBS of the Subthalamic Nucleus in Parkinson's Disease

We demonstrated that STN DBS is associated with profound alterations in body mass in patients with PD. Previous studies revealed that body mass gain occurs already in the first months after DBS implantation and appears to stabilize after one year. Interestingly, the Swedish Obese Subjects (SOS) study, which investigated the effects of bariatric surgery on subjects with obesity, found a mirrored effect. Here, subjects with obesity lost body mass very rapidly during the first months after surgery followed by a plateau phase [208].
However, body mass alterations are a known non-motor feature in PD. While both, low and high body mass, have been reported in PD, the following section will describe the body mass profile in PD.

4.1.1 Nutritional profile in Parkinson's disease

Importantly, body mass and body composition measurements are not consistent so far in PD research. Methods of body mass assessment included standing or sitting posture electronic scales, and out-patient weighing scales [67]. Also, the weighing procedure differed and included body mass measuring with light closes, with shoes on or off, and sometimes only depend on hospital medical reports or on recall by patients [67]. With regard to the assessment of body composition: air-displacement plethysmography has been promoted as gold standard technology for assessment of body mass and body composition [69,178,179,181,225,226] besides dual x-ray absorptiometry or the more complex four compartment model, The air-displacement plethysmography by using the Bod Pod System (Bod Pod(R), COSMED, Rome, Italy) is a non-invasive, fast, safe, comfortable, valid, reliable, and accurate method [178,179,209]. In consequence, variations in methodology in combination with demographical differences in studies may account for inconsistencies in study results. Surprisingly, there are no reports of the use of air-displacement plethysmography in PD patients so far [67]. Thus, a strength of the present thesis is its use to assess body composition preciously.

First of all, considerable body mass changes occur during the disease course of PD in both directions, disease-related malnutrition as well as treatment-related overfeeding [39]. Since the very first reports of James Parkinson in 1817 that body mass loss has been reported in PD, whereas longitudinal observations showed that body mass varied between the time of diagnosis and during subsequent years. The general observation was that PD patients in advanced disease stages have lower body mass and lower BMI than the general population [67]. However, this is not always the case. A contrary study indicated higher body mass in PD patients [157]. Several factors are discussed in this context such as age, disease severity,

motor symptoms, as well as alterations in energy expenditure and food intake that can be determined by impaired homeostatic regulation of hunger and satiety relating hormones and gastrointestinal dysfunction [39,67,163]. Furthermore, PD is characterized by numerous non-motor symptoms which may apparently affect body mass maintenance like taste and olfaction, gastrointestinal problems, mood and motivation of food intake, and cognition [39,67].

Body mass changes occur already in pre-motor stages of PD. It has been shown that patients start to lose body mass before the begin with levodopa treatment, which has been reported to be most prominent after 2 years of treatment [211]. In accordance to these findings, results of Study 1 indicate that body mass loss occurred prior to the diagnosis. In line, the lowest body mass in adulthood in both PD groups was prior diagnosis. Moreover, body mass at diagnosis was higher than the lowest body mass in adulthood, indicating a body mass increase that can be induced by start of treatment. The body mass at diagnosis was, however, lower than the reported highest body mass in adulthood. Furthermore, body mass at diagnosis seemed to be less than the body mass at T_0. In comparison to healthy control subjects, we found the highest body mass in adulthood at the time point of the measurements of Study 1. However, we found no body mass and BMI alterations in PD patients under best medical treatment over study duration. This new finding implies that it is still unclear how body mass will develop during PD progression due to the short interval. Whereas in contrast PD patients with DBS significantly increased in body mass and BMI over time.

As the patient sample in the systematic review had on average normal weight prior to surgery, whereas PD patients in Study 1 had normal weight, overweight, and some of them were obese according to BMI cut offs at baseline. These findings indicate that the postoperative body mass gain does not necessarily compensate for preoperative malnutrition or underweight which is well in line with recent evidence [8,36,39,67]. Nevertheless, it is unclear how body mass with develop with a stimulation duration greater than 12 months. The systematic review gave a first hint that body mass seems to stabilize with stimulation durations greater than 12 months, however, it needs to be addressed in further longitudinal studies. Study 2 revealed that the body mass gain is present at least 24 months after the operation. Due to this interesting finding, a more detailed assessment of body mass stages during PD progression is important.

Secondly, as previous mentioned PD patients that underwent DBS surgery had normal weight, overweight, and some of them were obese according to BMI cut offs at baseline in Study 1. None of our patients had underweight at any time point. BMI is a better biomarker than body mass alone, because BMI acts as an indicator for further cardiovascular and metabolic health risks [177]. After 12 months of stimulation, the number of patients with normal weight was reduced, whereas the number of patients with obesity class I was clearly increased in Study 1. One third of the patients were obese after stimulation durations of 12 months. These findings confirm again the results from the systematic meta-analysis.

Thirdly, results regarding PD-induced changes in body composition are conflicting. Most studies reported a low percentage of FM in PD patients [16,152,153,211,212]. In Study 1, the percentage FM was highly variable in both groups of PD patients, ranging from very low FM (8%) up to very high FM (48%). STN DBS surgery led to a continuous increase in FM. The systematic review reported that only a few studies assessed changes in body composition in detail. There is first evidence that females gained disproportionately more FM, whereas body mass gain in men was driven by both, FFM and FM [5,6,9,11,13,16,19,33,149]. At baseline, we found no differences in body composition between the three groups, and both control groups remained stable in their body composition over the study duration. These findings challenge previous reports of reduced body FM and lean body mass in PD, although the PD patients under best medical treatment had the lowest FM within this study [39]. PD patients with STN DBS revealed already 3 months after DBS device implantation an increase in FM and, vice versa, a reduction in FFM. Total body fat mass peaked regarding the FM 6 months after stimulation and remained then stable. Interestingly, we found in patients that did not gain body mass or that even experienced a reduction in body mass, an increase in FM. These findings were unexpected, because previous studies discussed that the increase in body mass after STN DBS reflects an increase in FFM [5,6,9,11,13,16,19,33,149]. Our findings, however, indicate a gain in FM and lose FFM as consequence of DBS only. This result highlights a new and important finding that there seems to be a stimulation-dependent effect leading to alterations in body composition, namely to the accumulation of FM. It is well known, that adipose tissue acts as a metabolic organ [213], indicating disruptions in the brain-adipose tissue crosstalk.

Fourthly, changes in body composition were also reflected by changes in body circumferences. The interpretation of the waist circumference [177], waist-to-hip ratio [177], and neck circumference [183] was done by standardized cut-off values. Neck circumference correlates with age, waist and hip circumferences, BMI, body mass, and systolic and diastolic blood pressure and other components of the metabolic syndrome [183]. In PD-DBS, we found a distinct increase in neck circumference, whereas the average neck circumference remained stable in both the control groups. Moreover, we found at baseline, that our PD cohort that underwent DBS surgery fulfilled on average already the criteria for visceral adiposity. These findings are in accordance with the BMI distribution in this cohort showing that a large proportion of PD-DBS group were overweight or obese (64%) already prior to surgery. Three months after DBS surgery, we found an increase in BMI as an obesity marker. The subsequent stabilization indicated a rapid change in body composition and body circumferences as a consequence of neuromodulation within the basal-ganglia circuitry.

To summarize, in accordance with previous findings [30], STN DBS impacts on body mass in the first line. Due to the fact that we saw no body mass changes within our control groups, our

results seem plausibly confirm our hypothesis I. Moreover, it interferes with body composition and body fat mass distribution. Since body mass results from balance between energy intake and energy expenditure [16], it is mainly determined by the metabolic activity of organs and tissues such as FFM including muscle mass and FM. Energy is predominantly stored in adipocytes. It is, however, not only a fat storage, but it also acts as an organ that secrets a plethora of hormones and cytokines [42,116]. These findings emphasize the metabolic relevance of body mass gain and FM distribution after STN DBS in PD patients, suggesting a communication between the brain and adipose tissue, which then in consequence may lead to a further accumulation of FM and alterations in adipokine release and signaling to the brain [5,6,13,39]. In this respect, the present thesis demonstrated the need for a differentiated consideration of body fat distribution within the respective patient group when it comes to an evaluation of body mass gain. It is further important to take into account that body mass has a highly interindividual variability and gender-specificity [16]. Therefore, these observations questioned whether body mass gain should be considered as deleterious in patients with higher body mass or as beneficial in some patients with lower body mass.

4.1.2 Metabolic predictors of body mass alterations in Parkinson's disease

For the interpretation of the previous findings, one has to consider that body mass gain after STN DBS is a multifactorial phenomenon influencing energy expenditure [16,33], metabolic changes [11,16,149], alterations in the hypothalamic regulation [13,161], alterations in dopamine signaling [39,215,216], and changes in eating behavior and food intake [8,104], respectively. Due to the findings that FM acts as a metabolic organ, metabolic alterations after STN DBS will be considered in the next paragraph.

Metabolic changes

Previous studies have proposed that body mass gain could be seen as a homeostatic response to the previous disease-related body mass loss [11,16,149] assuming that patients with PD may normalize their body mass back to their premorbid status. As STN DBS is associated with a body mass gain exceeding the previous body mass loss [11,156] this hypothesis is not convincing. Indeed, our review revealed that 88 % of the patients were overweight after one year of stimulation or were even obese as shown in Study 1. Moreover, STN DBS in PD is associated with alterations in energy metabolism. The basal energy expenditure was found to be decreased during active stimulation [6,16] as a result of decreased motor fluctuations, muscle stiffness, dystonia, levodopa-induced dyskinesia, severity of OFF fluctuations, improvement of sleep patterns, as well as LEDD reduction [6,10,67]. In context with body mass gain, patients with a greater improvement of motor dysfunction and a stronger reduction in LEDD were likely to gain less body mass arguing that an optimal lead localization in the sensorimotor part of the STN is associated with a lower

likelihood to develop this side effect [30]. This finding seems to be contractionary on the first view. On the one hand, DBS improves rigidity and resting tremor which would otherwise contribute to a higher preoperative energy expenditure that decreases postoperatively and leads to increased body mass. On the other hand, patients perform larger, faster and more movements and are more mobile than before the operation which should theoretically increase energy expenditure. Although the body mass gain is less pronounced in patients with an optimal lead positioning in the motor part of the STN, they may still gain body mass possibly through reduction in resting energy expenditure [6,11,109,149,157].

Moreover, a reduction in free living energy expenditure after treatment has been found [9]. Furthermore, STN DBS thus modifies the energy expenditure - energy intake balance resulting in reduced expenditure without decreasing energy intake [6,11,109,149,157]. The positive energy balance [75] may subsequently lead to an increase in body mass. For future studies, it would thus be important to assess the mobility of a patient using quantitative measures, e.g. by wearable sensors and to measure both, resting- and activity-dependent energy expenditure. Moreover, mechanisms other than changes in energy expenditure that contribute to postoperative body mass gain, e.g. changes in the hedonic control of food intake, should be taken into consideration.

A compelling hypothesis is a reduced secretion of growth hormones with consequently decreased lipolysis [67]. Furthermore, a drop of HDL cholesterol concentrations has been observed [18,33]. Additionally, one study found an increased glucose oxidation after DBS implantation [33]. These results remain contradictory as the basal glucose production and insulin sensitivity were reported to be unchanged in a different study [203]. To sum up, there is first evidence that STN DBS affects glucose and lipid metabolism, but this is still contrarily discussed [18,163].

Collectively, these results argue that body mass change is a significant non-motor feature in PD and can be significantly modulated by neurostimulation. Body mass homeostasis is a complex physiological process [67] that may thus be disturbed by neuromodulation. The mechanisms of postoperative body mass gain due to exact electrode position and its relation to body mass gain will be explained in the following section.

4.1.3 Effects of electrode localization on changes in body mass and body composition in Parkinson's disease

The exact postoperative location of the active DBS contact and the modulation of the electrical field now became possible with the use of modern toolboxes [186]. It has been proposed that STN DBS directly influences adjacent structures that are involved in eating behavior and energy balance by excitation of axons surrounding the electrode in combination with increased output from stimulated nuclei [31,39–41]. An estimation of the spread of the current has been

captured of approximately 2-4 mm radius around the active electrodes [218–220]. Moreover, given the functional and structural complexity of the basal ganglia circuitries [61], the current diffusion plays a role in the different basal ganglia circuitries causing thereby motor improvements as well as side effects of other motor or cognitive and limbic functions [41]. Thus, high-frequency stimulation could influence body mass homeostasis by modulation of structures that are involved in the regulation of energy expenditure, reward and food intake, such as the lateral hypothalamus [42,221], limbic subdivision of the STN [222–224], and the medial forebrain bundle [225]. These structures are located around the medical part of the subthalamic area [41]. Another assumption is that high-frequency stimulation could induce a dysfunctional information flow of cortico-striatal networks that are involved in the pathophysiology of obesity [29]. In conclusion, the position of the electrode relative to the intrinsic organization of the STN contributes differentially to clinical and metabolic outcomes [41].

First of all, the therapeutic benefit of DBS depend on the exact electrode position and its modulation of remote brain regions that are connected to the stimulation site. The exact electrode position within the dorsolateral part of the STN (sensorimotor subdivision) [226–228] as well as connected brain regions correlate with clinical responses and predict clinical outcome [229]. We could confirm in Study 1 an association between stimulation in the motor subdivision of the STN with improvement in clinical MDS-UPDRS-III scores: the more tissue within the STN motor subdivision is activated, the higher was the improvement in clinical motor signs [40,61,229]. This finding could not be replicated in Study 2. The present approach was, however, different between both studies which may have led to the varying outcomes. In Study 2, the enrolled patients were implanted at different centers had different times since DBS surgery and longer disease durations (mean 12.2 vs. 9.8 years). The major difference is that the difference of motor symptoms (MDS-UPDRS-III) was assessed between sessions (T0 vs. T6M) and in the best possible condition (Med ON vs. Med ON/DBS ON) whereas in Study 2, the immediate DBS-related difference was assessed (Med ON/DBS OFF vs. Med ON/DBS ON). Moreover, the datasets in Study 2 were analyzed retrospectively. No individual connectivity data were used in both studies. These individual connectivity data would refine the individual analysis by adding predictive values from connectivity analysis above and beyond anatomical modelled data [229]. Future work is therefore needed to determine clinical outcome parameters with normative connectomes, that have the advantage of large subject numbers, combined with patient-based connectomes, that might have the advantage of better matching of patient-specific brains, as well as functional and anatomical connectivity data of each patient to provide the best sensitivity for individual differences with the lowest signal to noise ratio as possible [84,88,88].

Changes in brain function induced by electrode position

Changes in mood and behavior are frequently observed by stimulation of the ventral-medial STN, where the current spreads to the limbic part of the STN, [40], for instance alterations in food intake, like increased appetite and hunger accompanied by compulsive and nocturnal eating disorders after STN DBS [39]. In this context, non-homeostatic food intake and reward-related mechanisms provide therefore a compelling hypothesis. The medial tip of the STN forms a circuitry with the basal ganglia and frontal cortex that is involved in limbic and motivational processing [8,41,61]. In detail, the STN is especially connected to the ventral tegmental area and ventral pallidum, which are key structures of the reward system [41]. Through its connections, stimulation of the STN may thus increase dopaminergic conveyance in the striatum [5,12]. Additionally, the medial part of the STN is conterminous to the medial forebrain bundle which contains essential projections underlying reward functions. Comprehensive research demonstrated the involvement of the medial forebrain bundle, mesolimbic system, and ventral pallidum in increase of food intake, desire for food rewards and in relation obesity [120,230,231]. For instance, animal studies indicate that both, STN lesions and DBS led to increased food-related incentive motivation in rats [67,160], but not to increased hunger [158]. Moreover, an electrophysiological study in monkeys revealed an increased firing rate of neurons in the STN related to the delivery of rewards [97,98]. Therefore, an active electrode in the vicinity of the medial STN, which is ideally located to co-stimulate the reward system, may influence food-related reward processing resulting in changes of motivational behaviors, food intake, and disruptions in body mass homeostasis [41]. Past research supports this assumption, because postoperative body mass gain correlated with arousal ratings elicited by food pictures in the STN during active stimulation. This finding suggesting an altered incentive salience and/or emotional relevance to rewarding cues [7,8].

Therefore, we hypothesized that a more medially located electrode (limbic and associative subdivision of the STN [40] led to a higher amount of body mass gain in these patients. Thus, the association between change in BM and BMI with activation pattern within the STN were assessed. While the association between BM and BMI only reached the level of significance between stimulation of the limbic STN and change in postoperative BM and BMI, we found a relationship between alterations in FM and active limbic STN stimulation highlighting the new role of the subthalamic area in metabolic functions, arguing for a manipulation of reward-related mechanisms. To briefly sum up, with Study 1 we provide evidence that body mass gain is inversely related to the distance of the contacts from the wall of the third ventricle, meaning that patients with volume of tissue activated in more medial areas within the STN experience greater body mass gain than those with active contacts in the motor subdivision of the STN. Study 2 revealed a weak negative association between stimulation of the associative part of the STN and body mass gain. These subjects, however, were not deeply phenotyped with

regard to metabolic parameters including body plethysmography, the weight was assessed retrospectively which is highly prone to recall errors and the association is weak and was not corrected for multiple comparisons. Thus, this association should be interpreted with caution. However, cognitive-associative functions as well as limbic functions are altered by STN DBS which could collectively influencing body mass [61]. Recent PET studies using 2-deoxy-2[18F]fluoro-D-glucose tracer found a correlation between STN DBS-related body mass gain and metabolic changes in associative and limbic brain areas, but no correlation with sensorimotor brain regions [158,196]. These findings suggest that the STN might be involved in motivational processing related to eating behavior [158].

Although the exact mechanisms remain elusive at this point, our results are consistent with the assumption that high-frequency stimulation of the STN exerts regional effects on adjacent structures involved in energy homeostasis [10,29,40,41,61]. The exact position of each implanted electrode was verified by visualization within the LEAD DBS Toolbox [186], we were therefore able to recognize that the different observations of associations with body mass gain and STN subdivision are not caused by electrode misplacement outside the STN. This finding imposes a change in adipocyte-brain crosstalk due to high-frequency stimulation.

Hypothalamic alterations in hormone release

In line with our new findings, it could be assumed that DBS current spread beyond the margin of the STN is responsible for a co-activation of the hypothalamus influencing energy metabolism and homeostatic pathways of food intake [41]. Only a few studies investigated the long-term effects of STN DBS on autonomic [39,67,69] and hormone [5,6,13,21,202] systems, providing no clear explanation for the body mass change phenomenon, which will be discussed in the following. Previous research revealed that patients with PD and STN DBS showed increased levels of the orexigenic neuropeptide Y (NPY) after DBS implantation [5,13]. The increased NPY levels correlated with a higher stimulation amplitude which could indicate that DBS may disrupt the melanocortin system by electric current diffusion to the hypothalamus [5]. Interestingly, the central hormone NPY exerts effects on food intake and body mass using different mechanisms including a relationship to the actions of glucocorticoids. Moreover, rodent models showed that neuropeptide Y levels are altered in neurodegenerative disorders like PD or Alzheimer's disease [232,233,234]. Furthermore, leptin and ghrelin as peripheral hormones are involved in the regulation of energy balance. Leptin is a long-term mediator for energy balance, whereas ghrelin is a fast-acting hormone for meal initiation. Both systems are disturbed in obesity [235] and are therefore important to consider in the context of body mass gain after DBS surgery. DBS is accompanied by increased serum leptin levels, reflecting an increased degree of adipose tissue. In addition, increased levels of ghrelin after STN DBS was likewise reported and could lead to a resistance to the anorexigenic effect of leptin within the

hypothalamus [5,6,11,13,69,156]. Also reduced growth hormone secretion has been described after STN DBS [155,236], which results in decreased lipolysis and thus to body mass gain.

One assumption for these endocrine alterations is that the spread of current beyond the margin of the STN, as discussed in the previous section, may influence the hypothalamic regulation of hormone secretion and energy homeostasis [67,161,194,202], and could disrupt the melanocortin system, which has been linked to obesity [5]. The disrupted hypothalamic hormone secretion leads to alterations in the central appetite mechanism [12,21,39].
Moreover, cortisol levels are normalized after STN DBS and the respective anabolic effect of this normalization process was hypothesized to drive the body mass gain [13,19,21,237]. In addition, cortisol levels decreased over time after DBS device implantation [13,202] and that this decrease was correlated with the position of the active electrode in the STN. The more medially the electrode was located, the greater was the decrease in cortisol levels. Furthermore, lower cortisol levels were strongly associated with body mass gain and higher trait anxiety [202].
These results seem to be contractionary to the relationship between cortisol levels and body mass gain with patients with abdominal obesity having increased cortisol levels. An important predictor of the impact of cortisol on metabolism is cortisol responsiveness. High cortisol responsiveness is associated with greater propensity to gain body mass in comparison to low responsiveness [202]. This difference in susceptibility is - at least in part - dependent on different physiological factors such as gender and pregnancy. Overall, cortisol modulates food intake and therefore impacts on body mass, but also different stressors are known to elicit different cortisol responses [234]. Thus, STN DBS may mimic the effect of chronic stress and disturbed limbic and motivational systems depending on the exact electrode position [202]. However, these findings are still contradictory, because one study revealed that hormone levels of the hypothalamic-adrenal-, hypothalamic-somatotropic-, hypothalamic-gonadal-axis were 3 or 6 months after DBS device implantation considered as normal [21,39]. Therefore, it is still under discussion how hormonal changes may contribute to body mass gain.

To briefly summarize, our findings are in accordance with previous research and support the hypothesis that body mass gain as side effect of STN DBS in patients with PD may, at least partially, determined by an regional effect of stimulation on adjacent structures that are involved in central regulation of reward and energy balance [41]. Unfortunately, we do not yet have corresponding hormone data to prove this assumption. Thus, body mass gain could result from increased sensitivity to food reward cues [8,41] and changes in eating behavior, including higher food intake, increased appetite, binge eating, or craving [18,22,36,40,96,157,158].

4.1.4 Effects of deep brain stimulation of the subthalamic nucleus on regulation of non-homeostatic food intake

The associations of high-frequency stimulation with alterations on hedonic eating, inhibition of eating behavior, and food intake were already discussed.

First of all, food intake is a complex process depending on homeostatic systems, cognitive control, emotional regulation and reward sensitivity [41]. Previous studies have been shown that PD patients did not report any changes in food intake, appetite or hunger in self-reported questionnaires [240–242]. However, inaccuracy of self-reported answers should be considered in the interpretation of the results, because small individual changes in the reward system and motivational behavior induced by STN DBS do not necessarily be reflected in subjective feelings of appetite or hunger [41]. We measured therefore in Study 1 emotional reactivity. Emotional reactivity depends on two major brain systems: the BAS and the BIS [243]. The BAS is thereby sensitive to reward signals that are associated with positive emotions and is assumed to represent the personality dimension of impulsivity [243]. The BIS in contrast, is sensitive to signals of punishment that are associated with negative emotions and is assumed to underlie the anxiety personality dimension [243–245]. Dopamine has thereby been indicated as the major mediator of reward-related impulsivity [215]. In line with that, PD is accompanied by reward-related impulsivity, as well as motor and cognitive inflexibility [39]. Moreover, PD has often been attributed to overactivation of the dopaminergic system due to antiparkinsonian medication [39]. Therefore, it is unclear how the aberrant impacts of reward are reflected in the BAS system. PD patients revealed increased reward responsiveness compared to healthy control subjects [215], but they did not differ in all other BAS scales as well as not in the BIS scale [215,246,247]. Interestingly, the BIS/BAS assessment has not been done in PD patients with STN DBS before. Here, we found, in contrast to previous findings, severer levels of emotional distress in PD patients. We observed decreased levels in fun seeking sub-scores as well as in the reward-responsiveness in the PD control group compared to healthy control subjects, but not in the DBS-treated group. Moreover, we found increased total BIS-score in the DBS-treated patients at T_{6M} and T_{12M} compared to PD patients under best medical treatment. Extending the previous findings, we have demonstrated for the first time that the BIS system seems to be disrupted due to subcortical high-frequency stimulation, whereas no change in behavioral activation system was observed. Of note, deficits of emotional self-awareness and difficulties in describing feelings has been associated with ICDs in PD [246]. This finding might be the first hint towards disturbed emotional inhibition system due to STN DBS, thereby causing ICDs. Further prospective studies are needed to assess these findings in more detail.

Changes in sensitivity to rewards and actual desires of food intake was further assessed in Study 1 with the assessment of hunger- and stress levels by a VAS. Moreover, extensive

studies and the length of the measurement day could induce subjective feelings of stress or increased hunger feelings in our participants of Study 1. All participants included in this study did not report high levels of adverse feelings throughout the measurement day. The most important symptoms and conditions for the present thesis, which will be discussed in more detail, comprises subjectively desires to eat, cravings for sweet and savory foods, as well as hunger and appetite levels in general. Some of these key symptoms were affected by stimulation. Baseline levels of general desire to eat were always higher rated before the breakfast compared to after the breakfast in all groups. Interestingly, this effect diminishes at the end of the measurement day. After the EEG measurement, the desire to eat was greater than before the EEG measurement, again in all groups. This observation suggests that, while viewing food images during the EEG, hedonic system of food intake could have been activated and thereby inducing increased desires to eat [121,122]. Concerning individual food cravings, DBS-treated patients tended to rate their desire for sweet foods higher after 6 months of stimulation than PD patients under best medical treatment and healthy control subjects in the present work. In contrast, no differences in the desire of savory foods was observed, neither at breakfast nor at EEG measurement. Moreover, in PD it is well known that patients show a preference for sweet foods [142–145]. In the present thesis, the absolute subjective ratings of craving for sweet foods were higher in DBS-treated patients and should be regarded as moderate in general. The interpretation, of the relevance of sweets cravings after DBS, as condition of increased energy intake, of the available data still seems to be difficult due to missing interaction effects and requires therefore further investigation. Important to consider in this respect is Study 2 employed in the present thesis to investigate sweet food preference in more detail in with an fMRI paradigm in chapter 4.3.

Interestingly, hunger and appetite levels were not significantly different rated by DBS-treated patients than PD patients under best medical treatment and healthy control subjects, although the hunger rating was decreased before the EEG measurement after 6 months of stimulation. These results are in line with previous studies suggesting that food intake and appetite were not changed due to high-frequency stimulation [41,240–242]. It is important to consider in this respect, that the assessment of desires to eat, cravings for sweet and savory foods, as well as hunger and appetite levels were recorded with subjective self-ratings. It is possible that subjective response biases in answering surveys, such as social desirability, may account for the present results. Furthermore, it could be again possible that the patients were insensitive to their slight alterations in behaviors or feelings or patients underreported and/or dissimulated symptoms to avoid being perceived as a person with higher drive to eat by others [248], because the present study used no cover story. Also methodological aspects such as small statistical power due to low sample size in the DBS-treated group could account for negative results.

Nevertheless, although no significant differences in hunger and appetite levels were detectable with self-ratings, the total amount of calories taken in during the 'Cookie-Test' showed differences between the groups, which was measured with standardized time after the last meals as well as at the end of the measurement day, indicating therefore levels of stress. At baseline, PD patients had in general a higher amount of total calorie intake than healthy control subjects. Six months after stimulation, the amount of total calories taken in increased further only in PD patients treated with STN DBS. This effect was observed in both sweet food cookie categories as well as in the amount of calories drunken with apple spritzer. These results argue for the hypothesis that overweight and obese individuals, shown in the large proportion of our patients had overweight or obesity after 6 months of stimulation, have a higher sensitivity to reward predicting a tendency for overeating and preferring sweet foods [41,231], as this effect was not observed in control subjects. This result is in line with the finding that STN lesioned rats preferred a more caloric solution to a sweeter but less caloric one [249,250]. In contrast, other animal studies revealed that STN stimulation or STN lesions increase motivation towards food [251], thereby producing an increased wanting without activating the liking component of reward [230]. We speculate that STN DBS in relation to an stimulation of the medial part of the STN, increases the sensitivity to reward, thereby modulating eating behavior, which would be more pronounced in patients with more medially located active contact [41]. Stimulation of the limbic part of the STN was positively associated with increase in FM, arguing for an excessive caloric intake due to stimulation [41].

In line, regulation of appetite and food intake is affected by numerous factors, for instance explicit and implicit food preferences and motivations referred as 'wanting' and 'liking' [119,120]. In particular, wanting is defined as the motivation to eat, whereas liking reflects both, sensitivity to rewards and sensory pleasure associated with eating [119,120]. Wanting, as the incentive salience of a reward or the motivational component of a reward has been linked to overeating and obesity. Liking is thereby a more general concept of the actual pleasurable impact of a reward. Both systems are mediated by the dopaminergic impacts [119,120]. We hypothesized an excessive amplification, specifically of psychological 'wanting' triggered by especially sweet food cues, without necessarily an amplification of 'liking' as consequence of STN DBS. Interestingly, both concepts were studied in the context of STN DBS in PD before, thereby pointing towards the critical role of dopamine in modulating wanting rather than liking [8]. In a specific go/no-go task, wanting for low calorie foods, and not liking, explained body mass gain after surgery [8]. Furthermore, this study suggested that especially individual features, such as attentional impulsiveness, impacts on the patients' vulnerability to gain body mass [8]. Interestingly, this effect has been found right after the DBS device implantation.

However, we found in the present thesis that neither wanting nor liking of high-calorie foods was affected by high-frequency stimulation of the STN. This finding suggests that although STN DBS increases FM due to an assumed excessive caloric intake, it may not be triggered by responses such as increased motivational food cravings in general or shifted food preferences towards high calorie food images on the first view. Furthermore, these findings seem to argue against previous reports that overweight and obese subjects reveal higher subjective ratings in wanting and liking [252]. Nonetheless, we could partially confirm previous findings, that the category of low calorie foods explains disruptions in body mass homeostasis. We found in contrast a change in liking for low calorie foods, and not in wanting, suggesting no clear association between STN DBS and impact on the hedonic system. This discrepancy may be due to several reasons. For instance, such a test as we performed here, not as a go/no-go task, has not been done before in PD patients to our knowledge, and therefore the expected results were only speculative. The results can again be influenced by longer stimulation durations and/or subjective biases towards social desirability [248]. Furthermore, as eating behavior is crucially influenced by the environment and social norms, so for instance are high-caloric foods considered as unhealthy and in consequence less socially accepted, it is possible that the patients understated their preferences for high-calorie foods [253], especially in the context of a study investigating body mass gain. In line with that, patients of the present study might consider low calorie foods more hedonic than foods with high calorie contents. Moreover, it should be noted that wanting and liking were highly variable rated overall patients, suggesting interindividual differences among them, such as individual characteristics or aspects of changes due to the surgery, that can account for these changes.

To sum up, all subjects from Study 1 revealed that they experienced the same levels of stress and hunger at the different measurement time points, indicating that the groups were comparable. Furthermore, STN DBS did not evoke relevant self-rated changes in behavioral activation system, accompanied by changes in food cravings and hunger ratings, and finally did not cause changes motivational components as regulators of appetite. Although, food preferences showed a tendency towards a preference for sweet foods in DBS-treated patients. As expected, high-frequency stimulation led to alterations in BIS, suggesting a shift towards rewarding stimuli. Inhibitory control is thereby a major factor influencing diet and food consumption. This systems acts on food intake in multiple ways, for instance by inhibiting an automatic response to eat palatable foods, refraining from overeating in response to emotional states and not acting on spontaneous food cravings [254]. Behavioral measures are thereby negatively correlated with body mass, assuming the subjects with overweight and obesity may have difficulties in withholding responses from palatable foods, in particular those with high fat and sugar contents [254,255]. Self-reported behavioral measures of impulsivity indicated that subjects with higher impulsivity ratings tend to eat more when food is present [256,257].

Results are still controversial and need further investigation. A compelling hypothesis is the relationship between motor improvement and body mass gain. This contributing factor will be explained in the following section.

4.2 Improvement in Clinical Scores after Deep Brain Stimulation of the Subthalamic Nucleus and its Relation to Body Mass Alterations in Patients with Parkinson's Disease

High-frequency stimulation of the STN is an effective technique for advanced motor complications in late stages of PD, which significantly improves motor impairments and quality of life of patients with PD. The most consistently reported outcome of STN DBS is the improvement of motor function in the medication-ON and -OFF states [6,10,11,13,16–20,22,24,33,95,96,149,156–158,161,162,162,195,196,200,202], activities of daily living [3], reduction of Anti-parkinsonian medication [5,6,8–11,13,16–20,24,33,95,149,156–158,162,195,196,200], and the reduction of dyskinesias[22] (levodopa-induced dyskinesia; LID) [10,16,17,95,158,163,195,196,259,260]. We were able to show that STN DBS improved clinical motor ratings on the MDS UPDRS-III scale, ranging from 23% in Study 2 up to 59% in Study 1, compared to a 48% in the systematic review. Differences in these clinical evaluations could be explained by differences in the time point of surgery or time since surgery. The patients in Study 2 experienced an average chronic stimulation duration of 24 months, whereas the stimulation duration in Study 1 was a maximum of 12 months. Moreover, improvements in motor functions depend on the optimal stimulation location in so-called 'sweet spots' for the best motor outcome [84], which varies between patients.

The results of our longitudinal approach indicate a typical initial decrease in MDS-UPDRS-III motor scores in PD patients with DBS, reflecting the so-called 'second honeymoon' phase of PD treatment [258]. Unfortunately, the motor improvements did not remain at the low level of the initial slump, but the scores increased again after 12 months of stimulation, which suggests that motor improvements are not stable in the long term. This finding is consistent with the literature, where improvements were observed after 1 year of stimulation, but deterioration after 5 years of follow-up [3,95]. However, evidence showed that DBS-induced improvements in tremor and rigidity are maintained for more than 5 years [3]. In contrast, beneficial effects on bradykinesia or axial symptoms observed 1 year after treatment started to decline after only 5 years of stimulation [3]. Interestingly, PD patients under best medical treatment also showed a decrease in motor scores observed at time T_{6M}, which is a short term effect of adjusting medication in these patients. The motor scores deteriorated again 6 months later indicating disease progression. Moreover, several studies showed that STN DBS significantly improves

[22] Of note, It is noteworthy that DBS has only limited therapeutic effects on axial symptoms, such as postural instability, postural abnormalities, freezing of gait (FOG), and other gait impairments. Although, FOG is likely to improve with DBS-treatment, postural instability and abnormalities may even worsen following DBS. Interestingly, also comorbidities are also associated with the onset and worsening of axial symptoms after DBS treatment, for instance, cognitive impairment or body mass gain [258]. Nevertheless, the most consistently reported outcome parameter of STN DBS is motor improvement in MDS-UPDRS-III and -IV scores [3].

medication-induced complications such as LIDs and motor fluctuations [2,3,31,95,157,261]. These improvements persist even after 5 years of stimulation [2,3,31,95,157,261]. In accordance with these studies, DBS-treated patients in our longitudinal clinical-experimental approach from Study 1 showed a 54% reduction in motor complications, which remained stable over the duration of the study. A similar reduction was found in the systematic review of about 38%. In PD patients under best medical treatment, the score of motor complications increased during the study period, again suggesting that the disease is progressing and that the medication is causing these severe side effects [2,3,31,95,157,261]. In accordance with these findings, DRT as a side effect was reduced by 45% in Study 1 and by 56% in the systematic review. Our findings are consistent with the literature, which shows in several studies that LEDD could be reduced by up to 50% after implantation of the DBS-device, which remained stable over 5 years of stimulation and beyond [2,3,31,95,157,261]. This reduction in dopaminergic medication is an indicator of the effectiveness of STN DBS in improving motor symptoms in PD patients, and in particular in minimizing the adverse effects of medications such as LIDs and hyperdopaminergic behavioral disorders [3].

To sum up, the results imply that stimulation-dependent modulation of sensorimotor brain networks lead to greater improvement of MDS-UPDRS scores, to a reduction of medication, and thus leads to the facilitating effects of STN DBS in PD. However, the mechanisms that are involved in these facilitating effects of STN DBS are not well understood and are complicated by the fact that the STN is connected to a variety of different brain regions, including the prefrontal-subthalamic hyperdirect pathway, basal ganglia, thalamus, substantia nigra, brainstem [262], and the cerebellum [64,65,263]. In accordance with the complexity of the DBS actions, the response to STN DBS is predicted by the localization of the DBS lead in the STN, and the associated connectivity profile to remote brain regions [229,262]. Structural connectivity between the active electrode and a widespread network, including the superior frontal gyrus [229,262] and the SMA [229], but also the thalamus [262], and the cerebellum [229], predicted a beneficial outcome of DBS [66]. For instance, high-frequency stimulation of the dorsal but not of the ventral STN was associated with changes in the anterior lobe of the cerebellum that were positively correlated with gait velocity [264]. Accordingly, we were able to show an association between VTA and motor improvements in Study 1. The more laterally the electrodes are located, meaning in the motor subdivision of the STN, the greater the improvement in motor functions in our PD patients. However, responses to electrical parameters could also predict beneficial clinical outcomes of STN DBS [66]. The amplitude of stimulation increases over time, which was observed in a 5 -year follow -up study [3,265]. This increase in amplitude was small and reflects adjustments due to disease progression [3]. Moreover, it could also reflect local changes around the electrode, as shown in one study by

a decrease in impedances over time [265]. Nevertheless, adjustments of frequency of stimulation improved control of symptoms in several studies [261,266,267].

The dynamic effects of STN DBS, and in particular, the motor improvements, in patients with PD may be involved in body mass gain after STN DBS as a result of the benefits of treatment [2,10,20,95,97,147,157,162,195]. Several factors appear to be associated with body mass changes after STN DBS in conjunction with motor impairments [30,67]. Among these multifactorial mechanisms, such as dyskinesias, tremor, muscle rigidity, dysphagia, but also problems with chewing and hand-to-mouth coordination were reported in connection with body mass changes [67]. Although it seems very plausible that impaired motor skills, which can restrict eating behavior, can cause changes in food intake in patients with PD, it has not been noticed in previous studies investigating changes in body mass after STN DBS. First of all, the results within the *Swallow subscale* indicate differences between the PD patients treated with STN DBS and healthy control subjects. DBS-treated patients showed great improvement in the *Swallow subscale* after 6 months of stimulation. This effect did not persist over time and worsened again with longer stimulation durations. In contrast, PD patients under best medical treatment showed a slight increase in dysphagia after 6 months, but remained then stable for another 6 months. However, dysphagia as possible cause for body mass changes seems to be more likely to be a feature of disease severity rather than a cause of body mass alterations. As PD progresses, the onset of sarcopenia, as a loss of muscle mass, is reported [67]. Sarcopenia can be discussed as a factor that contributes to changes in body mass in PD. Furthermore, other impaired motor features, such as oral dexterity, can be discussed in connection with the ability to eat independently in PD patients [67]. Therefore, the *Eating Procedure* subscale assesses these motor characteristics. Again, the first general observation was a significant difference between PD patients with STN DBS and healthy control subjects. The high-frequency stimulation did not improve motor skills regarding eating procedure after 6 months of stimulation. Apparently, the eating motor skills regarding eating procedure could not be maintained over time and deteriorated with longer stimulation durations. In contrast, PD patients under best medical treatment remained stable over the study duration. These results underline that DBS cannot completely achieve improvements in motor skills necessary for eating behavior. Moreover, rigidity and dyskinesias are also convincing factors for impaired eating motor skills. Therefore, the *Cutlery Use subscale* reflects an even more specific part of the eating procedure. In accordance with our previous findings, STN DBS affects this subscale with an improvement after 6 months of stimulation, but then again with deterioration after longer stimulation durations. PD patients under best medical treatment showed a slight increase in this subscale after 6 months after baseline measurement, but remained stable at the T_{12M}. Surprisingly, these results imply that stimulation-related improvements in eating motor skills are caused by short term benefits of STN DBS and therefore only lead to short

term effects on eating performance. Therefore, impairments of eating motor skills remain and may not be responsible for body mass gain after STN DBS. It should be mentioned that the applied scale is not an established validated tool in PD research.

Nevertheless, amelioration of motor sign severity in general and not motor impairments restricting eating behavior seems to be a plausible mechanism for postoperative body mass gain. The improved motor skills, i.e. due to reduction of rigidity, dyskinesias, limb akinesia, tremor, and improvement of gait, as well as reduction of dopaminergic medication collectively give rise to reduced energy expenditure [2,10,20,95,97,147,157,162,195]. In contrast, other studies found no correlation between body mass gain and changes in the UPDRS-III score [16,161,162]. Taking advantage of our systematic approach however, we found little or no body mass gain in patients with a higher improvement in terms of disease severity. This observation challenges the concept of reduced energy expenditure as a relevant mechanism, while the localization of DBS electrodes may have a stronger impact on body mass changes [10,40]. In keeping with this notion, the distance of the active electrode to the wall of the third ventricle in the mediolateral direction is inversely correlated with body mass gain and the UPDRS-III score of the contralateral extremities. Patients with more laterally located electrodes had a better motor improvement and gained less body mass than patients with at least one more medially located electrode [10]. In line with these findings, our systematic review showed that patients with a greater improvement in terms of motor dysfunction and a stronger reduction in LEDD were likely to gain less body mass, arguing that an optimal lead localization in the sensorimotor part of the STN is associated with a lower likelihood to develop this side effect. At first sight, this finding seems to be contractionary. On the one hand, DBS improves rigidity and rest tremor, which would otherwise contribute to a higher preoperative energy expenditure, which decreases postoperatively and leads to increased body mass. On the other hand, patients perform greater movements and are more mobile than before the operation, which theoretically should increase energy expenditure. In line with this, patients with a greater motor improvement and a stronger LEDD reduction were less likely to have an increased body mass postoperatively. Although the body mass gain is less pronounced in patients with an optimal lead positioning in the motor part of the STN, they may still gain body mass probably through the reduction in resting energy expenditure.

In contrast, the influence of possible changes in dopamine replacement therapy induced by STN DBS on body mass changes in patients with PD is rarely investigated and still controversial. Patients on levodopa significantly loose body mass within one year of treatment in comparison to patients on dopamine agonists [268]. Here, the effect was dose-dependent: higher LEDD at baseline in levodopa-treated patients was associated with a more rapid body mass loss [268]. In contrast, other studies found no clear relationship between body mass

changes and LEDD although the results may depend on the type of medication [67]. For example, ropinirole had no effect on body mass, whereas cabergoline and pergolide were associated with unintentional body mass loss, and pramipexole increased body mass in patients with PD [67]. Besides the role of dopamine in motivational and reward processing, catecholamines are also involved in the regulation of brown adipose tissue (BAT) thermogenesis. Recent evidence revealed that BAT-dependent non-shivering thermogenesis is involved in regulation of body mass and could increase insulin sensitivity [269]. One possible suggestion is that dopamine replacement therapy may facilitate mitochondrial UCP1-induced thermogenesis, which could potentially also influence body mass.

Do these results indicate that changes in body mass may be a surrogate for alterations in brain activity caused by STN DBS?

4.3 Changes in the Neural Circuit and Plasticity Mechanisms of Cognitive Control of Eating Behavior after DBS of the Subthalamic Nucleus in Parkinson's Disease

The neural regulation of eating behavior is complex because it involves the integration of information from the inner and outer environments with hedonic and cognitive processes. Environmental influences, particularly food cues, can greatly increase appetite beyond physiological needs, leading to dysfunctional eating patterns. In particular, this involves persistent food cravings, which lead to overeating and binge eating disorders. Tasty food cues stimulate excessive food search and intake through cognitive and hedonic processes [140,192,231,270]. PD patients in particular show changes in sensitivity to food rewards [8].

To briefly review, the brain circuitry that mediates reward and reinforcement is disrupted in PD [29]. Furthermore, neurodegenerative processes can affect dopaminergic reward mechanisms [204], leading to changes in action selection, goal-directed behavior, and habit formation [39,67,212]. Anticipatory pleasure (the experience of pleasure in relation to future activities) is impaired in PD, whereas consummatory pleasure (experience when we directly engage in an enjoyable activity) remains intact [120,230]. Consummatory and anticipatory pleasures correspond to liking and wanting concepts, as has already been discussed in the present work [120,230]. Moreover, motivational responses to food cues are altered in PD patients, as they react less motivated to images of food in comparison to control subjects [271]. Changes in the motivation to reward food stimuli were discussed to be involved in body mass gain after STN DBS [22,96]. In PD patients in whom the stimulation was switched ON and OFF compared to healthy control subjects, it was found that the arousal ratings of food images during active stimulation correlated with the postoperative body mass gain [22]. Furthermore, another study found that the degree of acoustic startle reflex inhibition correlated positively with food images, and the patients' arousal ratings correlated with body mass gain after DBS implantation [96]. In accordance with these studies, patients with at least one contact that was placed in the ventromedial area of the STN experienced a significantly higher body mass gain than patients with both active contacts placed laterally [10,40,41]. Moreover, correlations between brain metabolism in associative and limbic areas with postoperative body mass gain as a consequence of STN DBS were found [158], while the reverse correlation pattern was observed in a sample of patients with PD undergoing GPi DBS [260]. PD patients with binge eating disorder were found to have high levels of attentional impulsiveness [272]. This high attentional impulsiveness may increase the attraction exerted by palatable food cues and thus trigger eating behavior [272]. These results confirmed the view that cognitive and emotional mechanisms may be associated with changes in body mass after STN DBS. Attentional impulsiveness, in particular, could play a role in postoperative body mass gain.

In summary, changes in food reward seem to be present in PD, which highlights the role of the striatum. The striatum is important for reward sensitivity and salient events [273] and has also been involved in psychopathologies with aberrant reward processing [274]. Cognitive inflexibility, habit formation, and decision-making are caused by a dysregulation of the striatum and may be secondary consequences of STN DBS [275]. As far as we know, this is the first study to investigate the acute effects of DBS on food cues and different categories of food using an fMRI paradigm.

The direct group comparison for spatial whole-brain maps showed differential activation patterns during active stimulation in brain areas that are important for food cue processing. Furthermore, significant changes in functional connectivity were found in the different brain networks as a comparison between active stimulation, inactive stimulation, and healthy control subjects. Not surprisingly, within this broad network of brain regions, we found activations in exteroceptive (visual) and interoceptive (gustatory and somatosensory) regions that process food-relevant information [192]. Firstly, it was proposed to include the extrastriate visual network (VN) in the processing of the stimulus category, where higher correlations were found for food versus non-food conditions [121,131]. Moreover, this network is also influenced by calorie content, with high-calorie images causing the strongest response [121,131]. The visual system seems to play an important role in differentiating the calorie content of food stimuli. For instance, the lateral occipital cortex was identified to detect the energy values of food cues [276], and the fusiform gyrus triggered higher responses to high-calorie food images [277]. The calorie content, especially of high-calorie foods, appears to have the highest incentive value in processing food cues [121,131]. Furthermore, the VN is substantially affected by body mass and can be influenced by eating behavior, as the stimulus category showed an increased response in slim subjects, whereas obese individuals showed no significant modulation of food cue category, e.g. in the fusiform gyrus [122,278–280]. In addition, restrained eaters were found to have a reduced modulation of the visual system, attempting to reduce visual attention for food cues [121,131]. Since we found an effect of PD pathology on primary visual areas compared to healthy controls, we suggest that possible differences in body mass may be partly due to bottom-up deficiencies in sensory processing.

However, changes in top-down processing mediated by frontal areas may also influence body mass homeostasis [121,131]. The salience network as the core network of goal-oriented behavior was identified in our study as significantly altered due to the high-frequency stimulation of the STN. We found a significant correlation between the time course of the task and the salience network for food versus non-food as well as different image categories under different conditions. It has been discussed to modulate the salience network again by the caloric content of the food. Moreover, it has been suggested that a translational link between

emotion and cognition should be established [281]. In particular, the insula and ACC were found to respond to personal salience, including homeostatic, emotional, motivational, and cognitive processing and integration of information [282,283]. The interaction with the prefrontal and parietal cortex is overly involved in executive control, as evidenced by a certain salience of a cue that draws attention to relevant stimuli [284]. We observed differences between ON versus OFF states in functional connectivity of the salience network, leading to enhanced functional connectivity within the insula and the SMG during active stimulation and the processing of food versus non-food stimuli, as well as during processing of sweet foods images versus neutral images. Interestingly, the SMG is part of the association cortex, which is involved in the interpretation of stimuli. In line with this finding, the correlation analysis of the VTA of active leads and body mass gain showed a negative association between activation of the associative subdivision of the STN and body mass gain in Study 2, indicating that higher activation of the associative area of the STN led to lower body mass gain. As discussed above, these results should still be interpreted with care. These findings suggest that the functional connectivity of insula and SMG may drive body mass gain as a result of DBS. Functional connectivity in both areas was thereby increased during inactivated stimulation and even lower in healthy control subjects. This implies that the effect of high-frequency stimulation does not normalize connectivity patterns within the salience network, but rather increases functional connectivity during food cue processing. Therefore, as a mediator for top-down processing, salience network appears to induce increased visual processing and awareness of food cues during active stimulation, which could potentially lead to increased awareness and attention to food cues in PD, particularly with respect to sweet foods.

Up to this point, we have shown modulation elicited by STN DBS in functional connectivity in different brain networks. In particular, the salience network during active DBS was modulated by the stimulus category. Moreover, PD patients showed changes in FC when stimulation was switched while viewing sweet foods. In general, the insula has been identified to process gustatory information, emotional valence, and attention from stimuli to guide behavior [121,131,285–289].

Moreover, it is reasonable to expect that both reward sensitivity and motivational changes are likely to show an interaction in food intake and body mass gain after STN DBS. In particular, individual features, such as attentional impulsiveness, may increase the susceptibility of patients to experience body mass gain. In obese subjects, brain regions that mediate the motivation and attention salience of food cues, especially within the reward system, showed greater activation in response to food cues compared to lean individuals [290]. We therefore assessed functional connectivity changes in the reward network in a second step to identify neural correlates for changes in food-related motivational behavior. We found that active stimulation while viewing the food cue leads to reduced functional connectivity in the left

putamen and right lateral occipital cortex, left amygdala and right lateral occipital cortex, bilateral lateral occipital cortex and bilateral insula, as well as left hippocampus and left insula. In addition, for sweet foods, active subcortical stimulation led to reduced functional connectivity in the left NAcc and right lateral occipital cortex, right lateral occipital cortex, and bilateral insula and right lateral occipital cortex, and bilateral OFC. Interestingly, the insula and OFC are activated by the memory of rewarding effects of food and by the taste of palatable food [33-36,205,206]. Moreover, several studies pointed to the key role of the OFC in decision-making for rewards, and it appears to be responsible for cost-benefit calculations and rewarding value of taste [33-36,205-207]. Furthermore, the ventral pallidum encodes the 'liking' of tastes and the reward of food in humans [119,120,230]. The evidence from our study that active stimulation showed less activation in this area may indicate that PD patients may experience a greater reluctance to view food images during the reallocation of attention to food images. This finding could be analogous to our findings on the incentive salience, where no impact of food cues on incentive salience was observed in Study 1. This could be explained by various theories that have been put forward with regard to the reward system and its anatomical underpinnings. For instance, the Reward Surfeit Theory of Obesity [192,270,292] proposed that overeating is caused by a strong and lasting reward during the intake of palatable, high-calorie food. A refinement of this theory, on the other hand, suggests that reward responses are triggered by anticipatory visual cues, which down-regulate the reward system after repeated cue-reward associations and up-regulates habit formation driven by visual cues. This concept is similar to that of chronic addiction and drug abuse [192,293,294]. The modifications in the reward and habit system are driven by variations in dopaminergic neurotransmission [192,295–297]. On the other hand, Reward Deficit Theory of Obesity [298] has been proposed to induce overeating by reducing the sensitivity of the reward system to dopaminergic signals [192]. This theory was underlined by the initial evidence that blocking D2 receptors leads to obesity [192]. Moreover, the Refined Dynamic Vulnerability Model [299,300] points in the same direction by predicting overeating by blunted responses of the reward system to palatable, high-calorie food intake, thereby contributing to body mass gain [192]. There seems to be a U-shaped response in the ventral striatum to too low and too high dopamine levels, which leads to obesity via different mechanisms [192].

When interpreting these results, it is important to consider limitations. First, the food viewing paradigm could be confounded by different stimulation durations, disease duration, and disease progression. Activation during imaging may also be driven by the dopaminergic action of the Anti-parkinsonian medication which is different across patients. In addition, it may be possible that the activations found in regions related to attention, motivation, and food reward are not food-specific but are increased by general reward sensitivity, such as nicotine or money [192,301]. Furthermore, this phenomenon could be explained by the food images used in the

fMRI paradigm. PD patients may find the presented images unappetizing, which leads to greater dislike. Further studies should perform a food image evaluation of all food images presented during the fMRI to exclude the effect of processing due to the visual attributes of the images. Nonetheless, when interpreting the results, it should be taken into account that the signal-to-noise ratio was disrupted due to artifacts of the DBS device within the MR scanner. Therefore, the exact role of the STN and its acute stimulation in reward processing and response control needs further investigation. However, food cues and especially sweet foods exerted a strong motivating effect during active stimulation, which could result in overeating with high-calorie or high-carbohydrate foods. The relevance of higher sweet cravings in PD patients due to active stimulation compared to inactivated stimulation and age-matched healthy control subjects as a condition of possible increased energetic demands is difficult to interpret in the context of generally reduced activity of the reward system and requires further investigation.

To briefly sum up, we were able to confirm one of the most frequently reported findings in imaging studies on food perception: higher recruitment of regions involved in salience, such as the insula, in response to food-related stimulation [121,132,134,136,192,273]. The insular cortex has been linked to subjective experiences of several types of cravings, such as food cravings [192,285–287,289], substance abuse [192], and cigarette addiction [192,302], suggesting its role in cravings and addiction-like behaviors [192]. We could confirm an increased salience of food cues, reflecting an increased emotional balancing in accordance with the findings of co-activation of the associative and limbic areas of the STN as a result of STN DBS. Furthermore, we were able to highlight a new finding, namely support for the Refined Dynamic Vulnerability Model [299,300]. The theory is supported by our finding that visual food cues in regions involved in salience triggered an increased response to visual cues to food and at the same time blunted activations in reward areas. It was striking that we noticed increased salience responses towards sweet foods, confirming earlier evidence of sweet foods in PD [142–145]. Finally, our results indicate a potential imbalance between top-down and bottom-up processing of appetizing food cues, which could reflect a lack of control over the desire to eat and thereby cause an increase in body mass (Fig. 38).

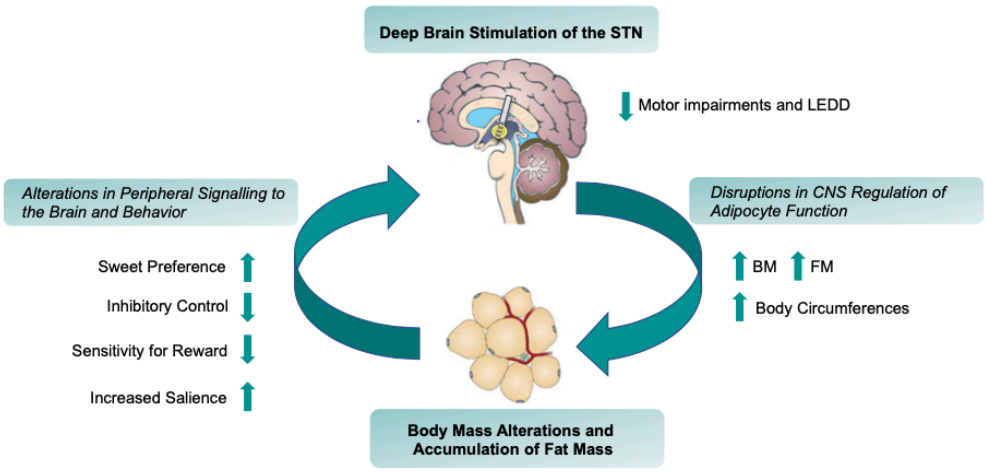

Figure 38. Summary of findings. Abbreviations: BM, body mass; FM, fat mass; STN, subthalamic nucleus; CNS, central nervous system.

4.4 Limitations and Strengths

First, the systematic review and meta-analysis were calculated on the basis of incomplete data sets, some of which were imprecise in terms of reporting on several variables of interest. The sub-analyses therefore included a varying number of subjects. Some relevant studies [22,96] could not be included because the exact time of post-surgery assessment was missing. Thus, we were not able to generate forest and funnel plots due to a lack of data. Given that only six studies contained sufficient information on control groups, it was not possible to calculate the required odds ratios.

Second, it is important to consider the limited sample size in Study 1. First of all, due to methodological aspects: A limited sample size reduces the statistical power and may explain negative results since the need to correct multiple comparisons often increases the likelihood of producing false-negative results. Next, it is relevant to consider sample size in relation to the variability of the degree of postoperative body mass gain in patients with PD after STN DBS. In fact, our results indicate the possible existence of factors that may make some patients more susceptible to body mass gain than others. Taking into account already small sample size and further missing data due to dropouts or due to single missing measurements, higher variability of data was observed. Nevertheless, a clear highlight of the present thesis is the sample size of PD-DBS group considering that STN DBS surgery is not that often performed and due to the limited time for graduation within the GRK1957.

Another challenge within the study design is that we do not have a cover story, and explaining the study objectives at the beginning might influence the development of body mass, which means that it is possible that patients monitor their body mass closely and try not to gain body mass[23] . Furthermore, we did not take into account other factors, such as hormones (e.g. adipocytokines) involved in energy metabolism, or changes in spontaneous physical activity, which are likely to play a crucial role in determining the risk of body mass gain. However, an advantage of the present thesis is the enrollment of control groups since we can exclude that body mass gain observed in patients may be linked to factors other from surgery. In addition, we have covered only a limited period of time. Therefore, future studies should enroll a larger cohort of patients, and longer assessment periods are justified in order to investigate the overall time course of body mass changes. Moreover, due to individual differences, such as circadian influences, differences in motor impairments, or the number of meals taken, eating diaries and control for normal eating behavior should be included. Another idea is to enroll additional control groups, such as ET or cervical dystonia, both treated with DBS. However, Study 1 was designed as a prospective and longitudinal study with multimodal assessment of

[23] A wife of a DBS-treated patient reported this observation.

contributing factors of body mass gain, which is a clear strength. Moreover, the control groups give collectively evidence that body mass alterations are caused by STN DBS.

Third, general limitations of the DBS treatment *per se* may include effects of focality or the exact position within the STN, interindividual anatomical variability, the variability in the efficacy of the treatment, and the fact that the expected or simulated electrical stimulation is not the actual response of the DBS (we do not know). Moreover, we do not know whether there are calcium plasticity effects through DBS, which means that it is not clear if we induce LTD or LTP, or first LTD then LTP as a long-term effect, which is possibly frequency-dependent. Furthermore, it is unknown how the effect of synaptic memory influences DBS. Finally, it is not clear how CSF affects DBS in terms of conductivity and current propagation. In addition, animal studies on body mass gain after STN DBS are rare, and sham studies are only difficult to achieve in humans, although we need them for very well-controlled studies.

Finally, the validity of the self-report measures used in our study is at the center of a long-standing debate. In some reports, no change in food intake, appetite, or hunger was observed which could be attributed to the fact that the self-reported intake was error-prone [156]. Although other measures have shown that they successfully discriminate between the participants' hunger state, it would be worth considering more objective tests [8]. In addition, since liking was assessed using a question without presenting the reward itself, it is possible that liking ratings may still be influenced by the participants' anticipatory pleasure toward the reward. In addition, we do not have positive controls in the 'wanting-liking' test, which means that we should have images where the patients should change their rating to check whether the subjects have understood the instructions. Moreover, these discrepancies in the questionnaires used to assess appetite and the hedonic effects of food cues may be due to individual differences, e.g. patients in our study might consider low-calorie foods more hedonic than high-calorie foods (unfortunately, we did not match the two food categories in terms of hedonic value).

5 Conclusion

Deep brain stimulation is an effective technique that significantly improves motor and non-motor symptoms and the quality of life of patients with PD. Unfortunately, it is associated with a rapid and undesirable postoperative body mass gain, which has been frequently reported in PD patients after STN DBS. The increase in body mass is fast and sustained in almost all patients. The risk of gaining body mass varies greatly among patients and differs between genders. However, both genders gained primarily in FM, indicating an increase in body mass that may not be tolerated due to metabolic repercussions and negative health implications. Postoperative body mass gain is thereby a multifactorial phenomenon and includes both motor and non-motor aspects.

The present thesis shows for the first time simultaneously that, according to previous research, body mass gain can be determined by a regional effect of stimulation on bordering structures involved in the central regulation of reward and energy balance. Body mass gain could thus result from increased salience of food cues, reflecting the increased emotional balance in accordance with the findings of co-activation of the limbic and potentially also the associative areas of the STN. Furthermore, we were able to highlight that the response to visual food cues has improved in regions of the salience network, especially for sweet foods, while at the same time, activations in reward areas have decreased. Finally, our results suggest a potential imbalance in both top-down and bottom-up processing of appetitive food cues that may reflect a lack of control in the desire to eat, changes in the sensitivity to food reward cues, and changes in eating behavior, including higher food intake, and increased appetite.

These findings underline the metabolic relevance of high-frequency stimulation of subcortical areas. In this respect, the clinical implications of our findings are that all patients should be informed that body mass gain may occur as a consequence of DBS. Potential candidates for this treatment should be monitored for initial changes in body mass and composition and possibly subsequent changes in body mass and composition. Strategies need to be developed to prevent postoperative body mass gain through preoperative nutritional counseling, physiotherapy, and sports therapy as well as continued therapy after implantation of the DBS device, to prevent rapid body mass gain. A promising option in clinical practice is current steering of the electrical field using segmented electrodes which enables the shaping of current distribution. Patients with a high likelihood of postoperative body mass gain or preoperative overweight or obesity could benefit from the implantation of such electrodes as they allow more postoperative adjustments. Based on the findings of this thesis, any attempt to optimize the stimulation of the sensorimotor STN and to avoid stimulation of the medial STN is urgently needed. Our promising findings could also be translated into new clinical approaches tailored to specific target groups, such as larger and better-controlled studies to determine the long-

term effectiveness of nutritional intervention studies. Moreover, the newly gained insights highlighted in the present thesis could provide new approaches to study DBS in the context of metabolic function and to develop new targets for DBS treatment with fewer side effects. In general, it should be recognized that patients may have the same signs, symptoms, or diagnosis, the underlying changes in the causal circuit may vary considerably from patient to patient. In view of this heterogeneity of neuropathology and the diversity of presentation, brain-circuitry-based precision medicine is a cornerstone for personalized therapies of movement disorders. Despite the well-established evidence that deep brain stimulation is an effective treatment option for movement disorders, many challenges remain both in the short and long term. Neuromodulation has thereby undergone a revolutionary revaluation in recent decades, with the emphasis on multidimensional data-driven approaches in order to achieve a higher level of individualization in therapy. These include better devices that allow finer control over the spatial distribution of current around the active contact, auto-adjusting devices based on biophysiological markers, closed-loop neurostimulation systems as well as computer-aided systems for surgical planning and postoperative programming.

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Appendix

Appendix A

Ethics Approval.

UNIVERSITÄT ZU LÜBECK

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Herrn
PD Dr. med. Brüggemann
Klinik für Neurologie
im Hause

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Aktenzeichen: 17-198
Datum: 03. November 2017

Sitzung der Ethik-Kommission am 06. Juli 2017, Nachreichung vom 30.10.2017
Antragsteller: Herr PD Dr. Brüggemann
Titel: Mechanismen der Gewichtszunahme bei Morbus Parkinson nach Tiefer Hirnstimulation

Sehr geehrter Herr Dr. Brüggemann,

in Ihrem Schreiben vom 30. Oktober 2017 gehen Sie auf die Kommentare der Kommission vom 13. Oktober 2017 ein und legen überarbeitete Unterlagen vor (Probandeninformation für gesunde Kontrollpersonen und für Patienten, undatiert).

Die Ethik-Kommission hat **keine Bedenken** mehr gegen die Durchführung des Studienvorhabens.

Bei Änderung des Studiendesigns sollte der Antrag erneut vorgelegt werden. Über alle schwerwiegenden oder unerwarteten und unerwünschten Ereignisse, die während der Studie auftreten, ist die Kommission umgehend zu benachrichtigen. Die Deklaration von Helsinki in der aktuellen Fassung fordert in § 35 dazu auf, jedes medizinische Forschungsvorhaben mit Menschen zu registrieren. Daher empfiehlt die Kommission grundsätzlich die Studienregistrierung in einem öffentlichen Register (z.B. unter www.drks.de). Die ärztliche und juristische Verantwortung des Studienleiters und der an der Studie teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethikkommission durch unsere Stellungnahme unberührt.

Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

Appendix B

B.1. Visual-analog scale of eating motor skills.

Fragebogen zur Essmotorik

Probanden-Nr: _____ Gruppe:_____ Datum:_____

Uhrzeit:_____ Sitzung: _____

1) Hatten Sie in der vergangenen Zeit Probleme beim Schlucken oder beim Essen Ihrer Mahlzeiten? Zum Beispiel: Mussten Sie Ihre Mahlzeiten zerkleinern oder zerdrücken, um ein Verschlucken zu vermeiden?

Gar nicht _____ Extrem

2) Hatten Sie in der letzten Zeit häufig Schwierigkeiten mit der Einnahme Ihrer Mahlzeiten generell?

Gar nicht _____ Extrem

3) Hatten Sie in der letzten Zeit häufig Schwierigkeiten mit dem Gebrauch Ihres Bestecks? Haben Sie zum Beispiel Schwierigkeiten beim Umgang mit Fingerfood oder im Gebrauch von Gabel, Messer, Löffel oder Stäbchen?

Gar nicht _____ Extrem

B.2. Visual-analog scale of symptoms I.

Name:	Sitzung:	Datum:	Uhrzeit:

*In welchem Ausmaß treffen folgende Aussagen zur Beurteilung ihres **momentanen** subjektiven Gefühles auf Sie zu?*
Bitte markieren Sie bei jeder Aussage die entsprechende Stelle auf der schwarzen Linie mit einem Kreuz.

Wie... fühlen Sie sich im Moment?

Überhaupt nicht	hungrig	Extrem
Überhaupt nicht	satt	Extrem
Überhaupt nicht	durstig	Extrem
Überhaupt nicht	ängstlich	Extrem
Überhaupt nicht	fröhlich	Extrem
Überhaupt nicht	gestresst	Extrem
Überhaupt nicht	schläfrig	Extrem
Überhaupt nicht	konzentriert	Extrem

Wie stark ist Ihr momentanes Bedürfnis nach Essen?

Überhaupt nicht stark	...generell	Sehr stark
Überhaupt nicht stark	...nach Süßem	Sehr stark
Überhaupt nicht stark	...nach Herzhaftem	Sehr stark

B.3. Visual-analog scale of symptoms II.

Code: Sitzung: Datum:

VAS zum aktuellen Befinden

In welchem Ausmaß treffen folgende Aussagen zur Beurteilung Ihres **momentanen** subjektiven Gefühles auf Sie zu? **Bitte markieren Sie bei jeder Aussage die entsprechende Stelle auf der schwarzen Linie mit einem Kreuz.**

Wie stark treffen die folgenden Symptome im Moment auf Sie zu?

Angst

Überhaupt nicht _____ Extrem

Schwitzen

Überhaupt nicht _____ Extrem

Körperliches Unwohlsein

Überhaupt nicht _____ Extrem

Innere Unruhe

Überhaupt nicht _____ Extrem

Kribbelgefühl

Überhaupt nicht _____ Extrem

Zittern

Überhaupt nicht _____ Extrem

Hunger

Überhaupt nicht _____ Extrem

Herzklopfen

Überhaupt nicht _____ Extrem

Verschwommenes Sehen

Überhaupt nicht _____ Extrem

Konzentrationsfähigkeit

Überhaupt nicht _____ Extrem

Durst

Überhaupt nicht _____ Extrem

Ärger

Überhaupt nicht _____ Extrem

Kopfschmerzen

Überhaupt nicht _____ Extrem

Sattheit

Überhaupt nicht _____ Extrem

Übelkeit

Überhaupt nicht _____ Extrem

Traurigkeit

Überhaupt nicht _____ Extrem

Atembeschwerden

Überhaupt nicht _____ Extrem

Freude

Überhaupt nicht _____ Extrem

Müdigkeit

Überhaupt nicht _____ Extrem

Schwindel

Überhaupt nicht _____ Extrem

Nervosität

Überhaupt nicht _____ Extrem

Appetit

Überhaupt nicht _____ Extrem

Juckreiz

Überhaupt nicht _____ Extrem

Schwäche

Überhaupt nicht _____ Extrem

Wärme

Überhaupt nicht _____ Extrem

Aktivität

Überhaupt nicht _____ Extrem

Völlegefühl

Überhaupt nicht _____ Extrem

B.4. Questionnaire of behavioral inhibition and activation system.

Probanden-Nr._____

Der folgende Fragebogen enthält eine Reihe von Feststellungen, mit denen man sich selbst beschreiben kann. Diese Feststellungen können genau auf Sie zutreffen, eher zutreffen, eher nicht oder gar nicht auf Sie zutreffen. Zur Beantwortung des Fragebogens setzen Sie ein Kreuz in das entsprechende Rechteck. Bitte beantworten Sie jede Feststellung, auch wenn Sie einmal nicht sicher sind, welche Antwort für Sie zutrifft. Kreuzen Sie dann diejenige Antwort an, die noch am ehesten auf Sie zutrifft.

(1) = ‚trifft für mich gar nicht zu'

(2) = ‚trifft für mich eher nicht zu'

(3) = ‚trifft für mich eher zu'

(4) = ‚trifft für mich genau zu'

1.	Eine eigene Familie ist die wichtigste Sache im Leben.	1	2	3	4
2.	Sogar wenn mir etwas Schlimmes bevorsteht, bin ich selten nervös oder ängstlich.	1	2	3	4
3.	Ich strenge mich besonders an, damit ich erreiche, was ich möchte.	1	2	3	4
4.	Wenn mir etwas gut gelingt, bleibe ich sehr gern bei der Sache.	1	2	3	4
5.	Ich bin immer bereit, etwas Neues zu versuchen, wenn ich denke, dass es Spaß machen wird.	1	2	3	4
6.	Es ist wichtig für mich, wie ich gekleidet bin.	1	2	3	4
7.	Wenn ich erreiche, was ich will, bin ich voller Energie und Spannung.	1	2	3	4
8.	Kritik oder Beschimpfungen verletzen mich ziemlich stark.	1	2	3	4
9.	Wenn ich etwas haben will, tue ich gewöhnlich alles, um es zu bekommen.	1	2	3	4
10.	Ich werde oft Dinge nur deshalb tun, weil sie Spaß machen könnten.	1	2	3	4
11.	Es ist schwierig für mich, Zeit für solche Dinge wie Friseurbesuche zu finden.	1	2	3	4
12.	Wenn ich eine Chance sehe, etwas Erwünschtes zu bekommen, versuche ich sofort mein Glück.	1	2	3	4
13.	Ich bin ziemlich besorgt oder verstimmt, wenn ich glaube oder weiß, dass jemand wütend auf mich ist.	1	2	3	4
14.	Wenn ich eine Gelegenheit für etwas sehe, das ich mag, bin ich sofort voller Spannung.	1	2	3	4
15.	Ich handle oft so, wie es mir gerade in den Sinn kommt.	1	2	3	4
16.	Wenn ich glaube, dass mir etwas Unangenehmes bevorsteht, bin ich gewöhnlich ziemlich unruhig.	1	2	3	4
17.	Ich wundere mich oft über das menschliche Verhalten.	1	2	3	4

18.	Wenn mir etwas Schönes passiert, berührt mich das sehr stark.	1	2	3	4
19.	Ich bin besorgt, wenn ich glaube, dass ich eine wichtige Sache schlecht gemacht habe.	1	2	3	4
20.	Ich brauche Abwechslung und neue Erfahrungen.	1	2	3	4
21.	Wenn ich etwas erreichen will, verfolge ich hartnäckig mein Ziel.	1	2	3	4
22.	Verglichen mit meinen Freunden habe ich sehr wenig Ängste.	1	2	3	4
23.	Ich fände es sehr aufregend, einen Wettbewerb zu gewinnen.	1	2	3	4
24.	Ich habe Angst, Fehler zu machen.	1	2	3	4

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OBESITY/NEUROBIOLOGY

WILEY OBESITY Reviews

A systematic review of body mass gain after deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease

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Summary

This systematic review investigated the effects of deep brain stimulation of the subthalamic nucleus on extent and time course of body mass changes in patients with Parkinson's disease. A computerized search identified relevant articles using *a priori* defined inclusion and exclusion criteria. A descriptive analysis was calculated for the main outcome parameters body mass and BMI. Thirty-eight out of 206 studies fulfilled the inclusion criteria (979 patients aged 59.0±7.5 years). Considering the longest follow-up time for each study, body mass and BMI showed a mean increase across studies of +5.71kg (p < .0001; d = 0.64) and +1.8kg/m^2 (p < .0001; d = 1.61). The time course of body mass gain revealed a continuous increase ranging from +3.25kg (d = 0.69) at 3 months, +3.88kg (d = 0.21) at 6 months, +6.35kg (d = 0.72) at 12 months, and +6.11kg (d = 1.02) greater than 12 months. Changes in BMI were associated with changes in disease severity (r = 0.502, p = .010) and pharmacological treatment (r = 0.440, p = .0231). Data suggest that body mass gain is one of the most common side effects of deep brain stimulation going beyond normalization of preoperative weight loss. Considering the negative health implications of overweight, we recommend the development of tailored therapies to prevent overweight and associated metabolic disorders following this treatment.

KEYWORDS

deep brain stimulation, Parkinson's disease, subthalamic nucleus, weight gain

Britta Wilms and Norbert Brüggemann contributed equally

1 | INTRODUCTION

Body mass changes in both directions, weight loss and weight gain, have been reported in patients with Parkinson's disease (PD)[1] and are often observed in response to treatment. Deep brain stimulation (DBS) of either the subthalamic nucleus (STN) or globus pallidus internus (GPi) is an efficient treatment option for severe motor complications in advanced PD. Hence, DBS significantly improves motor and non-motor fluctuations, rest tremor, dyskinesias as well as quality of life (QoL), and usually results in a decrease of dopaminergic medication.[2-7] Side effects may include speech disturbance, postural instability, mood changes, and significant body mass gain independent of the DBS target region.[8-10] The extent and time course of body mass gain after DBS surgery have not yet been systematically addressed[11] although some potential mechanisms of body mass gain have been suggested like improvement of resting tremor and dyskinesias,[4,12] reduction in energy expenditure,[13,14] changes in eating behaviour and food intake,[12,15-20] as well as alterations in hypothalamic adipokine release.[10,18,19,21-23]

The purpose of this study is to systematically analyze the extent and range of body mass gain after STN DBS. We selected available studies investigating postoperative body mass changes and conducted a systematic review to quantify stimulation-induced body mass changes. We aimed to clarify *i)* the magnitude of the relationship between STN DBS and body mass gain, *ii)* the extent of body mass gain and BMI gain, and *iii)* the time course of assumed body mass and BMI gain.

2 | METHODS

2.1 | Search Strategy

A systematic review was conducted on original studies that assessed body mass gain in patients with PD after STN DBS, following the PRISMA recommendations. A computerized search for all STN DBS studies in PD was performed in MEDLINE, Cochrane Library, Clinical Trials, and Livivio containing the following search terms (last search performed on November 11th, 2017): (((Parkinson) OR (Parkinson's disease) OR (PD)) AND (((weight) OR (BMI)) AND ((change) OR (gain) OR (increase))) AND ((STN DBS) OR (Subthalamic nucleus deep brain stimulation) OR (deep brain stimulation) OR (DBS) OR (GPi deep brain stimulation) OR (globus pallidus deep brain stimulation) OR (pallidal deep brain stimulation))). Search was performed for articles published between 1984 and 2017 and was restricted to English and German publications, but not to age and gender of subjects, as well as origin of publication.

2.2 | Study Selection and Data Collection

All abstracts and articles of the computerized search were independently screened by two investigators (JS, BW) for potential relevance. Any disagreements were resolved by further examination of a third investigator (NB) and via consensus.

The following studies were excluded: reviews, letters, commentaries, abstracts, posters, case reports, correspondences to articles, and double nominations of publications in different search portals. Furthermore, animal studies, studies including DBS of the GPi, ventral intermediate thalamic nucleus (VIM) or caudal zona incerta (cZi), studies with alternative surgical methods (e.g. pallidotomy), articles reporting non-weight related outcomes, studies assessing body mass gain in another disease and studies targeting other research questions were not considered.

The included studies had to contain at least one of the following outcomes: absolute body mass before and after STN DBS or body mass changes, absolute body mass index (BMI) before and after STN DBS or BMI changes. Normal weight (BMI: 18.5-24.9 kg/m^2), overweight (BMI: 25.0-29.9 kg/m^2) and obesity were defined according to the WHO definition. THE WHO defines overweight and obesity for adults as follows: overweight is a BMI greater than or equal to 25 and obesity is a BMI greater than or equal to 30. [24] Additionally, UPDRS III and IV scores, as well as levodopa equivalent doses (LEDD) were investigated to reveal the efficacy of the DBS treatment. Moreover, sufficiently specified numerical baseline and follow-up outcome data for body mass, BMI, UPDRS III, UPDRS IV, and LEDD were required as well as data on standard deviations (SD) or standard errors of the mean.

2.3 | Statistical analyses

Results are reported as mean ± SD. Data were analyzed using Excel Version 2016 (Microsoft, Redmond, WA), SPSS Statistics 22.0 (SPSS Inc, Chicago, IL), and GraphPad Prism version 7.03 (GraphPad Software, La Jolla, CA) for Windows®. Paired Student's t-test was used to test for changes in BM, BMI, UPDRS III and IV, and LEDD. The effect size of BM and BMI changes were described by Cohen's d. Variables associated with changes in the main dependent variables (i.e. BM, BMI) were analyzed by Pearson correlation. Missing outcome data and SDs were calculated if applicable. All results were considered as statistically significant at the 5% level.

3 | RESULTS

3.1 | Study Selection and Characteristics

The literature search identified 206 potentially relevant articles of which 154 studies were assessed for a more detailed evaluation (Figure 1). Following the selection process, 54 studies[1,2,4,6,8-10,12-21,23,25-58] fulfilled the inclusion criteria as described above. For the analysis, 38 studies could be included of which 18 (47%) were prospective case studies, 12 (32%) were prospective case-control studies, 4 (11%) were retrospective case studies, 2 (5%) were retrospective case-control studies, 1 (2.5%) was a cross-sectional, and 1 (2.5%) was a retrospective survey study. In sum, the 38 selected studies included 979 patients with PD and STN DBS and 287 controls comprising of non-stimulated patients with PD under medical treatment (N = 186) and healthy control subjects (N = 101).

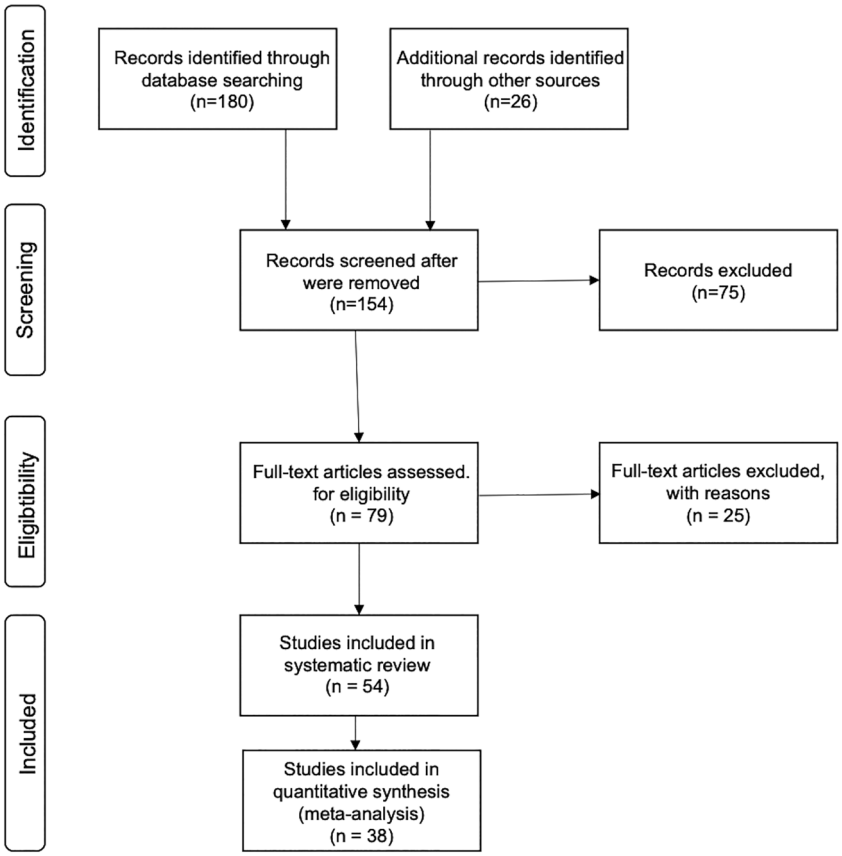

FIGURE 1 Systematic review and meta-analysis PRISMA flow diagram.

3.2 | Patient characteristics

Table 1 provides demographic information on subjects from each study. Study sample sizes ranged from 7 to 57 subjects (mean, 25.8 ± 11.6; N = 979) with a follow-up time between 1 month to 60 months after DBS implantation (mean, 17.8 ± 15.2 months). The mean age across studies was 59.0 ± 7.5 years (range, 54.9-66.0 years; N = 833). The mean disease duration prior to surgery was 12.4 ± 4.0 years (range, 8.5 years - 15.7 years; N = 680) at baseline. There was no specification of ethnicity of subjects in the studies.

3.3 | Body mass change

On average, we identified increases in body mass during the entire period. The analysis revealed a significant body mass gain in 21/21 studies (100%) with complete data sets at the latest follow-up.[1,4,8,13,14,16,17,23,25,31,32,38,40-44,54,56,59] For these 21 studies, the overall pooled mean body mass gain was +5.71 kg (baseline weight, 73.25 kg; range of body mass gain, 1.30 kg - 11.10 kg; 95% CI, -6,69, -4,74; N = 446; p < .0001; Figure 2) with a corresponding effect size of d = 0.64 (Suppl. material). To minimize a potential bias, a secondary analysis for different postoperative time points was performed at 3, 6, 12 months and greater than 12 months follow-up time.

The mean body mass gain 3 months after surgery was +3.25 kg (baseline weight, 73.70 kg; range body mass gain, 1.10 kg - 5.90 kg; 95% CI, -4.32, -2.18; N = 190; p < .001) with a corresponding effect size of d = 0.66. Mean change in body mass from baseline to 6 months following DBS was +3.88 kg (baseline weight, 74.98 kg; range body mass gain, 2.64 kg - 5.50 kg; 95% CI, -5.09, -2.68; N = 127; p < .001; d = 0.22). At 12 months follow-up, body mass increased by +6.35 kg (baseline weight, 71.39 kg; range body mass, 2.90 kg - 11.10 kg; 95% CI, -7.99, -4.71; N = 241; p < .0001; d = 0.72). Greater than 12 months follow-up, body mass gain remained stable with +6.11 kg (baseline weight, 69.23 kg; range body mass gain, 4.90 kg - 8.10 kg; 95% CI, -8.32, -3.91; N = 66; p = .003; d = 1.02).

3.4 | Change in BMI

Nineteen studies (N = 512) were available for the assessment of the BMI. All studies revealed an increase in BMI for the latest follow-up.[1,4,6,13-15,23,28,30,32,40-44,46,49,54] The overall pooled mean increase in BMI was +1.83 kg/m^2 (baseline BMI, 24.84; range BMI gain, 0.40-3.20 kg/m^2; 95% CI, -2.33, -1.31; p < .0001) with a mean effect size of d= 1.61 (Suppl. material) for the latest follow-up. The share of patients with overweight (BMI 25.0-29.9 kg/m^2) increased from 40% to 78%, and thus the share of patients with normal weight decreased from 60% to 22%.

TABLE 1 Overview about studies assessing changes of body mass in patients with PD after DBS device implantation.

Reference	Year	Study type	Stimulation Target	N enrolled	Mean follow-up (months)	Mean age at surgery (yrs)	Mean disease duration before surgery (yrs)	Mean preoperative levodopa dose (mg)	Mean increase of body mass (kg)	Mean effect size of body mass gain (Cohens' d)
Aiello *et al.*	2017	Prospective case -control study	bilateral STN DBS	18	6	60.17 ± 6.9	9.77 ± 4. 19	1113.56 ± 436.35	2.64	0.14
Balestrino *et al.*	2017	Prospective case study	bilateral STN DBS	32	12	60 ± 7	12 ± 4	1111.6 ± 396.7	6.7 ± 5.0	0.49
Bannier *et al.*	2009	Prospective case study	bilateral STN DBS	22	16	60.75 ± 2.1	9.8 ± 0.6	1135.4 ± 91.4	5.85 ± 1.15	2.19
Barichella *et al.*	2003	Prospective case study	bilateral STN DBS	30	12	60.0 ± 7.1	13.5 ± 3.7	831.4 ± 404.7	9.3 ± 6.2	NA
Escamilla-Sevilla *et al.*	2011	Prospective case -control study	bilateral STN DBS	20	6	58.0 ± 13.2	11.7 ± 3.9	1470.5 ± 666.4	3.6	0.25
Ford *et al.*	2004	Prospective case study	bilateral STN DBS	30	12	58.8	12.8	1665	2.7	NA
Foubert-Samier *et al.*	2012	Cross-sectional study between 1999–2006	bilateral STN DBS	47	55	56.9 ± 8.1	12.6 ± 5.2	1088.2 ± 354.9	7.2 ± 8.1	NA
Genty *et al.*	2011	Prospective case study	bilateral STN DBS	53	6	59.9 ± 8.3	11.5 ± 4.2	1138 ± 349	NA	NA
Guimares *et al.*	2009	Prospective case study	bilateral STN DBS	57	30	61 ± 6.8	14 ± 7.7	1024.5 ± 431	13.17 ± 10%	NA
Jorgensen *et al.*	2011	Prospective case study	bilateral STN DBS	10	12	61.7 ± 6.5	13.3 ± 4.8	878 ± 118	4.7 ± 1.6	1.76
Lee *et al.*	2011	Retrospective case-control study	bilateral STN DBS unilateral STN DBS	25 18	24	PD unilateral: 60 ± 2.5PD bilateral: 61.1 ± 1.1	PD unilateral: 10.3 ± 0.92PD bilateral: 12.7 ±1.4	unilateral: 1245 ± 114 bilateral: 1233 ± 67	3.9 ± 2.0 (unilateral) 5.6 ± 2.1 (bilateral)	NA
Limousin *et al.*	1998	Prospective case study	bilateral STN DBS	24	12	56 ± 8	14 ± 5	1224 ± 723	4.2	NA
Locke *et al.*	2011	Retrospective case study	STN DBS (bilateral and unilateral)GPi - DBS (bilateral and unilateral)	GPi: 23 (N=10 bilateral, N=13 unilateral)STN: 21 (N=15 bilateral, N=6 unilateral)	18	NA	NA	NA	4.29 ± 6.79 lb (Pounds)	NA
Macia *et al.*	2004		bilateral STN DBS	19	12	59.9 ± 6.60	15 ± 3.2	993 ± 408	9.7 ± 7.0	0.8

(Continues)

TABLE 1 (Continued)

Reference	Year	Study type	Stimulation Target	N enrolled	Mean follow-up (months)	Mean age at surgery (yrs)	Mean disease duration before surgery (yrs)	Mean preoperative levodopa dose (mg)	Mean increase of body mass (kg)	Mean effect size of body mass gain (Cohens' d)
		Prospective case-control study								
Markaki *et al.*	2012	Prospective case study	bilateral STN DBS	23	6	65.2 ± 8.9	12.7 ± 6	998 ± 252	3.09 ± 5.0	NA
Millan *et al.*	2017	Prospective case-control study	bilateral STN DBS	14	24	60 ± 6.8	2.2 ± 1.4	NA	NA	NA
Mills *et al.*	2012	Prospective case -control study	Bilateral STN DBSbilateral GPi DBS	61	12	61.5 ± 9.5	NA	NA	NA	NA
Moghaddasi & Boshtam	2010	Retrospective case study	bilateral STN DBS	15	3	51.8 ± 8.3	8.5 ± 1.5	NA	3.4	0.41
Montaurier *et al.*	2007	Prospective case -control study	bilateral STN DBS	24	3	61.51 ± 1.4	10.0 ± 1.05	1174 ± 89	3.4 ± 0.6	0.16
Moro *et al.*	1999	Prospective case study	bilateral STN DBS	7	16	57.4	15.4	1507.3 ± 821.5	7.9	1.34
Novakova *et al.*	2007	Retrospective survey study	bilateral STN DBS	25	45	55.0	15.0	NA	9.4	NA
Novakova *et al.*	2011	Prospective case study	bilateral STN DBS	27	12	56.8 ± 7.0	12.5 ± 4.0	1330 ± 538	5.2 ± 5.8	0.34
Ostergaard & Sunde	2006	Prospective case study	bilateral STN DBS	33	48	59 ± 8	NA	804 ± 364	4.9	0.30
Perlemoine *et al.*	2005	Prospective case-control study	bilateral STN DBS	19	13	59.9 ± 6.6 (SEM)	NA	1336 ± 408 (SEM)	9.7	NA
Rieu *et al.*	2011	Prospective case -control study	bilateral STN DBS	22	12	60.7 ± 1.5	9.6 ± 0.9	868.5 ± 105.6	8.4	NA
Romito *et al.*	2002	Prospective case study	bilateral STN DBS	22	23	56.3 ± 7.7	14.4 ± 5.9	1505.9 ± 722.8	8.1 ± 14.4	0.57
Rouille *et al.*	2015	Retrospective case-control study	bilateral STN DBS	36	6	60.3 ± 6.8	12.6 ± 4.1	1103.5 ± 341.5	NA	NA
Ruzicka *et al.*	2012	Prospective case study	bilateral STN DBS	20	18	56.6 ± 5.8	13.2 ± 4.5	NA	6.9 ± 4.0	NA

(Continues)

TABLE 1 (Continued)

Reference	Year	Study type	Stimulation Target	N enrolled	Mean follow-up (months)	Mean age at surgery (yrs)	Mean disease duration before surgery (yrs)	Mean preoperative levodopa dose (mg)	Mean increase of body mass (kg)	Mean effect size of body mass gain (Cohens' d)
Ruzicka *et al.*	2015	Prospective case study	bilateral STN DBS	20	17	56.6 ± 5.8	13.2 ± 4.5	NA	4.8	NA
Sauleau *et al.*	2009	Prospective case -control study	bilateral STN DBS bilateral GPi-DBS	32	6	57.7 ± 8.2	11.9 ± 3.9	1.337± 448	5.7 ± 5.4	NA
Sauleau *et al.*	2014	Prospective case study	bilateral STN DBS	23	12	NA	NA	1.115 ± 529	24.2 ± 5	NA
Schüpbach *et al.*	2005	Prospective case study	bilateral STN DBS	37	60	54.9 ± 9.1	15.2 ± 5.3	1468 ± 811	NA	NA
Seifried *et al.*	2013	Prospective case study	bilateral STN DBS	11	6	63 ± 7	14 ± 4	1054.0	5.1	0.34
Serranova *et al.*	2011	Prospective case-control study	bilateral STN DBS	20	NA	58.3 ± 6	15.7 ± 4	550.3 ± 479	8.1	0.64
Serranova *et al.*	2013	Restrospective case study	bilateral STN DBS	11	NA	56.3 ± 5	14.4 ± 3	643.8 ± 459.0	5.6	0.45
Strowd *et al.*	2016	Retrospective case-control study	unilateral STN DBS bilateral STN DBS	10 25	21	66 ± 8.1	10.3 ± 5.8	827 ± 495	2.9 ± 9.4	NA
Tuite *et al.*	2005	Restrospective case study	bilateral STN DBS	27	12	64	NA	NA	NA	NA
Walker *et al.*	2009	Prospective case-control study	unilateral STN DBS	39	12	59.1 ± 10.1	11.4 ± 6.1	1255.3 ± 611.7	4.2 ± 7.3	0.31

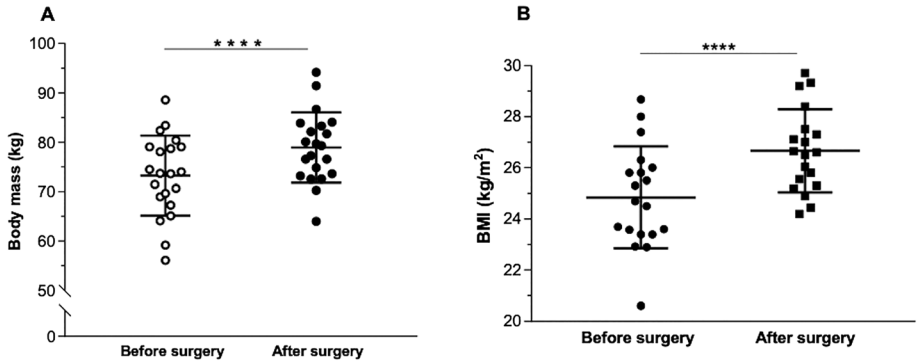

FIGURE 2 Weight changes in the study population. (A) Mean weight change over all studies as comparison between weight pre-surgery and at longest follow-up (N= 446, ****p < .0001). (B) Mean BMI change over all studies as comparison between BMI pre-surgery and at longest follow-up (N= 512, ****p < .0001). Values are means ± SD.

We also evaluated the time course of BMI gain and found an increase of +1.00 kg/m^2 already 3 months after DBS (baseline BMI, 25.14; range BMI gain, +0.10-1.27 kg/m^2; 95% CI, -1.29, -0.71; N = 185; p = .0042; d = 1.08; Figure 3). Here, the number of patients with overweight increased from 46% to 70%. The change in mean BMI from baseline to 6 months was +1.57 kg/m^2 (baseline BMI, 25.14; range BMI gain, 0.81-2.00 kg/m^2; 95% CI, -1,92, -1,21; N = 236; p = .0004; d = 0.87) with an increase in the proportion of patients with overweight from 55% to 77%. At 12 months follow-up, BMI increased by +2.12 kg/m^2 (baseline BMI, 24.49; range BMI gain, 0.40-4.70 kg/m^2; 95% CI, -3.33, -0.91; N = 199; p < .0001; d = 2.14). Thereby increased the proportion of patients with overweight from 52% at baseline to 88%. At a postoperative interval of greater than 12 months, the BMI increased by +1.97 kg/m^2 (baseline BMI, 23.9; range BMI gain, 0.87-2.90 kg/m^2; 95% CI, -4,52, 0,58; N = 103, p = .0031; d = 1.65) compared to the preoperative BMI. In this subgroup, 100% had normal weight before surgery, of which 44% developed overweight.

3.5 | Effects of STN DBS on motor function

In the 25 studies (N = 696) with complete UPDRS III datasets, [4,6,12-17,23,25,28-33,41,46-48,51,54-56] the overall pooled mean UPDRS III in the

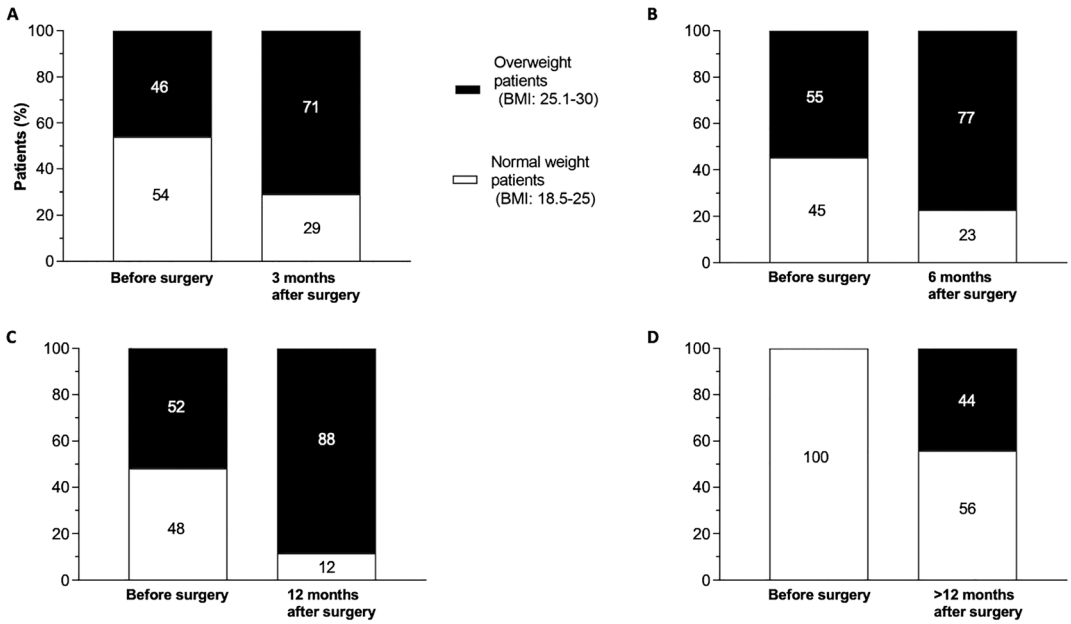

FIGURE 3 Distribution of weight in the study population measured with body mass index. BMI ≤ 25 normal weight, ≤ 30 overweight, ≥ 30 obese. (A) The number of patients who had overweight 3 months after surgery increased (N= 185, p = .0042). (B) The same results were seen 6 months after surgery (N= 236, p = .0004). (C) The proportion of patients who had overweight after surgery increased further 12 months after surgery (N= 199, p < .0001). (D) More than 12 months after surgery is a reduction in patients with overweight, which might implicate a plateau phase of weight gain after surgery (N = 102, p = .0031).

DBS ON state decreased from 34.7 (range 6.4 – 67.6) at baseline to 16.7 at the latest follow-up (range 5.0 – 39.3; 95% CI, 12.48, 23.53; $p < .0001$). Similarly, DBS led to an improvement of the mean dyskinesia score[4,14,15,28-30,32,51,56] in the UPDRS IV from 4.87 (range 1.45 – 11.00) to 1.88 (range 0.15 – 2.55; 95% CI, 1.54, 4.43; N = 252; $p = .0014$) postoperatively.

3.6 | Change in LEDD

In 24 studies[1,4,6,12-15,23,25,28-33,40-42,46,48,51,54,56] (N = 652), the overall pooled mean LEDD decreased from 1141 mg at baseline (range 831 mg – 1507 mg) by 56% to 644 mg at the latest available follow-up (range 402 mg – 1149 mg; 95% CI, 397,82, 596,44; N = 652; $p < .0001$). In keeping with other studies, our results thus confirm a clear improvement in motor function and a significant reduction in levodopa doses after stimulation.

3.7 | Predictors of weight gain following STN DBS

In search for predictive factors of body weight gain after surgery, we performed a correlation analysis of the following variables: delta weight, delta BMI, delta LEDD, delta UPDRS III, delta UPDRS IV, disease duration, age, as well as weight preoperatively. Change in weight was correlated with age (r = -0.4239, $p = .031$; Figure 4). Regarding the symptoms of PD, mean change in BMI was positively correlated with mean change in LEDD (r = 0.440, $p = .0231$) and with mean change in UPDRS III scores when 'on L-Dopa' (r = 0.502, $p = .010$; Figure 4). Postoperative mean change in LEDD was correlated with disease duration (r = -0.399, $p = .022$; Figure 4).

4 | DISCUSSION

The focus of this systematic review was to provide a comprehensive analysis of recently published studies that investigated body mass gain after STN DBS as a starting point for the development of new approaches to prevent this clinically relevant side effect. All but one study (50) reported weight gain after DBS with no study reporting weight loss. Thus, there is strong and consistent evidence for weight gain after STN DBS affecting the vast majority of patients.

The body weight gain occurs already in the first months after DBS implantation and appears to stabilize after one year. The maximum body mass gain across studies was 5.9 kg after one month [38] and 11.1 kg one year after DBS.[13] Nine studies investigated the body mass change 3 months after the surgery showing a mean increase in body weight of 3.25 kg. There was no detailed discussion about the exact mechanisms of this rapid weight gain in these articles. Interestingly, the Swedish Obese Subjects (SOS) study, which investigated the effects of bariatric surgery on subjects with obesity, found a mirrored effect. Here, subjects with obesity lost weight very rapidly during the first months after surgery followed by a plateau phase.[60] There seem to be general mechanisms that may drive these rapid body weight changes after interventions. Further investigations are required to address these effects more precisely.

As our patient sample had normal weight prior to surgery, the body mass gain does not necessarily compensate for preoperative malnutrition or underweight which is well in line with recent evidence.[1,18,34,35] In this context, it is also important to assess the changes in body composition after DBS-surgery. However, only a few studies reported in

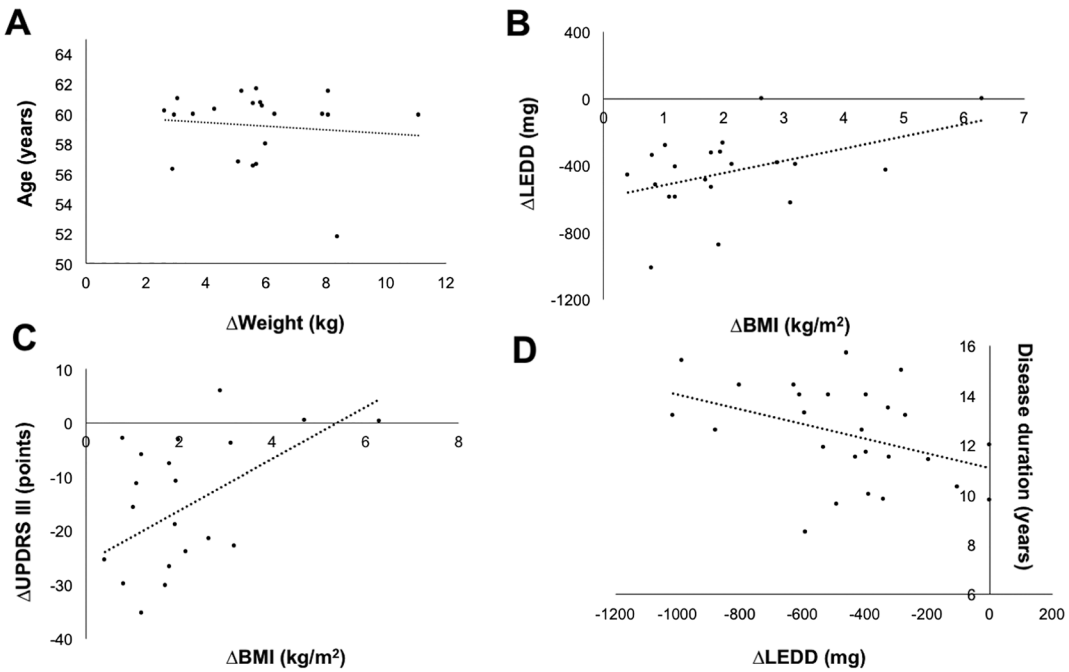

FIGURE 4 Predictive factors of weight gain after STN DBS in patients with PD. (A) Correlation of postoperative change in weight and age. (B) Correlation of mean change in BMI and mean change in LEDD. (C) Correlation of mean change in BMI and mean change in UPDRS III scores. (D) Correlation of mean change in LEDD and Disease Duration. All values mean differences between pre- and postoperative values.

detail on changes in body composition. There is evidence that females gained disproportionately fat mass while weight gain in men was driven by both, fat free mass and fat mass.[6,13,14,23,40-42,48,54]

Interestingly, patients with a greater improvement of motor dysfunction and a stronger reduction in LEDD were likely to gain less weight arguing that an optimal lead localization in the sensorimotor part of the STN is associated with a lower likelihood to develop this side effect. This finding seems to be contractionary on the first view. On the one hand, DBS improves rigidity and rest tremor which would otherwise contribute to a higher preoperative energy expenditure that decreases postoperatively and leads to increased weight. On the other hand, patients perform larger movements and are more mobile than before the operation which should theoretically increase energy expenditure. In keeping, patients with a larger motor improvement and a stronger LEDD reduction were less likely to have an increased weight postoperatively. Although the weight gain is less pronounced in patients with an optimal lead positioning in the motor part of the subthalamic nucleus (STN), they may still gain weight despite reduction in resting energy expenditure. For future studies, it would thus be important to assess the mobility of a patient using quantitative measures, e.g. by wearable sensors and to measure both, resting- and activity-dependent energy expenditure. Moreover, mechanisms other than changes in energy expenditure that contribute to postoperative weight gain, e.g. changes in the hedonic control of food intake, should be taken into consideration. In the revised version of the manuscript, we adjusted the discussion and have tried to solve these seemingly contradictory finding.

However, the effect of body mass gain following DBS is not limited to patients with PD and to the STN as stimulation target. Body mass gain after surgery has also been observed in other movement disorders including dystonia and essential tremor (ET).[8-10] Furthermore, body mass gain was reported in patients with PD treated with GPi DBS and unilateral pallidotomy.[8,36,47,51,53] The body mass increase, however, was significantly higher in patients with PD and bilateral STN DBS in comparison to unilateral STN stimulation and bilateral GPi DBS.[8,47,59] Similarly, patients with STN DBS gained more body mass than patients with stimulation in the GPi.[8] Interestingly, VIM DBS resulted in no weight change in patients with ET, but in a significant body mass gain in patients with PD.[10,20] These results collectively suggest that DBS may exert a general effect on physiological mechanisms of body mass homeostasis. It remains elusive to which extent the improvement of the underlying movement disorder is related to body mass changes. The target-dependent extent of body mass change may point towards to the involvement of different mechanisms that go beyond the pure normalization of abnormal movement patterns.

4.1 | Impact of dopamine replacement therapy

The impact of dopamine replacement therapy on weight changes in patients with PD are only rarely studied and are still controversial. It has been shown that patients on levodopa significantly loose body weight within one year of treatment in comparison to patients on dopamine agonists.[61] Here, the effect was dose-dependent: higher LEDD at baseline in levodopa-treated patients was associated with a more rapid weight loss.[61] In contrast, other studies found no clear relationship between BM changes and LEDD although the results may depend on the type of medication.[35] For example, ropinirole had no effect on BM, whereas cabergoline and pergolide led to unintentional weight loss, and pramipexole increased BM in patients with PD.[35]

Besides the role of dopamine in motivational and reward processing, catecholamines are also involved in the regulation of brown adipose tissue (BAT) thermogenesis. Recent evidence revealed that BAT-dependent non-shivering thermogenesis is involved in regulation of body weight and could increase insulin sensitivity.[62] One possible suggestion is that dopamine replacement therapy may facilitate mitochondrial UCP1-induced thermogenesis, which could potentially also influence BM.

4.2 | Physiological mechanisms

Body mass homeostasis is a complex and multifactorial process that is determined by physiological, metabolic, genetic, epigenetic, motivational, and behavioural factors.[34,35] In PD, body mass is a non-motor feature and body mass changes are known to occur at all stages of the disease. Low body mass is often reported in the prodromal stage of PD and further decrease in body mass has been shown during disease progression.[35] This process is associated with a continuous loss of fat mass. The body mass loss is associated with a variety of processes like difficulties with eating due to motor dexterity, decreased caloric intake, increased muscle rigidity, levodopa-induced dyskinesias, dysphagia, dysfunction of central energy homeostasis, increased metabolic demand due to motor symptoms, impaired olfaction and cognition, sarcopenia, as well as depression and an impact of dopaminergic medication.[21,34,35,49,52]

Body mass changes after DBS appear to have overlapping mechanisms with body mass loss in non-operated patients. In keeping with this notion, the observed DBS-related weight alterations involve changes in nutritional intake and eating behaviour, changes in energy expenditure, perturbations of homeostatic control, modulations by dopamine replacement therapy and dosage, changes in hormone- and neurotransmitter systems, as well as improvement in motor function as discussed in more detail below.[31,34,35,41,52]

4.3 | Changes in motor function

A plausible mechanism for postoperative body weight gain is the amelioration of motor sign severity. The improved motor function, i.e. due to reduction of rigidity, dyskinesias, limb akinesia, tremor and improvement of gait as well as reduction of dopaminergic medication collectively give rise to reduced energy expenditure.[4,12,25-29,37,51] In contrast, other studies found no correlation between body mass gain and changes of the UPDRS III score.[14,47,51] Taking advantage of our systematic approach however, we found less or no weight gain in patients with a higher improvement of disease severity. This

observation challenges the concept of reduced energy expenditure as a relevant mechanism whereas the localization of DBS electrodes may have a stronger impact on weight changes.[4,19] In keeping with this notion, the distance of the active electrode to the wall of the third ventricle in mediolateral direction is inversely correlated with body mass gain and UPDRS III score of the contralateral extremities. Patients with more laterally located electrodes had a better motor improvement and gained less body mass than patients with at least one more medially located electrode.[4] Moreover, it is well known that the CNS, and especially the hypothalamus plays an important role in the regulation of glucose homeostasis and peripheral insulin sensitivity. It has been shown that some of these neurons in these nuclei are assigned to glucoregulatory properties, which could potentially be co-stimulated due a more medial electrode position.[63-67] This finding suggests that the STN is involved or may even exert a regional effect on adjacent structures that are involved in the regulation of energy balance, reward, and food intake. If the active electrode is more located in the limbic subdivision of the STN, stimulation could act as an internal stressor to the limbic system. At the current state of knowledge, DBS represents a 'noise source' considered to disrupt abnormal bursting activity in the parkinsonian basal ganglia[43,68] and influences thereby motivational processing and the reward system, because the limbic cortico-basal ganglia loop is not only involved in reward processing and hedonic control of food intake but additionally interconnected with the hypothalamus, which regulates energy homeostasis.[68]

4.4 | Metabolic changes

Previous studies have proposed that the weight gain could be seen as a homeostatic response to the previous disease-related weight loss [6,14,41] assuming that patients with PD may normalize their weight back to their premorbid status. As STN DBS is associated with a weight gain exceeding the previous weight loss[33,41] this hypothesis is not convincing. Indeed, our review revealed that 88% of the patients were overweight after one year of stimulation.

STN DBS in PD is associated with profound alterations in energy metabolism. The basal energy expenditure was found to be decreased during active stimulation[13,14] possibly due to a reduction in non-exercise activity thermogenesis as a result of decreased motor fluctuations, muscle stiffness, dystonia, levodopa-induced dyskinesia, severity of OFF fluctuations, improvement of sleep patterns, as well as LEDD reduction.[4,13,35] Another change in energy expenditure was reported by Jorgensen and colleagues (2012), who found a reduction in free living energy expenditure after treatment.[40]

STN DBS thus modifies the energy expenditure - energy intake balance resulting in reduced expenditure without decreasing energy intake.[5,6,12,13,41] The positive energy balance[63] may subsequently lead to an increase in body mass. Interestingly, the distribution of body mass changes seems to be gender-specific with women gaining more absolute and truncal fat mass whereas men show an increase in both, fat and fat-free mass. Further, men may have an additional gain in muscle mass due to an increase in physical activity after STN DBS.[14,33,41,57]

A compelling hypothesis is a reduced secretion of growth hormones with consequently decreased lipolysis.[35] Furthermore, a drop of HDL cholesterol concentrations has been observed.[32,48] Additionally, one study found an increased glucose oxidation after DBS implantation.[48] These results remain contradictory as the basal glucose production and insulin sensitivity were reported to be unchanged in a different study.[58] To sum up, there is first evidence that STN DBS affects glucose and lipid metabolism, but this is still contrarily discussed.[20,32]

4.5 | Changes of brain function

Recent PET studies using 2-deoxy-2[18F]fluoro-D-glucose tracer found a correlation between STN DBS-related weight gain and metabolic changes in associative and limbic brain areas, but no correlation with sensorimotor brain regions.[15,30] These findings suggest that the STN might be involved in motivational processing related to eating behaviour.[15] Indeed, the STN is connected to the limbic system, especially to the ventral tegmental area and ventral pallidum, which are key structures of the reward system.[57] Through its connections, stimulation of the STN may thus increase dopaminergic conveyance in the striatum.[42,59] Additionally, the medial part of the STN is adjacent to the medial forebrain bundle which contains essential projections underlying reward functions. Animal studies have shown that STN lesions and DBS led to increased food-related incentive motivation in rats,[35,36] but not to increased hunger.[15] Moreover, an electrophysiological study in monkeys revealed an increased firing rate of neurons in the STN related to the delivery of rewards.[37,52] Therefore, an active electrode in the vicinity of the medial STN may influence food-related reward processing resulting in changes of motivational behaviours, food intake, and body weight.[57] Body mass gain thus could result from increased sensitivity to food reward cues[1,57] and changes in eating behaviour, including higher food intake, increased appetite, binge eating, or craving.[12,15-19,32,69]

4.6 | Hypothalamic alterations in adipokine release

Patients with PD and STN DBS showed increased levels of the orexigenic neuropeptide Y (NPY) after DBS implantation.[23,42] The increased NPY levels correlated with a higher stimulation amplitude which could indicate that DBS may disrupt the melanocortin system by electric current diffusion to the hypothalamus.[42] Interestingly, the central hormone NPY exerts effects on food intake and body weight using different mechanisms including a relationship to the actions of glucocorticoids. Moreover, rodent models showed that neuropeptide Y levels are altered in neurodegenerative disorders like PD or Alzheimer's disease.[63,70,71] Furthermore, leptin and ghrelin as peripheral hormones are involved in the regulation of energy balance. Leptin is a long-term mediator for energy balance, whereas ghrelin is a fast-acting hormone for meal initiation. Both systems are disturbed in obesity[72] and are therefore important to consider in the context of weight gain after DBS surgery. It has been shown that DBS is accompanied

with increased serum leptin levels, reflecting an increased degree of adipose tissue. In addition, increased levels of ghrelin after STN DBS was likewise reported and could lead to an resistance to the anorexigenic effect of leptin within the hypothalamus.[13,23,33,41,42,65,73] Also reduced growth hormone secretion has been described after STN DBS,[74,75] which results in decreased lipolysis and thus to body mass gain.

One assumption for these endocrine alterations is that the spread of stimulation current beyond the borders of the STN may influence the hypothalamic regulation of hormone secretion, energy homeostasis,[2,35,47,55] and may disrupt the melanocortin system, which has been linked to obesity.[42] The disrupted hypothalamic hormone secretion leads to alterations in the central appetite mechanism.[34,43,59]

Moreover, it has been shown that cortisol levels are normalized after STN DBS and the respective anabolic effect of this normalization process has been hypothesized to drive the body mass gain.[23,43,54,76] In addition, it has been shown that cortisol levels decreased over time after DBS[23,55] and that this decrease was correlated with the position of the active electrode in the STN. The more medially the electrode was located, the greater was the decrease in cortisol levels. Furthermore, lower cortisol levels were strongly associated with weight gain and higher trait anxiety.

These results seem to be contractionary to the relationship between cortisol levels and body mass gain with patients with abdominal obesity having increased cortisol levels. An important predictor of the impact of cortisol on metabolism is cortisol responsiveness. High cortisol responsiveness is associated with greater propensity to gain body mass in comparison to low responsiveness. This difference in susceptibility is - at least in part - dependent on different physiological factors such as gender and pregnancy. Furthermore, inter-individual differences in stress response are also determined by genetic background. Putting this foreword, cortisol responsiveness may be different within the assessed subjects. Overall, there is strong evidence that cortisol modulates food intake and therefore impacts on body weight, but also different stressors are known to elicit different cortisol responses.[71] Thus, STN DBS may mimic the effect of chronic stress and disturbed limbic and motivational systems.[55] However, these findings are still contradictory, because one study revealed that hormone levels of the hypothalamic-adrenal-, hypothalamic-somatotropic-, hypothalamic-gonadal-axis were 3 or 6 months after DBS device implantation considered as normal.[34,43] Thus, it is still under discussion how hormonal changes may contribute to body mass gain.

4.7 | Limitations

Our meta-analysis was calculated based on incomplete data sets that in part were imprecise with regard to the reporting of several variables of interest. The sub-analyses in this article therefore included different numbers of subjects. Some relevant studies, e.g.[16,17] could not be included as the exact time point of assessment after surgery was missing.

Thus, we were not able to generate forest and funnel plots due to missing data. Given that only six studies included sufficient information about control groups, it was not possible to calculate the necessary odds ratios.

Further limitations are the limited range of clinical disease severity due to guidelines for the treatment with DBS and the impossibility to randomize groups. Some reports found no change in food intake, appetite, or hunger which could be due to the fact of inaccuracy of self-reported intake.[33] In addition, most studies covered only a limited time period (in most cases 12 months). Longer assessment periods are warranted to investigate the complete time course of body mass changes.

5 | CONCLUSIONS

Deep brain stimulation is an efficacious technique that greatly improves motor and non-motor symptoms and the quality of life of patients with PD. Our results, however, suggest that body mass gain is one of the most common side effects of DBS. Body mass gain occurs rapidly and persistently in almost all patients. Postoperative body mass gain is a multifactorial phenomenon and can have negative health implications. Some patients with PD might develop postoperative obesity and related insulin resistance, and in the long-term diabetes and cardiovascular diseases.

Therefore, the clinical implications from our results is that all patients should be informed that weight gain may occur as a consequence of DBS. Potential candidates for this treatment may be given preoperative nutritional counseling, physiotherapy, and sports therapy after the implantation to prevent rapid weight gain leading to obesity.

Moreover, larger and better controlled trails are needed to establish long-term efficacy of nutritional intervention studies.

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CONFLICTS OF INTEREST

No conflict of interest was declared.

AUTHOR'S CONTRIBUTION

1. Research project: A. Conception, B. Organization, C. Execution.
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix D

Supplementary Table D.1. Coordinates of individual electrodes for the left and right hemisphere in MNI space.

	Right Hemisphere			Left Hemisphere		
	x	y	z	x	y	z
Subject 1	9.86	-15.39	-10.60	-11.07	-17.38	-8.50
Subject 2	7.88	-15.39	-10.67	-10.82	-17.91	-11.17
Subject 3	11.03	-15.86	-8.98	-11.63	-16.72	-8.84
Subject 4	10.84	-15.62	-9.45	-9.42	-16.45	-10.91
Subject 5	12.55	-14.64	-10.51	-11.16	-20.14	-12.21
Subject 6	9.66	-18.55	-9.59	-8.48	-16.15	-10.15
Subject 7	8.72	-19.06	-9.62	-6.96	-16.89	-6.94
Subject 8	11.77	-14.84	-7.66	-13.81	-15.79	-6.63
Subject 9	5.76	-13.09	-9.33	-6.82	-14.11	-8.98
Subject 10	10.10	-16.53	-6.91	-9.64	-16.20	-10.29
Subject 11	9.69	-12.72	-7.42	-10.43	-16.56	-7.04
Subject 12	11.84	-13.67	-8.58	-9.43	-14.64	-8.38
Subject 13	10.89	-14.66	-10.23	-9.94	-15.26	-10.08
Subject 14	8.83	-16.06	-7.88	-13.84	-15.57	-7.66
Mean	9.96	-15.43	-9.10	-10.25	-16.41	-9.13
SD	1.78	1.80	1.24	2.09	1.48	1.73

Overview of Contributions

All the experiments presented in this doctoral thesis were conducted under first supervision of Prof. Dr. Norbert Brüggemann (Department of Neurology, Institute of Neurogenetics, University Hospital Schleswig-Holstein, Lübeck, Germany) and second supervision of PD Dr. Britta Wilms (Institute of Endocrinology & Diabetes, University Hospital Schleswig-Holstein, Lübeck, Germany).
Comprehensive expert consultation and support was also provided by Prof. Dr. Thomas Münte (Department of Neurology, Institute of Psychology II, University Hospital Schleswig-Holstein, Lübeck, Germany), Dr. Marcus Heldmann (Department of Neurology, Institute of Psychology II, University Hospital Schleswig-Holstein, Lübeck, Germany), and Prof. Dr. Sebastian Schmid (Institute of Endocrinology & Diabetes, University Hospital Schleswig-Holstein, Lübeck, Germany), who furthermore substantially contributed to the published manuscripts.

Data collection for Study 1 cohort were acquired together with medical student Laura Lokowandt and PD Dr. Britta Wilms. Laboratory measurements of blood samples were conducted together with Laura Lokowandt, Anne Windjäger, Franziska Richter, Dr. Svenja Meyhöfer, and Katja Scheer. Additional clinical assessment of PD patients were performed from Prof. Dr. Norbert Brüggemann (MD), Dr. Vera Tadic (MD), Henrike Hanßen (MD), Dr. Jannik Prasuhn (MD), Dr. Max Borsche (MD), and Dr. Martje Pauly (MD). Data preparation of Study 1 was done by Laua Lokowandt, Sinja Großer, Catharina Fiensch and myself. All statistical analyses of the acquired data were performed by myself.

Data for Study 2 cohort were acquired together with medical doctor Henrike Hanßen. Data preparation of Study 1 was done by Henrike Hanßen and myself. All statistical analyses of the acquired data were performed by myself.

The analysis of fMRI data were partially conducted at the Danish Research Center for Magnetic Resonance in Copenhagen (Denmark), in cooperation with Prof. Dr. Hartwig Siebner and under supervision of Dr. David Meder.

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