Long-term effects of deep brain stimulation on non-motor symptoms in Parkinson's disease

Inauguraldissertation

zur Erlangung des Doktorgrades

der Humanwissenschaftlichen Fakultät

der Universität zu Köln

nach der Promotionsordnung vom 18.12.2018

vorgelegt von

Stefanie Theresa Jost

aus Bonn

Köln, Januar 2021

Acknowledgements

Throughout the writing of this dissertation I have received a great deal of support and assistance.

I would first like to thank my research supervisor, Dr. Haidar Dafsari, whose expertise was invaluable and who pushed me to sharpen my thinking. I want to thank you for your patient support, your enthusiastic encouragement, and for all the opportunities I was given to further my research. Haidar, I cannot find words to express my gratitude, without your persistent help, this project would not have been realized.

I would also like to express my gratitude to my other supervisors, Jun.-Prof. Dr. Simone Vossel and Prof. Dr. Josef Kessler, who guided me throughout the project and for your valuable and constructive suggestions when finalizing this thesis. Joe, you made a significant contribution to my decision to take this path. You always made me feel confident in my abilities and I am so thankful to have you as my mentor.

My sincere thanks also goes to Prof. Dr. Michael Barbe, who provided me an opportunity to join his lab and who gave me access to the research facilities. I would like to acknowledge my colleagues at the University Hospital Cologne and the other research centres for the wonderful collaboration. I would particularly like to single out Dr. Anna Sauerbier for her unwavering support and Dr. Jan Niklas Petry-Schmelzer for his extensive knowledge and insightful suggestions.

I also wish to acknowledge the support of my parents, my sister Charlotte, and my grandparents. I would particularly like to single out my grandfather Stephan Hochhaus, this thesis would not have been possible without you. Finally, I would like to express my deepest gratitude to my closest friends, in particular to Jana Orthey and Charlotte Schedlich-Teufer who have always been there for me and for being my biggest critic and fan.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

COMT	Catechol-O-methyltransferase
DBS	Deep brain stimulation
DMNV	Dorsal motor nucleus of the vagal nerve
EDS	Excessive daytime sleepiness
GPi	Globus pallidus internus
HADS	Hospital Anxiety and Depression Scale
ICD	Impulse control disorder
LEDD	Levodopa equivalent daily dose
LC	Locus ceruleus
MAO-B	Monoamine oxidase-B
MCI	Mild cognitive impairment
MED	Standard-of-care medical therapy
MedON	On-medication state
MedON/-StimON	Medication and stimulation ON state
NILS	Non-motor International Longitudinal Study
NMDA	N-Methyl-D-aspartate
NMS	Non-motor symptoms
NMSS	Non-Motor Symptoms Scale
NNT	Number needed to treat
PD	Parkinson’s disease
PDQ-8 SI	8-item Parkinson’s Disease Questionnaire Summary Index
PDSS	Parkinson’s Disease Sleep Scale
PPN	Pedunculopontine nucleus
QoL	Quality of life
RBD	Rapid eye movement sleep behavior disorder
REM	Rapid eye movement
RLS	Restless leg syndrome
RpN	Raphe nuclei
SCOPA	Scales for Outcomes in PD
SCOPA-A	Scales for Outcomes in PD-motor examination
SCOPA-B	Scales for Outcomes in PD-activities of daily living
SCOPA-C	Scales for Outcomes in PD-motor complications
STN	Subthalamic nucleus
UPDRS	Unified Parkinson’s Disease Rating Scale

Abstract

Non-motor symptoms (NMS), such as neuropsychiatric, neuropsychological, autonomic, sensory, and sleep symptoms, are a key component in Parkinson's disease (PD) with a major influence on quality of life (QoL). Deep brain stimulation of the subthalamic nucleus (STN-DBS) improves QoL, motor symptoms and NMS in PD patients. Non-motor effects have been observed in uncontrolled studies with follow-up periods up to two years in clinician-rated and laboratory-based investigations. However, little is known about the progression of NMS beyond the two-year follow-up period. Furthermore, it is unclear, which parameters influence the evolution of long-term QoL, as there is a large proportion of patients who do not experience clinically relevant QoL improvement following STN-DBS. Moreover, studies comparing non-motor effects of different DBS targets, such as the STN and the Globus pallidus internus (GPi) are lacking.

The aim of the first study was to examine 36-month effects of STN-DBS on NMS in a prospective, observational, controlled, international multicentre design with a control group receiving standard-of-care medical treatment (MED). Propensity score matching was used to balance baseline demographic and clinical characteristics between the STN-DBS and MED groups. We observed beneficial effects of STN-DBS compared with MED on QoL, NMS overall burden and specific non-motor aspects including sleep/fatigue, urinary symptoms, inability to smell/taste, and pain. Non-motor outcomes were significantly correlated with improvements of QoL.

Sleep disturbances and neuropsychiatric symptoms, such as depression and anxiety, are amongst the most common NMS in PD and are major predictors of negative health-related QoL. Therefore, the second study aimed at investigating the long-term effects of STN-DBS and MED on quality of sleep and neuropsychiatric symptoms in a more detailed analysis. This analysis was based on the results of a former study of our group, reporting non-motor

effects of STN-DBS on quality of sleep in an uncontrolled design at 24-month follow-up (fourth study in this thesis). At 36-month follow-up, we observed beneficial effects of STN-DBS compared to MED on overall quality of nights' sleep, sleep onset and maintenance insomnia, nocturia, nocturnal motor symptoms, and sleep refreshment, whereas no differences were found for depressive and anxiety symptoms. Sleep quality, depressive and anxiety symptoms were separately influenced by STN-DBS and not associated with changes in dopaminergic medication requirements.

The third study examined predictors of long-term QoL outcome after STN-DBS. At 36-month follow-up, 61.6% were classified as "QoL non-responders". We observed that patients with younger age at intervention, worse baseline QoL, and specific NMS profiles, including a higher burden of anhedonia and concentration impairment and less severe fainting experienced greater QoL improvement. Clinically relevant QoL improvement at 36-month follow-up could be predicted with 75% accuracy.

In the fifth study, non-motor effects of STN- and GPi-DBS at short-term follow-up were compared. Both, STN- and GPi-DBS improved global NMS burden, however, distinct profiles were found for specific NMS: The attention/memory and miscellaneous domains only improved in the STN-DBS group, whereas cardiovascular and sexual function domains solely improved in the GPi-DBS group.

In conclusion, this thesis provides Class IIb evidence for beneficial effects of STN-DBS on NMS at 36-month follow-up, which also correlated with QoL improvements. The mechanisms that may mediate the observed effects are discussed. Our results further provide evidence that 36-month QoL changes depend on baseline QoL and NMS burden. These findings highlight the importance of a comprehensive assessment of QoL and a wide range of non-motor and motor symptoms when selecting individuals for DBS therapy and choosing a DBS target. Implementing these assessments in clinical practice, could pave the way to personalized patient care in PD.

1. Theoretical Section

1.1 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (Dorsey et al., 2018). PD prevalence increases with age and ranges from 41 people per 100,000 in the fourth decade of life to more than 1,903 people per 100,000 among those who are 80 years and older (Pringsheim, Jette, Frolkis, & Steeves, 2014). Due to an ageing population, PD prevalence and incidence is likely to rise over time, and the number of patients with PD is expected to double from 2005 to 2030 (Dorsey et al., 2018; Lix et al., 2010). Men are more frequently affected than women (1.4:1.0 male-to-female ratio) (Dorsey et al., 2018). The reasons for this male preponderance are not fully understood yet, however, it has been suggested that female sex hormones, sex-associated genetic mechanisms, and sex-specific disparities in environmental factors and health care might play a role. Most cases of PD are idiopathic but there are genetic risk factors and environmental contributions (e.g. pesticide, herbicide associated with increased PD risk; smoking and caffeine associated with decreased risk) (Kouli, Torsney, & Kuan, 2018).

PD is a complex multisystem disorder defined by motor and non-motor symptoms (NMS) (Klingelhoefer & Reichmann, 2017). Bradykinesia, rigidity, rest tremor, and postural instability are considered the cardinal motor features in PD. Secondary motor symptoms include micrographia, hypomimia, hypophonia, dysarthria, dysphagia, sialorrhoea, short step length, decreased arm swing, freezing, dystonia, and glabellar reflexes (Armstrong & Okun, 2020; Jankovic, 2008). The pathophysiology of PD is multifactorial and involves a widespread distribution of Lewy type-α synucleinopathy as well as coexisting pathology, e.g. Alzheimer's disease, cerebrovascular disease, and cerebral amyloid angiopathy (Adler & Beach, 2016).

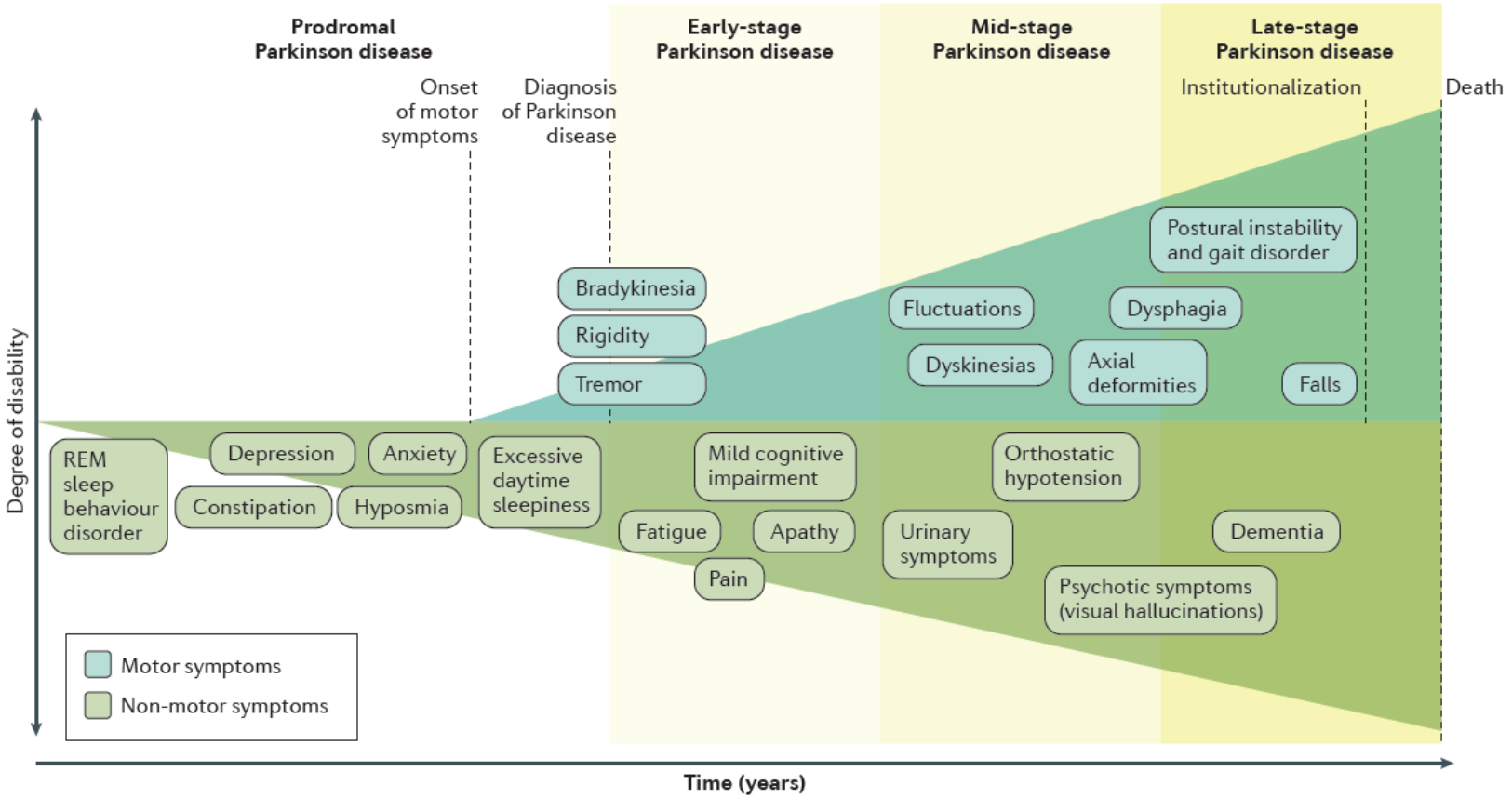

Figure 1 – Clinical symptoms associated with Parkinson's disease.

Reprinted by permission from Springer Nature: Nature Reviews Disease Primers, Parkinson disease, Poewe et al. (2017)

Furthermore, disruptions of basal ganglia-thalamo-cortical circuitry, have been suggested to play an essential role (Kurtis, Rajah, Delgado, & Dafsari, 2017). When motor dysfunction manifests clinically, the pathology of PD has already reached an advanced stage. As suggested by Braak et al. (2003), α-synuclein pathology starts in the peripheral nervous system and the olfactory bulb and progressively engages more brain regions as the disease progresses, before the substantia nigra becomes involved and motor symptoms become evident. This so-called prodromal phase of PD may start 12–14 years before the diagnosis (Postuma et al., 2012) and is characterized by specific NMS, such as olfactory dysfunction, constipation, and rapid eye movement (REM) behaviour disorder (RBD) (Berg et al., 2015). Figure 1 illustrates the clinical symptoms associated with the different stages of PD.

As the diagnosis of PD is still primarily based on clinical features and exclusionary criteria according to the Movement Disorder Society Clinical Diagnostic Criteria for PD (see table 1; Postuma et al., 2015), NMS are highly relevant for an earlier diagnosis of PD (Athauda & Foltynie, 2015; Berg et al., 2015).

The accuracy of the diagnosis can be improved by dopamine transporter single-photon emission computed tomography that enables to detect a possible presynaptic dopaminergic deficit (Armstrong & Okun, 2020). This helps to distinguish between PD and other movement disorders, such as essential tremor or drug-induced parkinsonism. However, it will not differentiate from other neurodegenerative causes of parkinsonism, such as atypical parkinsonian syndromes (Williams-Gray & Worth, 2016) and a definitive diagnosis of PD is only possible post-mortem. A good response to levodopa as well as an asymmetric onset of symptoms can help to confirm the diagnosis of PD (Williams-Gray & Worth, 2016).

Table 1 – Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease.

Diagnosis of parkinsonism
• Bradykinesia • At least one of rest tremor or rigidity
Supportive criteria
• Clear and dramatic beneficial response to dopaminergic therapy • Presence of levodopa-induced dyskinesia • Rest tremor of a limb, documented on clinical examination • The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy
Absolute exclusion criteria
• Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities • Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades • Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, within the first 5 years of disease • Parkinsonian features restricted to the lower limbs for more than 3 years • Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism • Absence of observable response to high-dose levodopa despite at least moderate severity of disease • Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia • Normal functional neuroimaging of the presynaptic dopaminergic system • Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician feels that an alternative syndrome is more likely than Parkinson's disease
Red flags
• Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset • A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment • Early bulbar dysfunction: severe dysphonia or dysarthria or severe dysphagia within first 5 years • Inspiratory respiratory dysfunction • Severe autonomic failure in the first 5 years of disease. This can include: a) Orthostatic hypotension in the absence of dehydration, medication, or other diseases b) Severe urinary retention or urinary incontinence in the first 5 years of disease, that is not simply functional incontinence. • Recurrent (>1/year) falls because of impaired balance within 3 years of onset • Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years • Absence of any of the common non-motor features of disease despite 5 years disease duration. These include sleep dysfunction, autonomic, hyposmia, or psychiatric dysfunction

- Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- Bilateral symmetric parkinsonism

Legend: The first essential diagnostic criterion is parkinsonism. The diagnosis of *clinically established Parkinson's disease* further requires the absence of absolute exclusion criteria, at least two supportive criteria, and no red flags. The diagnosis of *clinically probable Parkinson's disease* requires the absence of absolute exclusion criteria. Furthermore, the presence of red flags need to be counterbalanced by supportive criteria (if 1 red flag is present, there must also be at least 1 supportive criterion; if 2 red flags, at least 2 supportive criteria are needed; no more than 2 red flags are allowed). Adapted from Postuma et al. (2015).

As PD involves progressive neurodegeneration, symptom burden worsens over time. In advanced disease stages, motor symptoms and NMS may become resistant to medical therapy and thus more difficult to manage. Furthermore, complications associated with long-term levodopa treatment, such as dyskinesia, psychosis or impulse control disorders (ICD) may occur. Postural instability and freezing of gait may result in falls, while dementia and hallucinations can develop in some patients (Kouli et al., 2018). The progression of PD is highly variable, in a meta-analysis of post-mortem studies, increased but heterogeneous mortality ratios were observed, with approximately 1.5 times higher mortality in PD compared with controls (Macleod, Taylor, & Counsell, 2014). When patients die from PD-related symptoms, the most common cause of death is pneumonia, however, most patients die with PD and not from it (Pennington, Snell, Lee, & Walker, 2010).

1.2 Non-motor symptoms in Parkinson's disease

It has become apparent that NMS are a key component in PD. NMS may appear in all stages of the disease and can be used as clinical biomarkers in the prodromal phase of PD. NMS burden has been identified as the most important contributor to quality of life (QoL) of PD patients (Martinez-Martin, Rodriguez-Blazquez, Kurtis, & Chaudhuri, 2011). Moreover, NMS lead to increased overall cost of care and rates of nursing home

placement with hallucinations being the strongest predictor of the need for institutionalization (Aarsland, Larsen, Tandberg, & Laake, 2000). The importance of NMS for diagnosis and management of PD is of growing recognition in the scientific community (Pfeiffer, 2016), as NMS are often overshadowed by the dominance of motor symptoms due to a combination of under-reporting of NMS by patients, as well as a lack of awareness from their doctors (Gallagher, Lees, & Schrag, 2010). In a study by Shulman et al. (2002), depression, anxiety, and fatigue were not recognized by neurologists in half of the consultations and sleep dysfunction in over 40%.

In the following, specific NMS, including neuropsychiatric symptoms, sleep disturbances, cognitive impairment, autonomic dysfunctions, pain, olfactory impairment and weight changes will be described.

1.2.1 Neuropsychiatric symptoms

Neuropsychiatric symptoms including depression, anxiety disorders, hallucinations, ICDs, and apathy are the most common non-motor complaints in PD patients affecting about 67% of the patients at some point of the disease (Barone et al., 2009). It is difficult to calculate the prevalence of neuropsychiatric disorders in PD because of possible overlaps with the movement disorder, side effects of antiparkinsonian medication, and other treatment induced complications and due to the coexistence of motor and non-motor fluctuations (Gallagher & Schrag, 2014).

Depression has been consistently observed to be a major contributor to health-related QoL (Schrag, 2006). Depression in PD is complex and likely to result from an interaction of psychological (for instance adjustment to the disease) and neurobiological factors (for instance monoamine neurotransmitter depletion) (Gallagher et al., 2010; Weintraub & Burn, 2011). It is still unclear whether depression in PD has the same anatomical basis

as depression in the general population (Weintraub & Burn, 2011). Prevalence estimates of **anxiety** in PD range between 25–40% (Pfeiffer, 2016). Anxiety disorders that often occur in PD include generalized anxiety disorder, panic disorder or phobic disorders (Pfeiffer, 2016). Depression and anxiety syndromes can occur in the prodromal phase of PD, which is in line with the neuroanatomical staging system proposed by Braak et al. (Braak & Del Tredici, 2009; Braak et al., 2003).

Apathy is another behavioural and very common symptom of PD, which can be very frustrating especially for caregivers. Apathy is defined as an 'absence or lack of feeling, emotion, interest or concern' (Levy & Dubois, 2006, p. 916). There is an overlap between apathy and depression, but they can be distinguished by the indifference of the patients, which is characteristic for apathy (Meyer et al., 2014).

Hallucinations in PD are usually of visual nature and occur especially in the later stage of the disease in about one quarter of PD patients (Fenelon, Mahieux, Huon, & Ziegler, 2000). In previous studies, the presence of hallucinations was the strongest predictor for nursing home placement (Aarsland et al., 2000; Goetz & Stebbins, 1993). The pathophysiology of hallucinations in PD is not fully understood and involves an interaction between intrinsic (e.g. visual processing deficits, such as lower visual acuity or functional brain abnormalities; structural abnormalities and genetics), and extrinsic factors, such as the use of anti-parkinsonian dopaminergic medication, which plays a prominent role in PD psychosis (Zahodne & Fernandez, 2008).

ICDs in PD are characterised by an "inability to resist an impulse, drive or temptation to perform an act out of character for that person that may ultimately cause harm to themselves or others" (Wolters, van der Werf, & van den Heuvel, 2008, p. 50). They typically emerge as pathological gambling, hypersexuality or dopamine dysregulation

syndrome which refers to addictive and compulsive use of dopaminergic medication that usually occurs as a consequence of dopamine replacement therapy (Mizushima, Takahata, Kawashima, & Kato, 2012; Wolters et al., 2008).

1.2.2 Sleep-related dysfunction

Sleep problems are common and disabling in PD and include sleep disturbances caused by nocturnal motor symptoms, restless leg syndrome (RLS), RBD, nocturia, and/or hallucinations as well as excessive daytime sleepiness (EDS) (Rye & Iranzo, 2005; Williams-Gray & Worth, 2016). In a multicentre survey with a large cohort of 1072 PD patients (the PRIAMO study), sleep disorders were the second most prevalent NMS after psychiatric complaints affecting 64% of patients across all disease stages (Barone et al., 2009). Polysomnography studies have revealed objective sleep dysfunctions such as sleep fragmentation, poor sleep efficiency, and abnormal movements including increased blinking, blepharospasm, RBD, periodic limb movements in sleep, and tremor (Rye & Iranzo, 2005). Some forms of sleep dysfunction, such as RBD may even precede the development of motor symptoms by years (Olson, Boeve, & Silber, 2000). The nocturnal disturbances may become more severe as the disease progresses (Kumar, Bhatia, & Behari, 2002). The disturbances have many potential causes, they can be directly disease-related, age-related or induced by anti-parkinsonian medication, mood disturbances and comorbidities (Roychowdhury & Forsyth, 2012; Rye & Iranzo, 2005).

The most common form of insomnia in PD patients is sleep fragmentation, characterised as frequent nocturnal awakenings, followed by early morning awakening (Tandberg, Larsen, & Karlsen, 1998). Gjerstad, Wentzel-Larsen, Aarsland, and Larsen (2007) found an association between insomnia and female sex, disease duration, depression, and higher antiparkinsonian medication dosage.

RBD is characterised by vigorous body movements associated with violent dreaming and nightmares during REM sleep, the dreams appear to be “acted-out” (Arnulf, 2012). It is of relevance to PD as it may predate its onset. A recent meta-analysis of longitudinal studies showed that 96% of RBD patients converted to a neurodegenerative disease at 14 year follow-up of which the most frequent disorder was PD (43%) (Galbiati, Verga, Giora, Zucconi, & Ferini-Strambi, 2019). RBD not only affects the patients but also their bed partners who suffer the consequences of the patient’s sleep disturbance, as they are at risk for injury (Pfeiffer, 2016).

Sleep fragmentation may also appear due to RLS, periodic limb movements in sleep or sleep apnea. **RLS** is highly prevalent in PD and characterised by a marked urge to move (most commonly the legs), typically in night-time hours and during periods of inactivity. Moving eases the uncomfortable sensation but it returns when the movement stops (Keir & Breen, 2020; Yang et al., 2018). **Periodic limb movements in sleep** are characterised as repetitive limb movements, usually the legs, which occur mainly during non-REM sleep (Comella, 2008). RLS and periodic limb movements in sleep often co-exist with 81% of RLS patients showing periodic limb movements in sleep (Ondo, 2014). **Obstructive sleep apnea** is another cause for increased sleep fragmentation in PD, however, it is unclear whether the prevalence of obstructive sleep apnea is higher in PD patients than in the general population as previous studies reported conflicting results (Cochen De Cock et al., 2010; Maria et al., 2003).

EDS is also common in PD and indicated by 14%–76% of PD patients, compared with about 2% of the healthy elderly (Brodsky, Godbold, Roth, & Olanow, 2003; Tan et al., 2002). EDS is defined as self-reported inappropriate sleepiness or unintended sleep onset severe enough to interfere with activities of daily living (Frauscher & Poewe, 2014). EDS is frequently induced by antiparkinsonian medication such as dopamine agonists

(Knie, Mitra, Logishetty, & Chaudhuri, 2011), however, other potential causes including overnight sleep disturbances, such as RBD, periodic limb movements in sleep, and obstructive sleep apnea as described above must not be overlooked.

Fatigue can be described as a sense of exhaustion and diminished energy level and is prevalent in about 50% of PD patients (Siciliano et al., 2018). It encompasses cognitive, physical and psychosocial aspects, and seems to be influenced by multiple factors including motor symptoms, depression, and EDS (Friedman et al., 2007; Valko et al., 2010). However, fatigue is also present among patients without depression and somnolence, indicating that it is an independent symptom in PD patients despite the overlap between these three NMS (Alves, Wentzel-Larsen, & Larsen, 2004). It may also be present in the premotor phase of PD and persists or even worsens over the disease course.

1.2.3 Cognitive impairment and dementia

Cognitive dysfunction and dementia are frequently associated with PD. Newly diagnosed PD patients may already experience cognitive deficits (Kandiah et al., 2009). **Cognitive impairment** in PD may occur in different domains, including executive function, memory, attention, visuospatial function, and language (Litvan et al., 2012). **Dementia** is a common long-term outcome, affecting up to 80% of patients in a longitudinal study with an 8-year study period (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). Dementia in PD can be distinguished from Alzheimer's disease by more prominent impairment in executive functions, verbal fluency, and visuospatial skills. Memory may also be impaired, but recall is relatively spared in comparison with Alzheimer's disease (Janvin et al., 2006). The concept of mild cognitive impairment (MCI) was originally derived from the area of Alzheimer's disease, and is characterised as a state of cognitive decline that is not severe enough to impair activities of daily living and thus warrant a

diagnosis of dementia (Aarsland et al., 2017; Litvan et al., 2012). In nondemented PD patients, MCI occurs in approximately 25% (Aarsland et al., 2010; Litvan et al., 2012). PD-MCI patients have an increased risk of eventually developing dementia, but considerable variability in prognosis of MCI has been observed with some patients remaining stable or even reverting to normal cognition (Pedersen, Larsen, Tysnes, & Alves, 2013).

1.2.4 Autonomic dysfunction

Autonomic dysfunction in PD can manifest as cardiovascular, gastrointestinal, urogenital, sexual, or thermoregulatory symptoms (Pfeiffer, 2016). Most of the dysautonomic symptoms develop in the later stages of the disease but some, such as constipation, may appear in early PD even before the motor symptoms become evident (Pfeiffer, 2016). As is the case for most of the NMS, autonomic dysfunction cannot solely be explained by side effects of antiparkinsonian medication but constitutes an intrinsic part of the disease itself. In neuropathological studies, Lewy bodies and neurites were observed to be widely distributed throughout the peripheral autonomic nervous system (Leclair-Visonneau et al., 2018).

Nonspecific **cardiovascular autonomic symptoms** commonly described by PD patients are transient visual impairment, nausea, light-headedness, dizziness, and scarcely loss of consciousness (Jost, 2017). Mild orthostatic hypotension affects approximately 60% of PD patients, however, symptomatic orthostatic hypotension occurs only in a minority of these patients (Pfeiffer, 2016). Due to falls and concomitant vascular diseases, orthostatic hypotension is of great relevance as it implies an increased mortality (Sanchez-Ferro, Benito-Leon, & Gomez-Esteban, 2013).

Regarding **urinary disturbances**, patients, particularly male patients, commonly complain about urinary urgency, frequency, nocturia, and urge incontinence produced by detrusor overactivity (Jost, 2013). Explanations of urinary disturbances include the degeneration of the dopaminergic system, as dopamine has an inhibitory effect on micturition (Jost, 2017). Urinary symptoms occur more frequently as PD progresses, but may also develop in early PD (Pfeiffer, 2016).

Sexual dysfunction may occur in both men and women with PD, with men typically describing lower sexual satisfaction due to erectile dysfunction, difficulty reaching orgasm, or premature ejaculation and women stating lower sexual desire and difficulties with arousal and orgasm (Pfeiffer, 2016). However, although common, sexual dysfunction is one of the most neglected NMS in PD, as patients and also physicians may feel uncomfortable to talk about the topic and patients may also think that reduced sexual urge and performance may be inevitable in old age (Bhattacharyya & Rosa-Grilo, 2017). However, sexual expression and the need for intimacy are major contributors of QoL (Bronner, 2011) and should be an integral part of the assessment of the patients' symptoms.

The entire gastrointestinal tract may be affected in PD patients, causing several **gastrointestinal symptoms** such as dysphagia, drooling, decreased frequency of bowel movement, nausea due to impaired gastric emptying, constipation, and defecatory dysfunction (Fasano, Visanji, Liu, Lang, & Pfeiffer, 2015; Pfeiffer, 2020). There is growing evidence for synucleinopathy accumulation outside the brain, throughout the enteric nervous system, along the entire gastrointestinal tract and the dorsal motor nucleus of the vagus (Cersosimo & Benarroch, 2012). Drooling in PD is not caused by excess saliva production but by less frequent and inefficient swallowing, which has several negative implications, such as social stigma, bad breath, increased intra-oral occult bacteria,

difficulty eating and speaking, and increased risk of aspiration pneumonia (Fasano et al., 2015; Pfeiffer, 2020; Srivanitchapoom, Pandey, & Hallett, 2014). As levodopa must reach the small intestine in order to be absorbed, delayed gastric emptying may have implications for effective levodopa absorption and may aggravate motor fluctuations (Fasano et al., 2015). Constipation is the most prominent gastrointestinal symptom in PD, as it is one of the earliest markers of the beginning of PD processes and may emerge decades before motor features (Abbott et al., 2007). Although less prominent, difficulty with the act of defecation itself including increased straining, painful defecation, and incomplete emptying is just as common as constipation and may equally affect patients' QoL (Pfeiffer, 2020).

Thermoregulatory dysfunction may occur in the form of hyperhidrosis, heat or cold intolerance in PD and has received only little attention, although it is experienced frequently (Pfeiffer, 2020). Drenching sweats without an explaining stimulus like physical exertion or high temperature are reported by approximately 50% of people with PD (Jost, 2017). Patients may receive sweating problems as very stigmatizing and they may have a significant negative impact on their QoL (Pfeiffer, 2016). Sweating problems may occur simultaneously with motor off-state, but can also appear independent of it (Ossig et al., 2016; Pursiainen, Haapaniemi, Korpelainen, Sotaniemi, & Myllyla, 2007). The pathophysiology of thermoregulatory dysfunction in PD comprises central components including involvement of the hypothalamus and brainstem and peripheral mechanisms, such as small fiber peripheral neuropathy (Pfeiffer, 2020).

1.2.5 Other non-motor symptoms

Pain is also common and present in a majority of approximately three-quarters of PD patients (Valkovic et al., 2015). Hardly surprising, pain can severely impact the patients'

QoL (Antonini et al., 2018; Pfeiffer, 2016). There have been several classifications suggested for pain in PD. Chaudhuri and Schapira (2009) propose a classification into PD-related chronic pain (e.g. central pain), fluctuation-related pain (e.g. due to dystonia or dyskinesia), nocturnal pain (e.g. due to akinesia, RLS or periodic limb movements in sleep), coat-hanger pain, oro-facial-pain, and peripheral limb or abdominal pain. Pathophysiology of pain in PD may involve central and peripheral compartments of the nociceptive pathways (Rukavina et al., 2019).

Olfactory impairment is present in more than 95% of PD patients (Haehner et al., 2009), often already at the time of diagnosis. As hyposmia occurs early in the disease course, it is a sensitive marker for the early and differential diagnosis of PD (Doty, 2012). Relating to the high prevalence of hyposmia in PD, it seems to be valid to question a diagnosis of PD in patients with a normal sense of smell (Haehner et al., 2009).

Weight loss, mainly due to fat rather than muscle loss, is a common finding in PD patients which may occur before the diagnosis and tends to continue during the disease process (Chen, Zhang, Hernan, Willett, & Ascherio, 2003; Markus, Tomkins, & Stern, 1993). The reasons have not been fully understood, but other NMS, such as sensory dysfunctions (e.g. loss of olfaction/taste), neuropsychiatric symptoms (e.g. depression, apathy), and gastrointestinal dysfunctions have been associated with weight loss in PD due to decreased energy intake (Fasano et al., 2015). However, previous studies have shown that weight loss cannot solely be explained by reduced energy intake, but by an increase in energy expenditure (Chen et al., 2003; Markus, Cox, & Tomkins, 1992). Conversely, weight gain is also frequently observed in PD patients and associated with dopamine agonists treatment, impulse control disorder with compulsive eating, and after surgical procedures, such as subthalamic deep brain stimulation (DBS), possibly due to effects on limbic areas (Fasano et al., 2015; Sauleau et al., 2014).

1.2.6 Non-motor fluctuations

In the context of long-term levodopa treatment, NMS may show a pattern of fluctuation similarly to levodopa-induced motor fluctuations (Storch et al., 2013). Non-motor fluctuations tend to correlate with motor fluctuations with higher frequency and intensity of NMS during motor off periods (Storch et al., 2013). In a study by Witjas et al. (2002), the most frequent fluctuating NMS were anxiety (66%), drenching sweats (64%), slowness of thinking (58%), and fatigue (56%). A proportion of 28% of the patients stated that their non-motor fluctuations were more disabling than their motor fluctuations.

1.2.7 Pathophysiology of non-motor symptoms

Most NMS are currently thought to reflect the involvement of PD-related lesions of nervous system structures other than the dopaminergic nigrostriatal pathway (Tolosa, Gaig, Santamaria, & Compta, 2014). Figure 2 illustrates the anatomic substrates for NMS in PD. Apart from nigrostriatal dopamine deficiency, extranigral aspects of PD include several brain stem nuclei (e.g. locus ceruleus, pedunculopontine nucleus, raphe nuclei, and dorsal motor nucleus of the vagal nerve), olfactory and limbic structures, the peripheral autonomic nervous system, and several cortical regions (Chaudhuri, Healy, Schapira, & National Institute for Clinical, 2006; S. Y. Lim, Fox, & Lang, 2009).

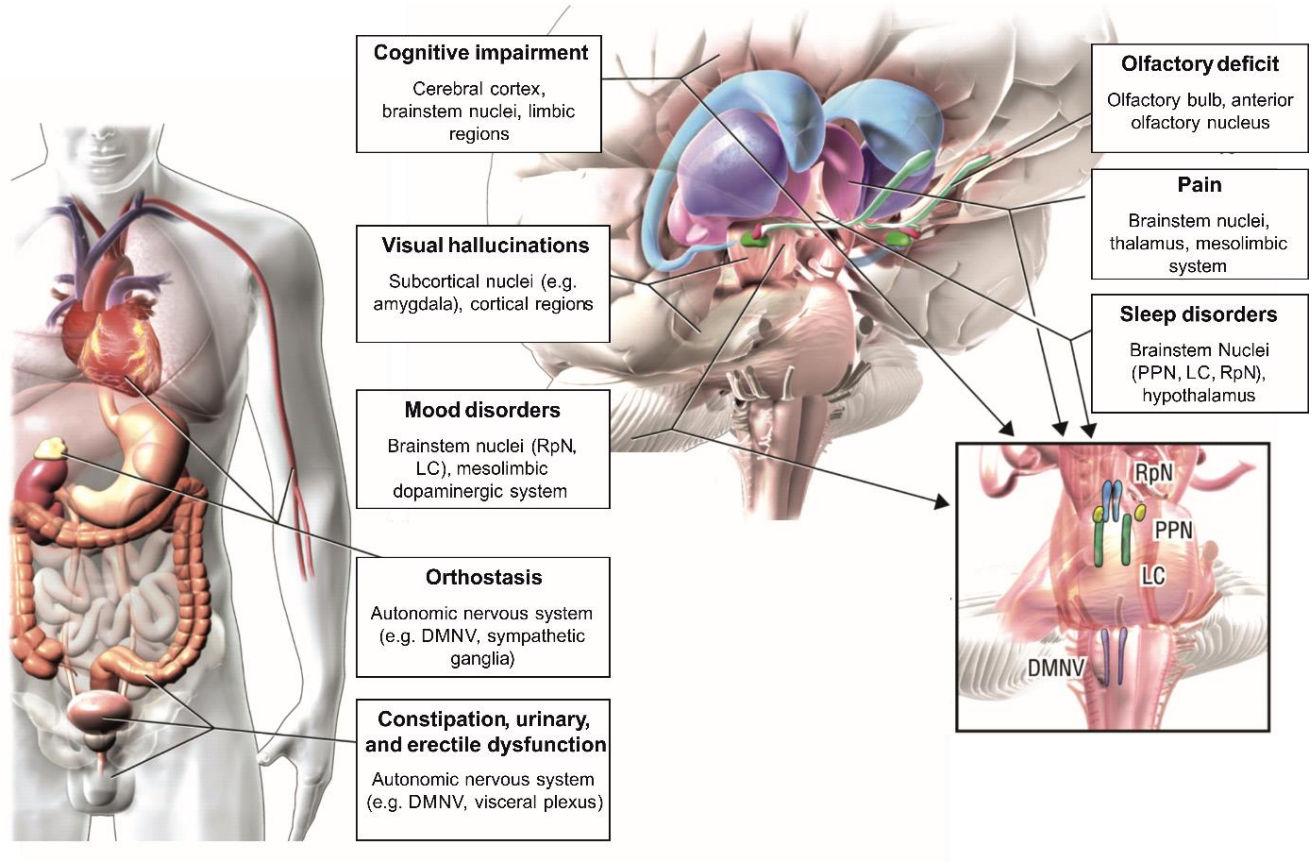

Figure 2 – Anatomic substrates for non-motor symptoms in Parkinson's disease.

Abbreviations: **DMNV** = dorsal motor nucleus of the vagal nerve; **LC** = locus ceruleus; **PPN** = pedunculopontine nucleus; **RpN** = raphe nuclei. Reproduced with permission from JAMA Neurology. 2009. 66 (2): 167–172. Copyright© (2021) American Medical Association. All rights reserved.

1.3 Management of Parkinson’s disease

In spite of many clinical trials, there is still no neuroprotective or disease-modifying treatment for PD (Berg et al., 2015). Recently, high-intensity exercising has gained attention in the context of neuroprotection: In a phase 2 randomized multicentre study of high-intensity treadmill exercise in PD patients within 5 years of diagnosis, significantly less worsening of motor function was observed in the high-intensity exercise group compared with the usual care control group (Schenkman et al., 2018). However, further investigation is warranted to determine whether exercise modifies PD progression

(Armstrong & Okun, 2020). Current treatments are directed at treating PD symptoms, enabling people to sustain good QoL for years (Ahlskog, 2008). This chapter addresses the different treatment options available in PD, including drugs and advanced treatments, such as DBS, intrajejunal levodopa infusion, apomorphine infusion, and focused ultrasound. The different treatment options are illustrated in figure 3.

1.3.1 Medical treatment

To date, there are no established disease-modifying or neuroprotective drugs in PD (AlDakheel, Kalia, & Lang, 2014). Symptomatic treatment should be started when patients feel functionally impaired or embarrassed by their symptoms (Connolly & Lang, 2014).

The core mechanism of the cardinal motor symptoms in PD is dopamine deficiency in the substantia nigra leading to striatal dopamine depletion and dysfunctions in striato-cortical loops (Poewe et al., 2017). After more than 50 years of use in the treatment of PD, levodopa has remained the gold standard and practically all PD patients eventually take levodopa throughout their disease course (LeWitt & Fahn, 2016). However, levodopa use bears the risk of the development of motor complications, including motor response fluctuations and dyskinesia (Poewe et al., 2017). Motor complications are caused by discontinuous drug delivery due to the short half-life of levodopa and its erratic gastrointestinal absorption (Poewe & Antonini, 2015). Until recently, levodopa was avoided for treatment of early PD, but recent research did not support this approach (Espay & Lang, 2017). Due to pathophysiologic changes throughout the disease course, dopaminergic medication loses its long-duration response and the short-duration response decreases (Chou et al., 2018). Moreover, dopamine which was produced internally or provided via medication cannot be stored for later usage anymore. Consequently, PD patients commonly require higher doses and more frequent administration of levodopa over time (e.g., every 2–3 hours).

Figure 3 – Management of motor symptoms in Parkinson's disease.

Pharmacological treatment options

Early stage PD

Younger patients/higher life expectancy

- MAO-B inhibitors (selegiline, rasagiline) and/or
- non-ergoline dopamine agonists (pramipexole, ropinirole, rotigotine, piribedil)
- ergoline dopamine agonists (bromocriptine, cabergoline, pergolide) only in exceptional cases (Cave: risk of fibrosis)
- levodopa (second choice)

In cases of intolerance or insufficient effect:

- switch to another non-ergoline dopamine agonist
- add NMDA-antagonist amantadine (budipine just in exceptional cases)
- add anticholinergics in patients with persistent tremor (just in exceptional cases, not for older patients or patients with cognitive impairment) or propanolol

In cases of non-response or deterioration

- levodopa + decarboxylase inhibitors (benserazide, carbidopa)
- retarded release levodopa for nocturnal akinesia

Older patients/lower life expectancy/ comorbidities

- levodopa + decarboxylase inhibitors
- extended release levodopa + decarboxylase inhibitors for nocturnal akinesia

Advanced stage PD

- add-on treatment to levodopa therapy with COMT inhibitors (first choice entacapone, second choice tolcapone) for PD patients experiencing motor fluctuations ('wearing-off')
- or add-on treatment with MAO-B inhibitor rasagiline to reduce 'Off' times (selegiline is not recommended to reduce 'Off' times)
- or combination of MAO-B inhibitors and COMT inhibitors
- dopamine agonists to reduce motor complications (not suitable for patients with cognitive impairment, dementia and/or psychosis)
- amantadine to reduce dyskinesia with levodopa induced motor complications (rasagiline not suitable for treatment of dyskinesia)
- extended release levodopa + decarboxylase inhibitors
- deep brain stimulation
- intrajejunal levodopa infusion to reduce 'Off' times and dyskinesia
- apomorphine infusion to reduce 'Off' times and dyskinesia

+

Non-pharmacological treatment options

Physiotherapy

- training of gait
- training of balance
- strength and stretching exercises
- training of aerobic capacity
- training of movement amplitude
- training of movement initiation
- training of mobility and autonomy in activities of daily living
- training of movement strategies
- prevention of falls

Speech therapy

Occupational therapy

Abbreviations: **COMT** = Catechol-O-methyltransferase; **MAO-B** = Monoamine oxidase-B; **NMDA** = N-Methyl-D-aspartate; **PD** = Parkinson's disease. Adapted from Deutsche Gesellschaft für Neurologie (2016), Kapitel: Extrapyramidalmotorische Störungen, S3-Leitlinie: Idiopathisches Parkinson-Syndrom (Langversion)

Useful alternatives to levodopa for the therapy of early PD include dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors. They are associated with a lower risk for dyskinesia but also with less robust symptom relief. Furthermore, they only need to be taken 1–3 times daily throughout the course of the disease, which is another advantage over levodopa that requires more frequent dosing as the disease progresses (Ahlskog, 2008; Armstrong & Okun, 2020).

Unlike levodopa, dopamine agonists directly stimulate the postsynaptic dopamine receptors, as they do not require metabolic conversion (Sit, 2000). The most frequently used dopamine agonists are pramipexole and ropinirole (Ahlskog, 2008). In addition, rotigotine is available as a transdermal patch enabling sustained drug delivery (Poewe et al., 2017). Common side effects in individuals treated with dopamine agonists comprise sleep disturbances and ICDs often accompanied by withdrawal symptoms such as anxiety, drug cravings or irritability, when the use of dopamine agonists is discontinued (Armstrong & Okun, 2020; Chaudhuri & Logishetty, 2009; Garcia-Ruiz et al., 2014). MAO-B inhibitors and Catechol-O-methyltransferase inhibitors may be useful levodopa adjuncts, as they prolong the benefits of levodopa by blocking enzymes that degrade dopamine (Armstrong & Okun, 2020).

Amantadine is commonly added to reduce dyskinesia and is generally well tolerated (Fox et al., 2018). Anticholinergics may be added in exceptional cases for the treatment of young individuals (<60 years) with prominent tremor and no cognitive impairment or hallucinations (Connolly & Lang, 2014). However, caution is advised because of the long-term risk of memory impairment and other adverse events (Fox et al., 2018).

1.3.2 Deep brain stimulation

Since its introduction into clinical practice in the late 1990s, DBS has become a gold standard treatment for patients with advanced PD suffering from motor fluctuations or pharmacotherapy-refractory tremor (Deuschl et al., 2006; Lee, Lozano, Dallapiazza, & Lozano, 2019). In the EARLYSTIM trial, superior outcomes following DBS have been observed compared with medical treatment alone in relatively early-stage PD (Schuepbach et al., 2013).

DBS involves unilateral or bilateral surgical placement of leads transcranially in certain brain regions. The surgery is commonly performed bilaterally although unilateral DBS can be considered in cases where PD symptoms are highly asymmetric (Taba et al., 2010). The leads are connected to a battery under the skin in the upper chest region (Armstrong & Okun, 2020).

DBS is a complex treatment and considerable interindividual variability in DBS outcomes has been observed (Dafsari, Weiss, et al., 2018). Successful treatment requires a careful selection of appropriate candidates for DBS treatment, as well as optimal placement of the electrodes (S. Lim, Moro, Tan, & Lang, 2014). Potential risks and benefits, surgical approach, and brain target selection should be assessed by an experienced multidisciplinary team preoperatively (Armstrong & Okun, 2020). Postoperatively, individuals treated with DBS attend programming visits to adjust stimulation parameters and medications (Armstrong & Okun, 2020).

The two most common DBS targets are the subthalamic nucleus (STN) and the globus pallidus interna (GPi) (Lee et al., 2019) and it continues to be debated which of the two is the better target (Krack & Hariz, 2013). Randomized controlled trials demonstrate that both targets provide comparable efficacy in terms of motor outcomes (Follett et al., 2010;

Odekerken et al., 2013; Okun et al., 2009). STN-DBS usually allows for a reduction of dopaminergic drug use, whereas GPi-DBS seems to be slightly more effective for the control of dyskinesia (Follett et al., 2010; Odekerken et al., 2013). However, as the reduction in dopaminergic medication with STN-DBS may indirectly lead to similar improvements in dyskinesia as with GPi-DBS, STN-DBS became the preferred target in most centres (Krack & Hariz, 2013; Odekerken et al., 2013).

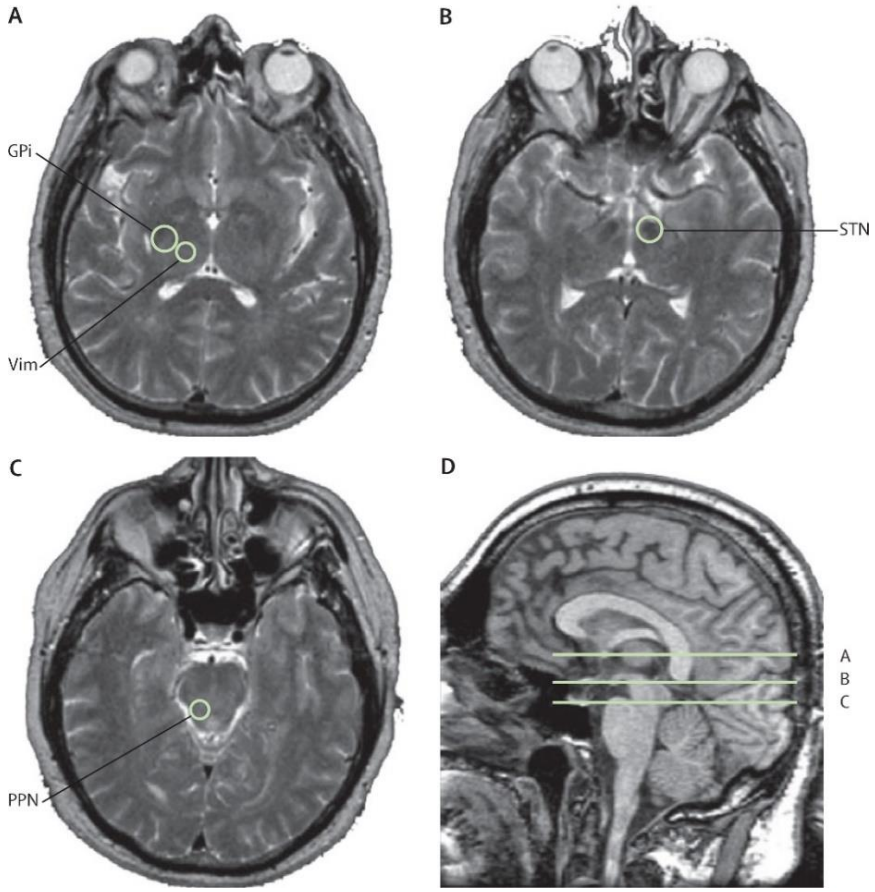

Figure 4 – Main target structures of deep brain stimulation, as they appear on T2-weighted brain MRI.

Abbreviations: **GPi** = globus pallidus internus; **PPN** = pedunculopontine nucleus; **STN** = subthalamic nucleus; **Vim** = ventralis intermedius nucleus. Reprinted from the Lancet, 11, Fasano, Daniele, and Albanese, Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation, 429–442, Copyright 2012 with permission from Elsevier.

Less commonly used targets comprise the ventral intermediate nucleus and the pedunculopontine nucleus (PPN). Neurostimulation of the ventral intermediate nucleus of the thalamus has been observed to improve tremor but no other motor symptoms in PD (Armstrong & Okun, 2020; S. Lim et al., 2014). The procedure is used in very selected cases with tremor-dominant PD, but has largely been replaced by STN- or GPi-DBS (S. Lim et al., 2014). The PPN is a new target for DBS currently being studied for the management of axial signs that fail to respond to levodopa and conventional DBS targets. The available evidence supports that PPN-DBS has the potential to alleviate freezing of gait and falls in some patients (Thevathasan et al., 2012; Yu, Ren, Guo, Li, & Li, 2020). However, PPN stimulation is still an experimental therapy, as the published literature is limited and high variability in the benefits of PPN-DBS has been observed (Thevathasan et al., 2012). Therefore, PPN-DBS is not used in routine clinical practice at this time (S. Lim et al., 2014).

1.3.3 Other advanced treatment options

Subcutaneous **apomorphine infusion** is self-administered via an injection pen and clinically established for PD patients with severe motor fluctuations not sufficiently controlled by oral medication (Armstrong & Okun, 2020; Katzenschlager et al., 2018). In the randomized, multicenter, double-blind TOLEDO study, apomorphine infusion resulted in significantly reduced off time compared with placebo (Katzenschlager et al., 2018).

Intrajejunal levodopa infusion (also referred to as levodopa-carbidopa enteral suspension or levodopa-carbidopa intestinal gel infusion) is another strategy aimed at decreasing motor fluctuations and dyskinesias in advanced PD (Virhammar & Nyholm, 2017). A levodopa gel is administered continuously via a percutaneous endoscopic gastrostomy with jejunal extension, resulting in more constant plasma levels of levodopa

than oral administration (Armstrong & Okun, 2020). Treatment with intrajejunal levodopa infusion significantly decreases off-time and increases on-time without dyskinesias (L. Wang, Li, & Chen, 2018). Distinct effect profiles of STN-DBS, apomorphine, and levodopa infusion on motor symptoms, QoL and NMS have been recently reported by Dafsari et al. (2019).

Focused ultrasound thalamotomy uses highly focused ultrasound energy to create discrete intracranial lesions while using magnetic resonance imaging (MRI) guidance to target and monitor the extent of the lesion (Armstrong & Okun, 2020). MR-guided focused ultrasound has been approved by the Food and Drug Administration for treatment of essential tremor and, more recently, for tremor-dominant PD based on two randomized, sham-controlled trials (Bond et al., 2017; Elias et al., 2016). In tremor-dominant PD, focused ultrasound thalamotomy led to 62% improvement of on-medication tremor scores (Bond et al., 2017).

2. Empirical Section

2.1 Objectives of the thesis

When I started my doctoral thesis, there was no evidence-based treatment of a wide range of NMS yet (Kurtis et al., 2017). However, the importance of NMS for diagnostic purposes and their contribution to patients' QoL emphasize that research in the effects of anti-parkinsonian medication and advanced treatment options on NMS was an unmet need. Previous studies have provided level IV evidence for beneficial effects of STN-DBS on NMS for follow-up periods up to two years in clinician-rated and laboratory-based investigations, including poly-somnography for sleep, urodynamic examinations for urinary symptoms, sniffing sticks for olfaction, as well as sensory signs such as thermal detection thresholds and pain thresholds (Kurtis et al., 2017). However, little was known about the progression of NMS beyond the two-year follow-up period and higher level evidence based on controlled studies, comparing the effects of STN-DBS on NMS with the progression of NMS in patients undergoing standard-of-care medical treatment (MED) were missing. Interestingly, on the individual level, 43-49% of patients experience no clinically relevant improvement of QoL postoperatively at 6-month follow-up and specific demographic and clinical parameters have been identified as predictors of short-term QoL improvement (Dafsari, Weiss, et al., 2018; Daniels et al., 2011). However, predictors of long-term QoL outcome have not been investigated yet. Moreover, although some data suggested slight advantages of GPi-DBS on mood and cognition (Anderson, Burchiel, Hogarth, Favre, & Hammerstad, 2005; Okun et al., 2009), comparative studies, investigating the differential effects of STN- and GPi-DBS on other NMS were also lacking.

The present thesis aimed at investigating the long-term effects of STN-DBS compared to MED on a wide range of NMS. Furthermore, predictors of long-term QoL outcome after STN-DBS were examined. Finally, the effects of STN- and GPi-DBS on NMS were compared. The empirical section comprises five publications which address the following research questions:

1. Are there beneficial motor and non-motor effects of STN-DBS compared to MED at 36-month follow-up?
2. Are there beneficial effects of STN-DBS compared to MED on sleep disturbances? How is the relationship between changes in sleep disturbances, mood symptoms, dopaminergic medication, and QoL following STN-DBS?
3. Is QoL outcome at 36-month follow-up following STN-DBS predictable by specific demographic and preoperative clinical parameters?
4. Are there differential effects of STN- and GPi-DBS on NMS burden?

We prospectively recruited patients at the University Hospital Cologne as part of the Non-motor International Longitudinal Study (NILS) of the ‘Non-Motor PD study group’ of the ‘International Parkinson’s disease and Movement Disorders Society’. The NILS study is an international, multicenter, open-label study with non-motor profiling of PD as the primary outcome measure investigating the progression of NMS and treatment responses to medication and advanced treatments (German Clinical Trials Register #6735). To address the previously described research questions, we analyzed selected data of patients from the DBS and medication arms of the NILS database.

Jost, Sauerbier, Visser-Vandewalle et al. (2020). J Neurol Neurosurg Psychiatry, 91, 687-694

2.2 A prospective, controlled study of non-motor effects of subthalamic stimulation in Parkinson's disease – results at the 36-month follow-up

Jost, S. T., Sauerbier, A., Visser-Vandewalle, V., Ashkan, K., Silverdale, M., Evans, J., ... Dafsari, H. S. (2020). A prospective, controlled study of non-motor effects of subthalamic stimulation in Parkinson's disease: results at the 36-month follow-up. *J Neurol Neurosurg Psychiatry, 91*(7), 687-694. doi:10.1136/jnnp-2019-322614

Jost, Sauerbier, Visser-Vandewalle et al. (2020). J Neurol Neurosurg Psychiatry, 91, 687-694

A prospective, controlled study of non-motor effects of subthalamic stimulation in Parkinson's disease – results at the 36-month follow-up

Stefanie T. Jost, MSc,[1] Anna Sauerbier, MD/PhD,[1,2] Veerle Visser-Vandewalle, MD/PhD,[3] Keyoumars Ashkan, MD/PhD,[2] Monty Silverdale, MD/PhD,[4] Julian Evans, MD/PhD,[4] Philipp A. Loehrer, MD,[5] Alexandra Rizos, MSc,[2] Jan Niklas Petry-Schmelzer, MD,[1] Paul Reker, MD,[1] Gereon R. Fink, MD/PhD,[1] Jeremy Franklin, PhD,[6] Michael Samuel, MD/PhD,[2] Alfons Schnitzler, MD/PhD,[7] Michael T. Barbe, MD,[1] Angelo Antonini, MD/PhD,[8,9] Pablo Martinez-Martin, MD/PhD,[10] Lars Timmermann, MD,[5] K. Ray Chaudhuri, MD/PhD,[2,11] Haidar S. Dafsari, MD[1]

On behalf of EUROPAR and the International Parkinson and Movement Disorders Society Non-Motor Parkinson's Disease Study Group.

[1]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany

[2]Parkinson Foundation International Centre of Excellence, King's College Hospital, London, United Kingdom

[3]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Stereotaxy and Functional Neurosurgery, Cologne, Germany

[4]Department of Neurology and Neurosurgery, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Greater Manchester, United Kingdom

[5]Department of Neurology, University Hospital Giessen and Marburg, Campus Marburg, Marburg, Germany

[6]University of Cologne, Institute of Medical Statistics and Computational Biology (IMSB), Cologne, Germany

[7]Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

[8]Parkinson and Movement Disorders Unit, IRCCS Hospital San Camillo, Venice, Italy

[9]Department of Neurosciences (DNS), Padova University, Padova, Italy

[10]Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), Carlos III Institute of Health, Madrid, Spain

[11]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

Corresponding Author:
Haidar S. Dafsari
Department of Neurology
University Hospital Cologne
Kerpener Str. 62
50937 Cologne, Germany
Tel: +49 221 478-37445
email: haidar.dafsari@uk-koeln.de

Abstract

Objective: To examine 36-month effects of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) on non-motor symptoms (NMS) compared with standard-of-care medical treatment (MED) in Parkinson's disease (PD).

Methods: Here we report the 36-month follow-up of a prospective, observational, controlled, international multicentre study of the NILS cohort. Assessments included NMSScale (NMSS), PDQuestionnaire-8 (PDQ-8), Scales for Outcomes in PD (SCOPA)-motor examination, -activities of daily living, and -complications, and levodopa equivalent daily dose (LEDD). Propensity score matching resulted in a pseudo-randomised sub-cohort balancing baseline demographic and clinical characteristics between the STN-DBS and MED groups. Within-group longitudinal outcome changes were analysed using Wilcoxon signed-rank and between-group differences of change scores with Mann-Whitney U test. Strength of clinical responses was quantified with Cohen's effect size. In addition, bivariate correlations of change scores were explored.

Results: Propensity score matching applied on the cohort of 151 patients (STN-DBS n=67, MED n=84) resulted in a well-balanced sub-cohort including 38 patients per group. After 36 months, STN-DBS significantly improved NMSS, PDQ-8, SCOPA-motor examination and -complications and reduced LEDD. Significant between-group differences, all favouring STN-DBS, were found for NMSS, SCOPA-motor complications, LEDD (large effects), motor examination and PDQ-8 (moderate effects). Furthermore, significant differences were found for the sleep/fatigue, urinary (large effects) and miscellaneous NMSS domains (moderate effects). NMSS total and PDQ-8 change scores correlated significantly.

Conclusions: This study provides Class IIb evidence for beneficial effects of STN-DBS on NMS at 36-month follow-up which also correlated with quality of life improvements. This highlights the importance of NMS for DBS outcomes assessments.

2.3 Subthalamic Stimulation improves quality of sleep in Parkinson disease: a 36-month controlled study

Jost, S. T., Ray Chaudhuri, K., Ashkan, K., Loehrer, P. A., Silverdale, M., Rizos, A., . . . Dafsari, H. S. (2020). Subthalamic stimulation improves quality of sleep in Parkinson disease: a 36-month controlled study. *Journal of Parkinson's Disease,* 11(1): 323-335. doi:10.3233/JPD-202278

Jost, Chaudhuri, Ashkan et al. (2020). J Parkinson Dis, 11(1), 323-335

Subthalamic Stimulation improves quality of sleep in Parkinson disease: a 36-month controlled study

Stefanie T. Jost, MSc,[a] K. Ray Chaudhuri, MD/PhD,[b,c] Keyoumars Ashkan, MD/PhD,[b] Philipp A. Loehrer, MD,[d] Monty Silverdale, MD/PhD,[e] Alexandra Rizos, MSc,[b] Julian Evans, MD/PhD,[e] Jan Niklas Petry-Schmelzer, MD,[a] Michael T. Barbe, MD,[a] Anna Sauerbier, MD/PhD,[a,c] Gereon R. Fink, MD/PhD,[a,f] Veerle Visser-Vandewalle, MD/PhD,[g] Angelo Antonini, MD/PhD,[h] Pablo Martinez-Martin, MD/PhD,[i] Lars Timmermann, MD,[d] Haidar S. Dafsari, MD[a]

On behalf of EUROPAR and the International Parkinson and Movement Disorders Society Non-Motor Parkinson's Disease Study Group.

[a] Department of Neurology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

[b] Parkinson Foundation International Centre of Excellence, King's College Hospital, London, United Kingdom

[c] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

[d] Department of Neurology, University Hospital Giessen and Marburg, Campus Marburg, Marburg, Germany

[e] Department of Neurology and Neurosurgery, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Greater Manchester, United Kingdom

[f] Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Centre Jülich, Jülich, Germany

[g] Department of Stereotaxy and Functional Neurosurgery, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

[h] Department of Neurosciences (DNS), Padova University, Padova, Italy

[i] Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), Carlos III Institute of Health, Madrid, Spain

Corresponding Authors:

Stefanie T. Jost
Department of Neurology
University Hospital Cologne
Kerpener Str. 62
50937 Cologne, Germany
Tel: +49 221 478-86180
email: stefanie.jost@uk-koeln.de

Haidar S. Dafsari
Department of Neurology
University Hospital Cologne
Kerpener Str. 62
50937 Cologne, Germany
Tel: +49 221 478-37445
email: haidar.dafsari@uk-koeln.de

Abstract

Background: Sleep disturbances and neuropsychiatric symptoms are some of the most common nonmotor symptoms in Parkinson's disease (PD). The effect of subthalamic stimulation (STN-DBS) on these symptoms beyond a short-term follow-up is unclear.

Objective: To examine 36-month effects of bilateral STN-DBS on quality of sleep, depression, anxiety, and quality of life (QoL) compared to standard-of-care medical therapy (MED) in PD.

Methods: In this prospective, controlled, observational, propensity score matched, international multicenter study, we assessed sleep disturbances using the PDSleep Scale-1 (PDSS), QoL employing the PDQuestionnaire-8 (PDQ-8), motor disorder with the Scales for Outcomes in PD (SCOPA), anxiety and depression with the Hospital Anxiety and Depression Scale (HADS), and dopaminergic medication requirements (LEDD). Within-group longitudinal outcome changes were tested using Wilcoxon signed-rank and between-group longitudinal differences of change scores with Mann-Whitney *U* tests. Spearman correlations analyzed the relationships of outcome parameter changes at follow-up.

Results: Propensity score matching applied on 159 patients (STN-DBS n=75, MED n=84) resulted in 40 patients in each treatment group. At 36-month follow-up, STN-DBS led to significantly better PDSS and PDQ-8 change scores, which were significantly correlated. We observed no significant effects for HADS and no significant correlations between change scores in PDSS, HADS, and LEDD.

Conclusions: We report Class IIb evidence of beneficial effects of STN-DBS on quality of sleep at 36-month follow-up, which were associated with QoL improvement

independent of depression and dopaminergic medication. Our study highlights the importance of sleep for assessments of DBS outcomes.

2.4 Non-motor predictors of 36-month quality of life after subthalamic stimulation in Parkinson disease

Jost, S. T., Visser-Vandewalle, V., Rizos, A., Loehrer, P., Silverdale, M., Evans, J., ... Dafsari, H.S. (2021). Non-motor predictors of 36-month quality of life after subthalamic stimulation in Parkinson disease. *npj Parkinson's disease,* 7(1): 48.

Jost, Visser-Vandewalle, Rizos et al. (2020). NPJ Parkinson Dis, 7(1): 48

Non-motor predictors of 36-month quality of life after subthalamic stimulation in Parkinson disease

Stefanie T. Jost, MSc,[1] Veerle Visser-Vandewalle, MD/PhD,[2] Alexandra Rizos, MSc,[3] Philipp A. Loehrer, MD,[4] Monty Silverdale, MD/PhD,[5] Julian Evans, MD/PhD,[5] Michael Samuel, MD/PhD,[3] Jan Niklas Petry-Schmelzer, MD,[1] Anna Sauerbier, MD/PhD,[1,6] Alexandra Gronostay,[1] Michael T. Barbe, MD,[1] Gereon R. Fink, MD/PhD,[1,7] Keyoumars Ashkan, MD/PhD,[3] Angelo Antonini, MD/PhD,[8] Pablo Martinez-Martin, MD/PhD,[9] K. Ray Chaudhuri, MD/PhD,[3,6] Lars Timmermann, MD,[4] Haidar S. Dafsari, MD[1]

On behalf of EUROPAR and the International Parkinson and Movement Disorders Society Non-Motor Parkinson's Disease Study Group.

[1]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany
[2]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Stereotaxy and Functional Neurosurgery, Cologne, Germany
[3]Parkinson Foundation International Centre of Excellence, King's College Hospital, London, United Kingdom
[4]Department of Neurology, University Hospital Giessen and Marburg, Campus Marburg, Marburg, Germany
[5]Department of Neurology and Neurosurgery, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Greater Manchester, United Kingdom
[6]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[7]Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Centre Jülich, Jülich, Germany
[8]Department of Neurosciences (DNS), Padova University, Padova, Italy
[9]Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), Carlos III Institute of Health, Madrid, Spain

Corresponding Authors:

Stefanie T. Jost
Department of Neurology
University Hospital Cologne
Kerpener Str. 62
50937 Cologne, Germany
Tel: +49 221 478-86180
email: stefanie.jost@uk-koeln.de

Haidar S. Dafsari
Department of Neurology
University Hospital Cologne
Kerpener Str. 62
50937 Cologne, Germany
Tel: +49 221 478-37445
email: haidar.dafsari@uk-koeln.de

Abstract

In this ongoing, prospective, multicenter international study (Cologne, Manchester, London) including 73 patients undergoing STN-DBS, we aimed to identify predictors of 36-month follow-up quality of life (QoL) outcome after bilateral subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson's disease (PD).

We assessed the following scales preoperatively and at 6-month and 36-month follow-up: PDQuestionnaire-8 (PDQ-8), NMSScale (NMSS), Scales for Outcomes in PD (SCOPA)-motor examination, -activities of daily living, and -complications, and levodopa equivalent daily dose (LEDD). We analyzed factors associated with QoL improvement at 36-month follow-up based on (1) correlations between baseline test scores and QoL improvement, (2) step-wise linear regressions with baseline test scores as independent and QoL improvement as dependent variables, (3) logistic regressions and receiver operating characteristic curves using a dichotomized variable "QoL responders"/"non-responders".

At both follow-ups, NMSS total score, SCOPA-motor examination and -complications improved and LEDD was reduced significantly. PDQ-8 improved at 6-month follow-up with subsequent decrements in gains at 36-month follow-up when 61.6% of patients were categorized as "QoL non-responders". Correlations, linear, and logistic regression analyses found greater PDQ-8 improvements in patients with younger age, worse PDQ-8, and worse specific NMS at baseline, such as 'difficulties experiencing pleasure' and 'problems sustaining concentration'. Baseline SCOPA scores were not associated with PDQ-8 changes.

Our results provide evidence that 36-month QoL changes depend on baseline neuropsychological and neuropsychiatric non-motor symptoms burden. These findings highlight the need for an assessment of a wide range of non-motor and motor symptoms when advising and selecting individuals for DBS therapy.

2.5 Beneficial effect of 24-month bilateral subthalamic stimulation on quality of sleep in Parkinson’s disease

Dafsari, H. S., Ray-Chaudhuri, K., Ashkan, K., Sachse, L., Mahlstedt, P., Silverdale, M., . . . Timmermann, L. (2020). Beneficial effect of 24-month bilateral subthalamic stimulation on quality of sleep in Parkinson's disease. *J Neurol, 267*(6), 1830-1841. doi:10.1007/s00415-020-09743-1

Dafsari, Chaudhuri, Ashkan et al. (2020). J Neurol, 267, 1830-1841

Beneficial effect of 24-month bilateral subthalamic stimulation on quality of sleep in Parkinson's disease

Haidar S. Dafsari[1, 2], MD, K. Ray-Chaudhuri[2, 3], MD/PhD, Keyoumars Ashkan[2], MD/PhD, Lena Sachse[1], Picabo Mahlstedt[1], Monty Silverdale[4], MD/PhD, Alexandra Rizos[2], MSc, Marian Strack[1], Stefanie T. Jost[1], MSc, Paul Reker[1], MD, Michael Samuel[2], MD, Veerle Visser-Vandewalle[5], MD/PhD, Julian Evans[4], MD/PhD, Angelo Antonini[6, 7], MD/PhD, Pablo Martinez-Martin[8], MD/PhD, Lars Timmermann[1, 9], MD,
On behalf of EUROPAR and the IPMDS Non Motor PD Study Group.

[1] Department of Neurology, University Hospital Cologne, Cologne, Germany
[2] National Parkinson Foundation International Centre of Excellence, King's College Hospital, London, United Kingdom
[3] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[4] Department of Neurology and Neurosurgery, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Greater Manchester, United Kingdom
[5] Department of Stereotaxy and Functional Neurosurgery, University Hospital Cologne, Cologne, Germany
[6] Parkinson and Movement Disorders Unit, IRCCS Hospital San Camillo, Venice, Italy
[7] Department of Neurosciences (DNS), Padova University, Padova, Italy
[8] National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain
[9] Department of Neurology, University Hospital Giessen and Marburg, Campus Marburg, Germany

Co-investigators: see separate file "Members of the Non-motor Parkinson's Disease Study Group of the International Parkinson's and Movement Disorders Society"

Corresponding Author:
Dr. Haidar S. Dafsari
Department of Neurology
University Hospital Cologne
Kerpenerstr. 62
50937 Cologne, Germany
Tel.: 0221-478-37445
E-mail: haidar.salimi-dafsari@uk-koeln.de

Abstract

Background: Subthalamic nucleus (STN) deep brain stimulation (DBS) improves quality of life (QoL), motor, and sleep symptoms in Parkinson's disease (PD). However, the long-term effects of STN-DBS on sleep and its relationship with QoL outcome are unclear.

Methods: In this prospective, observational, multicenter study including 73 PD patients undergoing bilateral STN-DBS, we examined PDSleep Scale (PDSS), PDQuestionnaire-8 (PDQ-8), Scales for Outcomes in PD-motor examination, -activities of daily living, and -complications (SCOPA-A, -B, -C), and levodopa-equivalent daily dose (LEDD) preoperatively, at 5 and 24 months follow-up. Longitudinal changes were analyzed with Friedman-tests or repeated-measures ANOVA, when parametric tests were applicable, and Bonferroni-correction for multiple comparisons. Post-hoc, visits were compared with Wilcoxon signed-rank/t-tests. The magnitude of clinical responses was investigated using effect size.

Results: Significant beneficial effects of STN-DBS were observed for PDSS, PDQ-8, SCOPA-A, -B, and -C. All outcomes improved significantly at 5 months with subsequent decrements in gains at 24 months follow-up which were significant for PDSS, PDQ-8, and SCOPA-B. Comparing baseline and 24 months follow-up, we observed significant improvements of PDSS (small effect), SCOPA-A (moderate effect), -C, and LEDD (large effects). PDSS and PDQ-8 improvements correlated significantly at 5 and 24 months follow-up.

Conclusions: In this multicenter study with a 24 months follow-up, we report significant sustained improvements after bilateral STN-DBS using a PD-specific sleep

scale and a significant relationship between sleep and QoL improvements. This highlights the importance of sleep in holistic assessments of DBS outcomes.

2.6 Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson’s disease

Dafsari, H. S., Dos Santos Ghilardi, M. G., Visser-Vandewalle, V., Rizos, A., Ashkan, K., Silverdale, M., . . . Timmermann, L. (2020). Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson's disease. *Brain Stimul, 13*(6), 1697-1705. doi:10.1016/j.brs.2020.09.019

Dafsari, dos Santos Ghilardi, et al. (2020) Brain Stim 13, 1697-1705

Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson's disease

Haidar S. Dafsari[a, b], MD, Maria Gabriela dos Santos Ghilardi[c], MD, Veerle Visser-Vandewalle[d], MD/PhD, Prof., Alexandra Rizos[b], MSc, Keyoumars Ashkan[b], MD/PhD, Prof., Monty Silverdale[e], MD/PhD, Julian Evans[e], MD/PhD, Prof., Raquel C.R. Martinez[c, f], MD/PhD, Rubens G. Cury[c], MD/PhD, Stefanie T. Jost[a], MSc, Michael T. Barbe, MD[a], Prof., Gereon R. Fink[a, g], MD, Prof., Angelo Antonini[h, i], MD/PhD, Prof., K. Ray-Chaudhuri[b, j], MD/PhD, Prof., Pablo Martinez-Martin[k], MD/PhD, Prof., Erich Talamoni Fonoff[c, f], MD/PhD, Prof., Lars Timmermann[a, l], MD, Prof.,
On behalf of EUROPAR and the IPMDS Non Motor PD Study Group.

[a] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany

[b] National Parkinson Foundation International Centre of Excellence, King's College Hospital, London, United Kingdom

[c] Division of Functional Neurosurgery of Institute of Psychiatry, Department of Neurology, University of São Paulo Medical School, São Paulo, Brazil

[d] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Stereotaxy and Functional Neurosurgery, Cologne, Germany

[e] Department of Neurology and Neurosurgery, Salford Royal Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Greater Manchester, United Kingdom

[f] Laboratory of Neuromodulation, Institute of Teaching and Research, Hospital Sirio-Libanês, São Paulo, Brazil

[g] Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Centre Jülich, Jülich, Germany

[h] Parkinson and Movement Disorders Unit, IRCCS Hospital San Camillo, Venice, Italy

[i] Department of Neuroscience, University of Padua, Padua, Italy

[j] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

[k] National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain

[l] Department of Neurology, University Hospital Giessen and Marburg, Campus Marburg, Germany

Corresponding Author:
Dr. Haidar S. Dafsari
Department of Neurology
University Hospital Cologne
Kerpenerstr. 62
50937 Cologne, Germany
Tel.: 0221-478-37445
E-mail: haidar.dafsari@uk-koeln.de

Abstract

Background: Subthalamic (STN) and pallidal (GPi) deep brain stimulation (DBS) improve quality of life, motor, and nonmotor symptoms (NMS) in advanced Parkinson's disease (PD). However, few studies have compared their nonmotor effects.

Objective: To compare nonmotor effects of STN-DBS and GPi-DBS.

Methods: In this prospective, observational, multicenter study including 60 PD patients undergoing bilateral STN-DBS (n=40) or GPi-DBS (n=20), we examined PDQuestionnaire (PDQ), NMSScale (NMSS), Unified PD Rating Scale-activities of daily living, -motor impairment, -complications (UPDRS-II, -III, -IV), Hoehn&Yahr, Schwab&England Scale, and levodopa-equivalent daily dose (LEDD) preoperatively and at 6-month follow-up. Intra-group changes at follow-up were analyzed with Wilcoxon signed-rank or paired t-test, if parametric tests were applicable, and corrected for multiple comparisons. Inter-group differences were explored with Mann-Whitney-U/unpaired t-tests. Analyses were performed before and after propensity score matching which balanced out demographic and preoperative clinical characteristics. Strength of clinical changes was assessed with effect size.

Results: In both groups, PDQ, UPDRS-II, -IV, Schwab&England Scale, and NMSS improved significantly at follow-up. STN-DBS was significantly better for LEDD reduction, GPi-DBS for UPDRS-IV. While NMSS total score outcomes were similar, explorative NMSS domain analyses revealed distinct profiles: Both targets improved sleep/fatigue and mood/cognition, but only STN-DBS the miscellaneous (pain/olfaction) and attention/memory and only GPi-DBS cardiovascular and sexual function domains.

Conclusions: To our knowledge, this is the first study to report distinct patterns of beneficial nonmotor effects of STN-DBS and GPi-DBS in PD. This study highlights the importance of NMS assessments to tailor DBS target choices to patients' individual motor and nonmotor profiles.

3. General Discussion Section

The present doctoral thesis investigated the long-term effects of subthalamic stimulation compared with a control group receiving standard-of-care medical therapy on a wide range of NMS. Furthermore, demographic and clinical predictors of long-term QoL outcome following STN-DBS were examined. Finally, differential non-motor effects of STN- and GPi-DBS were explored. These research aims were addressed in the context of a prospective, observational, international, multicentre study. The following section will summarize the obtained results and discuss them considering the current literature.

3.1 Summary of the results

This thesis reports Class IIb evidence for beneficial effects of STN-DBS on a wide range of NMS in a controlled design at 36-month follow-up. Patients treated with STN-DBS experienced a better outcome of total NMS burden and specific non-motor aspects including sleep/fatigue, urinary symptoms, inability to smell/taste, and pain, compared with patients treated with standard-of-care medical therapy. In a more detailed analysis of the effects of STN-DBS on subjective sleep dysfunction, we observed beneficial effects on overall quality of nights' sleep, sleep onset and maintenance insomnia, nocturia, nocturnal motor symptoms, and sleep refreshment. Depressive and anxiety symptoms remained unchanged from baseline to 36-month follow-up. The observed effects were significantly correlated with improvements of QoL and not associated with changes in dopaminergic medication requirements. In our cohort, clinically relevant QoL improvement at 36-month follow-up could be predicted with 75% accuracy and patients with younger age at intervention, worse baseline QoL, and a higher burden of specific NMS, such as anhedonia and concentration

impairments experiencing greater QoL improvement. Both, STN- and GPi-DBS improved global NMS burden and differential effects on specific aspects of NMS were observed.

3.2 Non-motor effects of subthalamic stimulation

In accordance with previous studies with long-term follow-ups, STN-DBS resulted in a significant improvement of **motor function** and **QoL** (Schuepbach et al., 2013; Weaver et al., 2012). In the MED group, standard-of-care stabilized motor symptoms, activities of daily living, and QoL at 36-month follow-up. As expected, STN-DBS led to a significant LEDD reduction (30%), while medication requirements remained stable in the MED group over the 36-month course.

In line with the results at 12-month follow-up in a study by Holmberg, Corneliusson, and Elam (2005), we observed no significant differences in **cardiovascular** outcomes between the STN-DBS and MED groups at 36-month follow-up. However, in the within-group analysis of the matched cohort, a significant worsening of cardiovascular symptoms following STN-DBS was observed. Studies investigating the effect of STN-DBS on cardiovascular dysfunction, such as orthostatic hypotension have produced variable results. As reviewed recently, the majority of studies found STN-DBS to have no effect on cardiovascular dysfunction (Bunjo, Bacchi, Chandran, & Zacest, 2020). Two studies investigated cardiovascular dysfunction in STN-DBS turned on and off, and suggested a worsening as well as differential effects of STN-DBS and levodopa on cardiovascular autonomic function (Hou, Wu, & Lai, 2009; Li et al., 2017). However, studies assessing the effect of chronic subthalamic stimulation at long-term follow up are missing. In the present investigation of the unmatched, original cohort, cardiovascular symptoms remained unchanged at 36-month follow-up following STN-

DBS. Cardiovascular baseline impairment was higher in the STN-DBS original cohort than in the matched sub-cohort. This finding is consistent with the result of our third study in which we observed that higher cardiovascular baseline impairment (fainting) is a significant predictor of worsened QoL at long-term follow-up. The underlying mechanisms warrant further investigation and future studies should investigate the long-term effects of STN-DBS on cardiovascular symptoms in dependence of different baseline cardiovascular impairments.

To our knowledge, this is the first study reporting sustained improvements in various aspects of **sleep dysfunction** following STN-DBS in a controlled design at 36-month follow-up. Our results are consistent with previous uncontrolled studies demonstrating beneficial effects of STN-DBS on subjective sleep symptoms with follow-up periods up to three years (Choi et al., 2019; Dafsari, Silverdale, et al., 2018; Kurtis et al., 2017). The significant correlation between improvements of PDSS total score and PDQ-8 SI indicates the close connection between sleep and QoL outcomes.

In line with the results of Choi et al. (2019), we report an improvement of **sleep onset and maintenance insomnia** at 36-month follow-up. As a new observation, we observed that this improvement was significantly better in the STN-DBS group compared to a MED control group. This finding is also supported by studies using polysomnography with evidence of improved total sleep time, sleep continuity, and depth (Arnulf et al., 2000; Baumann-Vogel et al., 2017). In line with previous studies that reported significant improvements of RLS following STN-DBS up to two years postoperatively, we observed an improvement of **nocturnal restlessness** at 36-month follow-up (Baumann-Vogel et al., 2017; Klepitskaya et al., 2018). Our study extends the time frame of beneficial effects on nocturnal restlessness to 36 months. In the STN-group, **nocturia** remained unchanged at 24-month and 36-month follow-up, which is

in accordance with previous studies with shorter follow-up periods up to 4 months (Hjort, Ostergaard, & Dupont, 2004). As we observed a significant worsening of nocturia in the MED group at 36-month follow-up, the between-group comparison resulted in a significantly better outcome of STN-DBS compared to MED. Furthermore, confirming negative results by Hjort et al. (2004), we found no evidence for an improvement of **nocturnal psychosis** at 36-month follow-up. Moreover, we report beneficial effects on **nocturnal motor symptoms** at 36-month follow-up, which is in line with the results from Choi et al. (2019). Conversely, in the MED control group, a significant worsening of nocturnal motor symptoms was observed. Relating to **sleep refreshment**, we found favourable effects of STN-DBS at 24-month and 36-month follow-ups. At 36-month follow up, STN-DBS resulted in better outcomes than MED, as sleep refreshment deteriorated in the MED group, whereas it was stabilized in the STN-DBS group. The observation of unchanged sleep refreshment at 36-month follow up was also supported by Choi et al. (2019). Although daytime sleepiness or sleep attacks are a well-known side effect of dopaminergic medication, in particular dopamine agonists medication (Homann et al., 2002), we found no association between LEDD reduction and the sleep refreshment outcome, possibly due to patient-specific adverse events thresholds. Further studies are needed to investigate possible higher-order relationships between sleep refreshment and dopaminergic medication requirements.

Dopamine agonists may help to improve sleep quality. Especially, dopamine agonists with sustained drug delivery mechanisms, i.e., the rotigotine transdermal patch, may be effective for sleep-related NMS such as RLS, RBD, and nocturia, as they provide a more continuous form of dopaminergic stimulation during sleep (Chaudhuri & Logishetty, 2009). On the other hand, dopamine agonists may also cause sleep-related

adverse events, such as EDS, sleep attacks, and the risk of ICDs. In our cohort, no relationship was found between changes of sleep symptoms and changes of dopaminergic and specifically dopamine agonist medication. Therefore, medication side effects are unlikely causes for the observed changes of sleep symptoms.

In line with a study by Weaver et al. (2009), we observed no significant changes of **mood/apathy** in the STN-DBS group at 36-month follow-up. However, in another study, improved depression has been reported at 3-year follow-up after STN-DBS (Funkiewiez et al., 2004). Recent studies have reported that depressive symptom change following STN-DBS was linked to structural connectivity profiles between the stimulation site and the left prefrontal cortex (Irmen et al., 2020), indicating that the placement of active contacts may influence the depression outcome. The variability of changes in depressive symptoms may be due to cohort differences, variations in measuring tools and electrode placement, and differences in postoperative management and medication changes (Kurtis et al., 2017). The observation that improvements of sleep dysfunction, anxiety, and depression were not significantly correlated indicates that sleep and mood disorders are separately influenced by STN-DBS. Further long-term studies addressing the mutual influence of depression, anxiety, apathy, and other neuropsychiatric disorders such as hypomania and ICDs are needed.

Only few studies have investigated the effect of STN-DBS on **hallucinations**. In our cohort, we observed beneficial effects on perceptual problems/hallucinations at 6-month and 24-month follow-up (Dafsari, Silverdale, et al., 2018), which is in line with the results of Yoshida et al. (2009) who report an improvement of pre-existing hallucinations following STN-DBS at 6-month follow-up. In the present investigation, this effect was not significant anymore at 36-month follow-up. Future studies should

address the hallucination outcome and its interplay with dopaminergic medication, psychotropic co-medication, and other neuropsychiatric aspects of PD.

We observed no significant within-group changes and no inter-group differences between STN-DBS and MED in the **attention/memory** domain at 36-month follow-up. The effect of DBS on cognition is still controversial. There is evidence for a small decrease in verbal fluency, working memory, and executive functions following STN-DBS when compared with best medical therapy (Parsons, Rogers, Braaten, Woods, & Troster, 2006; Witt et al., 2008). However, the authors conclude that STN-DBS seems to be relatively safe from a cognitive point of view, as the declines were of small size. In other studies, e.g. in a large randomized prospective trial by Williams et al. (2010), no significant differences in cognitive decline were observed between STN-DBS and best medical treatment at 1-year follow-up. Furthermore, in line with our results, in previous studies with longer follow-up periods, no significant change of global cognitive functions and attention and memory subscales was found 3 years postoperatively (Funkiewiez et al., 2004). Moreover, in a controlled 3-year follow-up study by Zangaglia et al. (2009), stable performances in memory tasks following STN-DBS were observed, whereas verbal fluency performance worsened.

A modulation of **gastrointestinal** symptoms by STN-DBS has been reported in a study by Zibetti et al. who observed a significantly lower prevalence of constipation at 24-month follow-up (Zibetti et al., 2007) and also in a previous study of our group (Dafsari, Silverdale, et al., 2018). At 36-month follow-up, we did not observe a significant change of gastrointestinal symptoms in our cohort anymore.

To our knowledge, this is the first report of a 36-month improvement in **urinary symptoms** following STN-DBS as well as advantageous effects compared with a MED

control group. This is in concordance with previous studies including clinician-rated scales, urodynamic bladder examinations, and PET imaging with shorter follow-up periods (Dafsari, Silverdale, et al., 2018; Herzog et al., 2006; Witte et al., 2018). Nonetheless, long-term effects of STN-DBS on urological outcomes are conflicting as Yamamoto et al. (2018) found no significant improvement in urodynamic parameters 3 years postoperatively. However, this result was limited by a very small sample size, as only 10 persons completed the 3-year follow-up.

In the present thesis, we observed an improvement of **sexual functions** in the STN-DBS group at 36-month follow-up, which is in line with earlier studies with shorter follow-up periods (Dulski et al., 2019). Furthermore, previous studies suggest that the effect of STN-DBS might depend on gender: While Castelli et al. (2004) reported an improvement of sexual function in male PD patients undergoing STN-DBS at a 9–12 month follow-up, no significant change of sexual function was observed in female PD patients in another study at 4-month follow-up (Castelli et al., 2004; Kurcova et al., 2018).

We observed beneficial effects of STN-DBS on the miscellaneous domain in the within-group comparison from baseline to 36-month follow-up and in the between-group comparison (STN-DBS vs MED). Confirming the results of previous studies which reported an improvement of **pain** at 1-year and 8-year follow-up in patients undergoing STN-DBS (Cury et al., 2014; Jung et al., 2015), we observed a significant improvement of pain in our cohort at 36-month follow-up.

To our knowledge, this study is the first to report an improvement of subjective **olfactory symptoms** in the STN-DBS group at 36-month follow-up. This extends the time frame of studies showing beneficial immediate effects on odour identification

(Hummel, Jahnke, Sommer, Reichmann, & Muller, 2005) as well as at 6- and at 12-month follow-up (Guo et al., 2008). The authors discuss that the effect possibly indicates an improvement of cognitive processing of olfactory information (Hummel et al., 2005). Our study adds to the evidence for beneficial effects of STN-DBS on olfaction and extends the time frame to 36 months after surgery.

We found no effect of STN-DBS on **weight changes** at 36-month follow-up and no differences between the STN-DBS and MED groups. The effect of subthalamic stimulation on weight changes is still a matter of debate. Our finding is in contrast to previous studies that commonly report weight gain after STN-DBS, which may negatively affect the metabolic status of the patients (Chen et al., 2003; Kurtis et al., 2017). Furthermore, in a study comparing weight changes in patients undergoing unilateral STN-DBS and best medical treatment, greater weight gain was observed in the surgical group (Walker et al., 2009). However, this may be explained by the fact that the follow-up periods of the available studies were short. On the other hand, weight changes were only assessed with one item of the NMSS and not measured objectively in our study. Further studies including longer follow-up periods are needed to investigate this issue.

Previous studies suggested beneficial effects of STN-DBS on **sweating function** at short-term and up to 24-month follow-up (Dafsari, Silverdale, et al., 2018; Trachani et al., 2010). In the present thesis, we observed no significant improvement in excessive sweating at 36-month follow-up and no significant difference between the STN-DBS and the MED group, which may indicate that the effect of STN-DBS on sweating function decreases over time.

3.3 Predictors of quality of life outcome after subthalamic stimulation

On the individual level, only 38% of the patients experienced a sustained clinically relevant QoL improvement at 36-month follow-up compared with preoperative baseline. We were able to identify preoperative factors that predict QoL outcome at 36-month follow-up with 75% accuracy. Younger age at intervention, worse baseline QoL, more severe anhedonia and concentration impairment as well as less severe fainting predicted greater long-term QoL improvement.

These results are partly in line with earlier studies with shorter follow-up periods. For example, the association between younger age at intervention and greater QoL improvement was previously described by Soulas et al. (2011) at 12-month follow-up. Furthermore, Schuepbach et al. (2019) reported a significant relationship between worse preoperative QoL impairment and greater postoperative QoL improvement at 24-month follow-up. In our study, the odds of postoperative QoL improvement increased by 5% with every additional point in the preoperative PDQ-8 Summary Index score. The strength of this relationship is in concordance with a previous study of our group at 6-moth follow-up (Dafsari, Weiss, et al., 2018) as well as with the results of the Cleveland Clinic cohort (Floden, Cooper, Griffith, & Machado, 2014). Also confirming results of earlier studies, sex, disease duration, motor examination, and dopaminergic medication requirements at preoperative baseline were not associated with QoL outcome (Chandran et al., 2014; Daniels et al., 2011; Lezcano et al., 2016; Siderowf et al., 2006).

Moreover, specific NMS including anhedonia, subjective concentration problems and fainting were associated with QoL outcome. The predictive potential of anhedonia extends the time frame of the study by Schuepbach et al. (2019) who reported greater

QoL improvement at 24-month follow-up in patients with worse baseline scores in two depression scales. Furthermore, as a novel finding, we observed that patients with more severe baseline concentration deficits experienced greater QoL improvements at 36-month follow-up. Concentration deficits are often accompanied by global cognition impairment in patients with PD, but preoperative global cognition scores were not predictive for QoL outcome. However, one must acknowledge that preoperative multi-disciplinary assessments including psychological interviews, neuropsychological assessments, and neurological examinations resulted in a highly-selected cohort with preserved global cognition and low baseline depression scores similar to other DBS cohorts (Dafsari et al., 2019; Deuschl et al., 2006; Schuepbach et al., 2019). Therefore, our findings cannot be generalized to patients with clinically relevant depression or cognitive impairment. To our knowledge, our study is the first to report an association between the presence of preoperative fainting and worse QoL outcome at 36-month follow-up. A possible explanation is the fact that syncope has been shown to have an adverse impact on QoL and we observed worsening of cardiovascular symptoms (such as fainting/syncopes) following STN-DBS at 36-month follow-up (McCarthy, Ward, Romero Ortuno, & Kenny, 2020). The exact mechanism that underlie the worsening of cardiovascular symptoms in STN-DBS need to be clarified in future studies.

3.4 Differential effects of subthalamic nucleus and globus pallidus internus deep brain stimulation

In line with previous studies, similar improvement of motor outcomes was observed for both DBS targets, whereas dopaminergic medication requirements were only reduced in the STN-DBS group (Follett et al., 2010; Odekerken et al., 2016). Also confirming the results of previous studies (Xie et al., 2016), we observed greater improvement in QoL following GPi-DBS based on greater relative changes, larger effect sizes, and

smaller NNT compared with STN-DBS at 6-month follow-up. Only few studies have investigated the effects of STN-DBS and GPi-DBS on NMS (Kurtis et al., 2017). We observed beneficial effects for both, STN-DBS and GPi-DBS and no significant difference between both targets on global NMS burden.

GPi-DBS seems to be advantageous relating to mood outcome, which is in line with previous studies and with the guidelines on STN- and GPi-DBS (Follett et al., 2010; Rughani et al., 2018). Furthermore, as a novel observation, we report beneficial effects on cardiovascular and sexual function only for GPi-DBS. In contrast, in the STN-DBS group, cardiovascular function was unchanged at 6-month follow-up and even worsened at 36-month follow-up.

Confirming the results from the randomized controlled NSTAPS trial, we observed improvements of sleep/fatigue for both DBS targets (Odekerken et al., 2013). No significant target differences were observed for weight changes which is in line with previous studies (Locke et al., 2011; Mills, Scherzer, Starr, & Ostrem, 2012).

Conversely, urinary symptoms were only improved by STN-DBS and remained unchanged following GPi-DBS, which is also confirming previous studies including urodynamic examinations (Herzog et al., 2006; Mock et al., 2016; Witte et al., 2018). Moreover, STN-DBS seems to be more efficacious than GPi-DBS in improving perceptual problems/hallucinations probably connected to the reduction of dopaminergic medication following STN-DBS.

Previous studies have suggested less non-motor morbidity and also fewer adverse events following GPi-DBS, which is in line with our observation of slightly advantageous non-motor outcome of GPi-DBS based on larger effect sizes and smaller NNT (Fasano et al., 2012; Moro et al., 2010; Rouaud et al., 2010). However,

the perception of a larger number of adverse events after STN-DBS may partly result from a reporting bias, as STN-DBS is performed much more frequently (S. Lim et al., 2014).

To conclude, these observations highlight that both sites are feasible targets. In the absence of a difference in motor outcomes, the choice of the target can reasonably take into consideration the differential nonmotor effect profiles. However, these results are limited by small sample sizes for GPi-DBS of most studies and further studies with larger cohort sizes are needed to confirm these results.

3.5 Mechanisms of effects of deep brain sitmulation on non-motor symptoms

As NMS are defined by exclusion, they result from heterogeneous neurodegenerative processes in multiple brain networks and neurotransmitter systems (Kurtis et al., 2017; Petry-Schmelzer et al., 2019; Qamar et al., 2017). Grey matter volume loss and white matter changes have been identified in PD patients suffering from NMS such as depression (van Mierlo, Chung, Foncke, Berendse, & van den Heuvel, 2015) or cognitive decline (Hall & Lewis, 2019). Therefore, the mechanisms that may mediate the observed motor and nonmotor effects of DBS are diverse.

1) Firstly, **improved motor function** may be an important contributor to changes in specific NMS. Improved mobility may exert a positive influence on e.g. mood symptoms or sleep dysfunction. This is in line with our observation of significantly better daytime and nocturnal motor outcomes following DBS, which were significantly associated with e.g. improvements in sleep disturbances. This observation indicates the relative importance of nocturnal motor symptoms for subjective sleep outcomes. Therefore,

improvements in sleep symptoms were at least partly mediated by a modulation of the motor circuitry. However, the relationship between changes in QoL and sleep disturbances was still significant when controlling for motor symptoms indicating that the changes in sleep dysfunction have a positive effect on QoL which goes beyond the effect of enhanced motor function.

2) **Direct effect:** In line with the concept of a tripartite topographical organization within the STN and the GPi (Alkemade, Schnitzler, & Forstmann, 2015; Krack, Hariz, Baunez, Guridi, & Obeso, 2010), neurostimulation of specific subdivisions of these targets leads to distinct outcomes. The tripartite division hypothesis suggests that the dorsolateral aspects of the STN are associated with motor circuits, the anteromedial region with the associative area, and the ventral portion with limbic regions (Alkemade et al., 2015). Previous studies have observed beneficial effects on mood and attention after neurostimulation of the ventral parts of the STN (Petry-Schmelzer et al., 2019), which have been shown to be involved in the processing of emotional information (Buot et al., 2013). Furthermore, neurostimulation of the somatosensory region of the GPi is associated with greater improvement in motor impairment (Middlebrooks et al., 2018).

3) **Network effects in basal ganglia-thalamo-cortical loops:** The basal ganglia are involved in three different functional and anatomical loops for sensorimotor, associative, and limbic processing (see figure 5) (Kurtis et al., 2017). As the STN and GPi form part of the basal ganglia, network effects of DBS have to be considered. Several functional imaging studies have observed that DBS influences the function of the basal ganglia circuitry in PD patients and thus modulates thalamo-cortical projections (Herzog et al., 2006). For example, a modulation of the motor circuitry may affect frontal cortical regions such as the supplementary motor area and hereby improve motor symptoms (Krack et al., 2010; Thobois et al., 2002). Blood flow changes

in cortical regions such as the dorsolateral prefrontal cortex and the anterior cingulate, which are part of the associative circuit are correlated with cognitive performance following STN-DBS (Accolla et al., 2016; Campbell et al., 2008). Furthermore, network effects of DBS on the thalamus could e.g. improve RLS (Driver-Dunckley et al., 2006).

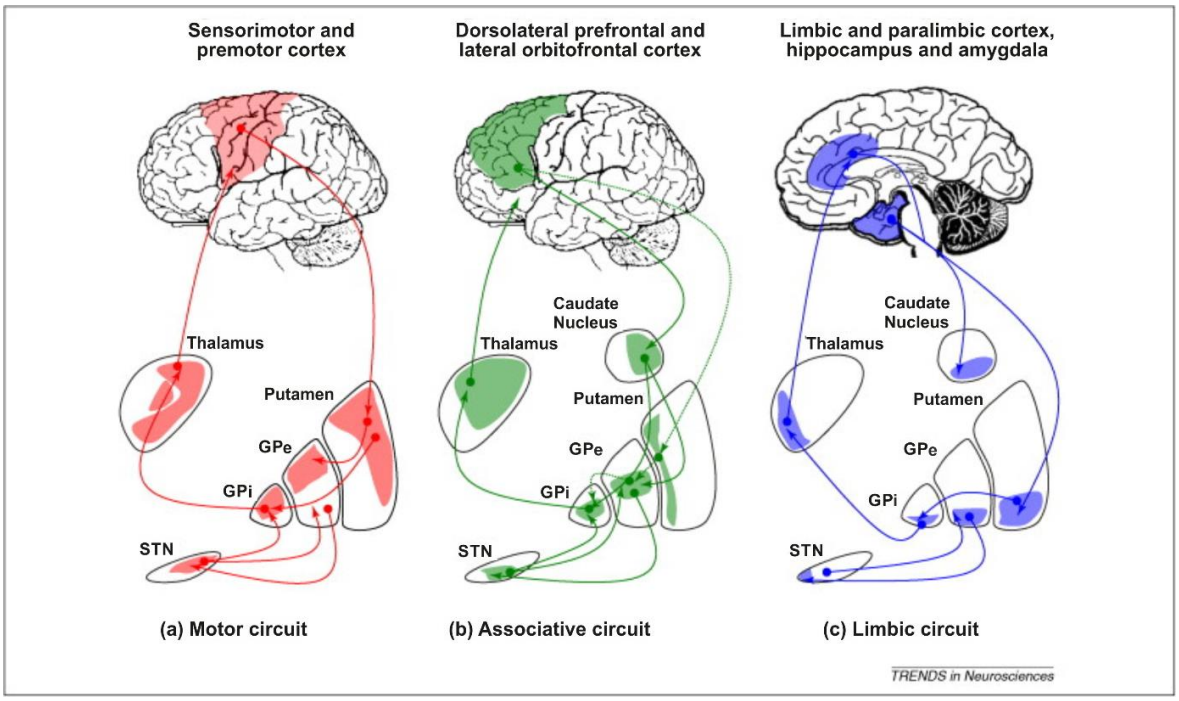

Figure 5 – Cortico-basal ganglia-thalamocortical circuits.

This figure shows a pseudo-anatomical arrangement of the motor, associative, and limbic pathways. **(a)** Motor circuit. Neurons from the sensorimotor cortex project to the posterolateral putamen. From the putamen there are two main projections topographically organized onto the posterolateral region of the target nuclei: (i) the direct circuit to the GPi and (ii) the indirect circuit connecting the posterior putamen to the GPe, the STN and the GPi. The GPi is the primary output nucleus of the basal ganglia to the cortex via the ventrolateral thalamus. **(b)** Associative circuit. This circuit originates in the dorsolateral prefrontal and lateral orbitofrontal cortices, which project to the caudate nucleus and anteromedial portion of the putamen. From the striatum it projects to the dorsomedial region of the GPi and anteromedial parts of the GPe and STN to converge onto the GPi and back to the cortex via the ventral anterior nuclei of the thalamus. **(c)** Limbic circuit. This loop starts in the hippocampus, amygdala and paralimbic and limbic cortices and projects to the ventral striatum (ventral portion of the caudate and putamen). The ventral striatum projects to the limbic portion of the GPe and medioventral STN and ventral GPi and to the cortex via the mediodorsal nucleus of the thalamus. Reprinted from Trends in Neurosciences, 33(10), Krack, Hariz, Baunez, Guridi, & Obeso, Deep brain stimulation: from neurology to psychiatry? 474–484, Copyright (2010), with permission from Elsevier.

Abbreviations: STN = subthalamic nucleus; **GPi** = globus pallidus internus; **GPe** = Globus pallidus externus

Regarding urinary symptoms, Herzog et al. (2006) observed that STN-DBS modulates neural activity in frontal cortical centres involved in urinary bladder control and this modulation was associated with improved bladder dysfunction. Furthermore, changes in glucose metabolism in the midbrain, cerebellum, and right frontal lobe during subthalamic stimulation were linked to improvements in olfactory function (Cury et al., 2018). Little is known about network effects of pallidal stimulation. Castillo et al. (2020) have recently reported improved symptoms of insomnia following neurostimulation of the globus pallidus externa and assume that this effect may be mediated by network effects on pallido-thalamo-cortical loops including the reticular thalamic nucleus which is associated with sleep and wake states. However, further studies on network effects of pallidal stimulation in particular for nonmotor outcomes are needed.

4) **Spread of current to anatomical structures in proximity of the target nuclei:** Beneficial effects of DBS on NMS may also be mediated by a spread of current to neighbouring structures of the STN. The pedunculopontine nucleus has previously been associated with the sleep-wake cycle and enhanced night-time sleep and EDS (Mena-Segovia, Bolam, & Magill, 2004; Peppe et al., 2012; Romigi et al., 2008), and is located approximately 5 mm ventral to the STN (Stefani et al., 2013). Projections from the STN to the globus pallidus externus may serve as another possible explanation for the observed improvements in sleep, as the globus pallidus externus has been associated with enhanced sleep symptoms as described above (Castillo et al., 2020; Qiu, Chen, Wu, Nelson, & Lu, 2016). Furthermore, a spread of current to the medial forebrain bundle located near the medial STN, which is a promising, although yet experimental, DBS target for major depression, may mediate improvements in mood symptoms (Coenen et al., 2018). However, at long-term follow up, we observed

no changes in mood symptoms and further studies are needed to investigate the mechanisms of chronic stimulation on mood symptoms.

5) Previous studies have observed improvements in **sensory gating** following STN-DBS. Sensory gating describes the process of filtering out redundant or irrelevant sensory information (Cromwell, Mears, Wan, & Boutros, 2008). Gulberti et al. (2015) reported enhanced auditory processing which was specific to neurostimulation and not observed for dopaminergic medication. Furthermore, Herzog et al. (2006) report improved sensory gating of urinary bladder afferents following STN-DBS. Depression and anxiety disorders have also been associated with impaired sensory gating (Y. Wang et al., 2009; Xiao et al., 2010) but further studies are needed to investigate the role of sensory gating in mood and other non-motor outcomes after subthalamic stimulation.

6) NMS result from **multi-neurotransmitter dysfunctions** and can be related to dopaminergic deficiency, non-dopaminergic pathogenesis or a combination of both (Qamar et al., 2017). Dopaminergic deficiency may be involved for example in sleep disturbances, apathy, and urinary symptoms; cholinergic dysfunction in cognitive impairment and constipation; noradrenergic dysfunction in cardiovascular dysfunction; and serotonergic dysfunction e.g., in depression, anxiety, hallucinations, and weight changes (Qamar et al., 2017). Neurotransmitters other than dopamine, such as noradrenaline or serotonin may be involved in the mechanisms of STN-DBS, as there are for example noradrenergic projections from the locus coeruleus to the STN as well as indirect projections between the STN and the serotonergic dorsal raphe nucleus via the lateral habenula (Jakobs, Fomenko, Lozano, & Kiening, 2019).

7) **LEDD reduction:** Non-motor outcomes may also be influenced by a reduction of dopaminergic medication requirements following STN-DBS. Side-effects of dopaminergic treatment, such as gastrointestinal symptoms, daytime sleepiness, and hallucinations may decrease with LEDD reduction (Chaudhuri & Schapira, 2009; Stowe et al., 2011; Yeung & Cavanna, 2014). The present thesis can only report "net effects" of neurostimulation and reduced dopaminergic medication, however, in line with previous studies, we observed no significant correlation between changes in dopaminergic medication requirements (for both LEDD total and LEDD of dopamine agonists) and NMS outcome following STN-DBS or GPi-DBS (Dafsari et al., 2020; Dafsari, Silverdale, et al., 2018). Further studies with larger cohorts are needed to distinguish between stimulation and medication effects on NMS.

In summary, network modulation achieved by DBS is currently being researched intensively (Husain, 2019; Irmen et al., 2020; Petry-Schmelzer et al., 2019). Mechanisms of action of DBS on NMS are heterogenous and are mediated by improvements in motor symptoms, reduction of dopaminergic medication requirements, as well as symptom-specific neural network effects depending on the location of neurostimulation. Little is known about the mechanisms of GPi-DBS and future studies are needed to investigate how non-motor effects of pallidal stimulation are mediated.

3.6 Limitations

The following section will discuss the limitations of the study design.

This thesis reports the results of a non-randomized controlled trial. A randomized controlled design was not suitable and ethically not justifiable as we were interested in the long-term effects of STN-DBS and this would have meant to withhold an effective

therapy from severely affected PD patients for three years. In “real-life”, observational, non-randomized studies, the groups may however differ systematically, and direct group comparisons may be misleading. For this reason, we chose propensity scores to match baseline characteristics between the STN-DBS and MED groups to increase causal inference. We chose a conservative calliper (0.25) and conducted strict balance diagnostics to implement a precise matching (Stuart & Rubin, 2007). However, although this method is a well-established tool in the previously described situations and diagnostic statistics indicated a well-balanced matching for the selected matching parameters, it cannot replace randomization. The method can only be applied to variables that were assessed clinically which implies that potential confounders, such as ICD or apathy, which were not measured, cannot be controlled.

One of the limitations of the first study was a notable group difference in the mean NMSS sleep/fatigue domain at baseline, which was higher in the STN-DBS group than in the MED group and might therefore have contributed to the greater improvement observed in the STN-DBS group. However, in the second study there was no significant baseline difference in sleep dysfunction between the groups and STN-DBS was still beneficial compared to MED, so that this limitation may be set aside.

In the original, unmatched cohort, patients in the MED group were less severely affected than patients undergoing STN-DBS. Consequently, to obtain groups with well-balanced baseline characteristics, the matching process led to the selection of *less* strongly affected patients within the STN-DBS group and *more* severely affected patients within the MED group. Thus, patients in the STN-DBS group with very severe PD symptoms could not be included in the matched cohort, as there were no eligible matching partners in the MED group. Therefore, the observed effects of STN-DBS cannot be generalized to very severely affected PD patients. An additional aspect that

relates to this limitation is that patients with very severe PD symptoms have a higher probability of being lost to follow-up, which may result in a systematic bias in studies with long-term follow-ups (Limousin & Foltynie, 2019).

In the third study, we investigated the dependence of STN-DBS outcomes on the levels of baseline impairments and whether certain baseline characteristics predict long-term QoL outcomes. Specific preoperative NMS, namely more severe anhedonia, problems with sustaining concentration, and less severe fainting were predictors for greater QoL improvement. However, this result is limited by the underrepresentation of patients with severe NMS, such as clinically relevant psychiatric disorders or cognitive impairment, as these patients were not eligible for DBS.

Furthermore, we did not conduct objective measurements of NMS, such as polysomnography for sleep or urodynamic examinations for urinary symptoms. However, in this real-life study, we were interested in the subjective perception of the different NMS, and some NMS, such as sleep refreshment or nocturia can only be captured by interviewing the patient.

In the broader context of treatment choices, patients in the MED group decided against surgical therapy due to several reasons such as patients' age, a short disease duration (mean 7.5 years in the original cohort MED group), dopaminergic medication requirements, and specific symptom profiles. However, we did not systematically assess those reasons, therefore, group differences relating to this aspect, such as e.g. psychological factors, cannot be ruled out.

Strictly speaking, our MED group was no best medical treatment group as for example in the EARLYSTIM trial, since medication changes were not actively managed by an independent expert panel (Schuepbach et al., 2013). However, we applied the same

criteria (Horstink et al., 2006), and no deterioration of clinical outcomes including motor scores, NMSS burden, and QoL was observed over the 36-month period, which may indicate an overall successful management of these aspects in the MED group.

As indicated above, another limitation was that ICD and apathy were not systematically assessed. Moreover, with regard to sleep dysfunction, we used the PDSS-1 that does not capture RBD or sleep apnea. Further studies are needed to investigate the effects of DBS on these specific NMS as well as their possible potential in predicting DBS outcomes. An assessment of apathy might have particularly improved our prediction model, as in previous research, patients with negative QoL outcome showed higher preoperative apathy scores (Maier et al., 2013).

Due to the focus of this thesis on NMS in PD, some motor aspects, such as the cumulative daily OFF time or severity of dyskinesia were not assessed in the described studies. Also, motor examination was not conducted in pre- or postoperative medication or stimulation OFF states. This is important, as these parameters might be relevant in predicting DBS outcomes. Further studies are needed to investigate the predictive potential of these parameters.

Moreover, in the comparison of non-motor effects following STN- and GPi-DBS, the follow-up period of six months was short, as long-term data of the GPi-DBS group was not available at that time. This is of great relevance, as previous studies have raised concern regarding the long-term efficacy of pallidal stimulation (Volkmann et al., 2004), whereas other studies report stable responses (Lyons, Wilkinson, Troster, & Pahwa, 2002). Consequently, subsequent studies with longer follow-up periods are needed to confirm the findings on differential non-motor effects of STN- vs. GPi-DBS presented here.

3.7 Conclusions and implications

The core research question of the present thesis concerns the long-term effects of STN-DBS compared with MED on a wide range of NMS. This was accomplished in a prospective, observational, controlled, international, multicentre study. Furthermore, predictors of long-term QoL outcome after STN-DBS were examined, as previous research has observed considerable interindividual variability in QoL outcomes. Additionally, in an explorative analysis, differential non-motor effects of STN- and GPi-DBS at 6-month follow-up were examined.

The present thesis provides Class IIb evidence for beneficial effects of STN-DBS compared with MED on NMS total burden and specific NMS. Non-motor outcomes were significantly correlated with QoL improvements after STN-DBS highlighting their importance and the relevance of holistic assessments of NMS in PD. A large proportion of patients did not experience clinically relevant QoL improvement at 36-month follow-up. Younger age at intervention, worse preoperative QoL, and specific NMS were predictive for beneficial long-term QoL outcome. Both, subthalamic and pallidal DBS improved global NMS burden at 6-month follow up. Distinct profiles were found for the attention/memory and miscellaneous domains, which improved in the STN-DBS group, and cardiovascular and sexual function domains, which improved in the GPi-DBS group.

Studies comparing effects of different treatment options, for example, for STN-DBS, GPi-DBS, and standard-of-care medical therapy as investigated in the present thesis, enable better informed treatment choices as well as selection of DBS targets for individual patients. The selection of the DBS target can reasonably take into consideration the non-motor profile of the patient, as motor outcomes of STN- and GPi

DBS did not differ significantly. The observation of greater QoL improvements at 36-month follow-up in patients with younger age at intervention, worse preoperative QoL, and specific NMS profiles contribute to the long-term goal of identifying patients who experience more considerable postoperative QoL improvement. This research helps to provide a basis on personalized medicine to patient's individual PD profiles to better identify patients with the greatest benefits of each treatment option. Further randomized, controlled trials investigating non-motor outcomes for different treatment options and DBS targets are required to compare their differential effects.

4. References

Aarsland, D., Andersen, K., Larsen, J. P., Lolk, A., & Kragh-Sorensen, P. (2003). Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol, 60*(3), 387-392. doi:10.1001/archneur.60.3.387

Aarsland, D., Bronnick, K., Williams-Gray, C., Weintraub, D., Marder, K., Kulisevsky, J., . . . Emre, M. (2010). Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology, 75*(12), 1062-1069. doi:10.1212/WNL.0b013e3181f39d0e

Aarsland, D., Creese, B., Politis, M., Chaudhuri, K. R., Ffytche, D. H., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson disease. *Nat Rev Neurol, 13*(4), 217-231. doi:10.1038/nrneurol.2017.27

Aarsland, D., Larsen, J. P., Tandberg, E., & Laake, K. (2000). Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc, 48*(8), 938-942. doi:10.1111/j.1532-5415.2000.tb06891.x

Abbott, R. D., Ross, G. W., Petrovitch, H., Tanner, C. M., Davis, D. G., Masaki, K. H., . . . White, L. R. (2007). Bowel movement frequency in late-life and incidental Lewy bodies. *Mov Disord, 22*(11), 1581-1586. doi:10.1002/mds.21560

Accolla, E. A., Herrojo Ruiz, M., Horn, A., Schneider, G. H., Schmitz-Hubsch, T., Draganski, B., & Kuhn, A. A. (2016). Brain networks modulated by subthalamic nucleus deep brain stimulation. *Brain, 139*(Pt 9), 2503-2515. doi:10.1093/brain/aww182

Adler, C. H., & Beach, T. G. (2016). Neuropathological basis of nonmotor manifestations of Parkinson's disease. *Mov Disord, 31*(8), 1114-1119. doi:10.1002/mds.26605

Ahlskog, J. E. (2008). Symptomatic Treatment Approaches for Early Parkinson's Disease. In S. A. Factor & W. J. Weiner (Eds.), *Parkinson's disease diagnosis and clinical management* (pp. 633-642). New York: Demos.

AlDakheel, A., Kalia, L. V., & Lang, A. E. (2014). Pathogenesis-targeted, disease-modifying therapies in Parkinson disease. *Neurotherapeutics, 11*(1), 6-23. doi:10.1007/s13311-013-0218-1

Alkemade, A., Schnitzler, A., & Forstmann, B. U. (2015). Topographic organization of the human and non-human primate subthalamic nucleus. *Brain Struct Funct, 220*(6), 3075-3086. doi:10.1007/s00429-015-1047-2

Alves, G., Wentzel-Larsen, T., & Larsen, J. P. (2004). Is fatigue an independent and persistent symptom in patients with Parkinson disease? *Neurology, 63*(10), 1908-1911. doi:10.1212/01.wnl.0000144277.06917.cc

Anderson, V. C., Burchiel, K. J., Hogarth, P., Favre, J., & Hammerstad, J. P. (2005). Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol, 62*(4), 554-560. doi:10.1001/archneur.62.4.554

Antonini, A., Tinazzi, M., Abbruzzese, G., Berardelli, A., Chaudhuri, K. R., Defazio, G., . . . Rascol, O. (2018). Pain in Parkinson's disease: facts and uncertainties. *Eur J Neurol, 25*(7), 917-e969. doi:10.1111/ene.13624

Armstrong, M. J., & Okun, M. S. (2020). Diagnosis and treatment of Parkinson disease: a review. *JAMA, 323*(6), 548-560. doi:10.1001/jama.2019.22360

Arnulf, I. (2012). REM sleep behavior disorder: motor manifestations and pathophysiology. *Mov Disord, 27*(6), 677-689. doi:10.1002/mds.24957

Arnulf, I., Bejjani, B. P., Garma, L., Bonnet, A. M., Houeto, J. L., Damier, P., . . . Agid, Y. (2000). Improvement of sleep architecture in PD with subthalamic nucleus stimulation. *Neurology, 55*(11), 1732-1734. doi:10.1212/wnl.55.11.1732

Athauda, D., & Foltynie, T. (2015). The ongoing pursuit of neuroprotective therapies in Parkinson disease. *Nat Rev Neurol, 11*(1), 25-40. doi:10.1038/nrneurol.2014.226

Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T. P., . . . Dotto, P. D. (2009). The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord, 24*(11), 1641-1649. doi:10.1002/mds.22643

Baumann-Vogel, H., Imbach, L. L., Surucu, O., Stieglitz, L., Waldvogel, D., Baumann, C. R., & Werth, E. (2017). The impact of subthalamic deep brain stimulation on sleep-wake behavior: a prospective electrophysiological study in 50 Parkinson patients. *Sleep, 40*(5). doi:10.1093/sleep/zsx033

Berg, D., Postuma, R. B., Adler, C. H., Bloem, B. R., Chan, P., Dubois, B., . . . Deuschl, G. (2015). MDS research criteria for prodromal Parkinson's disease. *Mov Disord, 30*(12), 1600-1611. doi:10.1002/mds.26431

Bhattacharyya, K. B., & Rosa-Grilo, M. (2017). Sexual dysfunctions in Parkinson's disease: an underrated problem in a much discussed disorder. *Int Rev Neurobiol, 134*, 859-876. doi:10.1016/bs.irn.2017.05.019

Bond, A. E., Shah, B. B., Huss, D. S., Dallapiazza, R. F., Warren, A., Harrison, M. B., . . . Elias, W. J. (2017). Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant Parkinson disease: a randomized clinical trial. *JAMA Neurol, 74*(12), 1412-1418. doi:10.1001/jamaneurol.2017.3098

Braak, H., & Del Tredici, K. (2009). Neuroanatomy and pathology of sporadic Parkinson's disease. *Adv Anat Embryol Cell Biol, 201*, 1-119.

Braak, H., Del Tredici, K., Rub, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging, 24*(2), 197-211. doi:10.1016/s0197-4580(02)00065-9

Brodsky, M. A., Godbold, J., Roth, T., & Olanow, C. W. (2003). Sleepiness in Parkinson's disease: a controlled study. *Mov Disord, 18*(6), 668-672. doi:10.1002/mds.10429

Bronner, G. (2011). Sexual problems in Parkinson's disease: the multidimensional nature of the problem and of the intervention. *J Neurol Sci, 310*(1-2), 139-143. doi:10.1016/j.jns.2011.05.050

Bunjo, Z., Bacchi, S., Chandran, A. S., & Zacest, A. (2020). Orthostatic hypotension following deep brain stimulation in Parkinson's disease: a systematic review. *Br J Neurosurg, 34*(5), 587-590. doi:10.1080/02688697.2019.1639617

Buot, A., Welter, M. L., Karachi, C., Pochon, J. B., Bardinet, E., Yelnik, J., & Mallet, L. (2013). Processing of emotional information in the human subthalamic nucleus.

J Neurol Neurosurg Psychiatry, 84(12), 1331-1338. doi:10.1136/jnnp-2011-302158

Campbell, M. C., Karimi, M., Weaver, P. M., Wu, J., Perantie, D. C., Golchin, N. A., . . . Hershey, T. (2008). Neural correlates of STN DBS-induced cognitive variability in Parkinson disease. *Neuropsychologia, 46*(13), 3162-3169. doi:10.1016/j.neuropsychologia.2008.07.012

Castelli, L., Perozzo, P., Genesia, M. L., Torre, E., Pesare, M., Cinquepalmi, A., . . . Lopiano, L. (2004). Sexual well being in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry, 75*(9), 1260-1264. doi:10.1136/jnnp.2003.034579

Castillo, P. R., Middlebrooks, E. H., Grewal, S. S., Okromelidze, L., Meschia, J. F., Quinones-Hinojosa, A., . . . Wharen, R. E., Jr. (2020). Globus Pallidus Externus Deep Brain Stimulation Treats Insomnia in a Patient With Parkinson Disease. *Mayo Clin Proc, 95*(2), 419-422. doi:10.1016/j.mayocp.2019.11.020

Cersosimo, M. G., & Benarroch, E. E. (2012). Pathological correlates of gastrointestinal dysfunction in Parkinson's disease. *Neurobiol Dis, 46*(3), 559-564. doi:10.1016/j.nbd.2011.10.014

Chandran, S., Krishnan, S., Rao, R. M., Sarma, S. G., Sarma, P. S., & Kishore, A. (2014). Gender influence on selection and outcome of deep brain stimulation for Parkinson's disease. *Ann Indian Acad Neurol, 17*(1), 66-70. doi:10.4103/0972-2327.128557

Chaudhuri, K. R., Healy, D. G., Schapira, A. H., & National Institute for Clinical, E. (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol, 5*(3), 235-245. doi:10.1016/S1474-4422(06)70373-8

Chaudhuri, K. R., & Logishetty, K. (2009). Dopamine receptor agonists and sleep disturbances in Parkinson's disease. *Parkinsonism Relat Disord, 15 Suppl 4*, S101-104. doi:10.1016/S1353-8020(09)70845-4

Chaudhuri, K. R., & Schapira, A. H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol, 8*(5), 464-474. doi:10.1016/S1474-4422(09)70068-7

Chen, H., Zhang, S. M., Hernan, M. A., Willett, W. C., & Ascherio, A. (2003). Weight loss in Parkinson's disease. *Ann Neurol, 53*(5), 676-679. doi:10.1002/ana.10577

Choi, J. H., Kim, H. J., Lee, J. Y., Yoo, D., Im, J. H., Paek, S. H., & Jeon, B. (2019). Long-term effects of bilateral subthalamic nucleus stimulation on sleep in patients with Parkinson's disease. *PLoS One, 14*(8), e0221219. doi:10.1371/journal.pone.0221219

Chou, K. L., Stacy, M., Simuni, T., Miyasaki, J., Oertel, W. H., Sethi, K., . . . Stocchi, F. (2018). The spectrum of "off" in Parkinson's disease: what have we learned over 40 years? *Parkinsonism Relat Disord, 51*, 9-16. doi:10.1016/j.parkreldis.2018.02.001

Cochen De Cock, V., Abouda, M., Leu, S., Oudiette, D., Roze, E., Vidailhet, M., . . . Arnulf, I. (2010). Is obstructive sleep apnea a problem in Parkinson's disease? *Sleep Med, 11*(3), 247-252. doi:10.1016/j.sleep.2009.05.008

Coenen, V. A., Sajonz, B., Reisert, M., Bostroem, J., Bewernick, B., Urbach, H., . . . Madler, B. (2018). Tractography-assisted deep brain stimulation of the superolateral branch of the medial forebrain bundle (slMFB DBS) in major depression. *Neuroimage Clin, 20*, 580-593. doi:10.1016/j.nicl.2018.08.020

Comella, C. L. (2008). Sleep disorders. In S. A. Factor & W. J. Weiner (Eds.), *Parkinsons's disease: diagnosis and clinical management* (pp. 119-125). New York: Demos.

Connolly, B. S., & Lang, A. E. (2014). Pharmacological treatment of Parkinson disease: a review. *JAMA, 311*(16), 1670-1683. doi:10.1001/jama.2014.3654

Cromwell, H. C., Mears, R. P., Wan, L., & Boutros, N. N. (2008). Sensory gating: a translational effort from basic to clinical science. *Clin EEG Neurosci, 39*(2), 69-72. doi:10.1177/155005940803900209

Cury, R. G., Carvalho, M. J., Lasteros, F. J. L., Dias, A. E., Dos Santos Ghilardi, M. G., Paiva, A. R. B., . . . Fonoff, E. T. (2018). Effects of subthalamic stimulation on olfactory function in Parkinson disease. *World Neurosurg, 114*, e559-e564. doi:10.1016/j.wneu.2018.03.033

Cury, R. G., Galhardoni, R., Fonoff, E. T., Dos Santos Ghilardi, M. G., Fonoff, F., Arnaut, D., . . . Ciampi de Andrade, D. (2014). Effects of deep brain stimulation on pain and other nonmotor symptoms in Parkinson disease. *Neurology, 83*(16), 1403-1409. doi:10.1212/WNL.0000000000000887

Dafsari, H. S., Dos Santos Ghilardi, M. G., Visser-Vandewalle, V., Rizos, A., Ashkan, K., Silverdale, M., . . . Timmermann, L. (2020). Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson's disease. *Brain Stimul, 13*(6), 1697-1705. doi:10.1016/j.brs.2020.09.019

Dafsari, H. S., Martinez-Martin, P., Rizos, A., Trost, M., Dos Santos Ghilardi, M. G., Reddy, P., . . . Ray Chaudhuri, K. (2019). EuroInf 2: Subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease. *Mov Disord, 34*(3), 353-365. doi:10.1002/mds.27626

Dafsari, H. S., Silverdale, M., Strack, M., Rizos, A., Ashkan, K., Mahlstedt, P., . . . Timmermann, L. (2018). Nonmotor symptoms evolution during 24 months of bilateral subthalamic stimulation in Parkinson's disease. *Mov Disord, 33*(3), 421-430. doi:10.1002/mds.27283

Dafsari, H. S., Weiss, L., Silverdale, M., Rizos, A., Reddy, P., Ashkan, K., . . . Timmermann, L. (2018). Short-term quality of life after subthalamic stimulation depends on non-motor symptoms in Parkinson's disease. *Brain Stimul, 11*(4), 867-874. doi:10.1016/j.brs.2018.02.015

Daniels, C., Krack, P., Volkmann, J., Raethjen, J., Pinsker, M. O., Kloss, M., . . . Witt, K. (2011). Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable? *Mov Disord, 26*(14), 2516-2521. doi:10.1002/mds.23907

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schafer, H., Botzel, K., . . . Voges, J. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med, 355*(9), 896-908. doi:10.1056/NEJMoa060281

Deutsche Gesellschaft für Neurologie. (2016, 20.01.2021). Kapitel: Extrapyramidalmotorische Störungen, S3-Leitlinie: Idiopathisches Parkinson-

Syndrom (Langversion). Retrieved from https://www.awmf.org/uploads/tx_szleitlinien/030-010l_S3_Parkinson_Syndrome_Idiopathisch_2016-06.pdf

Dorsey, E. R., Elbaz, A., Nichols, E., Abd-Allah, F., Abdelalim, A., Adsuar, J. C., . . . Murray, C. J. L. (2018). Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol, 17*(11), 939-953. doi:10.1016/s1474-4422(18)30295-3

Doty, R. L. (2012). Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol, 8*(6), 329-339. doi:10.1038/nrneurol.2012.80

Driver-Dunckley, E., Evidente, V. G., Adler, C. H., Hillman, R., Hernandez, J., Fletcher, G., & Lyons, M. K. (2006). Restless legs syndrome in Parkinson's disease patients may improve with subthalamic stimulation. *Mov Disord, 21*(8), 1287-1289. doi:10.1002/mds.20911

Dulski, J., Schinwelski, M., Konkel, A., Grabowski, K., Libionka, W., Waz, P., . . . Slawek, J. (2019). The impact of subthalamic deep brain stimulation on sleep and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord, 64*, 138-144. doi:10.1016/j.parkreldis.2019.04.001

Elias, W. J., Lipsman, N., Ondo, W. G., Ghanouni, P., Kim, Y. G., Lee, W., . . . Chang, J. W. (2016). A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med, 375*(8), 730-739. doi:10.1056/NEJMoa1600159

Espay, A. J., & Lang, A. E. (2017). Common myths in the use of levodopa in Parkinson disease: when clinical trials misinform clinical practice. *JAMA Neurol, 74*(6), 633-634. doi:10.1001/jamaneurol.2017.0348

Fasano, A., Daniele, A., & Albanese, A. (2012). Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *Lancet Neurol, 11*(5), 429-442. doi:10.1016/S1474-4422(12)70049-2

Fasano, A., Visanji, N. P., Liu, L. W., Lang, A. E., & Pfeiffer, R. F. (2015). Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol, 14*(6), 625-639. doi:10.1016/S1474-4422(15)00007-1

Fenelon, G., Mahieux, F., Huon, R., & Ziegler, M. (2000). Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain, 123 (Pt 4)*(4), 733-745. doi:10.1093/brain/123.4.733

Floden, D., Cooper, S. E., Griffith, S. D., & Machado, A. G. (2014). Predicting quality of life outcomes after subthalamic nucleus deep brain stimulation. *Neurology, 83*(18), 1627-1633. doi:10.1212/WNL.0000000000000943

Follett, K. A., Weaver, F. M., Stern, M., Hur, K., Harris, C. L., Luo, P., . . . Group, C. S. P. S. (2010). Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med, 362*(22), 2077-2091. doi:10.1056/NEJMoa0907083

Fox, S. H., Katzenschlager, R., Lim, S. Y., Barton, B., de Bie, R. M. A., Seppi, K., . . . Movement Disorder Society Evidence-Based Medicine, C. (2018). International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord, 33*(8), 1248-1266. doi:10.1002/mds.27372

Frauscher, B., & Poewe, W. (2014). Excessive daytime sleepiness in Parkinson's disease. In K. Ray Chaudhuri, E. Tolosa, A. H. Schapira, & W. Poewe (Eds.), *Non-Motor Symptoms of Parkinson's Disease* (pp. 245-255). Oxford: Oxford University Press.

Friedman, J. H., Brown, R. G., Comella, C., Garber, C. E., Krupp, L. B., Lou, J. S., . . . Working Group on Fatigue in Parkinson's, D. (2007). Fatigue in Parkinson's disease: a review. *Mov Disord, 22*(3), 297-308. doi:10.1002/mds.21240

Funkiewiez, A., Ardouin, C., Caputo, E., Krack, P., Fraix, V., Klinger, H., . . . Pollak, P. (2004). Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry, 75*(6), 834-839. doi:10.1136/jnnp.2002.009803

Galbiati, A., Verga, L., Giora, E., Zucconi, M., & Ferini-Strambi, L. (2019). The risk of neurodegeneration in REM sleep behavior disorder: A systematic review and meta-analysis of longitudinal studies. *Sleep Med Rev, 43*, 37-46. doi:10.1016/j.smrv.2018.09.008

Gallagher, D. A., Lees, A. J., & Schrag, A. (2010). What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord, 25*(15), 2493-2500. doi:10.1002/mds.23394

Gallagher, D. A., & Schrag, A. (2014). Depression, anxiety and apathy in Parkinson's disease. In K. R. Chaudhuri, E. Tolosa, A. H. Schapira, & W. Poewe (Eds.), *Non-motor symptoms of Parkinson's disease* (pp. 139-157). Oxford: Oxford University Press.

Garcia-Ruiz, P. J., Martinez Castrillo, J. C., Alonso-Canovas, A., Herranz Barcenas, A., Vela, L., Sanchez Alonso, P., . . . Mahillo Fernandez, I. (2014). Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. *J Neurol Neurosurg Psychiatry, 85*(8), 840-844. doi:10.1136/jnnp-2013-306787

Gjerstad, M. D., Wentzel-Larsen, T., Aarsland, D., & Larsen, J. P. (2007). Insomnia in Parkinson's disease: frequency and progression over time. *J Neurol Neurosurg Psychiatry, 78*(5), 476-479. doi:10.1136/jnnp.2006.100370

Goetz, C. G., & Stebbins, G. T. (1993). Risk factors for nursing home placement in advanced Parkinson's disease. *Neurology, 43*(11), 2227-2229. doi:10.1212/wnl.43.11.2227

Gulberti, A., Hamel, W., Buhmann, C., Boelmans, K., Zittel, S., Gerloff, C., . . . Moll, C. K. (2015). Subthalamic deep brain stimulation improves auditory sensory gating deficit in Parkinson's disease. *Clin Neurophysiol, 126*(3), 565-574. doi:10.1016/j.clinph.2014.06.046

Guo, X., Gao, G., Wang, X., Li, L., Li, W., Liang, Q., & Zhang, H. (2008). Effects of bilateral deep brain stimulation of the subthalamic nucleus on olfactory function in Parkinson's disease patients. *Stereotact Funct Neurosurg, 86*(4), 237-244. doi:10.1159/000131662

Haehner, A., Boesveldt, S., Berendse, H. W., Mackay-Sim, A., Fleischmann, J., Silburn, P. A., . . . Hummel, T. (2009). Prevalence of smell loss in Parkinson's disease--a multicenter study. *Parkinsonism Relat Disord, 15*(7), 490-494. doi:10.1016/j.parkreldis.2008.12.005

Hall, J. M., & Lewis, S. J. G. (2019). Neural correlates of cognitive impairment in Parkinson's disease: a review of structural MRI findings. *Int Rev Neurobiol, 144*, 1-28. doi:10.1016/bs.irn.2018.09.009

Herzog, J., Weiss, P. H., Assmus, A., Wefer, B., Seif, C., Braun, P. M., . . . Fink, G. R. (2006). Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson's disease. *Brain, 129*(Pt 12), 3366-3375. doi:10.1093/brain/awl302

Hjort, N., Ostergaard, K., & Dupont, E. (2004). Improvement of sleep quality in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. *Mov Disord, 19*(2), 196-199. doi:10.1002/mds.10639

Holmberg, B., Corneliusson, O., & Elam, M. (2005). Bilateral stimulation of nucleus subthalamicus in advanced Parkinson's disease: no effects on, and of, autonomic dysfunction. *Mov Disord, 20*(8), 976-981. doi:10.1002/mds.20492

Homann, C. N., Wenzel, K., Suppan, K., Ivanic, G., Kriechbaum, N., Crevenna, R., & Ott, E. (2002). Sleep attacks in patients taking dopamine agonists: review. *BMJ, 324*(7352), 1483-1487. doi:10.1136/bmj.324.7352.1483

Horstink, M., Tolosa, E., Bonuccelli, U., Deuschl, G., Friedman, A., Kanovsky, P., . . . Sampaio, C. (2006). Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part II: late (complicated) Parkinson's disease. *Eur J Neurol, 13*(11), 1186-1202. doi:10.1111/j.1468-1331.2006.01548.x

Hou, J. G., Wu, L., & Lai, E. (2009). P2.035 Deep brain stimulation effects on orthostatic regulations in patients with Parkinson's disease. *Parkinsonism Relat Disord, 15*, S97-S98. doi:10.1016/s1353-8020(09)70386-4

Hummel, T., Jahnke, U., Sommer, U., Reichmann, H., & Muller, A. (2005). Olfactory function in patients with idiopathic Parkinson's disease: effects of deep brain stimulation in the subthalamic nucleus. *J Neural Transm (Vienna), 112*(5), 669-676. doi:10.1007/s00702-004-0207-y

Husain, M. (2019). Targeting network dysfunction in neurodegenerative diseases. *Brain, 142*(12), 3661-3662. doi:10.1093/brain/awz347

Irmen, F., Horn, A., Mosley, P., Perry, A., Petry-Schmelzer, J. N., Dafsari, H. S., . . . Kuhn, A. A. (2020). Left Prefrontal Connectivity Links Subthalamic Stimulation with Depressive Symptoms. *Ann Neurol, 87*(6), 962-975. doi:10.1002/ana.25734

Jakobs, M., Fomenko, A., Lozano, A. M., & Kiening, K. L. (2019). Cellular, molecular, and clinical mechanisms of action of deep brain stimulation-a systematic review on established indications and outlook on future developments. *EMBO Mol Med, 11*(4). doi:10.15252/emmm.201809575

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry, 79*(4), 368-376. doi:10.1136/jnnp.2007.131045

Janvin, C. C., Larsen, J. P., Salmon, D. P., Galasko, D., Hugdahl, K., & Aarsland, D. (2006). Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with lewy bodies and Alzheimer's disease. *Mov Disord, 21*(3), 337-342. doi:10.1002/mds.20726

Jost, W. H. (2013). Urological problems in Parkinson's disease: clinical aspects. *J Neural Transm (Vienna), 120*(4), 587-591. doi:10.1007/s00702-012-0914-8

Jost, W. H. (2017). Autonomic dysfunction in Parkinson's disease: cardiovascular symptoms, thermoregulation, and urogenital symptoms. *Int Rev Neurobiol, 134*, 771-785. doi:10.1016/bs.irn.2017.04.003

Jung, Y. J., Kim, H. J., Jeon, B. S., Park, H., Lee, W. W., & Paek, S. H. (2015). An 8-year follow-up on the effect of subthalamic nucleus deep brain stimulation on pain in Parkinson disease. *JAMA Neurol, 72*(5), 504-510. doi:10.1001/jamaneurol.2015.8

Kandiah, N., Narasimhalu, K., Lau, P. N., Seah, S. H., Au, W. L., & Tan, L. C. (2009). Cognitive decline in early Parkinson's disease. *Mov Disord, 24*(4), 605-608. doi:10.1002/mds.22384

Katzenschlager, R., Poewe, W., Rascol, O., Trenkwalder, C., Deuschl, G., Chaudhuri, K. R., . . . Lees, A. (2018). Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol, 17*(9), 749-759. doi:10.1016/S1474-4422(18)30239-4

Keir, L. H. M., & Breen, D. P. (2020). New awakenings: current understanding of sleep dysfunction and its treatment in Parkinson's disease. *J Neurol, 267*(1), 288-294. doi:10.1007/s00415-019-09651-z

Klepitskaya, O., Liu, Y., Sharma, S., Sillau, S. H., Tsai, J., & Walters, A. S. (2018). Deep brain stimulation improves restless legs syndrome in patients with Parkinson disease. *Neurology, 91*(11), e1013-e1021. doi:10.1212/WNL.0000000000006162

Klingelhoefer, L., & Reichmann, H. (2017). Parkinson's disease as a multisystem disorder. *J Neural Transm (Vienna), 124*(6), 709-713. doi:10.1007/s00702-017-1692-0

Knie, B., Mitra, M. T., Logishetty, K., & Chaudhuri, K. R. (2011). Excessive daytime sleepiness in patients with Parkinson's disease. *CNS Drugs, 25*(3), 203-212. doi:10.2165/11539720-000000000-00000

Kouli, A., Torsney, K. M., & Kuan, W. L. (2018). Parkinson's disease: etiology, neuropathology, and pathogenesis. In T. B. Stoker & J. C. Greenland (Eds.), *Parkinson's disease: pathogenesis and clinical aspects*. Brisbane (AU): Codon Publications.

Krack, P., & Hariz, M. I. (2013). Deep brain stimulation in Parkinson's disease: reconciliation of evidence-based medicine with clinical practice. *Lancet Neurol, 12*(1), 25-26. doi:10.1016/S1474-4422(12)70270-3

Krack, P., Hariz, M. I., Baunez, C., Guridi, J., & Obeso, J. A. (2010). Deep brain stimulation: from neurology to psychiatry? *Trends Neurosci, 33*(10), 474-484. doi:10.1016/j.tins.2010.07.002

Kumar, S., Bhatia, M., & Behari, M. (2002). Sleep disorders in Parkinson's disease. *Mov Disord, 17*(4), 775-781. doi:10.1002/mds.10167

Kurcova, S., Bardon, J., Vastik, M., Vecerkova, M., Frolova, M., Hvizdosova, L., . . . Kanovsky, P. (2018). Bilateral subthalamic deep brain stimulation initial impact on nonmotor and motor symptoms in Parkinson's disease: an open prospective

single institution study. *Medicine (Baltimore), 97*(5), e9750. doi:10.1097/MD.0000000000009750

Kurtis, M. M., Rajah, T., Delgado, L. F., & Dafsari, H. S. (2017). The effect of deep brain stimulation on the non-motor symptoms of Parkinson's disease: a critical review of the current evidence. *NPJ Parkinsons Dis, 3*, 16024. doi:10.1038/npjparkd.2016.24

Leclair-Visonneau, L., Magy, L., Volteau, C., Clairembault, T., Le Dily, S., Preterre, C., . . . Derkinderen, P. (2018). Heterogeneous pattern of autonomic dysfunction in Parkinson's disease. *J Neurol, 265*(4), 933-941. doi:10.1007/s00415-018-8789-8

Lee, D. J., Lozano, C. S., Dallapiazza, R. F., & Lozano, A. M. (2019). Current and future directions of deep brain stimulation for neurological and psychiatric disorders. *J Neurosurg, 131*(2), 333-342. doi:10.3171/2019.4.JNS181761

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex, 16*(7), 916-928. doi:10.1093/cercor/bhj043

LeWitt, P. A., & Fahn, S. (2016). Levodopa therapy for Parkinson disease: a look backward and forward. *Neurology, 86*(14 Suppl 1), S3-12. doi:10.1212/WNL.0000000000002509

Lezcano, E., Gomez-Esteban, J. C., Tijero, B., Bilbao, G., Lambarri, I., Rodriguez, O., . . . Zarranz, J. J. (2016). Long-term impact on quality of life of subthalamic nucleus stimulation in Parkinson's disease. *J Neurol, 263*(5), 895-905. doi:10.1007/s00415-016-8077-4

Li, K., Haase, R., Rudiger, H., Reimann, M., Reichmann, H., Wolz, M., & Ziemssen, T. (2017). Subthalamic nucleus stimulation and levodopa modulate cardiovascular autonomic function in Parkinson's disease. *Sci Rep, 7*(1), 7012. doi:10.1038/s41598-017-07429-9

Lim, S., Moro, E., Tan, A. H., & Lang, A. E. (2014). Non-motor symptoms of Parkinson's disease and the effects of deep brain stimulation surgery. In K. R. Chaudhuri, E. Tolosa, A. H. Schapira, & W. Poewe (Eds.), *Non-motor symptoms of Parkinson's disease* (pp. 394-419). Oxford: Oxford University Press.

Lim, S. Y., Fox, S. H., & Lang, A. E. (2009). Overview of the extranigral aspects of Parkinson disease. *Arch Neurol, 66*(2), 167-172. doi:10.1001/archneurol.2008.561

Limousin, P., & Foltynie, T. (2019). Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol, 15*(4), 234-242. doi:10.1038/s41582-019-0145-9

Litvan, I., Goldman, J. G., Troster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., . . . Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord, 27*(3), 349-356. doi:10.1002/mds.24893

Lix, L. M., Hobson, D. E., Azimaee, M., Leslie, W. D., Burchill, C., & Hobson, S. (2010). Socioeconomic variations in the prevalence and incidence of Parkinson's disease: a population-based analysis. *J Epidemiol Community Health, 64*(4), 335-340. doi:10.1136/jech.2008.084954

Locke, M. C., Wu, S. S., Foote, K. D., Sassi, M., Jacobson, C. E., Rodriguez, R. L., . . . Okun, M. S. (2011). Weight changes in subthalamic nucleus vs globus pallidus internus deep brain stimulation: results from the COMPARE Parkinson disease deep brain stimulation cohort. *Neurosurgery, 68*(5), 1233-1237; discussion 1237-1238. doi:10.1227/NEU.0b013e31820b52c5

Lyons, K. E., Wilkinson, S. B., Troster, A. I., & Pahwa, R. (2002). Long-term efficacy of globus pallidus stimulation for the treatment of Parkinson's disease. *Stereotact Funct Neurosurg, 79*(3-4), 214-220. doi:10.1159/000070834

Macleod, A. D., Taylor, K. S., & Counsell, C. E. (2014). Mortality in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord, 29*(13), 1615-1622. doi:10.1002/mds.25898

Maier, F., Lewis, C. J., Horstkoetter, N., Eggers, C., Kalbe, E., Maarouf, M., . . . Timmermann, L. (2013). Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. *J Neurol Neurosurg Psychiatry, 84*(11), 1273-1281. doi:10.1136/jnnp-2012-303670

Maria, B., Sophia, S., Michalis, M., Charalampos, L., Andreas, P., John, M. E., & Nikolaos, S. M. (2003). Sleep breathing disorders in patients with idiopathic Parkinson's disease. *Respir Med, 97*(10), 1151-1157. doi:10.1016/s0954-6111(03)00188-4

Markus, H. S., Cox, M., & Tomkins, A. M. (1992). Raised resting energy expenditure in Parkinson's disease and its relationship to muscle rigidity. *Clin Sci (Lond), 83*(2), 199-204. doi:10.1042/cs0830199

Markus, H. S., Tomkins, A. M., & Stern, G. M. (1993). Increased prevalence of undernutrition in Parkinson's disease and its relationship to clinical disease parameters. *J Neural Transm Park Dis Dement Sect, 5*(2), 117-125. doi:10.1007/BF02251202

Martinez-Martin, P., Rodriguez-Blazquez, C., Kurtis, M. M., & Chaudhuri, K. R. (2011). The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord, 26*(3), 399-406. doi:10.1002/mds.23462

McCarthy, K., Ward, M., Romero Ortuno, R., & Kenny, R. A. (2020). Syncope, fear of falling and quality of life among older adults: findings from the Irish longitudinal study on aging (TILDA). *Front Cardiovasc Med, 7*, 7. doi:10.3389/fcvm.2020.00007

Mena-Segovia, J., Bolam, J. P., & Magill, P. J. (2004). Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci, 27*(10), 585-588. doi:10.1016/j.tins.2004.07.009

Meyer, A., Zimmermann, R., Gschwandtner, U., Hatz, F., Bousleiman, H., Schwarz, N., & Fuhr, P. (2014). Apathy in Parkinson's disease is related to executive function, gender and age but not to depression. *Front Aging Neurosci, 6*(350), 350. doi:10.3389/fnagi.2014.00350

Middlebrooks, E. H., Tuna, I. S., Grewal, S. S., Almeida, L., Heckman, M. G., Lesser, E. R., . . . Holanda, V. M. (2018). Segmentation of the globus pallidus internus using probabilistic diffusion tractography for deep brain stimulation targeting in Parkinson disease. *AJNR Am J Neuroradiol, 39*(6), 1127-1134. doi:10.3174/ajnr.A5641

Mills, K. A., Scherzer, R., Starr, P. A., & Ostrem, J. L. (2012). Weight change after globus pallidus internus or subthalamic nucleus deep brain stimulation in Parkinson's disease and dystonia. *Stereotact Funct Neurosurg, 90*(6), 386-393. doi:10.1159/000340071

Mizushima, J., Takahata, K., Kawashima, N., & Kato, M. (2012). Successful treatment of dopamine dysregulation syndrome with dopamine D2 partial agonist antipsychotic drug. *Ann Gen Psychiatry, 11*(1), 19. doi:10.1186/1744-859X-11-19

Mock, S., Osborn, D. J., Brown, E. T., Stuart Reynolds, W., Turchan, M., Pallavaram, S., . . . Tolleson, C. M. (2016). The impact of pallidal and subthalamic deep brain stimulation on urologic function in Parkinson's disease. *Neuromodulation, 19*(7), 717-723. doi:10.1111/ner.12446

Moro, E., Lozano, A. M., Pollak, P., Agid, Y., Rehncrona, S., Volkmann, J., . . . Lang, A. E. (2010). Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov Disord, 25*(5), 578-586. doi:10.1002/mds.22735

Odekerken, V. J., Boel, J. A., Schmand, B. A., de Haan, R. J., Figee, M., van den Munckhof, P., . . . de Bie, R. M. (2016). GPi vs STN deep brain stimulation for Parkinson disease: three-year follow-up. *Neurology, 86*(8), 755-761. doi:10.1212/WNL.0000000000002401

Odekerken, V. J., van Laar, T., Staal, M. J., Mosch, A., Hoffmann, C. F., Nijssen, P. C., . . . de Bie, R. M. (2013). Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol, 12*(1), 37-44. doi:10.1016/S1474-4422(12)70264-8

Okun, M. S., Fernandez, H. H., Wu, S. S., Kirsch-Darrow, L., Bowers, D., Bova, F., . . . Foote, K. D. (2009). Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol, 65*(5), 586-595. doi:10.1002/ana.21596

Olson, E. J., Boeve, B. F., & Silber, M. H. (2000). Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain, 123*, 331-339. doi:10.1093/brain/123.2.331

Ondo, W. G. (2014). Parkinson's disease and restless legs syndrome. In K. R. Chaudhuri, E. Tolosa, A. H. Schapira, & W. Poewe (Eds.), *Non-motor symptoms of Parkinson's disease* (pp. 235-244). Oxford: Oxford University Press.

Ossig, C., Sippel, D., Fauser, M., Gandor, F., Jost, W. H., Ebersbach, G., & Storch, A. (2016). Assessment of nonmotor fluctuations using a aiary in advanced Parkinson's disease. *J Parkinsons Dis, 6*(3), 597-607. doi:10.3233/JPD-150764

Parsons, T. D., Rogers, S. A., Braaten, A. J., Woods, S. P., & Troster, A. I. (2006). Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol, 5*(7), 578-588. doi:10.1016/S1474-4422(06)70475-6

Pedersen, K. F., Larsen, J. P., Tysnes, O. B., & Alves, G. (2013). Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. *JAMA Neurol, 70*(5), 580-586. doi:10.1001/jamaneurol.2013.2110

Pennington, S., Snell, K., Lee, M., & Walker, R. (2010). The cause of death in idiopathic Parkinson's disease. *Parkinsonism Relat Disord, 16*(7), 434-437. doi:10.1016/j.parkreldis.2010.04.010

Peppe, A., Pierantozzi, M., Baiamonte, V., Moschella, V., Caltagirone, C., Stanzione, P., & Stefani, A. (2012). Deep brain stimulation of pedunculopontine tegmental nucleus: role in sleep modulation in advanced Parkinson disease patients: one-year follow-up. *Sleep, 35*(12), 1637-1642. doi:10.5665/sleep.2234

Petry-Schmelzer, J. N., Krause, M., Dembek, T. A., Horn, A., Evans, J., Ashkan, K., . . . Dafsari, H. S. (2019). Non-motor outcomes depend on location of neurostimulation in Parkinson's disease. *Brain, 142*(11), 3592-3604. doi:10.1093/brain/awz285

Pfeiffer, R. F. (2016). Non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord, 22 Suppl 1*, S119-122. doi:10.1016/j.parkreldis.2015.09.004

Pfeiffer, R. F. (2020). Autonomic dysfunction in Parkinson's disease. *Neurotherapeutics*. doi:10.1007/s13311-020-00897-4

Poewe, W., & Antonini, A. (2015). Novel formulations and modes of delivery of levodopa. *Mov Disord, 30*(1), 114-120. doi:10.1002/mds.26078

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., . . . Lang, A. E. (2017). Parkinson disease. *Nat Rev Dis Primers, 3*, 17013. doi:10.1038/nrdp.2017.13

Postuma, R. B., Aarsland, D., Barone, P., Burn, D. J., Hawkes, C. H., Oertel, W., & Ziemssen, T. (2012). Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord, 27*(5), 617-626. doi:10.1002/mds.24996

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., . . . Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord, 30*(12), 1591-1601. doi:10.1002/mds.26424

Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. (2014). The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord, 29*(13), 1583-1590. doi:10.1002/mds.25945

Pursiainen, V., Haapaniemi, T. H., Korpelainen, J. T., Sotaniemi, K. A., & Myllyla, V. V. (2007). Sweating in Parkinsonian patients with wearing-off. *Mov Disord, 22*(6), 828-832. doi:10.1002/mds.21422

Qamar, M. A., Sauerbier, A., Politis, M., Carr, H., Loehrer, P., & Chaudhuri, K. R. (2017). Presynaptic dopaminergic terminal imaging and non-motor symptoms assessment of Parkinson's disease: evidence for dopaminergic basis? *NPJ Parkinsons Dis, 3*, 5. doi:10.1038/s41531-016-0006-9

Qiu, M. H., Chen, M. C., Wu, J., Nelson, D., & Lu, J. (2016). Deep brain stimulation in the globus pallidus externa promotes sleep. *Neuroscience, 322*, 115-120. doi:10.1016/j.neuroscience.2016.02.032

Romigi, A., Placidi, F., Peppe, A., Pierantozzi, M., Izzi, F., Brusa, L., . . . Stefani, A. (2008). Pedunculopontine nucleus stimulation influences REM sleep in Parkinson's disease. *Eur J Neurol, 15*(7), e64-65. doi:10.1111/j.1468-1331.2008.02167.x

Rouaud, T., Dondaine, T., Drapier, S., Haegelen, C., Lallement, F., Peron, J., . . . Verin, M. (2010). Pallidal stimulation in advanced Parkinson's patients with contraindications for subthalamic stimulation. *Mov Disord, 25*(12), 1839-1846. doi:10.1002/mds.23171

Roychowdhury, S., & Forsyth, D. R. (2012). Sleep disturbance in Parkinson disease. *J Gerontol Geriatr, 3*(2), 53-61. doi:10.1016/j.jcgg.2012.04.002

Rughani, A., Schwalb, J. M., Sidiropoulos, C., Pilitsis, J., Ramirez-Zamora, A., Sweet, J. A., . . . Hamani, C. (2018). Congress of neurological surgeons systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson's disease: executive summary. *Neurosurgery, 82*(6), 753-756. doi:10.1093/neuros/nyy037

Rukavina, K., Leta, V., Sportelli, C., Buhidma, Y., Duty, S., Malcangio, M., & Ray Chaudhuri, K. (2019). Pain in Parkinson's disease: new concepts in pathogenesis and treatment. *Curr Opin Neurol, 32*(4), 579-588. doi:10.1097/WCO.0000000000000711

Rye, D. B., & Iranzo, A. (2005). The nocturnal manifestations of waking movement disorders - focus on Parkinson’s disease. In C. Guilleminault (Ed.), *Clinical neurophysiology of sleep disorders* (pp. 263-272). New York: Elsevier.

Sanchez-Ferro, A., Benito-Leon, J., & Gomez-Esteban, J. C. (2013). The management of orthostatic hypotension in Parkinson's disease. *Front Neurol, 4*, 64. doi:10.3389/fneur.2013.00064

Sauleau, P., Le Jeune, F., Drapier, S., Houvenaghel, J. F., Dondaine, T., Haegelen, C., . . . Verin, M. (2014). Weight gain following subthalamic nucleus deep brain stimulation: a PET study. *Mov Disord, 29*(14), 1781-1787. doi:10.1002/mds.26063

Schenkman, M., Moore, C. G., Kohrt, W. M., Hall, D. A., Delitto, A., Comella, C. L., . . . Corcos, D. M. (2018). Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo Parkinson disease: a phase 2 randomized clinical trial. *JAMA Neurol, 75*(2), 219-226. doi:10.1001/jamaneurol.2017.3517

Schrag, A. (2006). Quality of life and depression in Parkinson's disease. *J Neurol Sci, 248*(1-2), 151-157. doi:10.1016/j.jns.2006.05.030

Schuepbach, W. M., Rau, J., Knudsen, K., Volkmann, J., Krack, P., Timmermann, L., . . . Group, E. S. (2013). Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med, 368*(7), 610-622. doi:10.1056/NEJMoa1205158

Schuepbach, W. M., Tonder, L., Schnitzler, A., Krack, P., Rau, J., Hartmann, A., . . . Deuschl, G. (2019). Quality of life predicts outcome of deep brain stimulation in early Parkinson disease. *Neurology, 92*(10), e1109-e1120. doi:10.1212/WNL.0000000000007037

Shulman, L. M., Taback, R. L., Rabinstein, A. A., & Weiner, W. J. (2002). Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord, 8*(3), 193-197. doi:10.1016/s1353-8020(01)00015-3

Siciliano, M., Trojano, L., Santangelo, G., De Micco, R., Tedeschi, G., & Tessitore, A. (2018). Fatigue in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord, 33*(11), 1712-1723. doi:10.1002/mds.27461

Siderowf, A., Jaggi, J. L., Xie, S. X., Loveland-Jones, C., Leng, L., Hurtig, H., . . . Baltuch, G. (2006). Long-term effects of bilateral subthalamic nucleus stimulation on health-related quality of life in advanced Parkinson's disease. *Mov Disord, 21*(6), 746-753. doi:10.1002/mds.20786

Sit, S. Y. (2000). Dopamine agonists in the treatment of Parkinson s disease past, present and future. *Curr Pharm Des, 6*(12), 1211-1248. doi:10.2174/1381612003399581

Soulas, T., Sultan, S., Gurruchaga, J. M., Palfi, S., & Fenelon, G. (2011). Depression and coping as predictors of change after deep brain stimulation in Parkinson's disease. *World Neurosurg, 75*(3-4), 525-532. doi:10.1016/j.wneu.2010.06.015

Srivanitchapoom, P., Pandey, S., & Hallett, M. (2014). Drooling in Parkinson's disease: a review. *Parkinsonism Relat Disord, 20*(11), 1109-1118. doi:10.1016/j.parkreldis.2014.08.013

Stefani, A., Peppe, A., Galati, S., Bassi, M. S., D'Angelo, V., & Pierantozzi, M. (2013). The serendipity case of the pedunculopontine nucleus low-frequency brain stimulation: chasing a gait response, finding sleep, and cognition improvement. *Front Neurol, 4*, 68. doi:10.3389/fneur.2013.00068

Storch, A., Schneider, C. B., Wolz, M., Sturwald, Y., Nebe, A., Odin, P., . . . Ebersbach, G. (2013). Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology, 80*(9), 800-809. doi:10.1212/WNL.0b013e318285c0ed

Stowe, R., Ives, N., Clarke, C. E., Handley, K., Furmston, A., Deane, K., . . . Gray, R. (2011). Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson's disease. *Mov Disord, 26*(4), 587-598. doi:10.1002/mds.23517

Stuart, E. A., & Rubin, D. B. (2007). Best practices in quasi-experimental designs: matching methods for causal inference. In J. Osborne (Ed.), *Best practices in quantitative social science*. Thousand Oaks, CA: Sage.

Taba, H. A., Wu, S. S., Foote, K. D., Hass, C. J., Fernandez, H. H., Malaty, I. A., . . . Okun, M. S. (2010). A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. *J Neurosurg, 113*(6), 1224-1229. doi:10.3171/2010.8.JNS10312

Tan, E. K., Lum, S. Y., Fook-Chong, S. M., Teoh, M. L., Yih, Y., Tan, L., . . . Wong, M. C. (2002). Evaluation of somnolence in Parkinson's disease: comparison with age- and sex-matched controls. *Neurology, 58*(3), 465-468. doi:10.1212/wnl.58.3.465

Tandberg, E., Larsen, J. P., & Karlsen, K. (1998). A community-based study of sleep disorders in patients with Parkinson's disease. *Mov Disord, 13*(6), 895-899. doi:10.1002/mds.870130606

Thevathasan, W., Cole, M. H., Graepel, C. L., Hyam, J. A., Jenkinson, N., Brittain, J. S., . . . Brown, P. (2012). A spatiotemporal analysis of gait freezing and the

impact of pedunculopontine nucleus stimulation. *Brain, 135*(Pt 5), 1446-1454. doi:10.1093/brain/aws039

Thobois, S., Dominey, P., Fraix, V., Mertens, P., Guenot, M., Zimmer, L., . . . Broussolle, E. (2002). Effects of subthalamic nucleus stimulation on actual and imagined movement in Parkinson's disease : a PET study. *J Neurol, 249*(12), 1689-1698. doi:10.1007/s00415-002-0906-y

Tolosa, E., Gaig, C., Santamaria, J., & Compta, Y. (2014). Non-motor symptoms in the early motor stages of Parkinson's disease. In K. R. Chaudhuri, E. Tolosa, A. H. Schapira, & W. Poewe (Eds.), *Non-motor symptoms of Parkinson's disease* (pp. 24-43). Oxford: Oxford University Press.

Trachani, E., Constantoyannis, C., Sirrou, V., Kefalopoulou, Z., Markaki, E., & Chroni, E. (2010). Effects of subthalamic nucleus deep brain stimulation on sweating function in Parkinson's disease. *Clin Neurol Neurosurg, 112*(3), 213-217. doi:10.1016/j.clineuro.2009.11.015

Valko, P. O., Waldvogel, D., Weller, M., Bassetti, C. L., Held, U., & Baumann, C. R. (2010). Fatigue and excessive daytime sleepiness in idiopathic Parkinson's disease differently correlate with motor symptoms, depression and dopaminergic treatment. *Eur J Neurol, 17*(12), 1428-1436. doi:10.1111/j.1468-1331.2010.03063.x

Valkovic, P., Minar, M., Singliarova, H., Harsany, J., Hanakova, M., Martinkova, J., & Benetin, J. (2015). Pain in Parkinson's Disease: A Cross-Sectional Study of Its Prevalence, Types, and Relationship to Depression and Quality of Life. *PLoS One, 10*(8), e0136541. doi:10.1371/journal.pone.0136541

van Mierlo, T. J., Chung, C., Foncke, E. M., Berendse, H. W., & van den Heuvel, O. A. (2015). Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume. *Mov Disord, 30*(2), 245-252. doi:10.1002/mds.26112

Virhammar, J., & Nyholm, D. (2017). Levodopa-carbidopa enteral suspension in advanced Parkinson's disease: clinical evidence and experience. *Ther Adv Neurol Disord, 10*(3), 171-187. doi:10.1177/1756285616681280

Volkmann, J., Allert, N., Voges, J., Sturm, V., Schnitzler, A., & Freund, H. J. (2004). Long-term results of bilateral pallidal stimulation in Parkinson's disease. *Ann Neurol, 55*(6), 871-875. doi:10.1002/ana.20091

Walker, H. C., Lyerly, M., Cutter, G., Hagood, J., Stover, N. P., Guthrie, S. L., . . . Watts, R. L. (2009). Weight changes associated with unilateral STN DBS and advanced PD. *Parkinsonism Relat Disord, 15*(9), 709-711. doi:10.1016/j.parkreldis.2009.01.009

Wang, L., Li, J., & Chen, J. (2018). Levodopa-carbidopa intestinal gel in Parkinson's disease: a systematic review and meta-analysis. *Front Neurol, 9*(620), 620. doi:10.3389/fneur.2018.00620

Wang, Y., Fang, Y. R., Chen, X. S., Chen, J., Wu, Z. G., Yuan, C. M., . . . Cao, L. (2009). A follow-up study on features of sensory gating P50 in treatment-resistant depression patients. *Chin Med J (Engl), 122*(24), 2956-2960.

Weaver, F. M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W. J., Jr., . . . Group, C. S. P. S. (2009). Bilateral deep brain stimulation vs best medical therapy for

patients with advanced Parkinson disease: a randomized controlled trial. *JAMA, 301*(1), 63-73. doi:10.1001/jama.2008.929

Weaver, F. M., Follett, K. A., Stern, M., Luo, P., Harris, C. L., Hur, K., . . . Group, C. S. P. S. (2012). Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology, 79*(1), 55-65. doi:10.1212/WNL.0b013e31825dcdc1

Weintraub, D., & Burn, D. J. (2011). Parkinson's disease: the quintessential neuropsychiatric disorder. *Mov Disord, 26*(6), 1022-1031. doi:10.1002/mds.23664

Williams-Gray, C. H., & Worth, P. F. (2016). Parkinson's disease. *Medicine (Baltimore), 44*(9), 542-546. doi:10.1016/j.mpmed.2016.06.001

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., . . . Wheatley, K. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol, 9*(6), 581-591. doi:10.1016/S1474-4422(10)70093-4

Witjas, T., Kaphan, E., Azulay, J. P., Blin, O., Ceccaldi, M., Pouget, J., . . . Cherif, A. A. (2002). Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology, 59*(3), 408-413. doi:10.1212/wnl.59.3.408

Witt, K., Daniels, C., Reiff, J., Krack, P., Volkmann, J., Pinsker, M. O., . . . Deuschl, G. (2008). Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol, 7*(7), 605-614. doi:10.1016/S1474-4422(08)70114-5

Witte, L. P., Odekerken, V. J. J., Boel, J. A., Schuurman, P. R., Gerbrandy-Schreuders, L. C., de Bie, R. M. A., & group, N. s. (2018). Does deep brain stimulation improve lower urinary tract symptoms in Parkinson's disease? *Neurourol Urodyn, 37*(1), 354-359. doi:10.1002/nau.23301

Wolters, E., van der Werf, Y. D., & van den Heuvel, O. A. (2008). Parkinson's disease-related disorders in the impulsive-compulsive spectrum. *J Neurol, 255 Suppl 5*(5), 48-56. doi:10.1007/s00415-008-5010-5

Xiao, Z. P., Chen, X. S., Wang, J. J., Tang, Y. X., Zhang, T. H., Zhang, M. D., . . . Chen, C. (2010). Experimental study on sensory gating in generalized anxiety and obsessive compulsive disorders. *Zhonghua Yi Xue Za Zhi, 90*(3), 169-172.

Xie, C. L., Shao, B., Chen, J., Zhou, Y., Lin, S. Y., & Wang, W. W. (2016). Effects of neurostimulation for advanced Parkinson's disease patients on motor symptoms: a multiple-treatments meta-analysas of randomized controlled trials. *Sci Rep, 6*(1), 25285. doi:10.1038/srep25285

Yamamoto, T., Uchiyama, T., Asahina, M., Yamanaka, Y., Hirano, S., Higuchi, Y., & Kuwabara, S. (2018). Urinary symptoms are correlated with quality of life after deep brain stimulation in Parkinson's disease. *Brain Behav, 8*(12), e01164. doi:10.1002/brb3.1164

Yang, X., Liu, B., Shen, H., Li, S., Zhao, Q., An, R., . . . Xu, Z. (2018). Prevalence of restless legs syndrome in Parkinson's disease: a systematic review and meta-analysis of observational studies. *Sleep Med, 43*, 40-46. doi:10.1016/j.sleep.2017.11.1146

Yeung, E. Y. H., & Cavanna, A. E. (2014). Sleep attacks in patients with Parkinson's disease on dopaminergic medications: a systematic review. *Mov Disord Clin Pract, 1*(4), 307-316. doi:10.1002/mdc3.12063

Yoshida, F., Miyagi, Y., Kishimoto, J., Morioka, T., Murakami, N., Hashiguchi, K., . . . Sasaki, T. (2009). Subthalamic nucleus stimulation does not cause deterioration of preexisting hallucinations in Parkinson's disease patients. *Stereotact Funct Neurosurg, 87*(1), 45-49. doi:10.1159/000195719

Yu, K., Ren, Z., Guo, S., Li, J., & Li, Y. (2020). Effects of pedunculopontine nucleus deep brain stimulation on gait disorders in Parkinson's Disease: a meta-analysis of the literature. *Clin Neurol Neurosurg, 198*, 106108. doi:10.1016/j.clineuro.2020.106108

Zahodne, L. B., & Fernandez, H. H. (2008). Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs Aging, 25*(8), 665-682. doi:10.2165/00002512-200825080-00004

Zangaglia, R., Pacchetti, C., Pasotti, C., Mancini, F., Servello, D., Sinforiani, E., . . . Nappi, G. (2009). Deep brain stimulation and cognitive functions in Parkinson's disease: a three-year controlled study. *Mov Disord, 24*(11), 1621-1628. doi:10.1002/mds.22603

Zibetti, M., Torre, E., Cinquepalmi, A., Rosso, M., Ducati, A., Bergamasco, B., . . . Lopiano, L. (2007). Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *Eur Neurol, 58*(4), 218-223. doi:10.1159/000107943

5. Erklärung zum eigenen Anteil an der Dissertation

Die vorgestellten Studien sind ein Teil der Non-motor Longitudinal Interventional Study (NILS) der „Non-motor Parkinson's Disease Study Group" der „International Parkinson's and Movement Disorders Society". Das Studiendesign wurde von Herrn Dr. Haidar Dafsari und Prof. Dr. Ray Chaudhuri erstellt. Die Erhebung der klinischen Daten erfolgte seit 2012 durch medizinische Doktoranden und seit 2018 auch durch mich.

Bei den drei Erstautorenschaften „A prospective, controlled study of non-motor effects of subthalamic stimulation in Parkinson's disease: results at the 36-month follow-up", „Subthalamic Stimulation improves quality of sleep in Parkinson disease: a 36-month controlled study" und „Non-motor predictors of 36-month quality of life after subthalamic stimulation in Parkinson disease", welche in den Fachzeitschriften „Journal of Neurology, Neurosurgery, and Psychiatry", „Journal of Parkinson's disease" und „npj Parkinson's disease" veröffentlicht wurden, erfolgte die Konzeption und das Design der Datenanalyse durch mich und wurde durch Herrn Dr. Dafsari unterstützt. In den ersten beiden Studien wurden erstmals die Studienarme der Patienten, die eine Tiefe Hirnstimulation erhalten haben, mit Patienten verglichen, die ausschließlich medikamentös behandelt wurden. Die Auswertung der Daten sowie die Erstellung der Abbildungen und Tabellen erfolgte in eigenständiger Arbeit durch mich. Die Interpretation der Ergebnisse und das Erstellen der Manuskripte erfolgte durch mich und Herrn Dr. Dafsari in beratender Funktion.

Bei den Publikationen „Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson's disease" und „Beneficial effect of 24-month bilateral subthalamic stimulation on quality of sleep in Parkinson's disease" war ich an der

kritischen Revision des Manuskripts sowie durch die Ausarbeitung der Tabellen und Abbildungen als Koautorin beteiligt.