Modulation of attentional performance by deep brain stimulation of the pedunculopontine nucleus and of the substantia nigra pars reticulata in Parkinson's disease

Thesis

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by Dipl.-Psych. Julia Thein

born on 28-06-1985 in Magdeburg

Examiner: Prof. Dr. Tino Zähle

Prof. Dr. Tobias Staudigl

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Abbreviations

BG	Basal ganglia
COMT-Is	Catechol-O-methyl transferase inhibitors
CI	Cognitive impairment
CBD	Corticobasal Degeneration
DAT	Dopamine Transporter
DBS	Deep Brain Stimulation
DJ1	Protein Deglycase
DLB	Dementia with Lewy-Bodies
EF	Executive function
FOG	Freezing of gait
GBA	Glucocerebrosidase
GP	Globus pallidus
L-AAAD	L-Aromatic Amino Acid Decarboxylase
LB	Lewy bodies
LN	Lewy-neurites
LRRK2	Leucine Rich Repeat Kinase 2
MAO-B	Monoamine oxidase type B
MCI	Mild cognitive impairment
MDRS	Mattis Dementia Rating Scale
MLR	Mesencephalic locomotor region
MoCA	Montreal-Cognitive-Assessment
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
NMS	Non-motor symptoms
PIGD	Postural instability and gait disturbances
PD	Parkinson´s disease
PDD	Parkinson´s disease dementia
PD-MCI	Mild cognitive impairment in Parkinson´s disease
PET	Positron Emission Tomography
PINK 1	PTEN-Induced Kinase 1

PPN	Pedunculopontine nucleus
PRKN	Parkin RBR E3 Ubiquitin Protein Ligase
PSP	Progressive supranuclear palsy
RBD	REM sleep behavior disorder
RT	Reaction time
SNCA	Synuclein Alpha
SNpc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SPECT	Single Photon Emission Computed Tomography
STN	Subthalamic nucleus
TAP	Testing System for Attentional Performance
TMT	Trail Making Test
VIM	Ventral intermediate nucleus of the thalamus
VMAT2	Vesicular Monoamine Transporter Type 2
VPS35	Vacuolar Protein Sorting Ortholog 35
WCST	Wisconsin Card Sorting Test

I. Zusammenfassung

Das Parkinsonsyndrom (Morbus Parkinson) ist weltweit eine der häufigsten neurodegenerativen Erkrankungen. Bis heute ist die genaue Ursache nicht bekannt, es wird jedoch eine multifaktorielle Genese aus prädisponierenden genetischen sowie verschiedenen Umweltfaktoren angenommen. Während das Parkinsonsyndrom lange überwiegend durch das Auftreten der motorischen Kardinalsymptome charakterisiert wurde, ist inzwischen anerkannt, dass es sich um eine komplexe Systemerkrankung mit heterogener Symptomatik handelt und dass neben motorischen Symptomen auch eine Vielzahl nicht-motorischer Symptome auftreten können, die entscheidend zur Krankheitslast beitragen. Den Wechselwirkungen zwischen kognitiven und motorischen Funktionen und der Relevanz neuropsychologischer Einflussgrößen auf das Gangbild bei M. Parkinson wurde in den vergangenen Jahren zunehmend Bedeutung beigemessen.

Neben der medikamentösen Therapie, stellt das Verfahren der Tiefen Hirnstimulation (THS), vorrangig im subthalamischen Nucleus (STN), einen wesentlichen Ansatz zur Behandlung der motorischen Symptome des Parkinsonsyndroms dar. Während durch die THS vor allem bei der Behandlung von Tremor, Rigor und Bradykinese auch langfristig gute Ergebnisse erzielt werden können, zeigen sich bei der Behandlung axialer Symptome häufig nur kurzfristige Besserungen. Zur dauerhaften Therapieoptimierung wurde daher die Stimulation neuer Zielgebiete in Betracht gezogen. Dazu zählen der Pedunculopontine Nucleus (PPN) und die Substantia Nigra Pars Reticulata (SNr).

Aufgrund ihrer anatomischen Lage und auf Basis experimenteller Daten wird diesen beiden Strukturen eine Beteiligung nicht nur an motorischen, sondern auch an kognitiven Funktionen wie insbesondere Aufmerksamkeit und Exekutivleistungen zugeschrieben. Eine selektive Stimulation dieser beiden Zielgebiete könnte sich demnach nicht nur auf die Motorik, sondern auch auf die Aufmerksamkeitsleistung von Parkinsonpatienten auswirken.

Diese Arbeit untersuchte den möglichen Einfluss sowohl der PPN-Stimulation als auch der simultanen STN/SNr-Stimulation auf die Aufmerksamkeitsleistung bei Patienten mit M. Parkinson sowie atypischen Parkinsonerkrankungen.

Die Ergebnisse zeigten einen positiven Effekt der niederfrequenten PPN-Stimulation auf die Antwortzeiten in einer Einfachreaktionsaufgabe. Außerdem konnte eine Verbesserung der Reaktionszeitleistung auch unter simultaner THS in STN und SNr nachgewiesen werden. Basierend auf diesen Resultaten wird eine stimulationsinduzierte Steigerung der Aufmerksamkeitsleistung angenommen, durch die eine schnellere Reaktionsfähigkeit ermöglicht wird.

Unter Berücksichtigung der geringen Stichprobengröße sollten diese Ergebnisse in weiteren Studien an größeren Patientenpopulationen validiert werden. Dennoch ergeben sich daraus wichtige Hinweise auf die bedeutende Rolle des PPN und der SNr in Aufmerksamkeitsprozessen.

Die selektive Stimulation, sowohl des PPN als auch der SNr könnte eine Möglichkeit darstellen, um die Aufmerksamkeitsfunktionen bei Patienten mit Parkinsonsyndrom gezielt zu steigern. In Anbetracht der bedeutsamen Wechselwirkungen zwischen kognitiven und motorischen Funktionen könnten sich daraus neue Therapieansätze ergeben, um die Behandlung therapierefraktärer motorischer Symptome bei M. Parkinson zukünftig zu verbessern.

II. Summary

Parkinson's disease (PD) is a common and complex neurological disorder, resulting from a complicated interplay of genetic and environmental factors. While long being characterized primarily by the classical motor features of parkinsonism, it is now recognized that PD has a heterogeneous symptomatology that includes both motor and clinically significant non-motor features, which contribute equally to the disease burden. In recent years, the interaction between higher-level cognitive functions and gait disturbances in PD as well as the diverse neuropsychological influences on walking have been increasingly appreciated.

Alongside the available medical options, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an important therapeutic approach in order to improve the disabling motor features in PD. Stable long-term improvements have been observed in tremor, rigidity and limb bradykinesia. However, the efficacy of STN-DBS in addressing gait disturbances and axial symptoms, such as freezing of gait and postural instability, appears to gradually decline over time. Consequently, novel targets such as the pedunculopontine nucleus (PPN) and the substantia nigra pars reticulata (SNr) were considered, to allow continuous treatment.

Due to their anatomical location and based on experimental data, both the PPN and the SNr have been increasingly associated not only with motor but also with cognitive functions, particularly attention and executive functions. Assuming both, the PPN and the SNr, being involved in in cognitive functions such as attention, their selective stimulation could affect not only motor but also attentional performance in patients with PD. This work aims to investigate the possible influence of PPN- DBS and dual STN/SNr-stimulation on attentional performance in patients with PD and parkinsonian disorders.

The results revealed positive effects of both low-frequency PPN-DBS and dual STN/SNr -DBS on reaction time performance in a simple reaction time task, indicating an improvement in patients' attentional abilities and preparedness to react. This points to the possibility of enhancing attentional processes through selective stimulation of the PPN and through dual STN/SNr-stimulation. Limitations of this work, particularly with regard to the small sample size, have to be acknowledged and further studies are required to validate the results obtained. Nevertheless, this thesis provides further evidence for the significant roles of both, PPN and SNr, in attention.

Given the importance of attention to gait performance, the targeted modulation of attentional performance could be a promising approach to improve the treatment of therapeutically resistant aspects of Parkinson's gait disorder and therefore have implications for the future management of PD patients.

1. Introduction:

Parkinson´s disease (PD) is a progressive neurodegenerative disorder, named after James Parkinson, who was the first to describe its classical motor symptoms in his 1817 monograph “Essay on the shaking palsy”. For a long time, PD was primarily characterized by a complex motor disorder referred to as parkinsonism, a clinical syndrome that presents with a variety of symptoms including bradykinesia, muscular rigidity, rest tremor, postural instability, and gait impairment, resulting from the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). In the past decades, however, it was shown that the underlying pathology as well as the associated symptoms are more complex than initially assumed. The evolvement of the disease seems to result from a complicated interplay of genetic and environmental factors. PD is thought to involve multiple neurotransmitter pathways within the brain and autonomic nervous system and to manifest with a broad, heterogeneous range of symptoms including clinically significant non-motor features. A number of neurodegenerative disorders can mimic idiopathic PD, including Dementia with Lewy-Bodies (DLB), Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP) (Beitz, 2014). These disorders are referred to as atypical parkinsonian disorders. The progress in understanding the pathogenesis of idiopathic PD as well as parkinsonian disorders has been impressive, but still the cause remains unknown and a cure or preventive therapy are yet to be discovered. The available therapeutic approaches are only symptomatic and management strategies for many of the disabling features that occur in late stages of the disease are poor. The following chapter will give an overview of the epidemiological, clinical and pathogenetic evidence that has emerged since the first clinical descriptions of PD and several other parkinsonian disorders. A summary of the currently available medical and surgical therapeutic options and an introduction to the significant relationship between cognitive functions and gait will be given. With a focus on attentional deficits and their potential contribution to the parkinsonian gait disorder, this thesis aims to investigate the influence of stimulation in two different DBS targets on attentional performance in PD.

1.1 Epidemiology

PD is the second most common neurodegenerative disease after Alzheimer´s disease with median age-standardized annual incidence rates in high-income countries of 14 per 100000 people in the total population and 160 per 100000 people in populations aged 65 years and older (Hirtz et al., 2007). The incidence of PD is low before the age of 50 years, but

increases rapidly with age, peaking at around 80 years in most studies (Hirsch et al., 2016). The prevalence in industrialized countries is estimated at 0.3 % of the entire population and about 1 % in people over 60 years of age (Nussbaum & Ellis, 2003). With age being the most important risk factor and as a result of our aging society, PD prevalence is expected to rise dramatically, doubling in the next 20 years (Dorsey et al., 2018). Compared to non-affected individuals, mortality is not increased in the first decade after PD is diagnosed, but it increases afterwards (Pinter et al., 2015). Besides age, gender seems to be an established risk-factor for PD with some studies indicating an up to two-fold higher incidence in men than in women (Baldereschi et al., 2000). A contribution of genetics to PD is suggested by the increased risk of disease associated with a family history of PD or tremor (Noyce et al., 2012). Mutations in more than 20 genes have been associated with the disease (Blauwendraat et al., 2020). Approximately 5-10 % of PD cases can be attributed to monogenetic forms, for which there are several well-established genes, with autosomal dominant (*SNCA (α-synuclein)*, *LRRK2*, and *VPS35*) and autosomal recessive (*PRKN*, *PINK1*, *DJ1*) modes of inheritance (Jia et al., 2022). Alterations in the *GBA* gene are found in approximately 5-15 % of PD patients and thus represent the most important genetic risk factor known to date (Greuel et al., 2020; Smith & Schapira, 2022). Nonetheless, most PD cases seem to have a multifactorial etiology, resulting from the combined effects of environmental and genetic factors (Simon et al., 2020). Exposure to toxicant chemicals and head injury may increase the risk of PD, while lifestyle factors like regular physical activity and certain dietary patterns may lower the risk (Marras et al., 2018). Aside from PD, parkinsonism can also be found in several other neurodegenerative disorders. Among those parkinsonian disorders, dementia with Lewy-bodies is a common disease, with a prevalence of 0.4 % (400 per 100 000) in the elderly. Multiple system atrophy and progressive supranuclear palsy both have a prevalence of 5 to 10 per 100 000 persons while the prevalence of corticobasal degeneration is about 1 per 100 000 (J. Levin et al., 2016).

1.2. Neuropathology

1.2.1. Parkinson´s Disease

Basal Ganglia

PD is associated with a marked pathology in the basal ganglia (BG), a set of deep forebrain nuclei including the striatum (caudate and putamen), the globus pallidus (GP), the substantia nigra (pars compacta and reticulata) and the subthalamic nucleus (STN) [Fig.1]. The BG have become the focus of medical interest as damage in these structures has been shown to contribute to movement disorders such as PD and Huntington's Disease. Although

best known for their contribution to movement control, the BG are also implicated in the processing of higher order cognitive functions and behaviors (Pasupathy & Miller, 2005; Seger, 2006; Yin & Knowlton, 2006).

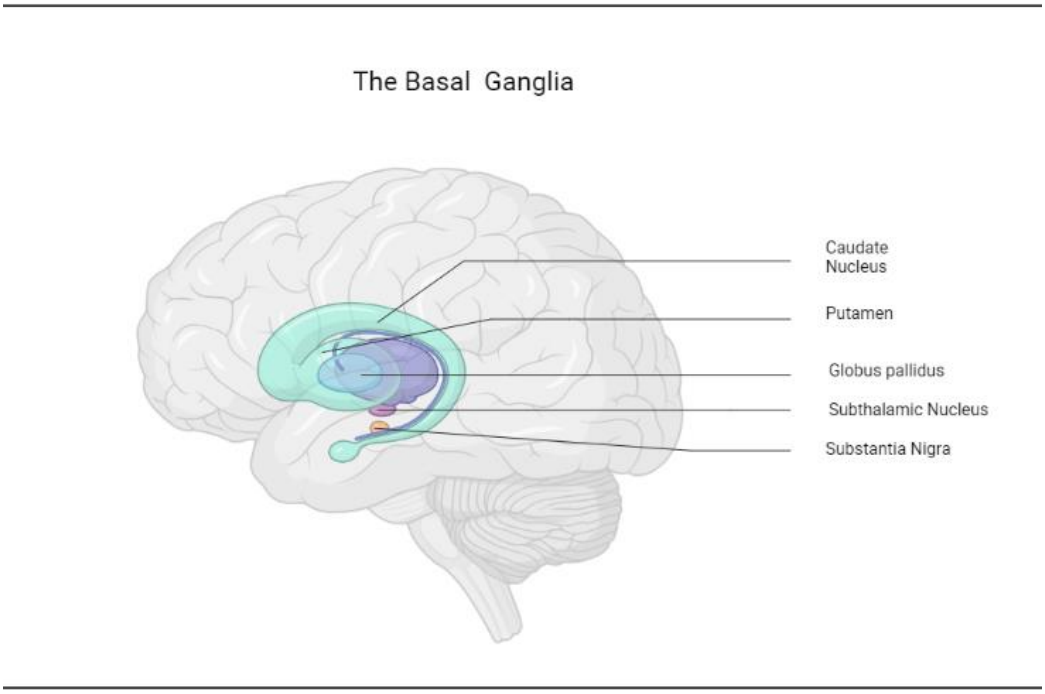

Figure 1: simplified representation of the main components of the basal ganglia (lateral view)

The BG and related nuclei can be broadly categorized as input nuclei, output nuclei and intrinsic nuclei. Input nuclei are those structures receiving incoming information from different sources, mainly cortical, thalamic and nigral in origin. The caudate nucleus, the putamen and the accumbens nucleus are all considered input nuclei. The output nuclei, involving the internal segment of the GP (GPi) and the substantia nigra pars reticulate (SNr) send basal ganglia information to the thalamus. Intrinsic nuclei, such as the external segment of the GP (GPe), the STN and the substantia nigra pars compacta are located between the input and output nuclei in the relay of information (Lanciego et al., 2012). The appropriate functioning of the basal ganglia system requires dopamine to be released at the input nuclei.

Studies in animal models of dopamine depletion have guided the development of a simplified circuit model of parkinsonism, more than two decades ago [Fig. 2]. In this classical

basal ganglia model, the hypodopaminergic state leads to an imbalance in the prokinetic direct and the inhibitory indirect striatal-pallidal pathways. According to this model, hypokinetic disorders such as PD result from a relative increase in the activity of inhibitory circuits (Albin et al., 1989; DeLong, 1990). Consequently, movement initiation and execution as well as the performance of sequential tasks are inhibited, giving rise to bradykinesia, a cardinal symptom of PD (Breit et al., 2004).

Much of this model has remained today, but has been modified and amplified with the emergence of new scientific data. Initially, the functional organization of the BG was conceived as a loop, in which cortical afferent activity is dispatched to and modulated by the basal ganglia, which then sends back a signal to the cortex to facilitate or inhibit motor activity. Current, extended concepts of the basal ganglia suggest that the BG are part of a complex network of neuronal circuits, organized in parallel to integrate activity from different cortical regions (Breit et al., 2004; Obeso et al., 2002; Pahapill, 2000).

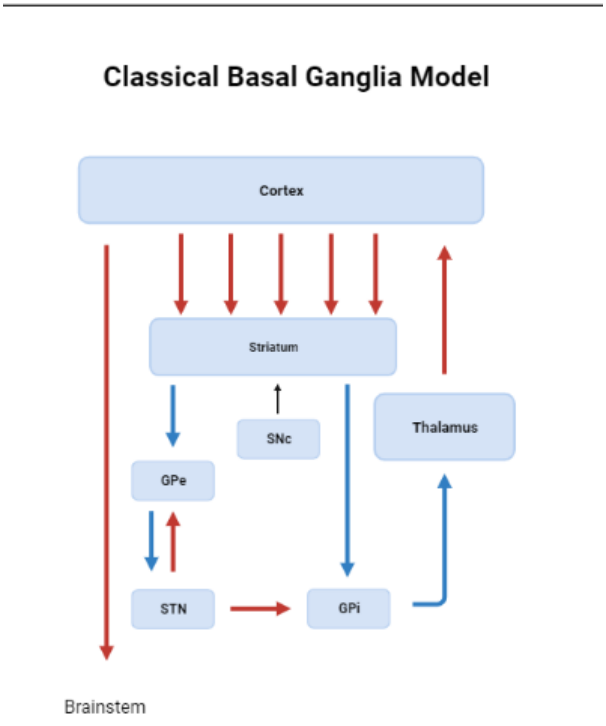

Figure 2: Schematic diagram of normal basal ganglia thalamocortical circuitry: classical basal ganglia model. Inhibitory connections shown as blue arrows, excitatory connections as red arrows, dopaminergic nigrostriatal projections shown as black arrows. Note: SNc substantia nigra pars compacta, GPe external part of the globus pallidus, STN subthalamic nucleus, GPi internal part of the globus pallidus

Dopamine Dysfunction

In PD, a dopamine dysfunction is caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [Fig. 3]. The progressive loss of these neurons leads to severe dopaminergic denervation of the striatum and causes a cascade of functional modifications involving all components of the basal ganglia circuitry (Blandini et al., 2000). The most severe affected area is typically the ventrolateral tier of the SNpc, although neuronal loss has been found to occur in many other brain regions, including the locus coeruleus, nucleus basalis of Meynert, pedunculopontine nucleus (PPN), raphe nucleus, dorsal motor nucleus of the vagus, amygdala and hypothalamus (Dickson, 2012). By causing degeneration in these structures, PD also detrimentally affects the noradrenergic, serotoninergic and cholinergic systems (Kehagia et al., 2013).

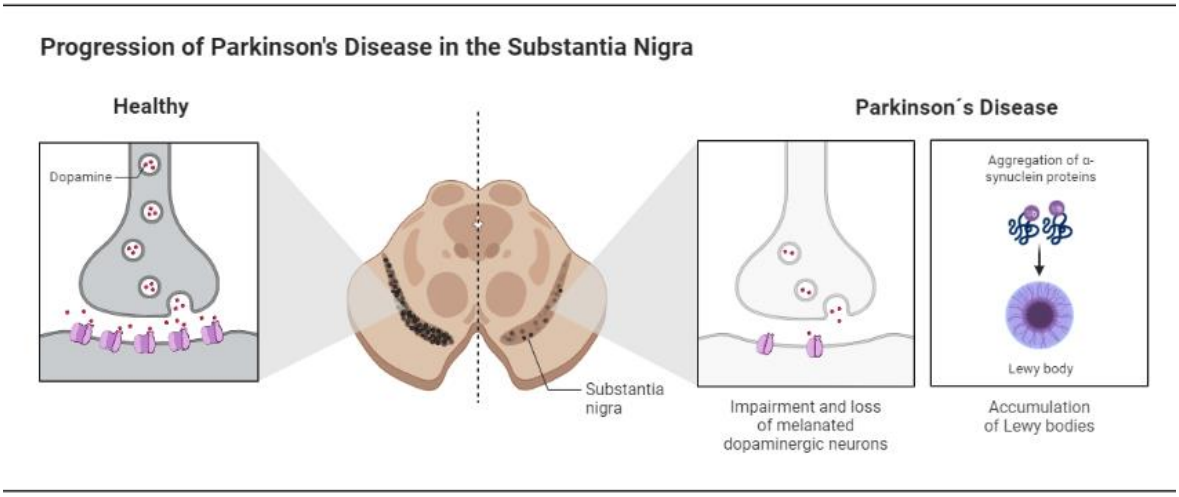

Figure 3: Progression of Parkinson´s Disease in the Substantia Nigra

Lewy Pathology

Another hallmark of PD is Lewy pathology, the presence of distinctive alpha-synuclein-containing cytoplasmic inclusions termed Lewy-bodies (LB) and Lewy-neurites (LN) (Angot & Brundin, 2009). LBs are intraneuronal, round inclusions with a hyaline core and a pale peripheral halo that are composed of more than 90 proteins (Wakabayashi et al., 2013), with their main components being alpha-synuclein and ubiquitin (Spillantini et al., 1997). In a misfolded state, alpha synuclein becomes insoluble and aggregates to form intracellular inclusions within the cell body (Lewy bodies) and processes of neurons (Lewy neurites) (Goedert et al., 2013).

Neither the loss of pigmented dopaminergic neurons in the SNpc nor the aggregation of alpha-synuclein in neurons is specific for PD, but these two neuropathologies are specific for a definite diagnoses of PD, when applied together (Poewe et al., 2017).

Pathological studies have suggested that the intracerebral formation of LB and LN begins at defined induction sites in the brainstem and advances in a topographically predictable sequence towards the cortex (Braak et al., 2004). The dorsal motor nucleus and olfactory bulb are reported to be initially involved (Braak stage 1) with progression thereafter through the pons and medulla (stage 2). By stages 3 and 4, the pathology has advanced to the stage where clinical symptoms emerge in response to nigro-striatal cell loss. By stages 5 and 6 neocortical areas are affected, which is associated with the development of cognitive impairment including dementia (Braak et al., 2005). Several recent studies suggest exceptions to this general order of progression (Burke et al., 2008; Halliday et al., 2008; Parkkinen et al., 2008) and it was reported that LB pathology could be more widespread than initially recognized. It can also be found in the spinal cord, the autonomic and peripheral nervous system, the skin, retina, submandibular gland, the cardiac nervous system and other organs (Djaldetti et al., 2009). Some studies suggest that the process of alpha-synuclein-misfolding might be initiated by e.g. viral infections in the intestine and the olfactory system (Braak et al., 2006) and also a “prion-like” propagation of misfolded alpha-synuclein has been suggested (Brundin et al., 2008). In addition, the roles of oxidative stress, mitochondrial dysfunction, inflammation and excitotoxicity have been discussed as potentially important mechanisms in pathophysiology (Macphee & Stewart, 2012). Nevertheless, the exact initialization mechanisms of PD remain unknown.

1.2.2. Parkinsonian Disorders

Neuronal loss in the SNpc is not only found in PD but also in a wide range of parkinsonian disorders, which can be broadly classified as those with and without alpha-synuclein pathology (Dickson et al., 2009).

Parkinsonian disorders like MSA and DLB are characterized by the abnormal deposition of the protein alpha-synuclein and therefore referred to as synucleinopathies. In MSA, the neurodegeneration not only affects the nigrostriatal dopaminergic pathway but also the cerebellar afferent pathways (pontocerebellar and olivocerebellar fibers). Neuronal inclusions in MSA are a minor component of the pathology, whereas alpha-synuclein inclusions within the cytoplasm of oligodendroglial cells are the major finding (Dickson, 2012). In DLB, there are three variations of alpha-synuclein pathology: brainstem predominant, limbic (or transitional) and neocortical. There is an overlap with Alzheimer’s

disease pathology, namely Tau and beta Amyloid deposition (Walker et al., 2015). The most common parkinsonian disorders that are not associated with alpha-synuclein pathology are the primary tauopathies, including PSP, CBD, frontotemporal degeneration with parkinsonism linked to chromosome 17, Guam Parkinson-dementia complex and dementia pugilistica (Dickson et al., 2009). In PSP and CBD, tau aggregates affect neurons, oligodendrocytes and astrocytes.

1.3. Clinical Presentation and Diagnosis

PD comprises a range of motor and non-motor features, which may vary in their expression between patients [Fig. 4]. However, all patients must exhibit the core clinical features and respond to dopaminergic therapy to satisfy the diagnostic criteria of PD (Berardelli et al., 2013; Postuma et al., 2015).

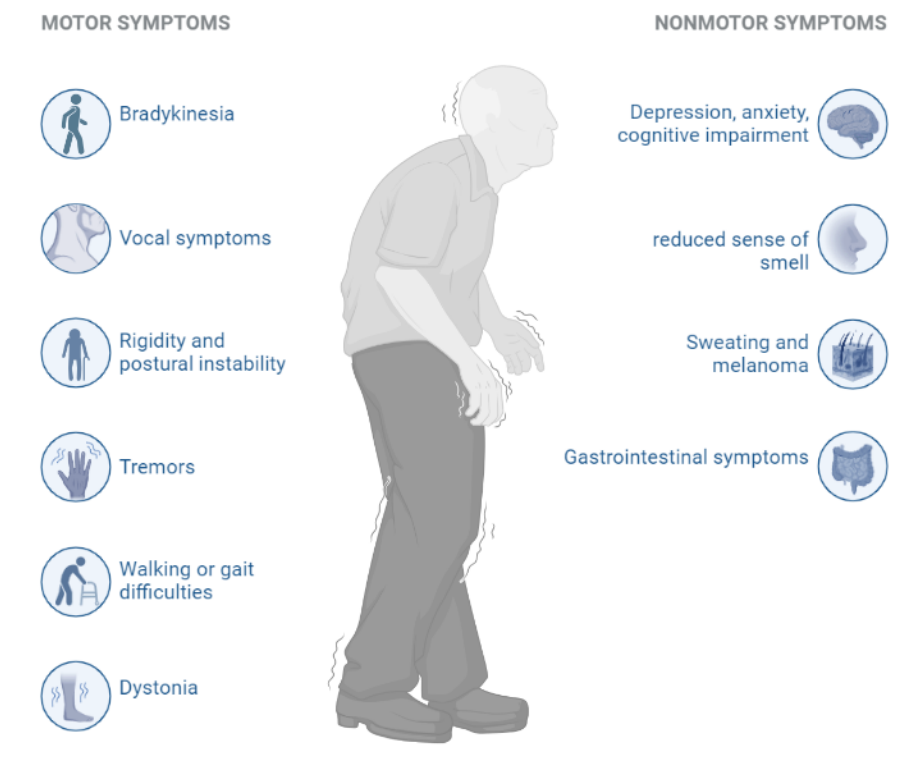

Figure 4: Motor and Nonmotor Symptoms of Parkinson´s Disease

1.3.1. Symptoms

PD is defined by the cardinal motor symptoms involving slowness of voluntary movement (bradykinesia), poverty of spontaneous movement (hypokinesia), failure of willed movement to occur (akinesia) as well as increased muscle tone (rigidity), tremor, and postural instability. Other motor features include postural anomalies (e.g. camptocormia, Pisa syndrome), gait disturbances and freezing of gait (FOG), defined as sudden and usually brief episodes of inability to produce effective stepping.

Onset of motor symptoms is usually unilateral, and asymmetry persists throughout the disease. In addition to the core motor features, PD is also associated with a variety of non-motor symptoms (NMS) including disorders of sleep-wake cycle regulation, cognitive impairment, disorders of mood and affect, autonomic dysfunction as well as sensory symptoms and pain (Chaudhuri & Schapira, 2009). Some of the NMS can be experienced years or even decades prior to the onset of motor features (Ross et al., 2012). The period when these symptoms arise has been conceptualized as the prodromal phase of PD (Schapira & Tolosa, 2010). NMS become increasingly prevalent over the course of the illness and represent a major determinant of quality of life and progression of overall disability (Poewe et al., 2017).

1.3.2 Diagnosis and Differential Diagnosis

To enhance the diagnostic accuracy of a clinical diagnosis of PD, the International Parkinson and Movement Disorder Society (MDS) has proposed a set of criteria that essentially represent a revised version of the Queens Square Brain Bank (QSBB) Criteria that have been the most commonly used over the past decades (Lees et al., 2009; Postuma et al., 2015). The diagnostic criteria for PD rely on the expert clinical neurological examination revealing a parkinsonian syndrome. It is clinically defined by bradykinesia in combination with at least one additional cardinal motor feature including rigidity or classical asymmetric 5-Hz resting tremor. The MDS Clinical Diagnostic Criteria for PD also require the presence of at least two supportive criteria (e.g., a beneficial response to dopaminergic therapy) and the absence of absolute exclusion criteria or red flags that might suggest an alternate cause of parkinsonism, including other neurodegenerative disorders, such as PSP, MSA or CBD.

The early diagnostic differentiation of PD from atypical parkinsonian disorders remains challenging since there is an overlap in clinical features and diagnostic tests or biomarkers still do not allow for a definite diagnosis from the earliest stages (Tolosa et al., 2021).

Imaging of the brain in patients with parkinsonism may increase the accuracy of differential diagnosis. Structural magnetic resonance imaging (MRI) can help to identify symptomatic parkinsonism (Mahlknecht et al., 2010) and a variety of MR techniques can reveal specific changes in the basal ganglia and infratentorial structures in atypical parkinsonism (Poewe et al., 2017). For example, abnormal T2-MRI-hypointensities in the putamen distinguish MSA-P from PD with 88% sensitivity and 89% specificity (Righini et al., 2002). Also, atrophy of the superior cerebellar peduncles and the frontal cortex helps differentiate between PSP and PD (Cordato et al., 2002; Paviour et al., 2005). Positron emission tomography (PET) and single photon emission computed tomography (SPECT) allow the detection of in vivo changes in the brain at the molecular level. In PD patients, PET and SPECT imaging of presynaptic dopaminergic function have shown marked reductions in vesicular monoamine transporter type 2 (VMAT2), dopamine transporter (DAT) and L-aromatic amino acid decarboxylase (L-AAAD) (Politis, 2014). In addition, I-ioflupane (DaTSCAN™) –SPECT has been shown to be a valid tool in the differential diagnosis between PD and non-degenerative tremors (Asenbaum et al., 1998; Benamer et al., 2000). However, despite substantial evidence of the utility of neuroimaging in improving diagnostic accuracy in PD, none of the currently available neuroimaging technique are specifically recommended for routine clinical use.

1.3.3 Parkinson´s Disease Subtypes

PD is notably heterogeneous regarding the age of onset, clinical presentation, rate of progression and treatment response. It has been established that genetically defined variants of the disease can differ from idiopathic PD in a number of clinical variables (Shu et al., 2018). Based on individual clinical features, several clinical subtypes of PD have been proposed.

The young-onset or early-onset PD subtype is usually defined by age at onset cut-offs below ages 40 or 50 years. It is characterized by slower progression, preserved cognition and an increased risk of treatment complications in response to levodopa (Schrag et al., 1998; Selikhova et al., 2009). Clinical presentations with a clinical predominance of rest tremor over other motor symptoms have been classified as tremor-dominant PD (Stebbins et al., 2013). This clinical subgroup has been associated with a slower progression and less cognitive decline compared to other clinical presentations (Selikhova et al., 2009; Simuni et al., 2016; Stebbins et al., 2013). Prominent postural instability and gait disorder have been classified as a postural instability and gait disturbances (PIGD) subtype represented by a rapid deterioration of motor function as well as cognition (Simuni et al., 2016). These

subtypes however should not be seen as rigid criteria, as patients my change categories with longer follow-up (Lee et al., 2019; Simuni et al., 2016). More recent cluster analyses have statistically confirmed the increasingly important role of NMS in Parkinson´s disease heterogeneity. In a prospective cohort study, three PD-subtypes were defined based on symptoms identified at baseline (Fereshtehnejad et al., 2015). According to this classification, the mainly motor/slow progression subtype represents PD patients with predominant motor manifestations and little evidence of depression or MCI at baseline. Patients in the intermediate subgroup showed orthostatic hypotension, but no cognitive impairment. NMS in this subgroup were moderate in severity, with motor traits broadly resembling the predominantly motor/slow progression phenotype. The third, diffuse/malignant subtype showed signs of orthostatic hypotension, REM sleep behavior disorder (RBD) and MCI at baseline as well as severe motor symptoms and more pronounced psychiatric disorders.

Despite similar age and disease duration, patients with the diffuse/malignant phenotype showed more rapid disease progression at prospective follow-up, affecting cognition and other NMS, motor signs, and global composite outcome. Consequently, the authors suggest screening patients with PD for MCI, orthostatic hypotension and RBD at baseline visits to identify the patients who are expected to have the fastest rate of progression.

1.4. Neuropsychological Characteristics of Parkinson´s Disease

Cognitive impairment (CI) is one of the most important non-motor manifestations of PD. It is six times more common in individuals with PD than in the healthy population (Aarsland et al., 2001) and contributes to a significant extend to the overall disease burden. Like motor symptoms, the characteristics of CI in PD can be variable regarding the impaired cognitive domains, the timing of onset and the rate of progression. The neuropsychological deficits in PD range from subjective cognitive symptoms to mild cognitive impairment (MCI) and eventually to dementia with progressive deficits severe enough to impair daily life. The following chapter provides an overview of the cognitive domains that can be affected in PD and outlines the important relationship between motor-symptoms and cognitive functioning.

1.4.1. Cognitive Impairment in Parkinson´s Disease

Approximately 20 to 33 % of patients experience mild cognitive impairment (PD-MCI) already at the time of PD diagnosis (Aarsland et al., 2010, 2021; Lawson et al., 2017;

Santangelo et al., 2015). In order to enable a uniform diagnostic procedure, the MDS proposed standardized diagnostic criteria for PD-MCI (Litvan et al., 2012). Therein PD-MCI is defined as a gradual cognitive decline, insufficient to significantly impair the patient's functional independence, and associated with a one to two standard deviation reduction in cognitive test performance. MCI can include executive dysfunction, impairment of attention and working memory, as well as deficits confined to memory, visuospatial domains, and language.

Executive Functions and Attention

The term executive function (EF) refers to a set of cognitive processes that control goal-directed behaviors from goal formulation and intention formation to successful execution and processing of the outcome. They include internal control of attention, set shifting, planning, inhibitory control, and dual task performance (Dirnberger & Jahanshahi, 2013). A decline in executive abilities is regarded the primary cognitive sequelae in PD (Dubois & Pillon, 1997; B. E. Levin et al., 1992) and has been reported to appear even in the earliest stages of PD. Even patients without global cognitive decline have been shown to exhibit impairments in working memory (Owen et al., 1997), trial-and-error learning (Postle et al., 1997), planning (Owen et al., 1995), response monitoring (Cooper et al., 1994), set shifting (Hsieh et al., 1995; Owen et al., 1992), and attentional control (Brown & Marsden, 1988b). The similarity of impairment seen in PD and in patients with frontal lobe lesions contributed to the concept of PD as a fronto-striatal syndrome (Robbins & Cools, 2014). The cognitive und behavioral deficits found in patients with PD are hypothesized to reflect the disruption of frontal-subcortical pathways due to nigrostriatal dopamine depletion (Green et al., 2002; Richards et al., 1993; Starkstein et al., 1990).

In terms of attention, there is some indication that certain areas of attention are better preserved than others. Digit span, representative of vigilance or sustained attention, remains fairly intact. On the other hand, performance on attentional tasks that demand speeded cognitive processing or require the patient to internally guide their attentional resources appear to be impaired (Pahwa et al., 1998; Raskin et al., 1990a; Ridenour & Dean, 1999). Patients with PD may also be affected on tasks of covert attention (Rafal et al., 1984). They seem to have more difficulty filtering out non-salient information in tasks of divided attention and show deficits in their ability to resist interference (Sharpe, 1992).

Memory

Memory deficits in PD are characterized by impairments of delayed recall, temporal ordering and conditional associate learning (Lichter & Cummings, 2001). It has been shown that

encoding of information as well as recognition are fairly preserved in non-demented patients with PD and that these patients are also able to benefit from external cueing (Brown & Marsden, 1988a; Cummings, 1986; B. E. Levin et al., 1992). This neuropsychological profile contrasts with the one seen in patients with Alzheimer´s disease (Huber et al., 1989; Mahler & Cummings, 1990) showing increased forgetting, poor recognition and an inability to benefit from external cueing (Cummings, 1986). It has been suggested that the poor performance on memory tasks seen in PD patients might relate to frontal/executive deficits resulting from a fronto-striatal dysfunction (Taylor et al., 1986). In contrast to patients with Alzheimer´s disease, impaired delayed recall appears to reflect an inefficient retrieval of information, not an encoding deficit (Raskin et al., 1990b; Taylor & Saint-Cyr, 1995). Accordingly, despite preserved encoding and recognition, PD patients may have difficulties in initiating and maintaining search strategies effectively.

Visuospatial Functions

Visuospatial skills include a number of cognitive abilities tied to the processing of visual information. This includes pattern recognition (facial recognition), constructional ability (figure drawing), color recognition (color naming) and spatial analysis (ability to perceive multiple objects in a visual field) (Watson & Leverenz, 2010). Various studies have reported visuospatial impairments, even in early PD (Grace et al., 2005; Montse et al., 2001; Uc et al., 2006).

Anatomically, posterior cortical areas have been associated with deficits in visual processing, including the occipital, parietal and temporal lobes. Neuroimaging suggests that visuospatial impairment in PD without dementia is associated with posterior cortical dysfunction (Abe, 2003). According to the “dual-syndrome-hypothesis” which has been introduced to explain the heterogeneous nature of cognitive deficits in PD, it is distinguished between dopaminergically mediated fronto-striatal executive impairments and a dementia syndrome with distinctive prodromal visuospatial deficits (Kehagia et al., 2013). Cognitive impairments related to temporal and posterior dysfunction are associated with a more rapid decline and a higher risk of later dementia. In contrast, frontostriatally based impairments such as deficits in attention and executive functions seem less likely to progress (Aarsland, 2016; Kehagia et al., 2013; Williams-Gray et al., 2007).

Speech and Language

PD patients show deficits in the motor aspects of speech (Raskin et al., 1990a). Deficits in speech output have been attributed to vocal-motor deficits such as dysarthria involving a reduction of speech volume and pitch (B. E. Levin et al., 1992). Compared to healthy

controls, patients with PD have demonstrated impairments on tasks assessing complex comprehension and grammar (Cummings et al., 1988).

1.4.2. Parkinson´s Disease Dementia

Within twelve years of disease duration, about 60-80% of patients develop Parkinson´s disease dementia (PDD) (Hely et al., 2008). It is defined as cognitive impairment in a patient with PD with deficits in at least two cognitive domains that are severe enough to significantly affect normal functioning beyond impairment caused by disease related motor and autonomic symptoms (Emre et al., 2007; Goetz et al., 2008). PDD is associated with a variety of cognitive deficits that extend the cognitive impairment seen in non-demented PD patients. In particular, the attentional impairment in PDD seems to go beyond problems in sustaining task focus and shifting attention, but can manifest as profound fluctuations in attention that can vary from day to day, or over the course of a day (Emre et al., 2007). In addition, patients with PDD show prominent deficits in visuospatial functions and memory (Emre et al., 2007; Goetz et al., 2008). Additionally, a wide range of neuropsychiatric symptoms is seen in PDD. The most common are hallucinations, apathy, depression, anxiety, and insomnia (Aarsland et al., 2007). Autonomic disturbances including urinary incontinence, orthostatic and postprandial hypotension are also frequent in PDD and it was suggested that orthostatic hypotension and cognition might be interrelated (McDonald et al., 2016).

1.4.3. Relationship between Motor-Symptoms and Cognitive Functioning

In the past years, the relationship between higher-level cognitive function and gait disturbances has attracted increasing interest. Gait is no longer viewed as largely automated motor process, but instead seen as affected by multifaceted neuropsychological influences such as attention and executive function (Giladi & Hausdorff, 2006; Yogev-Seligmann et al., 2008). A substantial body of evidence indicates that gait, even in healthy young adults, utilizes attention and that gait abnormalities in PD increase, when attention resources of patients are allocated to more than one task (Faulkner et al., 2006; Hollman et al., 2007; Yogev-Seligmann et al., 2008). Individuals with PD often show altered cognition compared to healthy adults (Dirnberger & Jahanshahi, 2013) and in many cases, patients with freezing of gait have even more pronounced cognitive dysfunction than those who do not suffer from FOG. In particular, FOG is associated with deficits in attention (Camicioli et al., 1997; Hall et al., 2014; Peterson et al., 2015), executive function such as shifting and

inhibition (Cohen et al., 2014; Matar et al., 2013) and visuospatial function (Almeida & Lebold, 2010; Lord et al., 2012; Matar et al., 2013). Mental conditions like stress, anxiety, depression and cognitively challenging situations also appear to play an important role in the pathogenesis of FOG (Giladi & Hausdorff, 2006). The attentional demands of gait have often been tested using dual tasking methodologies. It has been stated that simultaneous performance of two attention-demanding tasks not only causes a competition for attention, but also challenges the brain to prioritize the two tasks (Yogev-Seligmann et al., 2008). Gait disturbances in PD patients might hence result from an inappropriate prioritization (Bloem et al., 2001).

1.5. Treatment and Therapeutic Options

PD is still an incurable progressive disease, but treatment substantially improves quality of life and functional capacity. Substituting striatal dopamine loss via the systemic administration of the dopamine-precursor amino acid L-Dopa represented a revolutionary breakthrough in the treatment of PD, 50 years ago. Since then, the advanced understanding of the pharmacological players regulating nigrostriatal dopaminergic transmission has revealed multiple additional targets for dopaminergic therapies in PD. Despite the remarkable impact of dopaminergic therapy on the symptoms of PD, there is also a need for therapies that target other pharmacological systems. The following chapter will address the most relevant dopaminergic and non-dopaminergic pharmacological targets. In addition, the deep brain stimulation, a surgical treatment for PD will be discussed.

1.5.1. Dopaminergic Pharmacological Treatment

L-Dopa

L-dopa has remained the gold standard of pharmacological treatment in PD and over time practically all PD patients will require treatment with this agent (LeWitt & Fahn, 2016; PD Med Collaborative Group et al., 2014). In order to assure that L-dopa can be metabolized in the brain, the treatment is combined with a peripheral dopa decarboxylase inhibitor; carbidopa or benserazide. L-dopa has marked beneficial effects on the cardinal symptoms of PD. Nevertheless, chronic L-dopa treatment is associated with the evolution of motor complications including dyskinesia, dose related fluctuations („on-off“ syndrome) and psychiatric complications (Marsden et al., 1981). The mechanisms underlying these phenomena are still not completely understood, but it is suggested that discontinuous drug delivery resulting from the short half-life of L-dopa and erratic gastrointestinal absorption

plays a major role in the pathophysiology of these motor complications (Poewe & Antonini, 2015). Novel sustained-release formulations of L-dopa as well as continuous delivery (intestinally or subcutaneously) are being developed to address this problem (Poewe & Antonini, 2015). Also, the addition of dopamine agonists or COMT inhibitors plays an important role in order to maintain continuous receptor stimulation (Sian et al., 1999).

COMT-Inhibitors

Catechol-O-methyl transferase inhibitors (COMT-Is) are one of the recommended first-line levodopa add-on therapies for the amelioration of end-of-dose motor fluctuations in patients with advanced PD (Fabbri et al., 2022). COMT inhibitors such as tolcapone and entacapone suppress the activities of dopamine degradation enzymes and block peripheral dopamine metabolism, thus increasing the availability of L-dopa.

MAO-B-Inhibitors

Oxidation via monoamine oxidase type B (MAO-B) in glial cells is a major clearance mechanism for synaptically released dopamine. Inhibition of this enzyme prolongs and increases synaptic dopamine concentrations. The symptomatic efficacy of the MAO-B inhibitor selegiline as an adjunct to Levodopa was shown already in the 1970s (Birkmayer et al., 1977). More recent studies have established the antiparkinsonian efficacy of monotherapy with selegiline and the newer MAO-B inhibitor rasagiline, which has also been found to be effective when added to levodopa in patients with motor fluctuations (Fox et al., 2011).

DA-Agonists

Dopaminomimetics with direct activity to dopamine receptors (DA receptor agonists) were first introduced in the 1970s and have since become an important medical therapy for PD motor symptoms (Fox et al., 2011). They represent a class of agents that directly stimulate dopamine receptors mimicking the endogenous neurotransmitter dopamine. At first used as an adjunctive therapy in the advanced phases of the disease, over the years a significant role was found for DA monotherapy as a first approach in the initial stage of PD (Stocchi et al., 2016). Disadvantages arise from a reduced overall effect size when compared to L-dopa and their potential to induce drowsiness and a reduction of impulse control (Poewe et al., 2017).

1.5.2. Non-Dopaminergic Pharmacological Treatment

Glutamatergic, noradrenergic, serotonergic, and cholinergic systems play a critical role in the basal ganglia circuitry. Targeting these non-dopaminergic receptors therefore remains a focus of ongoing research to improve motor symptoms in PD, without the potential side effects of dopamine replacement therapy. Besides the complications of motor fluctuations and levodopa-induced dyskinesia, the occurrence of levodopa resistant motor features including treatment-resistant tremor, freezing of gait, postural instability and falls, swallowing and speech disturbances demands the use of alternative medical therapies. For treatment of motor fluctuations, safinamide, zonisamide and istradefylline are currently approved, with novel glutamatergic and serotonergic drug being under developement. Long-acting formulations of amantadine, which is thought to work as an NMDA antagonist (Fox et al., 2011), are approved for treatment of levodopa-induced dyskinesia. Cholinesterase inhibitors have shown beneficial effects on non-motor-features like cognitive dysfunction, depression, and autonomic failure. So far, no non-dopaminergic selective drug has shown significant long-term efficacy as monotherapy in PD (Gonzalez-Latapi et al., 2020).

1.5.2. Deep Brain Stimulation

Deep brain stimulation (DBS) is a minimally invasive neurosurgical procedure, which has become an established therapeutic tool for treating patients with PD and other movement disorders. It essentially represents the advancement of ablative stereotaxy, a surgical technique first introduced in the 1970s and based on the lesion of different functional targets within the BG. DBS is based on the observation that high-frequency electrical stimulation of specific brain targets can mimic the effect of ablation without irreversibly damaging the brain tissue (Benabid et al., 1989).

In DBS, an electrode is surgically implanted in specific target areas of the brain, providing continuous high frequency electrical stimulation. The electrodes are attached to an implantable pulse generator, which is typically placed subdermally below the collarbone [Fig. 5]. The stimulator settings can be adjusted telemetrically with respect to electrode configuration, current amplitude, pulse width, and pulse frequency (Volkmann, 2004).

The stimulation-induced improvement is closely linked to the responsiveness of motor symptoms to dopaminergic treatment as a good pre-operative response to L-dopa has been shown to be the best predictor of optimal DBS outcomes (Pahwa et al., 2003). The success of this therapeutic approach largely depends on the selection of suitable candidate patients.

Dementia, acute psychosis, and major depression are exclusion criteria (Bronstein et al., 2011). The following describes the DBS targets that are most important for the treatment of PD.

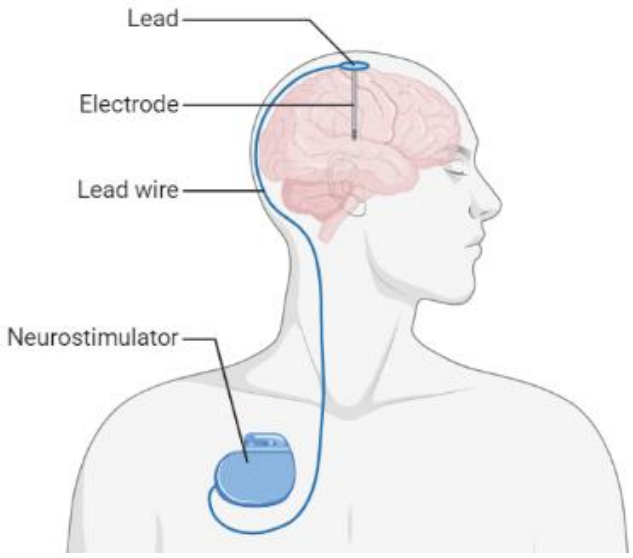

Figure 5: DBS electrodes and connection to the pacemaker

STN and GPi

Several clinical trials have established that DBS targeting either the subthalamic nucleus (STN) or the globus pallidus interna (GPi) is an effective treatment for moderate to severe PD (Anderson et al., 2005; Follett et al., 2010; Krack et al., 2003). The rationale of targeting specific structures within the BG is strongly supported by the current knowledge of the BG pathophysiology, which provides the theoretical basis for surgical therapy in PD (Breit et al., 2004). One of the roles of the BG is to modulate and streamline execution of movements through a balance between Gaba-ergic inhibitory and glutamatergic excitatory pathways. In PD, this balance is disturbed. Through a cascade of activity changes, dopamine deficiency leads to an increased neuronal activity of the STN and conversely of the GPi and SNr (Bergman et al., 1994; Filion, 1979).

DBS of the STN or GPi is hypothesized to 'silence' this pathological increased neuronal activity, leading to reduced parkinsonian symptoms and an improved movement pattern (Hariz & Blomstedt, 2022). With regard to the clinical effect of DBS, stimulation frequency seems to be a key factor (Breit et al., 2004). DBS is believed to mimic the clinical effects of lesioning in STN and GPi, when high-frequency (>100 Hz) stimulation is applied, whereas stimulation at lower frequencies results in little or no clinical effects (Volkmann, 2004).

Although the precise mechanisms of DBS have been the focus of intense scientific investigation and debate, they are not yet fully understood.

Due to the marked improvement in all major symptoms of the disease, the STN has become the most commonly used target for DBS in the treatment of PD worldwide (Breit et al., 2004). Bilateral STN-DBS has been shown to improve quality of life and motor scores compared to pre-operative medical off-state. Also, STN-DBS leads to a reduction of dopaminergic medication and consequently a decrease in dyskinesias and hypokinetic fluctuations (Deuschl & Agid, 2013).

The GPi is an alternative surgical target for the treatment of motor complications, including akinesia, rigidity and dyskinesias. Initially, the electrode placement in the STN was preferred, as it was reported to have a greater improvement in motor scores and a significant reduction of dopaminergic medication compared to GPi-DBS (Deep-Brain Stimulation for Parkinson's Disease Study Group et al., 2001; Krack et al., 1998). Nevertheless, pallidal stimulation is effective on all cardinal symptoms of PD. It is mainly considered in older patients, who may not tolerate levodopa withdrawal.and better tolerated than bilateral STN-DBS. Also, an easier postoperative adjustment of stimulator settings and medication might be arguments in favor of GPi-DBS. Although STN remains the preferred target, especially in younger patients, GPi may be considered in patients with speech disturbances, mild cognitive impairment or a history of depression, as STN-DBS sometimes exacerbates these symptoms (Anderson et al., 2005; Follett et al., 2010).

Randomized trials comparing the two targets have produced conflicting results of either similar motor benefits (Montgomery et al., 2013) or inferior long-term efficacy on motor function and motor fluctuations of GPi versus STN-DBS (Odekerken et al., 2016).

SNr

More recent studies suggested beneficial effects of combined stimulation of the STN and the substantia nigra pars reticulata (SNr) on gait impairment in PD (Chastan et al., 2008a; Weiss et al., 2013a). The SNr is one of the two output nuclei of the basal ganglia, embedded into a system of dense reciprocal interconnections with the pedunculopontine nucleus (PPN) and brainstem circuitries (Breit et al., 2001, 2005). In PD, a pathological overactivity of the SNr leading to inhibition of the locomotor network is considered one putative mechanism responsible for axial problems (Breit et al., 2006). To date, several studies have emphasized the crucial role of the SNr during locomotion (Deniau et al., 2007; Heilbronn et al., 2019; Lafreniere-Roula et al., 2010). Given the proximity of the STN to the SNr, their combined stimulation is feasible, and the operative approach closely resembles that of targeting the STN alone (Baumgartner et al., 2022) [Fig 6]. Advanced programming

techniques utilizing ‘interleaved pulses’ allow independent stimulation of STN and SNr contacts within the same electrode, employing different current amplitudes and pulse widths (Kovács et al., 2012; Weiss et al., 2011; Wojtecki et al., 2011).

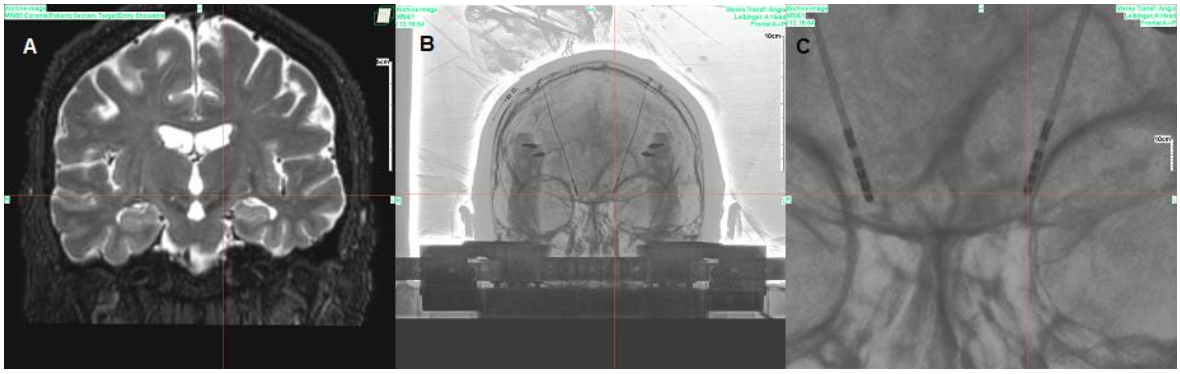

Figure 6: A: Pre-operative MRI image with the red cross visualizing the DBS target (STN); B: intraoperative X-ray for control of electrode position; C: intraoperative X-ray showing two DBS electrodes with four contacts each, the rostral contacts are located in the STN, the furthest caudal contact allows stimulation of the SNr.

VIM

The ventral lateral nuclei of the thalamus are populated by neurons that fire in synchronous bursts with timing similar to peripheral tremor (Guiot et al., 1962). The close temporal relation between tremor and burst of thalamic neuronal activity has led to the suggestion that these thalamic tremor cells could act as tremorigenic pacemakers (Lozano, 2000). DBS of the ventral intermediate nucleus (VIM) of the thalamus has been associated with an immediate and almost complete suppression of tremor (Benabid et al., 1996), with no effect on akinesia and rigidity.

PPN

With a focus on gait impairment and postural instability, the pedunculopontine nucleus (PPN) has been considered another potential target for DBS. It is part of the mesencephalic locomotor region (MLR), a functionally defined area of the midbrain that is associated with the initiation and control of locomotor movements. The PPN is located within the brainstem and exhibits reciprocal connections with basal ganglia structures and the spinal cord. Due to its location and based on physiological and anatomic data, an involvement of the PPN in the mechanisms of axial symptoms and postural instability in PD was suggested (Classen & Schnitzler, 2010; Hamani et al., 2007; Tsang et al., 2010). To date, small studies in

patients with PD have shown variable improvements in gait as well as a reduction in falls after PPN DBS (Moro, Hamani, et al., 2010). However, the benefit was limited within the small patient group and until now, this procedure remains experimental.

DBS is a complex therapy requiring a high level of interdisciplinary expertise in the correct surgical placement of the electrode, postoperative programming and the adjustment of neurostimulation and drug therapy (Bronstein et al., 2011). The most relevant adverse effects related to DBS are intracranial bleedings and device complications (e.g., infections and lead misplacements). Psychiatric sequelae of DBS including apathy, depression, impulsiveness and mania are not uncommon and might result from a complex interplay between disease related psychiatric symptoms, dopaminergic imbalance due to profound medication changes and stimulation-induced effects on limbic basal ganglia circuits (Kühn & Volkmann, 2017).

1.6. Aims of the Thesis

Parkinson's disease is a complex, age-related, neurodegenerative disease resulting from a pathophysiologic loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the development of neuronal Lewy Bodies. It comprises a range of motor and non-motor features and in recent years, increasing attention has been paid to the possible interactions between cognitive deficits and motor impairments in PD. A large body of evidence suggests that gait is affected by a variety of neuropsychological influences such as attention and executive function and that cognitive deficits might contribute to the parkisonian gait disorder (Giladi & Hausdorff, 2006; Yogev-Seligmann et al., 2008).

One therapeutic approach in order to improve the disabling motor features in PD is DBS, a neurosurgical procedure that allows targeted circuit-based neuromodulation. To date, DBS of the STN has become an established therapeutic tool in the treatment of PD. However, the efficacy of STN-DBS in addressing gait disturbances and axial symptoms, such as freezing of gait and postural instability, appears to gradually decline over time (Castrioto, 2011; Merola et al., 2011; Moro, Lozano, et al., 2010; Volkmann et al., 2009). In order to improve treatment of therapeutically resistant aspects of Parkinson´s gait disorder, novel targets such as the PPN and the SNr were considered. Due to their location within the brain and based on experimental data, both structures are assumed to be involved in motor as well as cognitive functions, especially attention and executive function (Sonne et al., 2022; Thevathasan et al., 2010, 2011). Consequently, stimulation of the PPN and the SNr might ameliorate not only motor impairment but also attention performance in PD.

Assuming that attention processes affect the gait pattern, the targeted modulation of attention parameters could be a promising therapeutic approach to improve gait disturbances in PD.

This thesis aims to investigate the effects of selective stimulation in two different DBS targets on attention performance in patients with PD and parkinsonian disorders. It is assumed that stimulation of the PPN as well as dual stimulation of the STN/SNr lead to an improvement in reaction times, reflecting enhanced attentional processing.

The first study was designed to examine the influence of PPN-DBS on attentional processing. The PPN is considered a part of the reticular activating system and involved in the regulation of attention and arousal (Mena-Segovia et al., 2008; Mesulam et al., 1989; Winn, 2006). Eight patients with parkinsonian disorders, implanted with electrodes in the bilateral PPN underwent computerized assessment of attention. To investigate the influence of the stimulation on attention, the performance in three standard reaction time tasks was assessed at five different stimulation frequencies in five consecutive sessions.

The second study aimed to investigate, whether STN-DBS with additional stimulation of the SNr might have beneficial effects on certain aspects of attention. Encouraging findings have already demonstrated advantageous effects of combined STN and SNr - stimulation on gait in PD (Villadóniga et al., 2022; Weiss et al., 2011, 2013a). Moreover, the SN is a critical brain region for the production of dopamine, which affects many systems of the central nervous system ranging from movement control, cognitive executive functions, and emotional limbic activity (Sonne et al., 2022). Neurobiological models on attention-deficit/hyperactivity disorder (ADHD) as well as findings from imaging studies suggest a crucial involvement of the substantia nigra in the pathogenesis of ADHD symptoms like inattention, excessive motor activity, and impulsivity (Krauel et al., 2010). Based on these findings, it was hypothesized, that additional, selective SNr-stimulation might improve not only motor performance but also have an impact on attentional processing in patients with PD.

2. Study 1: Modulation of attentional processing by deep brain stimulation of the pedunculopontine nucleus region in patients with parkinsonian disorders[1]

[1]The chapter is partially based on an article by Fischer, J., Schwiecker, K., Bittner, V., Heinze, H.-J., Voges, J., Galazky, I., & Zaehle, T. (2015). Modulation of attentional processing by deep brain stimulation of the pedunculopontine nucleus region in patients with parkinsonian disorders. *Neuropsychology*, *29*(4), 632–637. https://doi.org/10.1037/neu0000179

2.1. Introduction

Study 1 was designed to investigate the influence of PPN-DBS on certain parameters of attention in patients with parkinsonian disorders.

In addition to the well-established DBS of the STN, stimulation of the PPN was taken into account as a novel therapeutic target, when physiological and anatomical data indicated a reasonable association between the PPN and the initiation of gait and stereotyped movements (Classen & Schnitzler, 2010; Hamani et al., 2007; Tsang et al., 2010). In animal studies, stimulation of the PPN led to an increase in movement, whereas inhibition of PPN decreased it (Brudzynski et al., 1986; Garcia-Rill et al., 1987; Milner & Mogenson, 1988; Mogenson & Wu, 1988). Furthermore, a frequency dependent influence of PPN-stimulation on locomotion was proposed (Jenkinson et al., 2004; Nandi et al., 2002). Low frequent oscillations in the alpha range (7-11 Hz) were observed in the PPN after the administration of levodopa in patients suffering from PD (Androulidakis, Khan, et al., 2008). This prompted the suggestion that alpha band synchronization is a physiological feature of PPN function, possibly allied to motor related attentional processes. As effective therapeutic stimulation in the PPN is delivered at low frequencies (Jenkinson et al., 2004; Nandi et al., 2002), it was suggested that alpha band synchronization might be mimicked by low frequency stimulation of the PPN (Androulidakis, Khan, et al., 2008; Androulidakis, Mazzone, et al., 2008).

Considering PPN-DBS and movement control in parkinsonian disorders, clinical studies have shown heterogeneous results. Small observational studies with patients did indicate improved postural stability or gait with PPN-stimulation, but in small blinded trials, only a subjective reduction in falls with no other impact on postural instability and gait dysfunction was revealed (Follett & Torres-Russotto, 2012). Moro et al. examined the influence of unilateral PPN-stimulation on movement control in six advanced PD patients with significant gait and postural abnormalities. The authors found no significant improvement in motor scores on- versus off-medication three and twelve month after PPN-DBS, although patients

reported a significant reduction in falls in the on- and off-medication states. It was concluded that stimulation of the PPN-region may be effective in preventing falls in patients with advanced PD, but that further evaluation of this procedure is required (Moro, Hamani, et al., 2010). Despite its possible benefits on motor control and gait, to date PPN-DBS remains an experimental procedure, limited to a small patient group.

Besides having an influence on motor control, the PPN, as a component of the reticular activating system, is hypothesized to be involved in the regulation of attention and consciousness (Mena-Segovia et al., 2008; Mesulam et al., 1989). Over the past years, the relationship between higher-level cognitive function and gait disturbances has received increasing attention. Gait is no longer viewed as largely automated motor process, but instead seen as affected by multifaceted neuropsychological influences such as attention and executive function (Yogev-Seligmann et al., 2008). A substantial body of evidence indicates that gait, even in healthy young adults, utilizes attention and that, when attention resources of patients with PD are allocated to more than one task, gait abnormalities increase (Faulkner et al., 2006; Hollman et al., 2007; Yogev-Seligmann et al., 2008).

Taking into account the relevance of attention to the performance of gait, attentional deficits might contribute to the motor dysfunction in parkinsonian disorders. Accordingly, attentional augmentation could be one possible mechanism by which stimulation of the PPN-region might improve gait in parkinsonism (Thevathasan et al., 2010).

2.2. Methods

2.2.1. Participants

The study included 8 patients with parkinsonian disorders (5 female, mean age= 65, 63 ± 7,1 years; all right-handed, with bilateral DBS of the PPN. All Patients suffered from motor symptoms like freezing of gait (FOG) and postural instability (PI). The mean duration since DBS operation was 14, 25 ± 7, 8 months. Demographic and disease characteristics of each patient are listed in Table 1. During the testing, all patients remained on their prescribed dopaminergic medications in conjunction with DBS and were tested during the ON state of their medication cycle.

Electrodes were placed bilaterally in the PPN of all patients using standard stereotactic techniques as described previously (Voges et al., 2002, 2007). Briefly, macroelectrodes (Medtronic Model 3389) consisting of four platinum–iridium cylindrical contacts, each with diameter 1.27 mm, length 1.5 mm, and edge-to-edge separation of 0.5 mm, were implanted into the PPN using MRI-guided stereotaxy and intraoperative microelectrode recordings.

Stereotactic coordinates for macroelectrode placement were taken from a stereotactic brain atlas (Schaltenbrand & Wahren, 1977). The calculated target was modified according to the direct visualization of the PPN region on proton-density weighted magnetic resonance images (Zrinzo et al., 2008). Selection of final bipolar contacts and stimulation settings were determined on an individual basis to improve motor symptoms.

All patients were free of dementia (ensured by a Mattis dementia rating score ≥ 130) and did not show clinical levels of depression at the time of testing. Further exclusion criteria were: history of neurological condition other than PD/parkinsonian disorders, any psychiatric condition known to compromise executive cognitive functioning (e.g. schizophrenia, bipolar affective disorder, mood disorders) or any untreated or unstable medical conditions. All patients participated voluntarily and could cancel the test at any times. The local ethics committee (University of Magdeburg, Germany) approved the experiment.

Table 1: Demographic and clinical characteristics of patients

Patient #	Age [years]	gender	disease duration [years]	assessment post surgery [months]	MDRS	DBS voltage [V], pulse with [µs]	DBS contacts	LED [mg/d]	Co-DBS
1	68	f	7	24	131	2.0/60	0-1+/8-9+	-	bilateral STN
2	67	f	7	6	132	3,5/60	0-1+/8-9+	400	-
3	69	f	8	6	143	2.0/60	0-1+/8-9+	1200	-
4	5	m	8	25	140	2.0/60	0-1+/8-9+	2362	bilateral STN
5	73	m	8	18	133	2.0/60	0-1+/8-9+	250	-
6	74	f	7	3	142	1.0/60	0-1+/8-9+	300	-
7	52	f	16	24	144	1.5/60	2-C+/8-9+	1165	bilateral STN
8	70	m	10	17	139	2.0/60	0-1+/8-9+	1515	-

Note: LED: total daily Levodopa equivalent dose; MDRS: Mattis Dementia Rating Scale (max 144 P.); STN: Subthalamic Nucleus

2.2.2. Reaction-Time-Task

Patients underwent computerized assessment of attention, performing three subtests of the *Testing System for Attentional Performance* (TAP 2.2: Zimmermann and Fimm, 1996).

1a+b Alertness-Task: In this task, alertness is examined under two conditions. The first (unwarned) condition [Fig. 7 A], measures simple reaction times in response to a cross appearing on the monitor screen at varying intervals. Results of this task represent a measure of intrinsic alertness, meaning the ability to keep up a certain level of attention over time. In a second (warned) condition [Fig. 7 B], reaction time is measured in response to a critical stimulus preceded by a warning tone. The resulting short-term focus of attention on an expected event is described as phasic arousal. In both conditions, subjects are instructed to react to the appearing visual stimuli as fast as possible by pressing a response-button with the index finger of their dominant hand. Besides reaction time, also standard deviation as a measure of response stability and a parameter of phasic alertness are calculated, which indicates to what extend patients were able to benefit from the preceded warning tone.

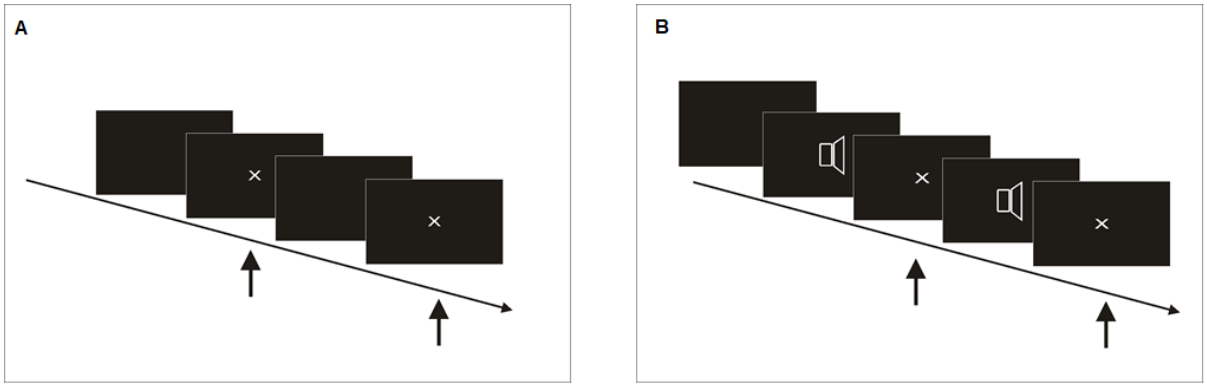

Figure 7: Sequence of the unwarned (A) and warned (B) condition of the Alertness-Task (TAP 2.2.: Zimmermann and Fimm, 1996)

2. Go-/NoGo-Task: In this task, the selective reaction to one of two presented stimuli is required. Patients have to press a button in response to a critical stimulus (cross) and omit a response to another stimulus (plus) [Fig. 8 A]

3. Divided-Attention task: In this dual-task a visual and an auditory task have to be proceeded simultaneously [Fig. 8 B]. Visual and auditory stimuli are presented in parallel,

and subjects are instructed to detect critical auditory and visual stimuli and respond to both by the press of a button.

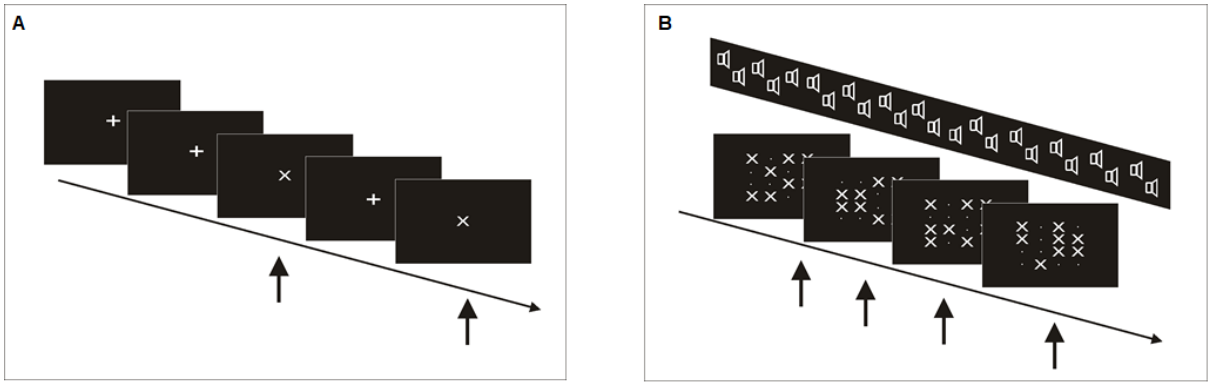

Figure 8: Sequence of the Go-/Nogo Task (A) and the Divided Attention Task (B) (TAP 2.2.: Zimmermann and Fimm, 1996)

A usual therapeutic frequency of 20-35 Hz has been suggested for bilateral and up to 70 Hz for unilateral PPN stimulation (Moro, Hamani, et al., 2010; Stefani et al., 2007). However, as the optimal frequency of PPN stimulation remained uncertain (Thevathasan et al., 2010), all Patients were tested at five different stimulation conditions (off-stimulation, 8 HZ, 20 Hz, 60 Hz, 130 Hz) to assess any frequency dependent stimulation effects on RT performance.

Patients were tested for five consecutive days, with one session a day. Testing sessions were scheduled in the morning with a minimum interval of twelve hours between change of stimulation frequency and assessment of performance. The order of the conditions was counterbalanced across patients. Both, patients as well as the experimenter were uninformed about the current stimulation frequency (double-blind-design). All further stimulation parameters (pulse width, voltage range) were kept constant across conditions. To avoid training effects, a practice trial was performed prior to each task.

2.3. Results

Performance data (median of the Reaction time [RT] and standard deviations) for the four stimulation conditions of all patients were compared with the OFF-condition for each subtests of the *TAP* separately, using pairwise T- statistics.

Electrical stimulation of the PPN at low frequencies significantly improved performance in a simple reaction time task (alertness-test) [Fig. 8]. Compared to OFF-Stimulation, patients'

RT in the *unwarned condition* of the Alertness-Test was significantly faster at stimulation frequencies of 8 Hz (T(7)=2,89, P=.02) and 20 Hz (T(7)=3,04, P=.02). Furthermore, there was a statistical trend for an improvement at 60 Hz (T(7)=2,34, P=.052). There was no statistical difference between RT under OFF and 130 Hz stimulation (T(7)=0,82, P=.45) [Fig. 9a]. Comparison of standard deviations as a parameter for reaction-stability revealed no significant difference among conditions. However, there was a trend for reduced reaction-stability under 20 Hz (T(7)=1,96, P=.09).

In the *warned condition* of the Alertness-Test there was a statistical trend for reduced RT under 20 Hz compared to the OFF condition (T(7)=2,13, P=.07). All other stimulation conditions (8 Hz, 60 Hz, 130 Hz) did not lead to a relevant change in performance [Fig. 9b]. Furthermore, no systematic stimulation dependent variation in the performance of the *go-/nogo* [Fig. 10A] and the *divided attention task* [Fig. 10 B-C] could be observed.

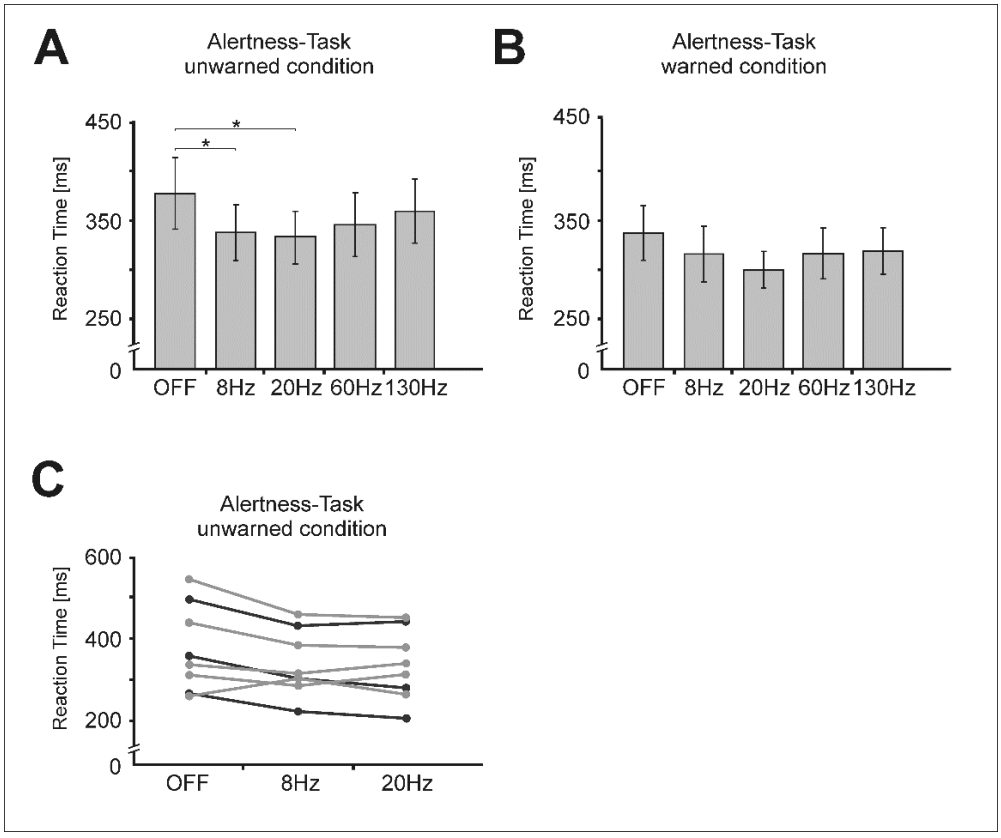

Figure 9: (A) Mean ± *SD* of reaction time in the unwarned condition of the Alertness task, and (B) mean ± *SD* of reaction time in the warned condition of the Alertness task under different stimulation frequencies. (C) Individual reaction times in the unwarned condition of the Alertness task for patients with PPN-stimulation (grey) and PPN-STN-costimulation (black). OFF = off-stimulation. * Significant differences between DBS conditions ($p < .05$).

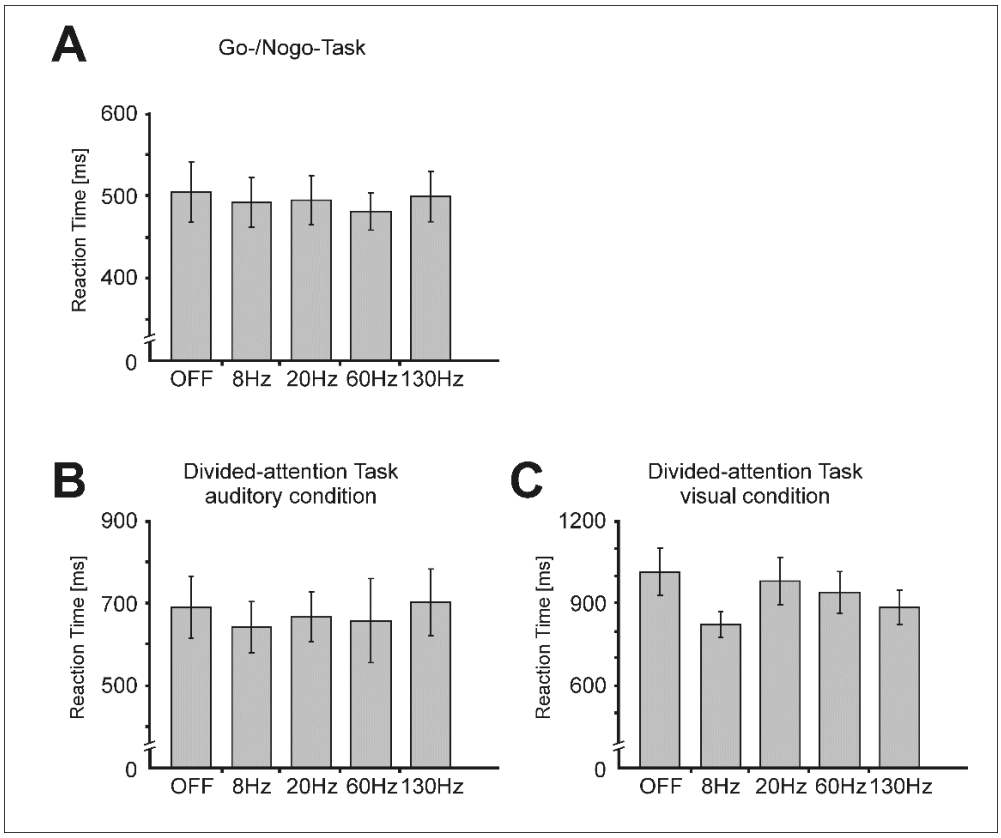

Figure 10*:* Mean ± *SD* of reaction time separately for the DBS frequencies in (A) go/no-go task, (B) divided attention (dual-task-auditory) task and (C) divided-attention (dual-task-visual) task. OFF=off-stimulation

2.4. Discussion

Study 1 revealed an improvement of performance in a simple reaction time task (alertness-task; unwarned condition) during PPN-DBS using very low frequencies (8Hz) and frequencies supposed to be therapeutically effective (20 Hz). Stimulation significantly improved patients' intrinsic alertness, suggesting an increased ability to build and keep up a certain level of attention. As performance in this task mainly represents basic attentional processing, these results indicate an influence of PPN-stimulation on these attentional sub-routines. Best performance was achieved at low-frequent stimulation of 8Hz and 20 Hz, which is in line with earlier results, reporting a frequency-dependent influence of PPN-stimulation in animal studies (Jenkinson et al., 2004).

The shortest simple reaction times were found at therapeutic frequencies of 20 Hz and a significant influence of low-frequent 8 Hz stimulation on reaction time performance was also evident. These findings support the notion that alpha oscillations in the PPN area may represent a physiological pattern of activity, possibly allied to motor related attentional processes and that this activity may be mimicked by low frequency stimulation of the PPN

(Androulidakis, Mazzone, et al., 2008). In accordance with earlier studies (Thevathasan et al., 2010), an effect of stimulation features on motor performance rather than attentional augmentation were considered.

Patients' performance in the two conditions of the alertness-task (warned and unwarned condition) - that both represent simple attention tasks with equal requirements on motor response and speed - revealed relevant changes in performance in the unwarned condition only. Accordingly, an influence on simple motor speed alone is unlikely to account for this selective improvement. Consequently, an influence of PPN-DBS on certain aspects of attentional processing is assumed.

Results of the *warned condition* (alertness-task) only showed a slight improvement at low-frequency stimulation (20Hz). As the preceded warning tone in this task already led to a short-term focus of attention on an expected stimulus, stimulation features attained no additional benefit. In line with this assumption, phasic-alertness-parameters did not show relevant changes among conditions.

Stimulation did not affect patients' performance in the *selective attention* nor in the more complex *divided-attention-task*. This is in line with the results of Thevathasan et al. (2010) who reported an influence of PPN-stimulation on performance in a simple reaction task only. PPN-stimulation therefore does not seem to influence complex attentional processing.

Summing up, study 1 showed an influence of PPN stimulation at low (8Hz) and therapeutic (20 Hz) frequencies on attentional processing, leading to an improved performance in a simple reaction time task. More complex demands like selective or divided-attention seem not to be influenced by stimulation. Possibly, these tasks require more complex cognitive functions of behavioral control, in particular execute functions like response inhibition and working memory that are basically associated with prefrontal regions (Aron et al., 2004; Sasaki et al., 1993).

Based on the above mentioned results it is assumed that PPN-DBS leads to attentional augmentation and accordingly to an improvement in reaction time performance in a simple reaction task. Consequently, attentional augmentation seems to be one essential aspect of how PPN-stimulation contributes to an improvement in motor action and gait in patients with parkinsonian disorders.

This study supports the notion of the PPN as a reticular nucleus, influencing basic aspects of attention and is also in line with the anatomical labeling of the PPN as a core component of the ascending reticular activating system, a group of upper brainstem nuclei that have a crucial role in maintaining behavioral arousal and consciousness.

Still, some limitations of this study have to be acknowledged at this point. Because to date DBS of the PPN-area is applied primarily in clinical studies, only a small number of patients could be included. Although data indicated an objective improvement in certain aspects of attention, no relevant change in attention functions was apparent in patients' everyday life. This underlines the investigational character of PPN-stimulation and stresses the need for further studies. For future works, a larger sample of patients and a focus on changes in patients' performance in everyday life would be eligible. Parkinsonian disorders provide a heterogeneous clinical picture, thus patients´ condition at the time of the assessment varied. All patients were examined within the time range of the clinical DBS-protocol but assessment intervals after surgery varied among the patient group. One should assume that a higher variance in patients and time of assessment would have led to a higher variance in data. Therefore, the effects reported in this study might have been more pronounced with a more homogenous patient group.

3. Study 2: Enhancing Attentional Performance in Parkinson´s Disease: The Impact of Combined Deep Brain Stimulation of the Substantia Nigra Pars Reticulata and the Subthalamic Nucleus[2]

[2]The chapter is partially based on an article submitted by Thein, J., Linnhoff, S., Haghikia, A., Voges, J., Galazky, I., & Zaehle, T. (2023). Enhancing Attentional Performance in Parkinson´s Disease: The Impact of Combined Deep Brain Stimulation of the Substantia Nigra Pars Reticulata and the Subthalamic Nucleus

3.1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established surgical intervention to alleviate motor symptoms and fluctuations in Parkinson´s disease (PD) (Deuschl et al., 2006; Kleiner-Fisman et al., 2006). It has been shown that STN-DBS can contribute to an improvement in motor symptoms and quality of life in patients with advanced PD and that a combination of STN-DBS and medical therapy is more effective, than medical management alone (Deuschl et al., 2006). However, concerns remain about the long-term effectiveness of STN-DBS (Rodriguez-Oroz et al., 2012). While stable long-term improvements have been observed in tremor, rigidity and limb bradykinesia, the efficacy of STN-DBS in addressing gait disturbances and axial symptoms, such as freezing of gait (FOG) and postural instability, appears to gradually decline over time, as the disease progresses (Moro, Lozano, et al., 2010; Volkmann et al., 2009). These gait and axial symptoms, prevalent in approximately 80% of advanced PD patients, are refractory to dopaminergic medication and surgical interventions (Giladi et al., 2001). They are associated with an increased risk of falls and hospitalization and thus contribute to a reduced quality of life for those affected.

In order to improve the treatment of therapeutically resistant aspects of the parkinsonian gait disorder, novel stimulation parameters and targets for DBS have been considered. One promising approach involves combined DBS of both the STN and the substantia nigra pars reticulata (SNr). The SNr is one of the two output nuclei of the basal ganglia, embedded into a system of dense reciprocal interconnections with the pedunculopontine nucleus (PPN) and brainstem circuitries (Breit et al., 2001). It has been suggested that different therapeutic outcomes observed in segmental and axial motor domains may reflect distinct functional sub-loops of pathological motor network processing (Weiss et al., 2013a). STN-DBS may primarily facilitate thalamo-cortico-spinal motor control, leading to improvements in segmental symptoms (Pötter-Nerger et al., 2008; Weiss et al., 2012). Conversely, gait disturbances in advanced PD stages are associated with impaired motor processing of mesencephalic locomotor pathways, including nigropontine projections to spinal motor

neurons (Chastan et al., 2008b; Thevathasan et al., 2011). The concept of dual STN and SNr stimulation aims to disrupt these altered basal ganglia circuits, thus enabling simultaneous treatment of both segmental and axial symptoms (Pötter-Nerger et al., 2008; Thevathasan et al., 2011). Given the proximity of the STN to the SNr, their combined stimulation is feasible, and the operative approach closely resembles that of targeting the STN alone (Baumgartner et al., 2022). Advanced programming techniques utilizing 'interleaved pulses' allows independent stimulation of STN and SNr contacts within the same electrode, employing different current amplitudes and pulse widths, thereby facilitating simultaneous stimulation of segregate functional motor loops (Weiss et al., 2011).

Encouraging findings have suggested beneficial effects of combined STN and SNr - stimulation on gait impairments in PD. A single-center, randomized, double-blind, controlled trial that included 12 PD patients, reported an improvement in freezing of gait with combined STN/SNr - stimulation, while axial symptoms assessed by the Unified Parkinson Disease Rating Scale (UPDRS) did not differ significantly between conventional STN-DBS and combined STN/SNr - stimulation (Weiss et al., 2011, 2013a). In a small cohort of PD patients with gait disorders unresponsive to dopaminergic treatment, standard STN-DBS resulted in some improvement, but the most significant benefits were observed with dual STN and SNr- stimulation (Valldeoriola et al., 2019). These findings are consistent with another preliminary study that prospectively compared the effect of dual STN and SNr - DBS versus conventional STN-DBS on gait disorders in advanced PD, demonstrating a more pronounced improvement with the combined stimulation (Villadóniga et al., 2022). Furthermore, the combined STN/SNr - stimulation has been shown to be safe with no clinically relevant neuropsychiatric adverse events (Weiss et al., 2013a).

Apart from its essential role in motor control, the substantia nigra (SN), as part of the basal ganglia circuitry, is also critically involved in various cognitive functions, including attention and executive functions (Sonne et al., 2022). Neurobiological models on attention-deficit/hyperactivity disorder (ADHD), as well as imaging studies in healthy participants highlighted the involvement of dopaminergic midbrain nuclei, particularly the SN, in the pathogenesis of ADHD symptoms such as inattention, excessive motor activity, and impulsivity (Krauel et al., 2010; Tomasi & Volkow, 2014). A recent study utilizing intraoperative microelectrode recordings of basal ganglia neurons during a supine stepping task revealed distinct roles of subthalamic and nigral neurons in parkinsonian gait control. While subthalamic neurons predominantly responded to motor aspects of the task, nigral neurons exhibited activity changes specifically associated with attentional aspects, highlighting the potential of the STN and SN as a cognition-motor interface for integrating

cognitive, emotional, and sensorimotor information for optimized action selection (Gulberti et al., 2023).

The relationship between attention and gait control has already been emphasized in numerous studies (Giladi & Hausdorff, 2006; Yogev-Seligmann et al., 2008). It has been proposed, that there are significant attentional requirements for postural control and that attentional deficits might contribute to gait disturbances in PD (Bond & Morris, 2000; Brown & Marsden, 1991). In this regard and with a focus on gait impairment and postural instability, earlier studies investigated the interactions between attention and gait in PD-patients with DBS of the pedunculopontine nucleus (PPN). It was hypothesized that PPN-stimulation might enable attentional augmentation und consequently lead to an improvement in gait (Fischer et al., 2015; Thevathasan et al., 2010).

Acknowledging the significant relationship between attention and gait and considering the pivotal role of the SN in both, motor and cognitive functions, dual STN/SNr - stimulation may not only address axial signs but also improve attentional performance in PD patients. The current study therefore investigated the influence of additional stimulation of the SNr on reaction time performance as an indicator of attentional processing in PD-patients with standard STN-DBS.

3.2. Methods

3.2.1. Participants

The study included twelve patients diagnosed with Parkinson's disease (PD) (1 female, mean age= 63.25 ± 9.93 years; one left handed), all of whom had undergone bilateral subthalamic nucleus deep brain stimulation (STN-DBS). Quadrupolar brain electrodes with two segmented contacts (Boston Scientific, MA, USA; Cartesia, directional lead, DB 2202) were bilaterally implanted into the STN using standard stereotactic techniques as previously described (Abdulbaki et al., 2021). Confirmation of electrode position was performed by intraoperative microelectrode recordings showing characteristic local field potential patterns for the STN and SN, clinical examination and stereotactic x-ray images (anterior-posterior and lateral direction). The impulse generator (Vercise TM, Boston Scientific, MA, USA) was implanted in the subclavicular area and subcutaneously connected to the intracerebral electrodes.

Patients with bilateral STN-DBS and confirmed contacts in the SNr were eligible for the study. The study included consecutive patients who were treated as inpatients in the Department of Neurology at the University Hospital Magdeburg between March 2022 and

June 2023. The mean duration since DBS surgery was 23.00 ± 18.01 months. Demographic, disease and stimulation characteristics of each patient are listed in Table 1. All patients were free of dementia (MDRS score > 130) and did not show clinical levels of depression at the time of testing. During the testing, all patients remained on their prescribed dopaminergic medication.

Table 2: Demographic and clinical characteristics of patients

Patient #	age [years]	gender	disease duration [years]	LED [mg/d]	assessment post surgery [month]	- STN - pulse width [µs], frequency [Hz], DBS current [mA]	- SNr - pulse width [µs], frequency [Hz], DBS current [mA]
1	58	m	11	200	12	60µs, 132 Hz, 3,1 mA (l), 3,7 mA (r)	1,5 mA, 60µs, 6 Hz (bil.)
2	55	m	13	1030,75	52	60µs, 139 Hz, 1,2 mA (l), 1,7 mA (r)	1,0 mA, 60µs, 6 Hz (bil.)
3	55	f	10	250	13	60µs, 119 Hz, 2,7 mA (l), 2,7 mA (r)	2,0 mA, 60µs, 6 Hz (bil.)
4	60	m	15	831,25	29	60µs, 119 Hz, 3,6 mA (l), 3,8 mA (r)	2,0 mA, 60µs, 6 Hz (bil.)
5	46	m	12	178	12	60µs, 139 Hz, 2 3,2mA (l), 4,2 mA (r)	2,5 mA, 60µs, 6 Hz (bil.)
6	51	m	8	500	14	60µs, 119 Hz, 2,5 mA (l), 2,3 mA (r)	2,0 mA, 60µs, 6 Hz (bil.)
7	70	m	11	150	12	60µs, 139 Hz, 2,4 mA (l), 2,4 mA (r)	1,5 mA, 60µs, 6 Hz (bil.)
8	73	m	11	300	25	60µs, 132 Hz, 1,7 mA (l), 5,5 mA (r)	1,5 mA, 60µs, 6 Hz (bil.)
9	70	m	11	864,5	17	60µs, 132 Hz, 4,0 mA (l), 2,1 mA (r)	2,0 mA, 60µs, 6 Hz (bil.)
10	77	m	14	465,5	9	60µs, 132 Hz, 2,3 mA (l), 2,4 mA (r)	2,0 mA, 60µs, 6 Hz (bil.)
11	68	m	8	0	12	60µs, 132 Hz, 2,5 mA (l), 2,8 mA (r)	1,5 mA, 60µs, 6 Hz (bil.)
12	76	m	14	275	69	60µs, 179 Hz, 3,2 mA (l), 2,1 mA (r)	1,5 mA, 60µs, 6 Hz (bil.)

LED: total daily levodopa equivalent dose, STN: subthalamic nucleus, SNr: substantia nigra pars reticulata

3.2.2. Reaction-Time-Task

Patients underwent computerized assessment of attention using the Alertness-task from the *Testing System for Attentional Performance* (TAP: 2.3.1 Zimmermann , P. and Fimm , B., 2020) a standard clinical procedure for examining attention functions.

Alertness, considered a component of attention, refers to the state of wakefulness that enables individuals to respond quickly and appropriately to specific stimuli (Sturm & Willmes, 2001). Alertness is a prerequisite for functional action and forms the basis of attentional performance.

The TAP alertness task, lasting approximately 10 minutes, assesses patients' reaction times (RTs) through four runs, consisting of 20 trials each, and incorporating two different conditions. The first condition (runs 1&4) referred to as the "unwarned" condition, measures simple reaction times in response to a cross appearing on the screen at varying intervals. The results of this task represent a measure of 'intrinsic alertness', which reflects the ability to sustain a certain level of attention over time. In a second condition (runs 2&3) referred to as the "warned" condition, the cross is preceded by a warning tone. The resulting short-term focus of attention on an expected event is referred to as 'phasic alertness'. In both conditions, participants are instructed to react to the visual stimulus as fast as possible by pressing a response-button with the index finger of their dominant hand. The results of this subtest provide information about a person´s alertness based on their basal responsiveness and general processing speed (Zimmermann , P. and Fimm , B., 2020)

All patients were tested under two different stimulation conditions: standard STN-DBS and combined STN/SNr-stimulation. The STN was stimulated with a high frequency of about 130Hz, which corresponds to the clinical standard of therapy (Abbasi et al., 2018). Co-stimulation of the SNr was performed with a low frequency of 6 Hz. According to individual side effects, DBS current of SNr-stimulation varied between 1.0 mA and 2.5 mA among patients.

Testing sessions were scheduled in the morning with a minimum interval of twelve hours between change of stimulation mode and assessment of performance. All other stimulation parameters, such as pulse width and voltage range, were kept constant across the conditions. To avoid training effects, a practice trial was conducted before each task. Because this was an ad-hoc-sample, the order of stimulation conditions could be randomized but not completely controlled. Thus, to account for potential order effects, we included stimulation order as a covariate into our statistical model.

All patients participated voluntarily and had the right to withdraw from the test at any time. The study was approved by the local ethics committee of the University of Magdeburg, Germany.

3.2.3. Statistical Analysis

Statistical analysis and production of all plots were performed using R Statistical Software (version 4.2.0, R Core Team, 2022). Linear mixed models (LMMs) were used to analyze the data of all participants. The lmer function from the *afex* package (Singmann, H.; Bolker, B.;Westfall, J. & Ben-Shachar, M., 2022) was employed to conduct the LMMs. The statistical significance of main effects and interactions was determined with the *anova*() function using F-Tests for LMMs. P-values were obtained using Sattersthwaite's approximation method. Single-trial reaction times (RTs) were considered as dependent variables. Response times over 1000 ms were not expected in this task and therefore excluded (N = 9 trials). Stimulation (dual-STN/SNr, standard-STN) and trial type ("unwarned", "warned"), as well as their interaction, were treated as fixed factors. Data from the off-stimulation condition in the *unwarned* trials were used as baseline. To account for individual-specific characteristics, subjects were included as random effects in the analysis (lmm_RT <- lmer(RT ~ trialnr + stim * WT + (1 | subid), data = data)).

We additionally added trial number as a covariate since the model explained significantly more variance with the factor included ($AIC_{without}$ = 22647, AIC_{with} = 22644, $\chi^2(1) = 4.559$, $p = .033$). Furthermore, to account for order effects, we also included order as a covariate. However, order as an additional factor did not enhance the model fit ($AIC_{without}$ = 22644, AIC_{with} = 22646, $\chi^2(1) = 0.129$, $p = .719$) and thus was not included in the final model. Also, variation of SNr-current among subjects had no relevant influence on RT performance ($AIC_{without}$ = 22644, AIC_{with} = 22645, $\chi^2(1) = 4.908$, $p = .179$)

3.3. Results

All patients were able to perform the tasks under both stimulation conditions. The linear mixed model (LMM) analysis predicting reaction times (RTs) revealed a significant main effect of *trial number* [$F(1,1894) = 4.554$, $p = .033$, $\eta_p^2 = .002$], indicating that RTs increased with each trial over time ,and a significant main effect of *trial type* [$F(1,1894) = 21.248$, $p < .001$, $\eta_p^2 = .01$], indicating that the presence of a warning tone affected RTs.

Importantly, the analysis revealed a significant main effect of *stimulation* [$F(1,1894) = 33.684$, $p < .001$, $\eta_p^2 = .02$], indicating that the two stimulation settings had an impact on RTs. Additionally, there was no significant interaction between *stimulation* and t*rial type* [$F(1,1894) = 1.917$, $p = .166$]. However, subsequent separate analysis for the two trial-types (unwarned; warned) revealed a significant improvement in RTs under dual STN/SNr-stimulation in unwarned trials (z = - 2.35, p = .016), but no significant RT-differences in the warned condition of the task (z = -1.96, p = .052).

Figure 11 A displays a linear regression plot illustrating the relationship between RTs and trial number. The data indicate a general slowing of RTs over time with an increase in RTs of on average 0.19 ms per trial [$\beta_{\text{trial number}} = 0.189$, CI (0.02 , 0.36)]. The presence of a warning tone significantly decreased RTs on average by 19 ms (18.86 ± 44.96 ms). Importantly, dual-STN/SNr stimulation significantly decreased RTs by on average 24 ms (23.83 ± 26.85 ms) over standard-STN stimulation (see also Figure 11B).

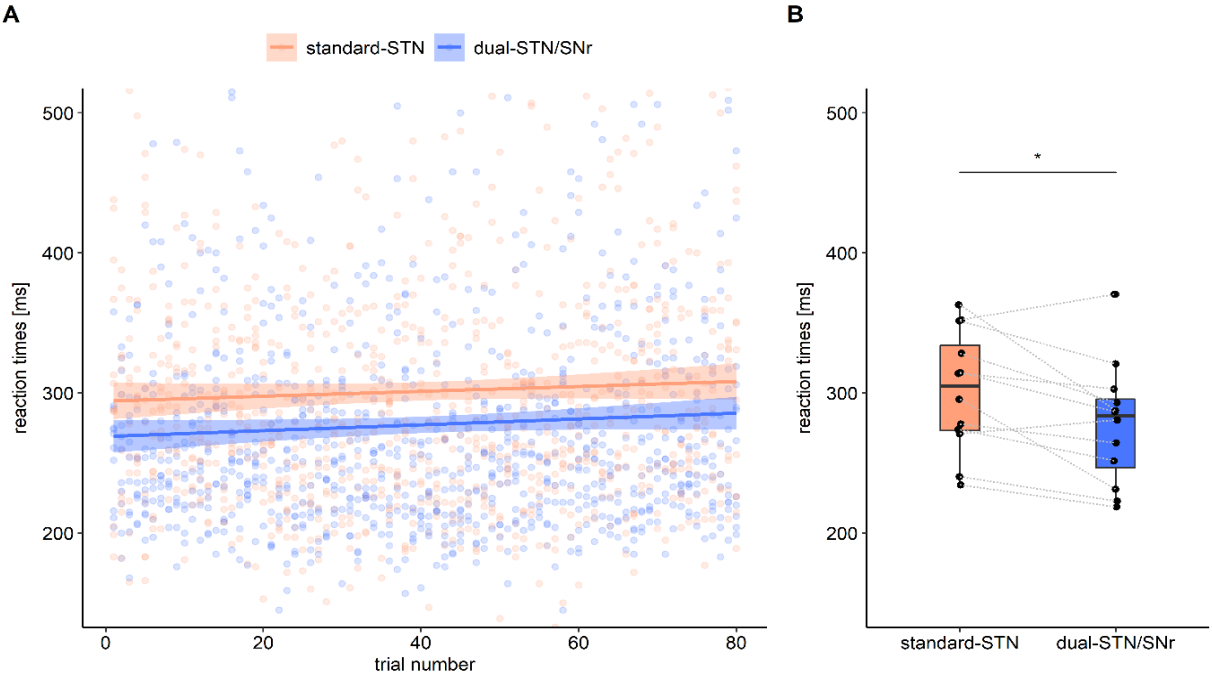

Figure 11: Results of reaction times analyses. A: Regression plot representing reaction times against trial number separate for the standard STN and dual STN/SNr stimulation condition. B: Boxplots showing mean reaction times separate for the standard-STN and dual-STN/SNr stimulation condition. *Wilcoxon signed ranks test z = -2.51, p = .009

3.4. Discussion

The present study investigated the impact of a simultaneous stimulation of the subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr) on attentional abilities in Parkinson's disease (PD) patients with standard STN-deep brain stimulation (DBS). Our findings demonstrate a beneficial effect of dual STN/SNr - DBS on reaction time performance, indicating an improvement in patients' alertness and preparedness to react.

Simultaneous STN/SNr - DBS is a promising approach in order to improve the treatment of therapeutically resistant axial signs in PD. The SN, as a critical brain region involved in dopamine generation, has been implicated not only in movement control but also in cognitive functions such as attention and executive functions (Sonne et al., 2022). Previous studies have highlighted the role of the SN in attention processes, supported by neurobiological models on attention-deficit/hyperactivity disorder (ADHD), imaging studies, and recent microelectrode recordings of nigral neurons (Gulberti et al., 2023; Krauel et al., 2010). Given this involvement of the SN in attention, it is plausible that dual STN/SNr-DBS could not only enhance motor control but also improve attentional processing in patients with PD.

Our data showed a general slowing of RTs with time-on-task, indicating an increase in patients' fatigability over time. Moreover, we found a general decrease in RTs in trials with a preceded warning tone, consistent with the concept of 'phasic alertness' (Posner & Boies, 1971; Posner & Petersen, 1990; Zimmermann , P. and Fimm , B., 2020) . Most importantly, we observed a significant enhancement in RTs under dual STN/SNr-DBS compared to standard STN – stimulation, indicating a positive impact of simultaneous STN/SNr-DBS on patients' alertness. When considering the different trial-types of the Alertness-Task, dual-STN/SNr-stimulation led to a significant RT improvement in unwarned trials only, with no significant influence on warned RTs. Unwarned RTs are considered a measure of intrinsic alertness and responsiveness. Warned RTs, on the other hand, provide information about the extent to which the ability to react can be increased through a preceded warning signal. Consequently, dual STN/SNr-stimulation seems to improve the intrinsic alertness and responsiveness in PD-patients. Since the warning tone already enables a short-term focus of attention on the expected stimulus in warned trials, we assume that the effect of dual-stimulation might not exceed the effect of phasic alertness.

To the best of our knowledge, this study is the first to investigate the effect of dual STN/SNr-stimulation on reaction time performance in PD-patients. Our results suggest a positive impact of simultaneous STN/SNr-DBS on responsiveness and attentiveness, leading to enhanced RTs.

We are aware that PD is a disease with dominant motor deficits and cannot completely rule out that an improvement in motor skills might also be responsible for the observed enhancement in RTs. Nevertheless, it should be noted that the task being performed places minimal motor skill demands and only requires pressing a response button with one finger. Additionally, dual STN/SNr-stimulation led to a significant improvement in RT performance only in unwarned trials, even though both trial types placed exactly the same demands on motor skills. Therefore, we assume that the demonstrated improvement in RT performance represents an increase in alertness and responsiveness rather than improved motor performance.

While previous studies have demonstrated beneficial effects of dual STN/SNr-DBS on gait (Valldeoriola et al., 2019; Weiss et al., 2011, 2013a), our findings further emphasize the role of the SN in cognitive functions, particularly attention. Considering the significant relationship between attention and gait performance, improvements in alertness and responsiveness through supplemental SNr stimulation could potentially lead to better treatment outcomes for gait disturbances and axial symptoms in PD. By addressing both motor and cognitive aspects of the disease, the combined STN/SNr-DBS may contribute to a more comprehensive and effective treatment of PD symptoms.

Given the limitations of this study, particularly with respect to the small sample size, further studies are needed to validate the results achieved. However, by demonstrating an improvement in ten out of twelve patients, this work provides important evidence for the beneficial effects of combined STN/SNr-stimulation on reaction time performance in PD. With regard to the therapeutic relevance of these results, further studies with a larger patient population would be desirable. In order to assess any frequency dependent stimulation effects on RT performance, the influence of SNr-stimulation should be examined at different stimulation frequencies. Furthermore, it should be investigated whether the co-stimulation of the SNr only influences the performance in simple reaction time tasks or can also be extended to more complex attention processes.

4. General Discussion

Parkinson's disease (PD) is a common and complex neurological disorder, resulting from a complicated interplay of genetic and environmental factors. It has long been characterized primarily by the classical motor features of parkinsonism associated with Lewy bodies and the loss of dopaminergic neurons in the substantia nigra. However, it is now recognized that PD has a heterogeneous symptomatology that includes both motor and clinically significant non-motor features, which contribute equally to the disease burden (Kalia & Lang, 2015). In recent years, there has been considerable interest in the interaction between higher-level cognitive functions and gait disturbances in PD and the diverse neuropsychological influences on walking as well as the interactions between mobility control and associated behaviors have been increasingly appreciated (Giladi & Hausdorff, 2006; Yogev-Seligmann et al., 2008).

Alongside the available medical options, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an important therapeutic approach in order to improve the disabling motor features in PD. However, since the therapeutic effect, particularly with regard to gait disturbances and axial symptoms, seems to diminish over time (Castrioto, 2011; Merola et al., 2011; Moro, Lozano, et al., 2010; Volkmann et al., 2009), novel targets such as the pedunculopontine nucleus (PPN) and the substantia nigra pars reticulata (SNr) were considered, to allow continuous treatment.

The PPN is part of the mesencephalic locomotor region (MLR) in the upper brainstem (French & Muthusamy, 2018) and intimately connected to the basal ganglia (BG), as well as other areas of the brain associated with motor control. It is thought to be involved in the initiation and modulation of gait and other stereotyped movements (Jenkinson et al., 2009). Based on observations in animal studies, it was suggested, that akinetic symptoms in PD might be partly caused by over-inhibition of the PPN and that stimulation of the PPN may provide greater benefit for axial symptoms (Pahapill, 2000).

The SNr is a major output nucleus of the BG and considered essential for the activation and adjustment of movement (Deniau et al., 2007; Heilbronn et al., 2019; Lafreniere-Roula et al., 2010). It has been established that in PD hyperactivity of the STN, due to dopamine deficiency, leads to a pathological overactivity of the major output structures of the basal ganglia, resulting in inhibition of motor projections to the thalamus and brainstem (Obeso et al., 2000). A combined stimulation of STN and SNr was proposed as another possible approach in order to disrupt the altered basal ganglia motor circuits (Weiss et al., 2011, 2013b) and improve motor features in PD.

Due to their anatomical location and based on experimental data, both the PPN and the SN have been increasingly associated not only with motor but also with cognitive functions (Sonne et al., 2022; Thevathasan et al., 2010, 2011). The PPN, as a part of the reticular activating system, has been suggested to be involved in the regulation of attention and consciousness (Mena-Segovia et al., 2008; Mesulam et al., 1989). The important role of the SN in attention and executive functions has been highlighted in several previous studies (Gulberti et al., 2023; Krauel et al., 2010; Romanos et al., 2010; Tomasi & Volkow, 2014).

Assuming that both PPN and SN are involved in cognitive functions such as attention, their selective stimulation could affect not only motor but also attentional performance in patients with PD.

This work aimed to investigate the possible influence of PPN - DBS as well as of dual STN/SNr-stimulation on attentional performance in patients with PD and parkinsonian disorders.

Study 1 examined reaction time (RT) performance in eight patients with PD and parkinsonian disorders under PPN stimulation in three different reaction time tasks: a simple reaction task (alertness task), a go/nogo-paradigm and a task for divided attention. Because the optimal frequency of PPN stimulation remained uncertain (Thevathasan et al., 2010), a range of frequencies (off-stimulation, 8 HZ, 20 Hz, 60 Hz, 130 Hz) were tested to assess any frequency dependent stimulation effects on RT performance.

The results showed an improvement in response times in a simple reaction time task (alertness-task; *unwarned condition*) during PPN-DBS with very low frequency stimulation (8Hz) and with therapeutic frequencies (20 Hz). No relevant change in reaction times was found in the *warned* condition of the alertness task. Consequently, it is suggested, that the preceded warning signal already increases attention to the expected stimulus and that stimulation features may not add any additional benefit. Consistent with the results of Thevathasan et al. (2010), who reported an influence of PPN-stimulation on simple reaction performance only, no significant changes in RT performance were found in the go/nogo paradigm and in the divided attention-task, regardless of stimulation frequency.

The best RT performance was demonstrated with low-frequency stimulation of 8 Hz and with therapeutic frequency stimulation of 20 Hz. This is consistent with previous animal studies that found beneficial effects of low frequency PPN stimulation on motor function (Jenkinson et al., 2004).

Given these results, one might assume that the faster response times under low frequency PPN-DBS are due to improved motor skills rather than increased attentional performance. However, patients' performance in the two conditions of the alertness-task (*warned* and *unwarned* condition) - that both represent simple attention tasks with equal requirements on motor response and speed - revealed an improvement of performance in the unwarned condition only. Accordingly, an influence on simple motor speed alone is unlikely to account for this selective improvement.

Interestingly, the most significant improvements in RT performance were found under low frequency stimulation of 8 Hz and 20 Hz. Based on earlier studies in which activity in the alpha frequency (8-13 Hz) was the most prominent oscillatory activity in the local field potential recorded from the PPN, it was hypothesized, that these activities play an important role in the function of the PPN (Androulidakis, Khan, et al., 2008; Androulidakis, Mazzone, et al., 2008). It has been shown, that alpha band power increases significantly following treatment with levodopa (Androulidakis, Mazzone, et al., 2008) and correlates with gait performance in PD (Tattersall et al., 2014; Thevathasan et al., 2012). Alpha oscillations are thought to play an important role in attentional processes (Palva & Palva, 2007) and it was suggested that alpha activity may indicate the process of actively suppressing cortical activity related to distractors while focusing attention on relevant targets (Ward, 2003). For example, alpha power increases with memory load during memory tasks, reflecting the individuals' efforts to suppress distraction (Jensen, 2002). With regard to the motor system, alpha activity is associated with the suppression of irrelevant processes in order to allow the smooth execution of motor programs (Pfurtscheller & Neuper, 1994; Suffczynski et al., 2001). As axial symptoms seem to be related to attentional deficits in PD (Giladi & Hausdorff, 2006; Okuma, 2006), alpha oscillations in the PPN could modulate attention to facilitate gait performance (Li & Zhang, 2015). Consequently, in view of the most significant improvement in RT performance exhibited under low frequent PPN stimulation in the alpha range, a stimulation-induced modulation of attentional performance is hypothesized.

Performance in the simple RT task primarily represents basic attentional functions, suggesting an impact of PPN-stimulation on basic attentional sub-routines rather than on complex attentional processing. This assumption is supported by the fact that there was no stimulation dependent effect on RT performance in more difficult attention tasks that require more complex cognitive functions of behavioral control, in particular execute functions like response inhibition and working memory. These functions are basically associated with prefrontal regions (Aron et al., 2004; Sasaki et al., 1993).

Based on the above-mentioned results, it is hypothesized that low-frequent PPN-DBS leads to an improvement in attentional performance, leading to an enhancement in response times in a simple reaction task. Consequently, attentional augmentation appears to be a key mechanism by which PPN-stimulation contributes to an improvement in motor action and gait in patients with parkinsonian disorders.

However, some limitations of this study must be acknowledged. Still, stimulation of the PPN is an experimental clinical procedure. By 2017, less than 100 cases of PD with PPN DBS have been published (Thevathasan et al., 2018). Consequently, only a small number of patients could be included. It should also be noted that parkinsonian disorders have a heterogeneous clinical picture and that the condition of the patients at the time of the assessment varied. In addition, although all patients were assessed within their regular follow-up periods, postoperative assessment intervals varied within the patient population. One might assume that greater variance in patients and timing of assessment results in greater variance in the data. Therefore, the effects reported in this study might have been even more pronounced in a more homogeneous patient group. Reaction time data indicated an improvement in basic attentional functions. Nevertheless, no relevant change in attention was apparent in patients' everyday life. This observation underlines the investigational character of this work and stresses the need for further studies, including a larger sample of patients. Also, a focus on changes in patients' performance in everyday life would be eligible.

In conclusion, Study 1 supports the contributing role of the PPN in attention, although some methodological limitations must be acknowledged.

Study 2 examined, whether co-stimulation of the SNr enhances reaction time performance in PD patients with standard STN-DBS. For this purpose, 12 patients with PD performed a simple RT-task (alertness task) under standard STN-DBS and under dual STN/SNr-stimulation. This investigation is based on the application of new programming techniques that allow STN and SNr contacts within the same electrode to be stimulated independently, using different current amplitudes and pulse widths (Kovács et al., 2012; Weiss et al., 2011; Wojtecki et al., 2011). The STN was stimulated with a high frequency of about 130Hz, which corresponds to the clinical standard of therapy (Abbasi et al., 2018). Co-stimulation of the SNr was performed with a low frequency of 6 Hz.

The results showed a significant improvement in response times in a simple reaction time task (alertness task, *unwarned condition*) under dual STN/SNr-DBS compared to standard

STN stimulation, suggesting positive effects of additional SNr-stimulation on attention and responsiveness.

Under combined STN/SNr-stimulation, a general decrease in RTs was also observed in trials with a preceded warning tone (alertness task, *warned condition)*, which is consistent with the concept of 'phasic alertness.' Consistent with study 1, it is hypothesized that the preceded warning signal already increases attention to the expected stimulus and that stimulation features may not provide any additional benefit.

As PD is a disease with dominant motor deficits, it was discussed whether the improvement in RTs could possibly be attributed to an improvement in motor skills rather than an increase in attention performance. In this regard, it should be noted that the task being performed places minimal motor skill demands. Additionally, dual STN/SNr-stimulation led to a significant improvement in RT performance only in unwarned trials, even though both trial types placed exactly the same demands on motor skills. Therefore, it is assumed that the demonstrated improvement in RT performance represents an increase in alertness and responsiveness rather than improved motor performance.

While recent studies have already demonstrated the beneficial effects of dual STN/SNr-stimulation on gait performance (Horn et al., 2021; Scholten et al., 2017; Valldeoriola et al., 2019; Weiss et al., 2011, 2013a), this work provides additional evidence that co-stimulation of the SNr can improve reaction time performance in PD. This underlines the important role of the SNr for cognitive functions, particularly attention.

Acknowledging the relevance of attention to gait performance (Faulkner et al., 2006; Hollman et al., 2007; Yogev-Seligmann et al., 2008), improvements in alertness and responsiveness through supplemental SNr stimulation could potentially lead to better treatment outcomes for gait disturbances and axial symptoms in PD. By addressing both motor and cognitive aspects of the disease, the combined STN/SNr-DBS may contribute to a more comprehensive and effective treatment of PD symptoms.

With respect to the small sample size, further studies are needed to validate the results achieved. However, by demonstrating a reaction time improvement in ten out of twelve patients, this work provides important evidence for the beneficial effects of combined STN/SNr-stimulation on attentional performance in PD. With regard to the therapeutic relevance of these results, further studies with a larger patient population would be desirable. In order to assess any frequency dependent stimulation effects on RT performance, the influence of SNr-stimulation should be examined at different stimulation frequencies. Furthermore, it should be investigated whether the co-stimulation of the SNr only influences the performance in simple reaction time tasks or can also be extended to

more complex attention processes. Moreover, as part of longer-term follow-up controls, it should be examined, whether simultaneous STN/SNr-stimulation permanently improves attentional performance.

In conclusion, this work aimed to investigate the possible influence of PPN- DBS as well as of dual STN/SNr-stimulation on attentional performance in patients with PD and parkinsonian disorders. Both studies point to the possibility of enhancing attentional processes through selective stimulation of the PPN and through co-stimulation of the SNr, providing further evidence for the significant roles of both, PPN and SNr, in attention. Given the importance of attention to gait performance, the targeted modulation of attentional performance could be a promising approach to improve the treatment of therapeutically resistant aspects of Parkinson's gait disorder and therefore have implications for the future management of PD patients.

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6. Anhang

Ehrenerklärung

Ich versichere hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; verwendete fremde und eigene Quellen sind als solche kenntlich gemacht. Ich habe insbesondere nicht wissentlich:

- Ergebnisse erfunden oder widersprüchlich Ergebnisse verschwiegen,
- statistische Verfahren absichtlich missbraucht, um Daten in ungerechtfertigter Weise zu interpretieren,
- fremde Ergebnisse oder Veröffentlichungen plagiiert,
- fremde Forschungsergebnisse verzerrt wiedergegeben.

Mir ist bekannt, dass Verstöße gegen das Urheberrecht Unterlassungs- und Schadensersatzansprüche des Urhebers sowie eine strafrechtliche Ahndung durch die Strafverfolgungsbehörden begründen kann.

Ich erkläre mich damit einverstanden, dass die Arbeit ggf. mit Mitteln der elektronischen Datenverarbeitung auf Plagiate überprüft werden kann.

Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form als Dissertation eingereicht und ist als Ganzes auch noch nicht veröffentlicht.

Magdeburg, 24.08.2023

Julia Thein