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RENÉ RANDVER

Parkinson's disease and depression: brain mechanisms and non-invasive brain stimulation based treatment strategies

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UNIVERSITY OF TARTU
Press

Institute of Psychology, University of Tartu, Estonia.

This dissertation has been accepted for the commencement of the degree of Doctor of Philosophy (in Psychology) on August 11, 2021 by the Council of the Institute of Psychology, University of Tartu.

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Commencement: October 15, 2021 in Näituse 2, Tartu.

Publication of this thesis is granted by the Institute of Psychology, University of Tartu, Estonia.

ISSN 1024-3291
ISBN 978-9949-03-692-9 (print)
ISBN 978-9949-03-693-6 (pdf)

University of Tartu Press
www.tyk.ee

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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, further referred to by respective Roman numerals:

I. Toomsoo, T., **Randver, R**., Liepelt-Scarfone, I., Kadastik-Eerme, L., Asser, T., Rubanovits, I., ... & Taba, P. (2017). Prevalence of depressive symptoms and their association with brainstem raphe echogenicity in patients with Parkinson's disease and non-PD controls. *Psychiatry Research: Neuroimaging*, *268*, 45–49. https://www.sciencedirect.com/science/article/abs/pii/S092549271730032X

II. **Randver, R.** (2018). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex to alleviate depression and cognitive impairment associated with Parkinson's disease: A review and clinical implications. *Journal of the Neurological Sciences*, *393*, 88–99. https://www.sciencedirect.com/science/article/abs/pii/S0022510X18303356

III. **Randver, R.,** Davel, K., & Toomsoo, T. (2019). High-frequency repetitive transcranial magnetic stimulation to the left dorsolateral prefrontal cortex of patients with Parkinson's disease and treatment-resistant depression: a pilot study. *Neurocase*, *25*(3–4), 80–90. https://www.tandfonline.com/doi/abs/10.1080/13554794.2019.1636069

The author of the dissertation contributed to the publications as follows:

- In **Study I**, set the aims and formulated the research hypothesis, designed and organized the study, analyzed the data, and wrote the manuscript as a co-author.
- In **Study II**, set the aims and formulated the research hypothesis, designed and organized the study, collected and analyzed the data, and wrote the manuscript as the main author.
- In **Study III**, set the aims and formulated the research hypothesis, designed and organized the study, participated in data collection, analyzed the data, and wrote the manuscript as the main author.

LIST OF ABBREVIATIONS

αS	alpha-synuclein
BDI	Beck Depression Scale
DBS	deep-brain stimulation
DLPFC	dorsolateral prefrontal cortex
HAM-D	Hamilton Depression Scale
HR-QoL	health-related quality of life
iTBS	intermittent theta-burst stimulation
MAO-A, MAO-B	monoamine oxidase A and B
NIBS	non-invasive brain stimulation
NMS	non-motor symptoms
NPS	neuropsychiatric symptoms
PD	Parkinson's disease
PD-MCI	mild cognitive impairment related to Parkinson's disease
PFC	prefrontal cortex
rTMS	repetitive transcranial magnetic stimulation
SSRI	selective serotonin reuptake inhibitor
TCS	transcranial sonography
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
TRD	treatment-resistant depression

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease with a global prevalence of 2–3% in people above 65 years of age (Poewe et al., 2017). Neurological disorders are now the leading source of disability globally, among which the growth of Parkinson's disease has been the fastest. From 1990 to 2015, the number of people with PD doubled to over 6 million. Driven principally by aging, this number is projected to double again to over 12 million by 2040. Additional factors, including increasing longevity, declining smoking rates, and increasing industrialization could raise the burden to over 17 million (Dorsey et al., 2018). For most of human history, PD has been a rare disorder − about 15% of the patients have positive family history for PD, and 5−10% have a specific monogenetic subtype of the disease. However, demographic change and the byproducts of industrialization have generated a surge in PD numbers, calling for heightened activism, focused planning, and novel approaches (Kalinderi et al., 2016).

Depression is a highly prevalent psychiatric disorder with a lifetime risk close to 20% and is associated with high levels of morbidity and mortality (Palazidou, 2012). PD is characterized by motor and non-motor features, including cognitive and neuropsychiatric disturbances. A number of studies have demonstrated the high prevalence of depression in patients with PD: epidemiological research has reported that the frequency of severe forms of depression is 5–20%, with milder forms occurring in an additional 10–30% of patients (Weintraub & Burn, 2011). A systematic review reported that premorbid depression was significantly more common in PD patients than in those without a diagnosis of PD, which suggests that depression may increase the risk of PD (Ishihara & Brayne, 2006). In a meta-analysis by Wang et al. (2018), depression was associated with a 2.2-fold increase in the incidence of PD. Despite the frequent occurrence of depression in patients with PD, the Global Parkinson's Disease Survey Steering Committee (2002) reported that only 1% of patients with PD recognized that they had depression. Depressed patients are at higher risk of serious physical health problems and worsening of the prognosis of other medical conditions (Palazidou, 2012), such as PD. Depression is a major factor in health-related quality of life (HR-QoL) in patients with PD (Jones et al., 2015), and may also be associated with more rapid deterioration in motor and cognitive functions (Ng et al., 2015; Santangelo et al., 2009). Depression in PD has also been associated with the severity of PD and the level of disability (Weintraub et al., 2004; see also Figure 1).

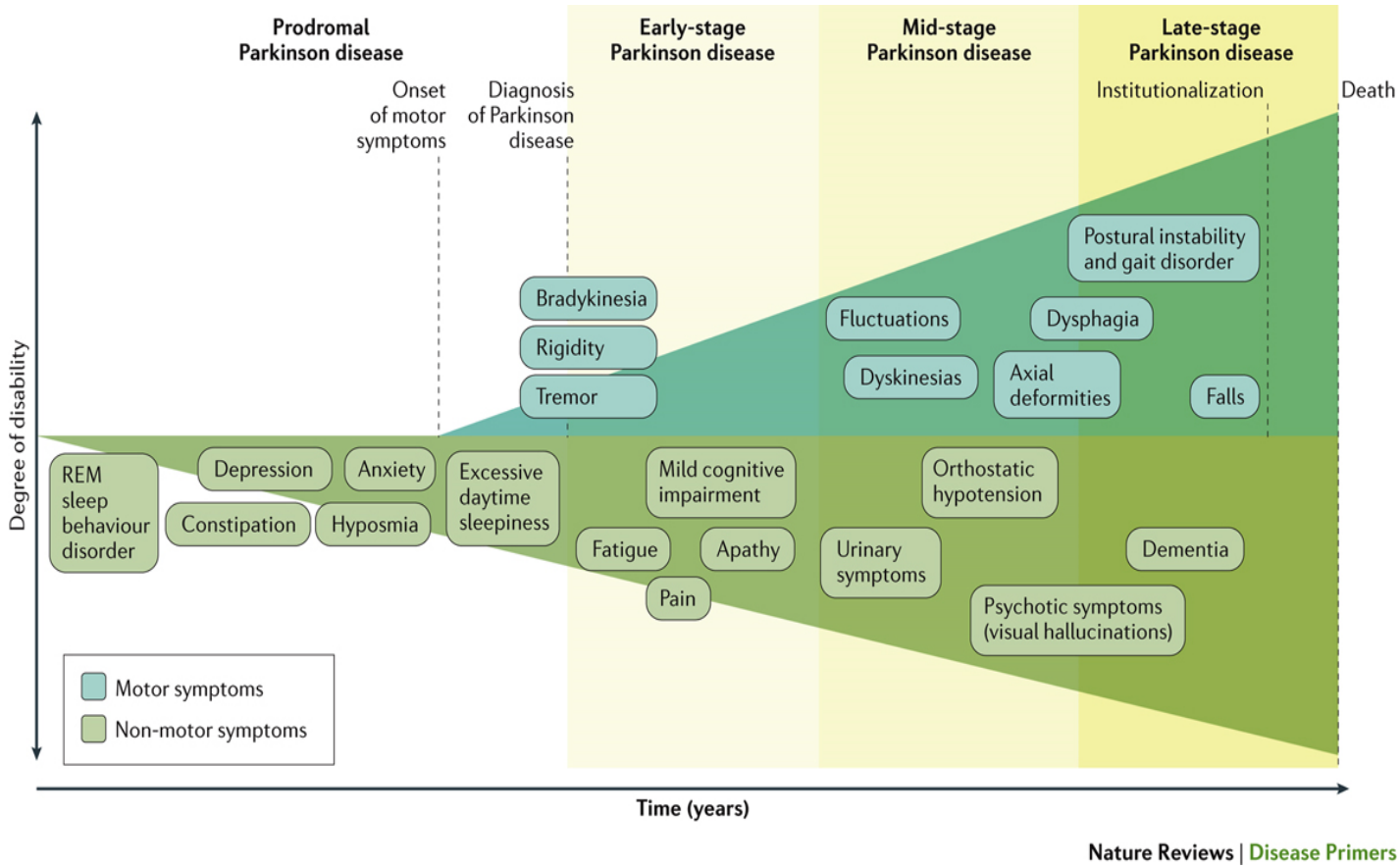

Figure 1. The influence of time and symptom type to the degree of PD-related disability (adapted from Poewe et al., 2017, with permission).

Follow-up studies show depression to be a long-term, relapsing condition with a tendency towards chronicity, and the risk of recurrence increases with each new episode (Palazidou, 2012). Three quarters of the patients experience more than one episode of depression, and the risk of recurrence is higher if the first episode occurs at a younger age and if there is a family history of depression (Hollon et al., 2006). Given these findings, the need for effective treatment starting from the first episode of depression is of critical importance. Maintenance treatment for several months during remission is essential after an acute episode of depression to prevent relapse, as well as long-term treatment to prevent recurrence in patients with more than one episode (Glue et al., 2010). In addition to the number of episodes, the prognosis is influenced by the duration of illness remaining untreated; the more protracted this is, the poorer the response to treatment and the lower the likelihood of achieving remission (Okuda et al., 2010). Subsyndromal states encourage relapse and progression to chronicity (Pintor et al., 2003). According to Palazidou (2012), many patients do not achieve full remission for various reasons which include poor compliance, premature ending of treatment, the use of inadequate treatment and other factors. Also, long-term depression (over 2 years) is common, clinically more serious than episodic depression, and associated with more functional impairment and high comorbidity. As the symptoms of depression increase during the progression of PD, they also raise direct healthcare costs such as examinations and treatment, and indirect costs such as disability-related job loss and caregiver burden (Huse et al., 2005; Johnson et al., 2013), causing preventable social expenditure at the national level. Multiple treatment types exist for depressed patients with PD, including pharmacotherapy, psychotherapy, and brain stimulation. Despite the substantial number of studies of PD-related depression in specific, its precise role in PD and respective treatment methods, especially newer ones such as repetitive transcranial magnetic stimulation, are insufficiently understood, and underdeveloped.

1.1. Key aspects of Parkinson's disease

In PD and related synucleinopathies, treating motor signs and symptoms (such as tremor, muscle rigidity, and bradykinesia, but also motor fluctuations and dyskinesias) resulting from the degeneration of dopaminergic neurons in the substantia nigra has long been the focus of disease management. However, in recent years, because of increased clinical recognition and relevance to the patient's quality of life, the non-motor aspects of such disorders have attracted increasing interest (Takamatsu et al., 2018).

Non-motor symptoms (NMS) in PD are common and contribute to diminished HR-QoL, increased dependency on caregivers, greater cognitive impairment, and more frequent subjective motor symptoms (Dhingra et al., 2021). According to the 2015 criteria by the Movement Disorder Society, the

core feature of PD is parkinsonism as defined by bradykinesia in combination with either resting tremor, rigidity, or both (Postuma et al., 2015). However, NMS are now being recognized as additional criteria within the prodromal period of PD.

Clinically, PD-related NMS consist of four domains: neuropsychiatric (e.g., depression, anxiety, apathy, hallucinations, mild cognitive impairment, dementia), autonomic (e.g., constipation, orthostatic hypotension, urinary changes, and sweating abnormalities), sleep (e.g., insomnia, sleep fragmentation, excessive daytime sleepiness, rapid eye movement sleep disorder, and restless leg syndrome), and sensory dysfunction (e.g., pain and olfactory dysfunction) (van Rooden et al., 2009; Modugno et al., 2013; Pellicano et al., 2015). Such diversity of NMS may be consistent with the widespread distribution of alpha-synuclein (αS) pathology in the gut (Shannon & Vanden Berghe, 2018; Stolzenberg et al., 2017) as well as in the brainstem and neocortex (Hawkes et al., 2007), in which multiple populations of aminergic neurons may be affected. In regard to cognition, the dopaminergic system of the brain is believed to be strongly involved in normal and pathological behavioral phenotypes of attention.

Consequently, in addition to PD, other synucleinopathies such as dementia with Lewy bodies and multiple system atrophy are associated with a wide range of non-motor symptoms, including cognitive impairment, depression and anxiety, sleep disorders, gastrointestinal symptoms, and autonomic failure. Thus, the classic Parkinsonian motor syndrome is now regarded as but one unitary symptom type among many disparate symptoms of these types of neurodegenerative diseases (Takamatsu et al., 2018).

1.2. Neuropsychiatry of Parkinson's disease

Neuropsychiatric disorders (such as affective, behavioral, and cognitive symptoms) are important non-motor features in PD, which occur at high frequency and have significant impact on the degree of disability and quality of life (Figure 1). These frequently affect PD patients from the very first stages of the disease, or even before the onset of motor symptoms (Baig et al., 2015; Kalia & Lang, 2015; Pont-Sunyer et al., 2015). Despite their major impact on the quality of life of patients with PD, they are underrecognized and untreated (Bologna et al., 2019), or the treatment may not be optimal.

Although PD is still considered a movement disorder and is diagnosed based on cardinal motor signs and symptoms (Postuma et al., 2015), the high prevalence of numerous neuropsychiatric symptoms suggests that it is more suitably conceptualized as a neuropsychiatric disorder (Weintraub & Burn, 2011). According to a study by Aarsland and colleagues (1999), the overall prevalence of neuropsychiatric symptoms in PD patients was 61%. The most common symptoms were depression (38%), hallucinations (27%), anxiety (20%) and apathy (16.5%). The less common symptoms are euphoria (7.0%) and disinhibition (6.5%). A later study (Aarsland et al., 2009) found that the prevalence of neuro-

psychiatric symptoms in early untreated PD patients was 56%. The most common symptoms reported in this study were depression (37%), apathy (27%), sleep disturbance (18%) and anxiety (17%), whereas psychotic symptoms were found to be very rare among untreated PD patients. For many PD patients and their families, neuropsychiatric disturbances are often more problematic and distressing than the motor aspects of disease (Hely et al., 2005).

According to Schrag and Quinn (2020), the focus of clinical management and treatment trials in PD in the early 1990s had been the development of better management options for the motor features and complications of therapy, such as motor fluctuations and dyskinesias. Clinical assessment, and in particular clinical trials, almost entirely relied on clinicians' judgement of severity of disease and its complications. However, in the late 1990s, this had started changing and the development of standardized scales to assess how patients evaluate their own health problems (i.e., HR-QoL measures) had recently enabled standardized quantitative assessment of patients' views. HR-QoL scales made it possible to assess impact on patients' lives, independent from clinicians' assessments, and to incorporate other aspects of HR-QoL, such as the emotional and social impact of the disease. While overall disability was an important factor, the key and overwhelmingly determining feature associated with poorer HR-QoL was the severity of depressive features, as assessed on the Beck Depression Inventory. Depression had been recognized as associated with PD but was often considered a consequence (Brown & Jahanshahi, 1995) although it had also been seen as a manifestation of brain dysfunction (Tandberg et al., 1997). We now know that, at least in part, it is an integral feature of the disease, and is significantly more common many years before the diagnosis (Ishihara & Brayne, 2006; Schrag et al., 2015) in people with a later diagnosis of PD than in controls.

Depression has been the most widely studied of all psychiatric disorders in PD (Weintraub & Burn, 2011), and major advances have been made in characterizing its frequency, clinical phenotype, and diagnosis (Weintraub, 2020). Worldwide, approximately 35–42% of PD patients have clinically significant depressive symptoms and 17–25% meet criteria for a major depressive disorder, which is notably higher than the prevalence rate of 13.5% in the general population (Beekman et al., 1999; Hely et al., 2005; Dissanayaka et al., 2011; Marsh, 2013; Pachana et al., 2013). Earlier epidemiological research has reported that the frequency of major (i.e., more severe) depression is 5–20%, with non-major forms (i.e., minor depression) occurring in an additional 10–30% of PD patients (Tandberg et al., 1996; Starkstein et al., 1998; Reijnders et al., 2008). Thus, up to 50% of PD patients experience depression at some point in the course of their illness. This is much higher than the prevalence of depression in adults in the local community (<10%) (Tandberg et al., 1996). Parkinson's patients with depression have significantly higher anxiety symptoms, pessimism, suicidal thoughts, and self-condemnation compared to Parkinson's patients without depression (Cummings, 1992; McDonald et al., 2003). Lee and colleagues (2016) analyzed 4,362 patients with PD and reported that the elderly with PD

had a two-fold higher risk of suicide compared to elderly without PD. In spite of the notions stated above, depression related to PD still remains underrecognized and undertreated (Althaus et al., 2008), even in specialty care settings (Shulman et al., 2002; Weintraub et al., 2003).

In a recent study by Fan et al. (2020), it was found that depression imposes a greater impact on PD patients' HR-QoL than motor function when co-occurring with cognitive impairment. Mild cognitive impairment related to PD (PD-MCI) is common − a relatively recent systematic review and meta-analysis (Saredakis et al., 2019) found that within three years, in those with PD and normal cognition, 25% converted to PD-MCI and 2% converted to dementia. Of those with PD-MCI, 20% converted to dementia while 28% reverted back to a state of normal cognitive function. After three or more years, the conversion rates to MCI and dementia were higher, and reversion rates lower. Although the cognitive deficits in PD have traditionally been classified as being "subcortical" in nature (i.e., relatively greater impairments in executive abilities, information-processing speed, and working memory compared with cortical functions like episodic memory storage and language skills), a review by Litvan and colleagues (2011) showed that a range of other cognitive domains are impaired in PD patients without dementia, including visuospatial, memory, and even language abilities. In addition, bradyphrenia as slowing of perceptual-cognitive information processing has been previously described in PD (Ransmayr et al., 1990; Bachmann et al., 1998; Shipley et al., 2002).

In addition to the most commonly studied neuropsychiatric symptoms such as depression, cognitive impairment (both mild cognitive impairment and dementia), and psychosis, other relatively common and clinically significant psychiatric complications include impulse control disorders, various anxiety symptoms, disorders of sleep and wakefulness, and apathy. A recent study (Kuhlman et al., 2019) suggested that in mild to moderate PD, in addition to the disability related to motor dysfunction, the most significant predictors of HR-QoL in PD are depression, anxiety, apathy, and excessive daytime sleepiness. The authors also pointed out that the non-motor symptoms of depression, anxiety, apathy, and excessive daytime sleepiness as a group accounted for 48% of the variance in HR-QoL in PD. A systematic review of studies using regression analysis to determine the impact of specific neuropsychiatric symptoms on HR-QoL in PD found depression to be most commonly associated with worse quality of life, and the most significant predictor of quality of life (Balestrino & Martinez-Martin, 2016).

As described by Gallagher and Schrag (2012), the pathophysiology of neuropsychiatric symptoms is complex, reflecting the widespread brainstem and cortical pathology in PD, with involvement of several neurotransmitters, among which dopaminergic, serotonergic, noradrenergic and cholinergic systems are found to be involved most often. The diagnosis of psychiatric conditions, in particular affective disorders, is challenging because of the overlap of somatic features of psychiatric disorders with the underlying movement disorder. The pathogenesis is likely to differ considerably from non-PD patients, and treat-

ments used in general psychiatry services may not be as effective in PD, warranting further elaboration in well-designed clinical studies. In order to understand the pathophysiology of PD better, brain imaging methods have become increasingly applied (Hu et al., 2015; Lou et al., 2015; Borgonovo et al., 2017; Nagy & Schrag, 2019; Lin et al., 2020). According to a systematic review by Wen and colleagues (2016), increased neural activity in the prefrontal regions and decreased functional connectivity between the prefrontal limbic networks in depressed patients have been consistently noted in previous research. Functional imaging studies point at an inverse correlation between dopaminergic density in the caudate and putamen with the severity of anxiety in PD. Prefrontal control of the patient's state in the combined PD and depression is clearly evident as shown in these studies, suggesting forms of treatment by intervention through manipulations of prefrontal functionality. This dissertation will delve into functional connectivity in more detail in later chapters.

Affective disorders (such as depression and anxiety), psychosis, impulse control disorders, and apathy are common and sometimes disabling psychiatric conditions in PD. There is inconsistent evidence that depression related to PD is distinct from clinical (i.e., non-PD) depression; some studies report higher rates of anxiety, pessimism, suicide ideation without suicide behavior, and less guilt and self-reproach in depressed PD patients compared with their non-PD counterparts (Leentjens, 2004). However, overall predictors or correlates of depression are similar between populations (Leentjens et al., 2013). Psychiatric aspects of PD are frequent and associated with numerous adverse outcomes, yet there remains incomplete understanding of their epidemiology, presentation, risk factors, neural substrate, and management strategies (Weintraub, 2020). Psychiatric features are typically co- or multimorbid, and there is great intra- and interindividual variability in presentation (Martinez-Martin et al., 2020). A significantly higher risk of anxiety and depression among the first-degree relatives of patients with PD has been shown, providing evidence for shared genetic and/or common environmental factors (Arabia et al,, 2007). With the introduction of levodopa and other medications and treatments into clinical practice, the increasing life span of both the general population and patients, and growing awareness and clinical research in the past half-century, PD-related neuropsychiatric disorders have been recognized as being very common and disabling long-term complications (Chaudhuri et al., 2006). In addition, they are associated with poor long-term outcomes and increased caregiver burden, requiring special clinical expertise for optimal management (Weintraub & Burn, 2011).

1.3. Treatment of neuropsychiatric symptoms of Parkinson's disease

Two major complementary paradigms have guided treatment development for neuropsychiatric disorders for nearly 70 years: a neurochemical paradigm positing that neuropsychiatric dysfunction results from abnormalities of (pri-

marily) neurotransmitters, and a behavioral/psychological paradigm purporting that dysfunction results from alterations of emotions, thought, and learning. The first has given rise to dozens of pharmacological agents to prevent and/or treat neuropsychiatric conditions, while the second has resulted in numerous psychotherapeutic approaches. Although these interventions are generally effective for most individuals with neuropsychiatric disorders, a substantial minority of patients continue to suffer despite treatment (Slaughter et al. 2001; Chen & Cheng, 2008; Lesenskyj et al., 2018).

Pharmacological agents used for the treatment of depression in general psychiatry practice include tricyclic antidepressants (TCA), the tricyclic-related drugs (e.g., trazodone), the selective serotonin reuptake inhibitors (SSRI), the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, the selective noradrenaline reuptake inhibitor (NRI) reboxetine, the presynaptic alpha-2 adrenoreceptor antagonist mirtazapine and the noradrenaline–dopamine reuptake inhibitor (NDRI) bupropion. All of them may have a role in treatment of mood disorders in PD. Approximately 20–25% of PD patients are on an antidepressant at any given time, even *de novo*, untreated patients (Smith et al., 2015; Martinez-Martin et al., 2020), most commonly a SSRI (Richard et al., 1997; Weintraub et al., 2003). Zhuo and colleagues (2017) completed a meta-analysis on the efficacy of antidepressant medications and found SSRIs to be most efficacious, however, they had more adverse effects compared to SNRIs which were considered the safest. Antidepressant use increases over the initial years of PD (Caspell-Garcia et al., 2017). Adverse effects of these medications can however limit their use, particularly in the elderly. According to Gallagher and Schrag (2012), autonomic phenomena commonly encountered in PD, such as orthostatic hypotension, are prone to exacerbation by the anti-cholinergic effects of TCAs, and to a lesser extent, SSRIs. The anti-cholinergic action of these drugs may worsen neuropsychiatric features of PD, such as cognitive impairment, visual hallucinations, and delusional thoughts. The SSRIs have important pharmacological interactions with the MAO-B inhibitors selegiline and, to a lesser degree, rasagiline, and thus theoretical predilection to serotonin syndrome.

Many depressed PD patients do not respond to pharmacotherapy or are reluctant to take additional medications, and thus may prefer psychotherapy (Oehlberg et al., 2008), which constitutes the second approach to depression treatment. Cognitive-behavioral therapy (CBT) has been shown to be efficacious for PD-related depression; for example, the results of a large RCT (n=80) using CBT showed Hamilton Depression Rating Scale (HAM-D) depression scores significantly decreased and symptoms remained stable at 1-month follow-up (Dobkin et al., 2011). Support is also present for group CBT for treatment of both depression and anxiety among patients with PD, with results maintained at 6-month follow-up (Troeung et al., 2014). Improvements through CBT have been seen not only in mood, but also in verbal memory and executive functioning (Dobkin et al., 2014). A fairly recent meta-analysis concluded that

exercise appears to have an impact on depressive symptoms in PD (Wu et al., 2017), but overall, it seems that the scientific evidence for this notion is limited.

The third approach to depression treatment development proposes that neuropsychiatric disorders result from the dysfunction of specific brain regions and/or networks of regions (Holtzheimer, 2018). Cortical dysfunction has been documented in PD by neuroimaging and neurophysiologic studies, showing either hypo- or hyperactivation of various brain areas (Lefaucheur, 2006; Lefaucheur, 2009). Both invasive and non-invasive brain stimulation methods can counter this imbalance in electrophysiological properties. In medicine, the term 'invasive' typically refers to procedures that breach the biological tissue or require implantation of a device into the body. Deep brain stimulation (DBS) is an established, although invasive treatment for PD that has been used for more than three decades. Although the mechanisms of DBS are still not fully understood, both subthalamic nucleus (STN) and internal globus pallidus (GPi) are effective targets to ameliorate complications such as motor fluctuation and dyskinesia related to long-term use of levodopa. In a study by Rätsep and Asser (2011), a comparison of mean clinical motor scores of six PD patients revealed a significant improvement of parkinsonian symptoms (in particular, arm rigidity) after DBS of the STN, also confirming that myotonometry is an objective method to evaluate rigidity in patients with PD. DBS has also been associated with improvement in mood, with mixed evidence from two meta-analyses that GPi lead location is preferred over the STN (Sako et al., 2014; Wang et al., 2016); if true, this is perhaps because GPi-stimulated patients undergo a smaller postoperative decrease in their PD medications (Weaver et al., 2009). For a review of clinical and electrophysiological effects and the future directions of invasive brain stimulation in PD (including DBS), see the work by Chen and Chen (2019).

Invasive brain stimulation techniques may not be an option for everyone, so non-invasive brain stimulation (NIBS) methods have also been developed. Although being one of the most used and highly effective NIBS techniques available for treatment-resistant depression, modern electroconvulsive therapy (ECT) has been associated with adverse cognitive effects that can lower the patient's quality of life. Less is known about ECT usage in PD. For severe, treatment resistant PD-related depression, ECT has been shown to be somewhat effective (Popeo & Kellner, 2009). There is still a growing need to safely, tolerably, and with minimal adverse effects help PD patients overcome treatment-resistant depression. NIBS techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have shown promise in addressing the fronto-striatal neural network via stimulation of the DLPFC (Kanno et al., 2004; Marcolin & Padberg, 2007), impacting cognitive as well as affective symptoms (Schulz et al., 2013). The basic principle of transcranial magnetic stimulation (TMS) is the application of short magnetic pulses over the scalp of a subject with the aim of inducing electrical currents in the cortical neurons of a predefined brain area. In a single-pulse TMS protocol, only a single impulse is applied. The objective is to measure the stimulation

effect on brain processes and/or behavior. In parallel, rTMS, first introduced in 1989, is a non-invasive technique of repeated stimulation of the cerebral cortex by a train of magnetic pulses. Since then, a large number of studies have involved rTMS as an investigational tool as well as a potential treatment for a variety of neurological and psychiatric disorders (Kamble et al., 2014). Since receiving FDA clearance as a reimbursable therapeutic method for treatment-resistant unipolar depression in 2008, rTMS has also stated to gain momentum as an attractive treatment method to alleviate other neuropsychiatric problems, including those associated with PD.

1.4. Aims of the thesis

As introduced in the preceding sections of this dissertation, depression is recognized as the most common neuropsychiatric symptom in PD. Depression in the context of PD is cause for concern because of associated faster cognitive and motor decline (Starkstein et al., 1992), poorer quality of life, and increased mortality (Hughes et al., 2004) seen in depressed patients with PD as compared to their non-depressed counterparts. Multiple treatment types exist for patients with PD-related depression, including pharmacotherapy, psychotherapy, and non-invasive brain stimulation. Advanced stage multimorbid PD patients with polypharmacy represent a relevant challenge for therapeutic safety (Chen & Cheng, 2008), and for achieving treatment response.

The general aim of the dissertation was to summarize the evidence and, where possible and appropriate, to fill the gaps and expand on knowledge regarding the effective therapeutic application of rTMS in patients with depression related to Parkinson's disease, with possible implications to neuropsychiatric phenomena outside the mood domain (e.g., cognitive impairment and anxiety), and consequently, the patients' quality of life. The approach undertaken was threefold: (a) to collate, participate in the validation of, and synthesize the available scientific evidence regarding the neural circuitry of depression within the context of PD, (b) to analyze the feasibility and specific parameters of using rTMS to treat depression in PD, and (c) to apply the knowledge from the previous two points to a clinically complex and heterogeneous sample of PD patients with treatment-resistant depression, with a goal to assess the role of individual differences in treatment response and gather direct data on any emerging practical issues in using NIBS in the aforementioned clinical setting. The latter serves as proof-of-concept to be used subsequently for developing an optimal treatment protocol for PD-related treatment-resistant depression.

Using transcranial sonography, it has been indicated that marked hyperechogenicity of the substantia nigra and reduced brainstem raphe echogenicity (suggestive of structural alterations at these sites) is particularly common and severe in patients who have both PD and depression, and these changes in the brain are associated with a history of depression before the development of PD (Walter et al., 2007a; Walter et al., 2007b). The precise nature of this relation-

ship is not entirely clear. The specific aim of **Study I** was to describe the prevalence and severity of depressive symptoms in PD and to analyze possible associations between specific brain-based biomarkers – in this case, the brainstem raphe – and depressive symptoms. The main expectations of the study were to confirm that neuroanatomical alterations of raphe nuclei in the brainstem (expressed in echogenicity levels) are involved in the pathogenesis of depressive disorders in PD, and that the degree of these changes is directly related to depressive symptom severity. Understanding that depressive symptom severity is an important factor modulating the clinical aspects of PD, an urgent need for new and effective treatments is raised (especially for PD patients with treatment-resistant depression).

The hypoactivity of the dorsolateral prefrontal cortex (DLPFC) in depression has been identified by many previous studies and now regarded as a critical hallmark for depression (Ring et al., 1994; Dragaševic et al., 2002; Mottaghy et al., 2002; Fregni et al., 2006; Cardoso et al., 2008; Bench et al., 2009; Koenings & Grafman, 2009). The DLPFC is regarded as most accessible for treatment with rTMS (Wassermann & Lisanby, 2001). **Study II** was set out to pool the available scientific literature on the therapeutic usage of a specific NIBS technique – rTMS – on neuropsychiatric symptoms of PD specifically associated with the dorsolateral prefrontal cortex (i.e. depression and cognitive impairment).

Following up on Study I and Study II and building on gained knowledge, the aim of **Study III** was to establish a preliminary effective, safe and tolerable evidence-based rTMS protocol for PD patients with treatment-resistant depression. Patients with PD-related TRD represent a heterogeneous clinical sample, stressing the interindividual variability in both clinical status and characteristics of treatment response. The study protocol will take these characteristics into account so as to be a viable approach in addressing PD-related treatment-resistant depression. The research questions addressed within the thesis are:

1. What is the current understanding of the neural circuitry of affective processing in depression related to PD?
2. How does depression influence the overall disease trajectory and quality of life of PD patients?
3. Can a NIBS method such as rTMS effectively, safely, and tolerably be applied to treat depression related to PD? In addition to treating depression, is there evidence regarding the treatment of other common neuropsychiatric problems associated with PD using rTMS?
4. What are the known obstacles and emerging questions to be mindful of when using rTMS to treat PD patients with treatment-resistant depression? How can the treatment process be optimized to achieve better outcomes?

2. INSIGHTS FROM AFFECTIVE AND COGNITIVE NEUROSCIENCE INTO DEPRESSION AND PARKINSON'S DISEASE

2.1. Neural circuits of affective processing

The neural circuits of affective processing include the limbic system and the prefrontal cortex (PFC). These brain areas and their connections are collectively responsible for maintaining emotional equilibrium, and thus, their malfunction is considered central to the pathophysiology of depression (Palazidou, 2012). The limbic system is a set of brain structures located on both sides of the thalamus, immediately beneath the medial temporal lobe of the cerebrum primarily in the forebrain. It supports a variety of functions including the processing of emotions, behavior, motivation, long-term memory, and olfaction.

The limbic system comprises of the amygdala, the cingulate gyrus, the hippocampus, the hypothalamus, and the anterior thalamic nuclei, as well as their connections surrounding the brainstem. The amygdala is one of two almond-shaped clusters of nuclei located deep and medially within the temporal lobes of the brain. Its primary role lies in the processing of emotional learning and memory, decision-making and emotional responses (including fear, anxiety, and aggression). It is involved in recruiting and coordinating cortical arousal and neuroendocrine response to underdetermined (surprising and ambiguous) stimuli. It also has connections with cortical and subcortical areas thought to be engaged in attentional and motivational processes (Holland & Gallagher, 1999; Davis & Whalen, 2001).

The PFC lies anteriorly to the premotor area (involved in the planning of complex motor actions) that itself is situated more rostrally from the primary motor area (involved in mediating conscious movement) of the frontal cortex. The PFC integrates complex sensorimotor information with motivation and affect. It is divided into three major sections: the dorsolateral, the paralimbic (orbital and medial aspects of PFC), and the anterior cingulate cortex (ACC) (Figure 2). The ventromedial (VMPFC) and the dorsolateral (DLPFC) prefrontal cortices connect with each other via the cingulate gyrus and the hippocampus. The VMPFC is necessary for the normal generation of emotions (in particular, social emotions) (Damasio et al., 1990) as well as the regulation of autonomic and neuroendocrine responses and modulation of pain, aggression, sexual and eating behaviours (Ongür & Price, 2000). The orbital PFC, or orbitofrontal cortex (OFC), plays a role in correcting behavioural or emotional responses (generated in part by the amygdala), while the DLPFC has been consistently implicated in cognitive control, solving complex tasks, maintenance and manipulation of information in working memory (Palazidou, 2012). According to Downar and Daskalakis (2013), the prefrontal regions do not function in isolation, but rather as nodes in larger networks involved in depression-related functions: cognitive control, rumination and self-reflection,

and the generation of visceral states sometimes known as somatic markers (Damasio, 1996). The anatomical projections from the medial prefrontal network to the amygdala, hypothalamus, periaqueductal grey (PAG), locus coeruleus, raphe nuclei, and brainstem autonomic nuclei play major roles in organizing the visceral and behavioral responses to stressors and emotional stimuli (Price & Drevets, 2010).

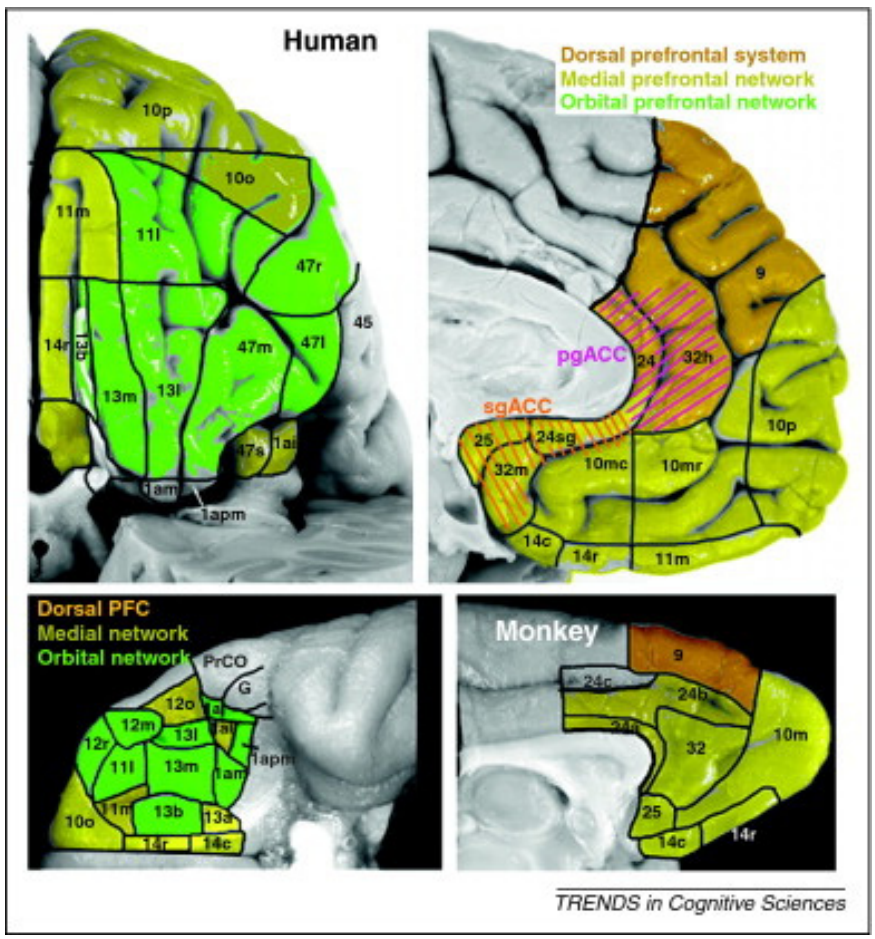

Figure 2. Maps of the orbital and medial surfaces of a human brain (above) and a macaque monkey brain (below), showing architectonic areas. The medial and orbital prefrontal networks are colored yellow and green, respectively. The networks have been defined based on connectional data. The regions referred to as the subgenual and pregenual anterior cingulate cortex (sgACC and pgACC) are indicated on the human brain with orange and red stripes (adapted from Price and Drevets, 2012, with permission).

Data from functional neuroimaging studies suggests that there is a complex network of brain regions that are involved in the pathophysiology of depression (Fitzgerald et al., 2008). Impaired reciprocal functional relationships between limbic (e.g., amygdala) and cortical (e.g., dorsolateral prefrontal cortex) structures are thought to correlate with emotional dysregulation and depression (Mayberg, 2003; Drevets et al., 2008). Functional neuroimaging studies have also implicated that variations in activity levels of the amygdala contribute to the development of depressive symptoms; for example, in depressed patients, Sheline and colleagues (2001) found a greater activation of the left amygdala during early stages of depression while also confirming that that after 8 weeks of antidepressant treatment, the activation decreased drastically. After increased amygdalar activation, decreased bilateral or left prefrontal cortical activation are also often reported functional anomalies in the imaging literature related to depression (Davidson et al., 2002a; Davidson et al., 2002b; Zhong et al., 2011). Because the DLPFC mediates a protective function against depression during the regulation of negative emotion (Phan et al., 2005; Eippert et al., 2007), hypoactivation in certain regions of the DLPFC could be linked to a failure to override other more automatic negative responses that might then lead to more severe negative mood states (Davidson et al., 2002a, Davidson et al., 2002b). These relationships will be further explored in the next sections of this chapter.

2.2. Structural and functional connectivity in clinical depression

The clinical phenomenology of depression implicates brain systems involved in the regulation of mood, anxiety, fear (e.g., panic attacks, phobias, and post-traumatic stress syndromes commonly occurring co-morbidly with depression), reward processing, attention, motivation, stress responses, social interaction, and neurovegetative function (i.e., sleep, appetite, energy, weight, libido) (Victor, 2013). Structural magnetic resonance studies have shown a reduction in the brain volume of depressed patients compared with healthy controls, with large volume reductions in the ACC and OFC, and moderate reductions in the hippocampus, the putamen and the caudate (Koolschijn et al., 2009). Functional brain imaging studies in depressed patients have shown abnormalities in regional cerebral blood flow and glucose metabolism in multiple structures involved in emotion processing, such as the PFC, cingulate gyrus, OFC, or deeper limbic regions like the amygdala, insula and hippocampus (Fitzgerald et al., 2006a; Steele et al., 2007). Fluorodeoxyglucose positron emission tomography (FDG-PET) studies of resting brain function in depression reveal bilaterally observable net hypoactivity in a widespread network that includes, in addition to the DLPFC and VMPFC, the dorsomedial prefrontal cortex (DMPFC), frontopolar cortex (FPC), and ventrolateral prefrontal cortex (VLPFC), along with hypoactivity in partner regions in the precuneus, lateral

parietal lobes and middle temporal gyri, and increased activity of amygdala, hippocampus, and brainstem raphe nuclei (Li et al., 2010; Price & Drevets, 2012). In depression, the VMPFC shows increased activity while the DLPFC shows a decrease in activity (Drevets, 1998). According to Palazidou (2012), decreased activity of the DLPFC in depression has been associated with psychomotor slowing and anhedonia. Response to treatment is associated with a decrease in metabolic activity, and long-term antidepressant drug treatment reduces metabolism in the amygdala and ACC in subjects with persistent, positive treatment response. In contrast, the persistence of the abnormal metabolic deficits in the dorsomedial/dorsal anterolateral PFC in depression during treatment may relate to histopathological changes reported in these regions in postmortem studies (Drevets et al., 2002). The structural changes in the brain, particularly the hippocampus and PFC, are believed to arise due to abnormalities in neuroplasticity rather than neurodegeneration. Nevertheless, it remains to be confirmed whether these changes are indeed always reversible, particularly in the PFC and also whether or not they predate the onset of depression.

Table 1. Functional and structural changes in the limbic and PFC areas implicated in depression (adapted from Palazidou, 2012, with permission).

Substrate	**Volume**	**Histological changes**	**Metabolic activity**	**Antidepressant effects**
OFC/VMPFC	↓	↓	↑	
ACC	↓			↓ Metabolic activity
Hippocampus	↓	↓		↑ Volume
Amygdala	↓?			↓ Metabolic activity
DLPFC	↓	↓	↓	

As summarized by Palazidou (2012), experimental lesioning studies, clinical observations of patients with degenerative disorders of the basal ganglia, and neuroimaging structural and functional studies in depressed subjects have provided strong evidence that deficits in normal functioning of the limbic-cortico-striato-pallido-thalamic circuits related to the medial and orbital PFC networks are among the main causes of depression. Consequently, abnormalities which interfere with the finely balanced interaction/communication within the neurocircuit, and in particular, a decrease in the inhibitory control of the limbic structures by the PFC, is associated with the characteristic emotional processing, cognitive performance, behavioral and other signs of depression as well as abnormalities in neurotransmitter activity, neuroendocrine function and pain modulation. Price and Drevets (2012) have proposed that impaired

function within the circuits involving the medial prefrontal network and related limbic structures can account for these disturbances in mood disorders.

The limbic-cortico-striato-pallido-thalamic circuit (Figure 3) is responsible for maintaining emotional stability and appropriate responses to emotional stimuli as well as regulating neurotransmission, autonomic and neuroendocrine function. This system also links with relevant structures in the midbrain/brain-stem (for example, the serotonergic raphe nuclei and the adrenergic locus coeruleus). In healthy humans, frontostriatal circuitry plays a crucial role in several different processes such as emotion, motivation and executive functions, including set-shifting, working memory and decision-making; this is probably because of its looped structure with cortical inputs to the striatum from where signals are projected back to the cortex via the thalamus (Alexander et al., 1986; Alexander & Crutcher, 1990). It has been hypothesized that in the depressed state the balance amongst the structures within the neurocircuit is disrupted as a result of decreased activity in the PFC which impairs its regulatory (inhibitory) action on the limbic structures which then become overactive. This dysregulation then leads to the manifestation of depressive symptoms (Palazidou, 2012).

One of the key questions in psychophysiology research concerns how individual differences in hemispheric asymmetry are manifested in motivation and personality. One dominant theory elaborated by Gray and colleagues, named the "reinforcement sensitivity theory" (Gray, 1982; Gray, 1987; Gray & McNaughton, 1996; Corr, 2004; McNaughton & Corr, 2004), suggests the operation of two general systems for coordinating adaptive behavior. The first system is referred to as the Behavioral Inhibition System (BIS). This system is sensitive to signals of conditioned punishment, non-reward, novelty, and innate fear stimuli. Its function is to increase attention toward aversive stimuli, to interrupt ongoing behavior and prepare for vigorous action or withdrawal, while processing potential threat cues. BIS is involved in the control of impulsive behavior. A second system has been referred to as the Behavioral Activation System (BAS) (Fowles, 1980; Fowles, 1988) or, alternatively, the Behavioral Approach System (Gray, 1982). The BAS is believed to mediate the experience of positive affect and behavioral disinhibition ('appetitive' behavior). Individual variation in the BAS predicts approach-related behavior and positive emotion in response to reward cues. Alpha band power is inversely related to activation (Lindsley & Wicke, 1974) and has been the measure most consistently used in studies of EEG asymmetry (Davidson, 1988) as a signature of BIS/BAS relative impact on the behavioral state and disposition. Davidson, and colleagues (1979) derived a measure of frontal alpha asymmetry to make inferences about emotional processes by subtracting alpha power of the left PFC from alpha power of the right PFC as a straightforward index. Positive emotional states have been found to be associated with a left > right activation asymmetry (Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001), whereas negative emotional states with a right > left activation asymmetry (Henriques and Davidson, 1990; Henriques & Davidson, 1991; Davidson & Henriques, 2000). Higher BIS scores have been associated with greater right PFC activity

(Shackman et al., 2009) whereas greater left PFC is associated with higher BAS scores (Harmon-Jones & Allen, 1997; Coan & Allen, 2003; Amodio et al., 2008; De Pascalis et al., 2013). In depressed individuals, BIS scores have been directly associated with depression severity (Wang et al., 2017). Higher BIS sensitivity may increase the avoidance goals and behaviors and amplify affective reactions to negative events (Gable et al., 2000) and is responsible for the excessive negative emotion observed in MDD. Consistently with this and with the theory, lower BAS functioning may be associated with approach deficits which limit the access to positive emotion and rewarding experiences (Trew, 2011) and in turn lead to sustained negative affect. According to a study by Wang et al. (2017), due to the evidence that prefrontally mediated cognitive control can either inhibit or augment reactions to achieve successful goal-directed behavior (Eippert et al., 2007), the altered prefrontal emotion regulatory network (DLPFC/VMPFC/VLPFC) in depressed patients demonstrated ineffective top-down modulation of emotion, as well as impaired modulatory role of approach/avoidance motivation in emotion regulation.

2.3. Structural and functional connectivity in depression as related to Parkinson's disease

Although the exact pathogenesis of behavioral and emotional disorders associated with PD remains to be clarified, several contributing mechanisms have been observed (Bologna et al., 2019). Several mechanisms have been proposed, including dopaminergic and nondopaminergic dysfunctions of several pathways at the subcortical and cortical levels, including in the limbic system (Diederich et al., 2016; Péron et al., 2012). In 1995, a unifying model of neurodegeneration in depression and PD was proposed (Mayberg & Solomon, 1995). This model suggests that primary degeneration of dopaminergic mesocortical and mesolimbic neurons leads to dysfunction of the orbitofrontal cortex, which secondarily affects serotonergic cell bodies in the dorsal raphe nuclei. Additional circuits that are proposed to be affected in patients with depression include the basotemporal limbic circuit, which links the orbitofrontal cortex to the anterior temporal cortex through the uncinate fasciculus, and the orbitofrontal cortex–basal ganglia–thalamic circuit. This model has received partial support from subsequent studies showing that patients with PD and depression had a profound loss of striatal dopamine transporter availability (Weintraub et al., 2005b) and frontal hypoperfusion compared with nondepressed PD patients (Matsui et al., 2006).

Because of the complex and important role of the basal ganglia in processing a wide range of motor and non-motor information (Grillner & Robertson, 2016; Stephenson-Jones et al., 2011), dysfunction in these structures is thought to play a key role in generating behavioral and emotional disorders in PD. It is believed that functional alterations in basal ganglia nuclei are relevant in the etiopathology of movement disorders such as PD. The main assemblages of serotonin-

synthesizing neurons are located in the brainstem raphe nuclei whose neurons receive efferents from the peripheral and the central nervous system, including the substantia nigra. Neurons from the dorsal raphe nuclei send descending and ascending projections to innervate almost all brain areas, including the basal ganglia. The basal ganglia form a complex, highly organized subcortical network that connects the thalamus with the cortex and plays an important role in the control of motor behavior, emotion and cognition. The main components of the basal ganglia are the striatum, consisting of both the dorsal (caudate nucleus and putamen) and the ventral part (nucleus accumbens and olfactory tubercle), the globus pallidus, the ventral pallidum, the substantia nigra, and the subthalamic nucleus (Fix, 2008). The substantia nigra consists of two parts: pars reticulata and pars compacta. The latter region provides dopaminergic input into the basal ganglia, and when it degenerates, it leads to neuronal dysfunction in these nuclei. In the classical basal ganglia model (Alexander et al., 1986), the loss of dopaminergic neurons in PD leads to disinhibition of the indirect pathway and a reduction in the inhibitory action of the direct pathway, resulting in elevated activity of the output nuclei (the substantia nigra, pars reticulata and the internal segment of the globus pallidus). The augmented activity of the basal ganglia output structures, which are inhibitory, reduces motor activity, resulting in PD motor symptomatology. By contrast, levodopa administered to treat PD symptoms causes the opposite effect of dopaminergic neuron loss, producing a decrease in the basal ganglia output nuclei activity (Aristieta et al., 2016; Obeso et al., 2008).

During the last decades, substantial knowledge concerning pathophysiology of depression in PD patients has been accumulated from structural and functional neuroimaging studies (Cardoso et al., 2009; Ring et al., 1994; Remy et al., 2005; Feldmann et al., 2008; Politis et al., 2010). High-resolution structural MRI studies have shown that PD patients with depression display abnormality in size of some areas, including the orbitofrontal gyrus, the superior temporal pole, and the mediodorsal thalamus, when compared with the patients with PD alone (Cardoso et al., 2009; Feldmann et al., 2008). In PD, the degeneration of dorsal raphe nuclei neurons occurs early. Functional neuroimaging techniques have also been used to study depression in PD patients (Cardoso et al., 2009; Ring et al., 1994). A PET study found decreased levels of regional cerebral blood flow (rCBF) in the medial prefrontal cortex and the cingulate cortex in depressed PD group, in contrast to the non-depressed PD group (Ring et al., 1994). Using fMRI, Cardoso and his colleagues observed decreased activity in the left mediodorsal thalamic nucleus and the left dorsomedial prefrontal cortex of depressed PD patients, but not of non-depressed PD patients (Cardoso et al., 2009). Depression in PD patients may thus be associated with abnormal alterations in the prefrontal-limbic network (Wen et al, 2013).

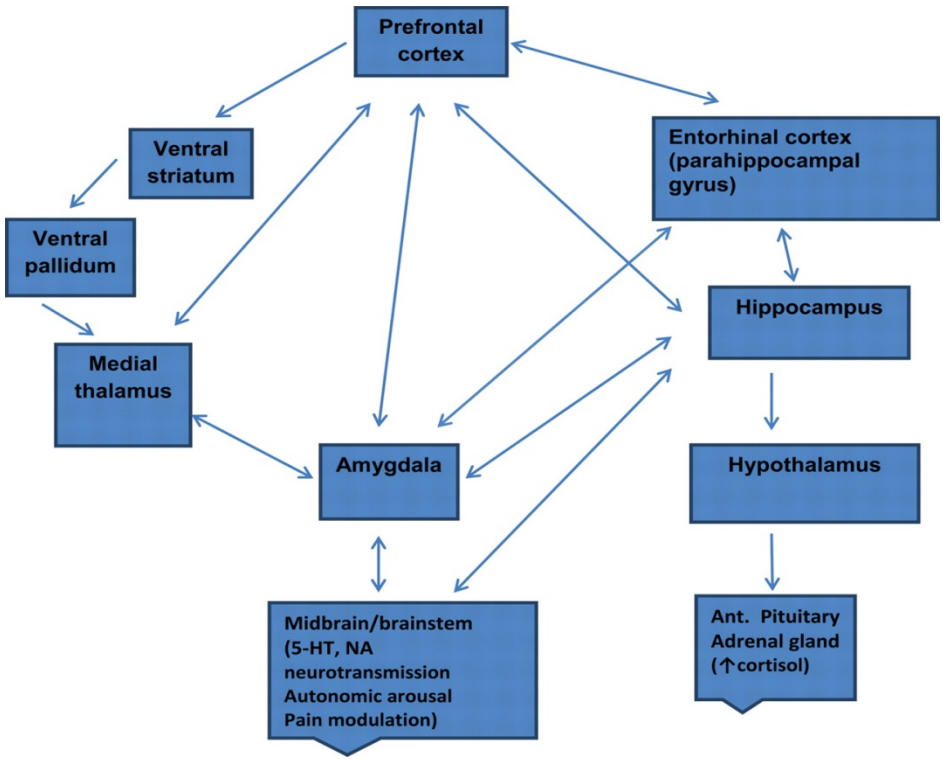

Figure 3. Schematic depiction of connections between the prefrontal cortex and limbic structures within the limbic-cortico-striato-pallido-thalamic circuits related to the medial and orbital prefrontal cortex networks implicated in depression. A decrease in the inhibitory control of the limbic structures by the PFC is associated with cognitive, behavioural and other signs of depression as well as abnormalities in neuroendocrine function, pain modulation and neurotransmitter activity (affecting the raphe, serotonergic nuclei and noradrenergic nucleus coeruleus), through its connections with the hypothalamus and the midbrain, in particular the periaqueductal area (adapted from Palazidou, 2012, with permission).

In a systematic review of neuroimaging studies investigating symptoms of apathy, depression, and anxiety in PD, frontostriatal circuits were identified as a shared pathway in the pathogenesis of all three of these affective disorders (Wen et al., 2016). PET studies have shown hypometabolism in the caudate and orbital-inferior frontal lobe, reduced cortical 5-HT1A receptor binding and a reduction in dopaminergic and noradrenergic binding in the limbic system in PD patients with depression, compared to non-depressed PD patients (Chen & Cheng, 2008). The organic hypothesis of depression associated with PD may be explained by dysfunction in the following brain regions, neural networks, and neurotransmitters: (1) subcortical nuclei and the frontal lobes; (2) cortical-striatal-thalamo-cortical and basal temporal limbic neural networks; and (3)

serotonergic, noradrenergic and dopaminergic neurotransmission mechanisms (Chen & Cheng, 2008). Previous research on the involvement of the serotonergic system, particularly as assessed by methods incorporating transcranial sonography, has revealed that raphe echogenicity is reduced in depressed versus non-depressed PD patients (Becker et al, 1997; Berg et al., 1999).

Postmortem studies (Kish, 2003) and in vivo neurochemical imaging investigations (Albin et al., 2008; Guttman et al., 2007; Kerenyi et al., 2003) have suggested that a brain serotonergic deficiency in PD could in part explain emotional and cognitive disturbances in PD patients (Boileau et al., 2008). Conversely, degenerative basal ganglia diseases and lesions of the striatum and orbitofrontal cortex increase the risk for developing major depressive episodes (Price & Drevets, 2010). Selective serotonin reuptake inhibitors, when chronically used to treat depression and anxiety, can induce motor side effects (tardive dyskinesia, parkinsonism, akathisia and dystonia) (Bilen et al., 2008; Leo, 1996). *In vivo* clinical studies have also revealed a relationship between non-motor symptoms and the dysfunction of the serotonergic system. In fact, PD patients receiving dopamine-rich grafts showed improvement in motor symptoms, but they still suffered from non-motor symptoms. In these patients, functional imaging showed that the dopaminergic neuron innervations were restored, but the serotonergic uptake binding was markedly reduced (Politis et al., 2012).

Concurrence of depression and cognitive dysfunction are well known in a wide range of clinical populations, including PD patients (Chaudhuri & Schapira, 2009; Marazziti et al., 2010). Neuroimaging studies provide further insight into the pathophysiology of this association in PD and indicate a crossroad, meaning a common pathway for depression and cognitive dysfunction. The mesocortical dopaminergic system facilitates working memory function via direct inputs to prefrontal cortex (Mattay et al., 2002). Neuropathologically, clinical changes in PD are mainly represented by dopaminergic neuronal loss occurring in the nigrostriatal tract and reduced dopamine projections to the striatum, which leads to inefficiencies in frontostriatal pathways (Jellinger, 2001). The cardinal feature of PD is represented by the deterioration of midbrain dopamine neurons, including dopamine projection to the ACC (Vogt, 2009; Thobois et al., 2010).

Taken together, PD-related depression may be related to dysfunction in the subcortical nuclei and the prefrontal cortex, the striatal-thalamic-prefrontal cortex circuitry and the basotemporal limbic circuit, as well as the brainstem monoamine and indolamine (i.e. dopamine, serotonin, and norepinephrine) systems (Murai et al., 2001; Mentis et al., 2002; Mayberg, 2003; Feldmann et al., 2008; Weintraub et al., 2005a; Weintraub et al., 2005b; Cardoso et al., 2009; Hesse et al., 2009; Felicio et al., 2010; Walter et al., 2010). Discrete components of frontostriatal pathways could generate individual differences in PD patients' neuropsychiatric manifestations. Expanding knowledge on the imaging biomarkers of depression related to PD represents both scientific and practical significance. The following part of this dissertation contributes to this aim.

2.4. STUDY I: Prevalence of depressive symptoms and their association with brainstem raphe echogenicity in patients with Parkinson's disease and non-PD controls

The aim of Study I was twofold: to describe the prevalence and severity of depressive symptoms in PD, as well as to analyze possible associations between brainstem raphe (BR) echogenicity and depressive symptoms in an Estonian sample of patients with PD (n=266) compared to age- and education-matched healthy (non-PD) controls (n=168). Transcranial sonography (TCS) is a method for distinguishing certain pathological processes in the brain. Low echogenicity of the mesencephalic midline, more precisely the brainstem raphe, is a common finding in 50–70% of patients with unipolar depression (Becker et al., 1994, Walter et al., 2007a), is associated with responsiveness to serotonin-reuptake inhibitors (Walter et al., 2007b), and thought to reflect an alteration of the serotonergic system. The first objective of the study was to confirm and elaborate on previous evidence whereby decreased echogenicity of the mesencephalic raphe had been demonstrated in 40–60% of patients with PD and depression (Becker et al., 1997, Walter et al., 2007a, Berg et al., 1999). Depression may in fact occur before the onset of motor symptoms, suggesting that in its early stages, the neuropathological process of PD itself increases the risk of depression (Schuurman et al., 2002; Leentjens et al., 2003, Reijnders et al., 2008).

The results of Study I implicated that severely depressed patients (with or without PD) showed significant BR hypoechogenicity. In the PD group, 38.7% had mild and 35.7% had severe depressive symptoms, while in the control group, 26.8% had mild and 28.6% had severe depressive symptoms. The percentage of controls with depressive symptoms exceeding normal limits was significantly lower than in the PD group ($p < 0.001$). Higher depressive symptom severity was associated with longer PD disease duration, more severe motor and cognitive impairment, and indicative of advanced disease stages.

As for the study's second objective to find possible associations between brainstem raphe echogenicity and the severity of depressive symptoms, it was found that BR echogenicity in both PD patients and non-PD controls was directly related to their total Beck Depression Inventory (BDI) score, although a significantly greater reduction of BR echogenicity in patients with PD and depressive symptoms was found compared to depressed non-PD controls. In the PD group, the direct relationship of depressive symptom severity and hypoechogenic BR remained significant even after accounting for age, disease duration, and Hoehn & Yahr stage – the level of affective disturbance directly reflected the anatomical changes in BR. Interestingly, 58.7% of controls with a normal BDI score showed partially reduced visibility of the BR. This number grew to 64.4% in a sub-sample of the control group with mild depressive symptoms. In the PD group, the respective percentages were 23.5 and 53.4. It was also noted that patients who were using antidepressants had significantly higher BDI scores than those who were not.

Study I, confirming that the prevalence of depressive symptoms in the patient sample was found to be significantly higher than in controls, demonstrated that depressive symptom severity is associated with the clinical aspects of PD. The findings were in concordance with previous reports whereby BR echogenicity was seen to be altered in individuals with depression (Becker et al., 1994, Walter et al., 2007b). The study underlined the growing importance and utility of brain-based biomarkers of depression in PD. Depression in PD patients is associated with abnormal alterations in the prefrontal-limbic network (Wen et al, 2013). Tying in to the notions that neuroanatomical alterations of the BR are involved in the pathogenesis of depressive disorders and a substantial number of depressed PD patients fail to respond to conventional antidepressive treatment, it was concluded that new – or additional – treatment methods to account for treatment-resistant depression in patients with a pronounced mono-aminergic deficit should be pursued.

3. NON-INVASIVE BRAIN STIMULATION AND DEPRESSION RELATED TO PARKINSON'S DISEASE

3.1. Non-invasive brain stimulation: a brief overview of known mechanisms

NIBS techniques include, among others, rTMS and tDCS. The rTMS method involves the application of a rapidly changing magnetic field in order to induce currents and action potentials in the underlying brain tissue. The tDCS involves the application of weak (1–2 mA) electrical currents to modulate neuronal membrane potential. This thesis will focus on the therapeutic applications of rTMS.

Despite the wide use and clinical potential, the neurobiological mechanisms of action of NIBS methods at the whole-brain level are still relatively poorly known. Most of what we know about these mechanisms is derived from neurophysiological studies focusing on the motor system. (Walsh & Cowey, 2000; Hallett, 2007). The combination of NIBS with neuroimaging is a powerful tool to investigate the effects of stimulation (Ko et al., 2013). Transcranial magnetic stimulation (TMS) is an established neurophysiological tool to examine the integrity of the fast-conducting corticomotor pathways in a wide range of diseases associated with motor dysfunction (Groppa et al., 2012). Single-pulse TMS is easy to employ because it is noninvasive, non- painful and safe. It can probe the function of many different parts of the cerebral cortex, excite, inhibit and assess aspects of excitability (Hallett, 2000). Growth in the research and diagnostic application of TMS prompted the rise of experimental protocols (including rTMS) that were designed to alleviate various clinical symptoms (George et al., 1999; Kobayashi & Pascual-Leone, 2003; Rossini & Rossi, 2007; Richards et al., 2008; Bhandari et al., 2016). rTMS can be used to excite (high-frequency rTMS) or inhibit (low-frequency rTMS) the underlying cortical tissue. The effects of rTMS propagate from the directly targeted cortical region to the connected nodes along neural networks (Eldaief et al., 2013; Shafi et al., 2012). The distributed effects are considered crucial for the clinical efficacy of rTMS (Fox et al., 2014). Studies have demonstrated the propagation of the stimulation effects to connected brain regions (Bergmann et al., 2016; Hallett et al., 2017).

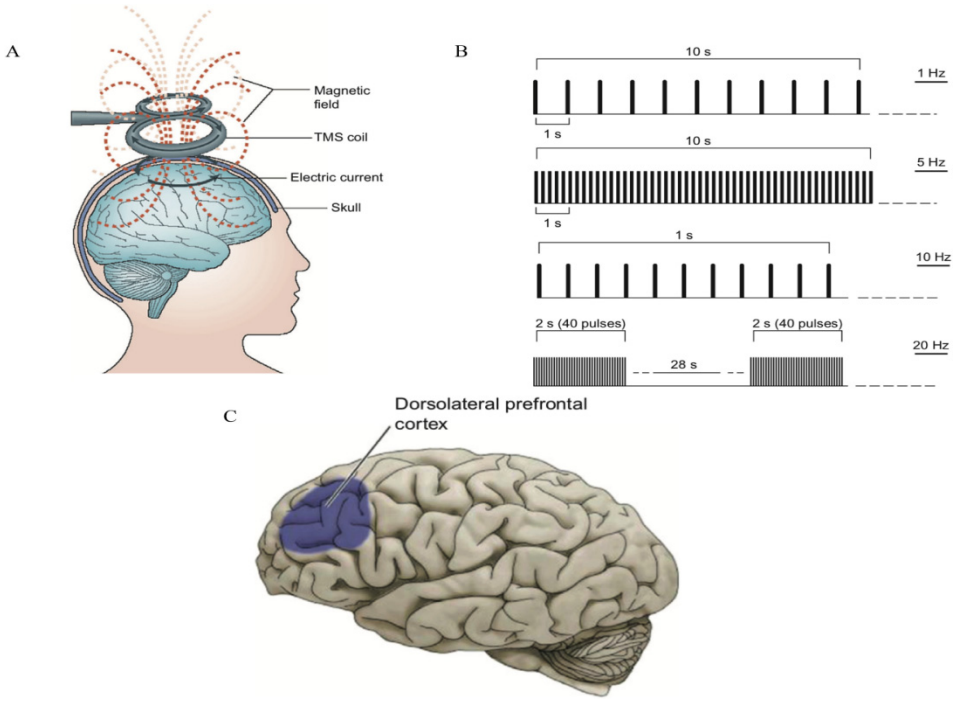

Figure 4. (A) Visual illustration of the induction of electrical currents in the brain through the magnetic pulses (dashed lines) applied by means of the coil; (B) Examples of 10 s of rTMS at 1 Hz (first trace) and at 5 Hz (second trace); 1 s of rTMS at 10 Hz and an example of 20 Hz application (trains of 2 s interleaved by a pause of 28 s); (C) Image of the location of the (left) dorsolateral prefrontal cortex in the brain (Adapted from Spronk, Arns, and Fitzgerald, 2011, with permission).

rTMS has been shown to modulate several neurotransmitter systems, increase neurotrophic factors, and induce changes on neuronal synapses via long-term potentiation (LTP) and long-term depression (LTD)-like mechanisms (Rektorová & Anderková, 2017; Rektorová & Biundo, 2019).

The physiological aftereffects of NIBS depend, among other factors, on the stimulation protocols and on the precise coil type and placement, as well as on the current "state" of the brain, with a varying effect across subjects (Anderkova et al., 2015; Bergmann et al., 2016, Hallett et al., 2017). The behavioral aftereffects of rTMS may outlast the duration of multiple sessions of stimulation by weeks or months and thus may have therapeutic potential (Biundo et al., 2017). In general, rTMS may modulate the abnormal brain reorganization caused by distinct brain pathology and/or interact with the normal processes of brain plasticity such that it enhances compensatory mechanisms and leads to an increased brain reserve, thus potentiating brain resilience (Priori et al., 2009). Classic studies have shown that high-frequency rTMS (usually 5 Hz or higher) increases (Pascual-Leone et al., 1994) whereas low-frequency (1 Hz or lower)

rTMS (Chen et al., 1997) decreases corticospinal excitability. These findings led to a large number of studies that explored the use of rTMS as a form of therapeutic non-invasive neuromodulation in neurological and psychiatric disorders. In these studies and interventions, some areas of the brain have turned out to be most promising targets for rTMS application. The DLPFC is regarded as most accessible for treatment with rTMS (Wassermann & Lisanby, 2001). In the following section, one of these areas − the DLPFC − will be focused upon, as it is one of the main brain areas of interest of this dissertation.

3.2. The dorsolateral prefrontal cortex as a stimulation target

The DLPFC is a key hub in the prefrontal-limbic network which connects to the orbitofrontal cortex, the thalamus, parts of the basal ganglia, the hippocampus, and primary and secondary association areas of the neocortex (Philip & Ulrich, 2002). It has an important role in cognitive, executive and emotional processes, especially the downregulation of negative emotional conditions (Barbas, 2000; Davidson et al., 2002a; Pena-Gomez et al., 2011). Abnormal activity in the DLPFC may lead to a cognitive and mental disorder, and partly contribute to interest or pleasure deficiency and cognitive decline exhibited by patients with depression (Bench et al., 1992; Dragaševic et al., 2002). The "frontal asymmetry hypothesis" of depression states that, in depression, there is an imbalance in left vs. right frontal brain activation (Henriques & Davidson, 1990). Early studies in the 1980s and early 1990s found a correlation between depression and hypoactivity in the left DLPFC, eventually leading to the selection of this region as a target for rTMS (George et al., 1994; Geroge et al., 1995). The converging evidence from lesion studies, stimulation studies, and connectivity studies backs correlative neuroimaging research in identifying the most central nodes of the brain's emotion-regulating networks (Downar & Daskalakis, 2013). The DLPFC, the VMPFC and the rostral ACC are parts of the prefrontal-limbic network which has been identified as being important for affective processing (Cardinal et al., 2002). Bennett (2011) identified that abnormal changes in the prefrontal-limbic network exist in patients with major depressive disorder. In addition, of the main brain regions known to be related to the pathophysiology of depression (e.g., prefrontal, cingulate, parietal, and temporal cortical regions, as well as parts of the striatum, thalamus, and hypothalamus), the DLPFC is regarded as one of the most accessible for treatment with rTMS (Wassermann & Lisanby, 2001). Similarly, DLPFC-targeted rTMS is one of the modes relatively more comfortable for the patient. The hypoactivity in the DLPFC in depression has been identified by a multitude of studies and regarded as a critical hallmark for depression, including PD-related depression (Bench et al., 1992; Ring et al., 1994; Dragaševic et al., 2002; Mottaghy et al., 2002; Fregni et al., 2006; Cardoso et al., 2008; Koenigs & Grafman, 2009). Similar results have been also found in depressed PD patients; a PET study reported a

decreased rCBF level in the DLPFC of depressed PD patients compared with non-depressed PD patients (Ring et al., 1994), and stimulating the DLPFC with rTMS can be effective in treating depression symptoms in PD (Dragaševic et al., 2002; Fregni et al., 2006). Together with these findings, it can be surmised that hypoactivation of the DLPFC may be an important factor for the genesis and development of depression in PD patients. A crucial variable to consider herein is laterality; in a study by Knoch et al. (2006) investigating the differences between left/right DLPFC and low-/high-frequency rTMS, the authors demonstrated a clear effect of laterality – the left versus right dorsolateral PFC activated different networks, in support of prefrontal hemispheric asymmetry. The referred findings corroborate and complement the studies using different neuroimaging modalities, such as fMRI and EEG, demonstrating the propagation of the stimulation effects to connected brain regions (Bergmann et al., 2016; Hallett et al., 2017).

3.3. Non-invasive brain stimulation and clinical depression

In recent decades, there has been increasing interest in treatment-resistant depression (TRD) (Berlim & Turecki, 2007b; Ruhe et al., 2012; Sackeim et al., 2019). Earlier estimates suggested that two-thirds of patients in a major depressive episode have substantial improvement following their first antidepressant medication trial (Klein et al., 1980; Souery et al., 1999). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al., 2004) challenged this perspective; in a large sample without a history of adequate antidepressant treatment failure in the current episode, approximately 30% remitted following treatment with citalopram. Non-remitters received up to three additional trials of antidepressant treatment (Rush et al., 2006). The likelihood of acute benefit decreased with each subsequent trial, and, if remission was obtained, the likelihood of relapse increased. For example, in STAR*D the probability of both remitting and sustaining that remission for a year was less than 5% in patients receiving their third antidepressant treatment (Conway et al., 2017). This prospective study and similar data (Fife et al., 2017; Mahlich et al., 2018; Rizvi et al., 2014; Saveanu et al., 2015; Thomas et al., 2013) have led to the estimate that approximately one-third of patients in a major depressive episode are characterized by TRD (Berlim & Turecki, 2007b; Cepeda et al., 2018; Fava, 2003; Thase, 2011). TRD is associated with increased morbidity and mortality (Banankhah et al., 2015; Reutfors et al., 2018; Souery et al., 2007), increased medical and psychiatric health care costs (Amos et al., 2018; Kubitz et al., 2013; Lepine et al., 2012; Mahlich et al., 2018; Olfson et al., 2018; Russell et al., 2004), and markedly reduced quality of life (Johnston et al., 2018; Mrazek et al., 2014).

It has been 25 years since the first trials of rTMS for TRD showed marked improvement with high-frequency stimulation of the left DLPFC (George et al., 1995; Pascual-Leone et al., 1996). Since then, dozens of trials have demons-

trated a statistically significant improvement in depressive symptoms with active over sham rTMS. Newer studies identified significant limitations in the earlier trials and sought to address them (Daskalakis et al., 2008). This new generation of studies has steadily improved rTMS outcomes via stronger or accelerated dosing regimens, longer treatment courses, bilateral stimulation protocols, individually tailored stimulation frequencies, new coil geometries, more precise neuronavigation technologies, and more accurate TMS navigation methods than the traditional "5 cm rule" for locating the DLPFC (Downar & Daskalakis, 2013). With such improvements, many studies have consistently achieved rTMS remission and response rates of around 30–35% and 40–55%, respectively (Levkovitz et al., 2009; Holtzheimer et al., 2010; Li et al., 2010; Fitzgerald et al., 2011; McDonald et al., 2011; Blumberger et al., 2012). Several of these trials enrolled up to 200 patients, while making use of improved techniques such as bilateral stimulation or MRI-based neuronavigation. Although the use of sham controls in large trials is no longer universal given the well-established superiority of active over sham rTMS, the reported outcomes in these trials are more than 5-fold better than the ∼5% remission/∼10% response rates consistently seen for sham stimulation in this refractory population (Lam et al., 2008). This near-doubling of rTMS efficacy represents a significant advance towards the viability of rTMS as a first-line treatment for refractory depression. In this population, rTMS remission rates now match or exceed the 23–33% remission rates seen for an open-label second medication trial or cognitive therapy in patients failing a first medication trial in the STAR*D study (Thase et al., 2007), or the 35% response and 22% remission rates seen for patients switching to psychotherapy after failing an antidepressant medication (Schatzberg et al., 2005). In 2014, HF-rTMS of the left DLPFC to treat depression received a recommendation corresponding to a Level A of evidence in the guidelines published by Lefaucheur et al (2014), further validated by updated guidelines in 2020 (Lefaucheur et al., 2020). Although rTMS therapy is nowadays applied worldwide in depressed patients, there is still a large heterogeneity in the published data concerning the populations included and the stimulation settings (Lefaucheur et al., 2020). The present recommendations are in favor of a definite antidepressant efficacy of HF-rTMS of the left DLPFC (using either a focal figure-of-8 coil or a deep H1-coil) and a probable antidepressant efficacy of LF-rTMS of the right DLPFC. They mostly apply to patients in an acute phase of a drug resistant MDD episode in the context of unipolar depression. Efficacy does not seem to differ significantly whether patients are concomitantly treated by antidepressant medication.

3.4. Non-invasive brain stimulation and Parkinson's disease

Available systematic reviews and meta-analyses have focused on rTMS' applicability in alleviating the motor symptoms of various movement disorders, including PD, and this has also been the main guiding principle upon selection of the stimulation target (mostly being M1 or SMA) (Arias-Carrión, 2008; Chou et al., 2015; Chung & Mak, 2016; Edwards et al., 2008; Fregni, 2005; Lefaucheur, 2006; Lefaucheur, 2009; Wagle-Shukla et al., 2016; Zhu et al., 2015). rTMS has been shown to positively influence the motor aspects of PD, lessening tremor and dyskinesias to some extent (Mally & Stone, 1999). A systematic review and meta-analysis by Wagle Shukla and colleagues (2016) indicated that rTMS therapy in patients with PD results in mild to moderate motor improvements and has the potential to be used as an adjunct therapy for the treatment of motor dysfunction in PD. Recently published guidelines have given a recommendation of possible efficacy for the effect of high-frequency rTMS (5–25 Hz) of bilateral (multiple) M1 areas on motor symptoms of PD (Lefaucheur et al, 2020). A detailed analysis of rTMS as a therapeutic method in alleviating motor symptoms of PD is outside the scope of this dissertation and the reader is referred to the references indicated above.

A recent review on the therapeutic use of rTMS have indicated probable antidepressant efficacy of HF-rTMS of the left DLPFC in PD patients (Level B) (Lefaucheur et al., 2020). As for the treatment of cognitive impairment in PD, there is no universal agreement on efficacy, on which stimulation protocols should be utilized, and for how long they should be applied. Only a few studies are available with preliminary results, and most concern depressed PD subjects (Rektorová & Anderková, 2017). Helmich and colleagues (2006) found that rTMS of the frontal cortex in order to regulate the dopamine system caused an increase in dopamine release in the basal ganglia which in turn improved the executive function of PD patients. Executive function, as a process of higher cognitive function, is usually closely related to the cooperation of multiple brain regions. It is feasible that stimulation of the DLPFC not only impacts cortical excitability directly within the stimulation area but also in the whole circuitry connected to it. A series of studies using PET have shown that short trains of 10 Hz of rTMS can stimulate subcortical dopamine release in the striatum (specifically, the caudate nucleus and putamen) in both healthy subjects and PD patients (Fuggetta et al., 2020), providing further evidence that the associative basal ganglia-thalamo-cortical loop is interconnected with the stimulated area (Strafella et al., 2001; Siebner & Rothwell, 2003).

As explained earlier in this dissertation, depression and cognitive dysfunction, specifically in the executive domain, might partially arise via dysfunctions of the same dopaminergic frontostriatal network. Depressive symptoms such as psychomotor slowing, concentration difficulties, and negative rumination may be explained by disruptions and malfunctioning of these projections. The deficits in executive functions reflect the damage to the frontal lobes of the brain,

particularly the DLPFC, which ultimately leads to the degradation of the nigrostriatal dopamine pathway and the midbrain pathway (Dalrymple-Alford et al., 2011). Due to the similar localization of cognitive and affective neural pathways within or connected to the frontal cortex, rTMS of the DLPFC represents a valid opportunity to address multiple PD-related neuropsychiatric issues simultaneously. An optimal set of clinical guidelines to address both the emotional and cognitive problems in patients with PD and depression using rTMS with maximal efficiency and safety has yet to be agreed upon. For this purpose, and in addition to experimental studies, systematic analysis of what has been empirically found so far is recommendable.

3.5. STUDY II: Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex to alleviate depression and cognitive impairment associated with Parkinson's disease: a review and clinical implications

While high-frequency rTMS to the left DLPFC is an approved treatment for medication-resistant depression in many countries, it is not approved for the treatment of other conditions. In many disorders such as PD, there are multiple small and medium sized studies but there are no large randomized controlled trials that are required for regulatory approval. Studies in the format of systematic reviews are particularly useful to assess the available evidence in these conditions.

The hypoactivity of the left DLPFC has been a critical hallmark in previous models of the pathophysiology of depression. Brain imaging studies in depressed patients have consistently found abnormalities in the prefrontal cortex, cingulate gyrus, orbitofrontal cortex, or deeper limbic regions like the amygdala, insula and hippocampus which are often reversible after clinical recovery (Fitzgerald et al., 2006a; Steele et al., 2007). Evidence in line with the "frontal asymmetry hypothesis" of depression has been demonstrated in rTMS studies incorporating functional brain imaging on PD patients with comorbid depression (Fregni et al., 2006; Cardoso et al., 2008). rTMS of the DLPFC has been shown to exert antidepressant-like effects superior to placebo and equivalent to standard psychopharmacological treatment.

The study's objective was to pool available scientific literature on the therapeutic usage of rTMS on non-motor symptoms of Parkinson's disease associated with the DLPFC (i.e. depression and cognitive impairment). The goal of the literature review was to obtain confirmation whether rTMS is an effective treatment method for emotional and cognitive problems associated with PD. 127 initial records were retrieved. After the identification of relevant articles, screening and eligibility analysis, 23 articles fit the inclusion criteria. 10 RCTs and 3 open-label studies centered on depression, whereas 6 RCTs and 4 open-label studies on cognition. Four of these included both mood and cognition pre-

and post-stimulation measures as outcomes. Nearly all studies included in the review that applied high-frequency rTMS over prefrontal brain regions found beneficial effects on mood, thereby alleviating depression associated with PD, insofar as evidence-based clinical recommendations, protocols and safety measures were applied.

To summarize the results of the review of studies that included mood/depression data from 314 subjects: presented here as a ready-to-use set of evidence-based clinical guidelines, rTMS using a f8-coil positioned on the left DLPFC, preferably with a stimulation frequency ranging between 1 and 15 Hz (i.e. high-frequency), with a treatment period of at least 2–4 weeks, will give a rapid therapeutic response comparable to an effective regimen of antidepressants in a majority of patients with depression related to PD. In regard to PD-related cognitive impairment, the results from rTMS studies were mixed, hindered by a modest number of high-quality RCTs.

4. PERSONALIZING TREATMENT WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

4.1. Known factors affecting treatment course

Previous studies have identified multiple factors, including female sex, older age, single status, education level, physical disease, family history of depression, cognitive disorders, smoking status, alcohol use, early childhood adversity, certain personality traits, and recent positive and negative life events, that can affect the progression of depression in PD patients (Global Parkinson's Disease Survey Steering Committee, 2002; Schrag, 2006; Reijnders et al., 2008; Leentjens et al., 2013). A study by Wichowicz and colleagues (2006) examined various clinical characteristics in association with depression in PD, and suggested that the severity of PD is related to depression. Longer duration of illness, a younger age of PD onset, frequent falls, a history of anxiety and memory problems are also associated with an increased rate of depression (Dissanayaka et al., 2011). The contribution of mood to patient´s QoL in PD is a consistent finding in the literature, even in studies using different methodologies (Karlsen et al., 1999; Schrag et al., 2001; Schrag, 2006; Santos-Garcia & de la Fuente-Fernández, 2013; Kadastik-Eerme et al., 2015). The magnitude of the effect of mood on QoL is greater for patients with longer disease duration (Santos-Garcia et al., 2020). Elderly subjects with late-onset depression show a higher prevalence of neuroimaging correlates of cerebrovascular disease relative both to age-matched healthy controls and to elderly patients with an early age at depression-onset (Drevets et al., 2008). The presence of pain has been found to be significantly associated with depression scores, even after adjusting for demographic and clinical variables (Ehrt et al., 2009). A recent study by Chang et al. (2020) found that depression in PD is strongly associated with anxiety and sleep disturbances, while the association with physical comorbidities was not significant.

The behavioral effects of rTMS have been found to depend on the frequency, intensity, and duration of stimulation (Padberg et al., 2002; Avery et al., 2006; Fitzgerald et al., 2006b; Fitzgerald et al., 2006c; O'Reardon et al., 2007). The most important parameters that rTMS protocols in depression can be distinguished on are the stimulation frequency and the stimulation location. The stimulation frequency refers to the number of pulses delivered per second, as can be programmed on the TMS device. High-frequency (HF-)rTMS usually includes frequency parameters of 5 Hz or above, whilst low frequency (LF-)rTMS incorporates stimulation frequencies of 1 Hz or below. In addition to studies applying solely HF-rTMS or LF-rTMS, combined approaches have been proposed. The excitatory HF-rTMS protocols are applied over the left DLPFC and inhibitory LF-rTMS protocols are applied over the right DLPFC. The choice of the stimulation frequency has been thus closely linked to the stimulation location (Spronk, Arns, & Fitzgerald, 2011). Consequently, when attempting to

treat PD-related depression by NIBS methods, right DLPFC excitability is advised to be suppressed and left DLPFC to be facilitated.

While rTMS treatment has been used with growing frequency over recent decades, its mechanisms and effects are still far from being transparent and unanimously recognized. Consequently, there are gaps in our knowledge and in the practices used. Multiple prior treatment failures are associated with reduced rates of response to subsequent depression treatment, including with rTMS; comparison of remission rates based on prior pharmacotherapy using data from the THREE-D trial (Blumberger et al., 2018) showed that three or more treatment failures may be associated with lower remission rates with rTMS (Hsu et al., 2019). Studies investigating rTMS effects on TRD associated with PD are scarce. A meta-analysis by Lesenskyj and colleagues (2018) qualitatively and quantitatively evaluated the use of rTMS for the treatment of refractory depression in patients with PD. Six of the 7 studies meeting inclusion criteria of the study reported significantly improved depression scores, large effect sizes, and significant p-values. When all study groups that applied rTMS to the DLPFC were considered together and weighted based on sample size, the effect size (1.37) suggested a notable reduction in depression following rTMS. However, the authors acknowledge that the findings reported in their meta-analysis could be a result of placebo and suggest rigorous control for possible placebo effects in planning future studies.

Taken together, an increasing amount of evidence is showing the therapeutic effects of rTMS on PD-related non-motor functions neuroanatomically linked to the DLPFC. However, the results vary, which presents a need for the refinement of possible stimulation parameters applicable to clinically heterogeneous patient sub-populations such as those with treatment-resistant depression and other neuropsychiatric comorbidities of the PD-related neurodegenerative process.

4.2. STUDY III: High-frequency repetitive transcranial magnetic stimulation to the left dorsolateral prefrontal cortex of patients with Parkinson's disease and treatment-resistant depression: a pilot study

It has been shown that 50–60% of PD patients do not achieve an adequate therapeutic response following a standard course of antidepressants (Fava, 2003). Even with a combination of psychotherapy, more than 30% of depressed patients are resistant to antidepressant treatment (Fekadu et al., 2009; Rush, 2007; Weintraub et al., 2005a). Advanced stage multimorbid PD patients with polypharmacy represent a relevant challenge for therapeutic safety (Chen & Cheng, 2008). As indicated earlier in the dissertation, rTMS has been shown to be an effective treatment option for major depressive disorder. There is less evidence on mood benefits associated with targeted rTMS use in patients with depression associated with PD, including those who are resistant to antidepressant treatment. Some studies have confirmed that high-frequency rTMS

(5–20 Hz) delivered to the left DLPFC for 2–4 weeks is able to produce potent antidepressant, anxiolytic and cognitive effects in PD patients while being functionally equivalent to pharmacological treatment with fluoxetine (Boggio et al., 2005; Fregni, 2004; Fregni et al., 2006). Other studies have indicated a moderately positive change after rTMS in the context of both treatment-naive depression and TRD associated with PD (Cardoso et al., 2008; Epstein et al., 2007; Pal et al., 2010). In a few instances, alleviation of cognitive dysfunction in addition to the mood disorder has also been observed when rTMS is applied to the left DLPFC (Lefaucheur, 2009). No specific guidelines were found for using rTMS to treat treatment-resistant depression in PD patients. Studies are still needed to clarify the effects of rTMS on rates of TRD in the context of PD.

The main objective of this prospective pilot study was to establish a preliminary effective, safe and tolerable rTMS protocol for PD patients with TRD, i.e., those who do not neatly fit within the available stimulation guidelines (Lefaucheur et al., 2014; Lefaucheur et al., 2020; Rossi et al., 2009; Rossini et al., 2015). Six PD patients [3m/3f, mean age of 61.3 yrs (SD = 11.89, range 42–76), mean education level of 13.2 yrs (SD = 2.86), and a mean PD duration of 5.2 yrs (SD = 1.72, range 3–7)] with TRD were treated with a regimen of high-frequency (10 Hz) rTMS targeted at the left DLPFC. The treatment was carried out in the amount of 500 impulses per stimulation session, two sessions per week for a period of six consecutive weeks, amounting to a total of 6000 impulses in 12 sessions. The individual effects of rTMS on motor function, mood and cognition were studied simultaneously in patients with both PD and TRD, also taking note of the possible functional impact on the level of everyday independence and quality of life. It is well known that the variability in coil placement can have a large impact on the biological effects, for example as demonstrated by stimulation site connectivity and clinical efficacy of rTMS in major depression by Fox and colleagues (2012). From an anatomical point of view, the most accurate method for targeting the DLPFC should be to use individual MRI data and a neuronavigation system, as suggested by several neuroimaging studies (Fox et al. 2012; Luber et al., 2017; Dubin et al., 2017). Consequently, in this study, a navigated rTMS system was chosen to be used in order to achieve maximal neuroanatomical precision. The subjects were carefully monitored for any possible change in various physical and psychological domains – both at fixed intervals of assessment and during individual stimulation sessions. Due to the clinically complex characteristics of the subject sample and lack of specific stimulation guidelines, the authors focused on individual scores and case reports rather than relying on group comparisons.

In the present study, there was a downward trend observed for individual BDI scores in all subjects apart from one individual. A non-deleterious effect of rTMS on most individual cognitive tasks and a short-term beneficial effect on self-reported cognitive functioning was found, although the latter had returned to baseline at the last assessment phase. The effects of rTMS were particularly evident in specific cases, which again stresses the interindividual variability in both clinical status and characteristics of treatment resistance. Diligent assess-

ment of key individual characteristics of the participants for prescribing specific rTMS protocols and delineating phenotype-dependent limitations of the practical usage of rTMS are important aspects of subsequent research. The impact of brain stimulation was directly related to the person's level of everyday independence and quality of life insofar as a distinctly alleviating effect on individual measures was observed. It is clear that some subjects possibly gained more, whereas in others, the intervention had little or no benefit. The few subjects with a clearly observed treatment response had high levels of anxiety, so the alleviation in mood problems may directly reflect the possible anxiolytic properties of rTMS treatment. Depressive symptoms may be part of an underlying anxiety disorder which would therefore be a direct representation of depression in PD being qualitatively different from "pure" major depressive disorder (Akhmadeeva et al., 2018).

Considering the modest number of subjects and many possible combinations of independent variables within repeated assessments, the dependent variables did not show a clear pattern of change, although possible trends emerged (e.g., in affective measures, as described above). While highlighting the large variability, the results of this prospective pilot study provided the basis for developing an extended treatment protocol, pending validation with a larger sample. The extent of possible beneficial effects as well as further exploration of risks and unforeseeable adverse effects in working with this highly specific and vulnerable segment of PD patients can thus become evident early on.

4.3. Future perspectives

There are a multitude of concepts, factors, and methods to consider in treating neuropsychiatric problems associated with PD that the research activities done within the scope of this thesis have implicated. A very recent critical review by Dhingra and colleagues (2021) outlined the clinical manifestation and treatment possibilities of neuropsychiatric symptoms including anxiety, depression, psychosis, impulse control problems, disordered sleep, and cognitive dysfunction, emphasizing their unique presentation in patients with PD. While only a part of them fit within the boundaries of this dissertation, they warrant consideration in further clinical studies looking to treat neuropsychiatric problems in PD. A brief and selective overview is presented below.

Anxiety

Compared to depression, anxiety in PD has received far less attention, which is somewhat surprising given that anxiety can be both mentally and physically disabling at times, particularly when frequent anxiety or panic attacks occur (Chang et al, 2020). Anxiety is indeed a common non-motor symptom in PD, with a prevalence of 25% to 49% (Pontone et al., 2009; Dissanayaka et al., 2010). The increase in the level of anxiety and the number of discrete anxiety attacks have been associated with non-motor fluctuations, particularly occurring

with the onset of "off" periods or at certain times of day (e.g., late afternoon or early evening) (Pontone et al., 2009; Dissanayaka et al., 2010). Similar to depression, an increased frequency of anxiety disorders can be observed up to 20 years prior to PD onset (Gonera et al., 1997; Shiba et al., 2000), but other than this finding − suggesting a contributing role for disease-related effects on brain monoaminergic nuclei in prodromal PD − not much is known about the etiology of anxiety in PD. It is known that 14% to 40% of PD patients are diagnosed with anxiety comorbid with depression (Schrag, 2004; Dissanayaka et al., 2010). Both anxiety and depression have been observed to induce similar changes in norepinephrine and serotonin systems; anxiety disorders may occur earlier than depression, and even before motor symptoms appear in PD. This progression may explain the occurrence of depression and anxiety in PD during the premotor phase (Weintraub et al., 2020). Given possible adverse effects associated with benzodiazepine use in PD, it is pertinent to consider non-pharmacological treatment approaches such as NIBS and CBT. At the same time, it is also important to consider other PD-related NPS such as psychosis, impulse control disorders and apathy. As acute anxiety episodes include difficulties of state control, NIBS protocols known to affect prefrontal control centers (e.g., right DLPFC) might also be viable direction of future research.

Young-onset PD

Study III of this dissertation included patients aged under 50 years. Young Onset Parkinson's disease (YOPD) occurs in people younger than 50 years of age. Most people with idiopathic, or typical, PD develop symptoms at 50 years of age or older (i.e. Late Onset Parkinson's disease, LOPD). Young adults are more likely to be employed and have younger children and, therefore, the impact on overall productivity and prognosis is greater for YOPD than LOPD (Calne & Kumar, 2008). Because YOPD patients also have longer disease duration by the time they reach the age of the LOPD patients (Schrag et al., 1998), they may suffer from more physical, economic, and psychological consequences. Non-motor features of PD seem to have a particularly distressing impact on HR-QoL of patients with YOPD (Mehanna & Jankovic, 2009). Impulse control disorders, such as gambling, compulsive shopping, and sexual addiction were reported with a nearly threefold increase in those taking dopamine agonists (often a preferred class of anti-PD drugs in YOPD) and a 50% increase associated with levodopa treatment (Voon et al., 2006). Dopamine dysregulation syndrome has been also associated with YOPD, especially in males (Barbosa et al., 2018). Although YOPD patients have a lower risk for dementia (Chaudhary et al., 2018), several studies have found that YOPD patients had a higher rate of depression and restless legs syndrome as well as sexual dysfunction than their older counterparts; for a review of these studies, please refer to the review by Mehanna and Jankovic (2019). Because of the above-mentioned undesirable side effects of dopaminergic treatment, NIBS may be preferred in cases where it holds the greatest potential of sufficient efficacy.

New developments in using rTMS

There has been an increasing interest in exploring the use of rTMS treatment protocols (including their accelerated versions) in recent years, as well as an increase in studies exploring the therapeutic benefits of theta-burst stimulation (TBS); a recently published direct parallel groups comparison by Fitzgerald and colleagues (2020) showed that an intermittent TBS (iTBS) protocol may be used to achieve similar therapeutic benefits as those obtained with a standard daily rTMS treatment schedule. In the study, iTBS produced similar clinical benefits to standard rTMS in terms of depression ratings, quality of life, and assessments of suicidality without the occurrence of any serious adverse events. An increased rate of treatment-emergent side effects or observable cognitive impairment was not observed. The THREE-D study demonstrated that iTBS is a non-inferior treatment compared to 10 Hz rTMS in patients with TRD (Blumberger et al., 2018). Based on an another study's (Trung et al., 2019) results, there is indication of a potential therapeutic effect of multiple-session iTBS on PD-MCI that is likely mediated by improved visuospatial functions.

NIBS approaches mostly target superficial cortical regions. One of the central challenges in NIBS research is how to achieve stimulation of deep brain regions when desired, because the electromagnetic fields applied during NIBS fall off in both intensity and focality with increasing depth (Bikson & Dmochowski, 2019). The superficial cortex has many regions directly implicated in cognition and behavior, as well as participating in brain-wide networks (Faber et al., 2012, Vaseghi et al., 2015, Cabib et al., 2016, Ironside et al., 2019). Nevertheless, some brain regions strongly implicated in neurological and psychiatric disorders are subcortical, for example the subthalamic nucleus in PD (Rodriguez-Oroz et al., 2000, Gunalan et al., 2018) or subcallosal cingulate for TRD (Lujan et al., 2013, Holtzheimer et al., 2017). Consequently, the ability to effectively stimulate deep brain regions with NIBS would open new avenues for treating brain disorders and cognitive and behavioral manipulation (Dmochowski & Bikson, 2017). This consideration is indirectly supported by the notion that traditional PD treatment has especially targeted subcortical structures, both with surgical approaches and medication.

As rTMS also has the potential to alleviate motor symptoms in PD, it is a valuable treatment method to consider. The rTMS guidelines based upon the available evidence are available for future studies (Lefaucheur et al., 2020). For example, a recent study found that high-frequency rTMS over the supplementary motor area (SMA) may be beneficial as an add-on therapy for alleviating freezing of gait in PD patients (Mi et al., 2019).

Transcranial direct current stimulation in PD

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that may help treat various neurological and psychiatric disorders (Fregni et al., 2021). It is administered via a constant electric current produced by a battery-operated current generator connected to at least two electrodes (anode and cathode) applied to specific head locations (or extra-

cephalic regions in case of the return electrodes). Earlier results support the idea that active stimulation of the DLPFC with tDCS could have beneficial, lasting effects on both affective and cognitive domains in patients with PD (Boggio et al., 2006; Doruk et al., 2014; Broeder et al., 2015). Positive effects of combined cognitive training and tDCS have been shown in cognitively impaired PD patients (Manenti et al., 2018). As per the newest guidelines of tDCS usage in neurological and psychiatric disorders (Fregni et al., 2021), anodal DLPFC tDCS, being a functional analogue of the facilitatory rTMS protocol, is probably effective for cognitive function in PD (Level B evidence). In regard to motor function in PD, anodal motor/premotor/SMA tDCS is possibly effective (Level C), whereas anodal prefrontal tDCS is probably not (Level B). tDCS-based home treatment could be a viable treatment option (Dobbs et al., 2018; Cucca et al., 2019), especially during viral pandemics and the need for self-quarantine, when face-to-face meetings and in-house medical procedures are not feasible.

Biomarkers of treatment response in clinical depression

Major depression is currently defined based on clinical criteria and encompasses a heterogeneous mix of neurobiological phenotypes (Drysdale et al., 2017). Only a few studies have focused on predicting outcomes following non-pharmacological treatment (Bailey et al., 2019). Knowledge of such predictors may allow clinicians to elucidate the sources of inter-individual variability in NIBS responses and provide more tailored therapeutic intervention (Rektorová & Biundo, 2019). For example, according to Iseger and colleagues (2019), autonomic functioning variables such as heart rate (HR) and heart rate variability (HRV) could serve as a potential target engagement mechanisms for optimizing and individualizing NIBS treatments in depression; the authors have emphasized the importance of including HR and HRV measurements during human depression studies, in particular those that conduct NIBS, to investigate to a better extent the acute effects of NIBS on autonomic functioning, and to establish the efficacy of electrocardiogram (ECG) metrics in target engagement of the frontal-vagal network. Depression in PD has also been suggested to relate to significant alterations in the composition of gastrointestinal microbiome profiles, likely resulting from imbalances of gut and central nervous system neurotransmitters (Dinan & Cryan, 2017; Lubomski et al., 2020).

Neuroimaging and neurophysiology can be utilized as readouts of neural changes induced by NIBS (Sverak et al., 2018). Online monitoring of the state of the brain has been suggested by several authors (Bergmann et al., 2016). The objective is to optimally tailor the NIBS treatment to meet the specific needs of individual patients. In an exploratory study by Avissar and colleagues (2017), TRD was marked by hypoconnectivity of executive and rostral motor fronto-striatal pathways, but normal connectivity of limbic and caudal motor fronto-striatal pathways. Higher baseline functional connectivity of the left DLPFC to the executive division of the striatum in depressed patients correlated with treatment response to TMS over the left DLPFC, suggesting that an intact pathway from the part of the cortex that is proximal to the stimulation site to

deeper structures may facilitate antidepressant effects. This raises the possibility that baseline functional connectivity could be used as a biomarker for treatment response to rTMS in clinical depression (Oliveira-Maia et al., 2017).

Resting-state EEG (rsEEG) may be able to identify treatment-predictive heterogeneity in depression. A recent study (Wu et al, 2020) using rsEEG and machine learning sought to identify a neurobiological signature of response to antidepressant treatment as compared to placebo. The authors developed a rsEEG-optimized latent-space computation model that was capable to robustly predict treatment outcome with the antidepressant sertraline and distinguish between response to sertraline versus placebo at the individual patient level and which may furthermore support treatment selection between medication and rTMS. These findings lay a path toward machine-learning-driven personalized approaches to treatment in depression, grounded in individual-level neurobiology.

Finally, as individual differences in resilience against and vulnerability to neurological disorders also depend on genetic variants based endophenotypes, fine-tuning individual NIBS protocols can be supported by the resuts of SNP genotyping. For example, association of depression and BDNF endophenotypes is well-established (Duman et al., 2021), substantiating NIBS-related research (Bocchio-Chiavetto et al., 2008; Cheeran et al., 2008; Krstic et al., 2014; Chan & Bota, 2019). It is not clear, however, whether the NIBS effects accrue as mediated by the motor areas or whether higher cognitive functions may also be involeved. A study by Tulviste and collegues (2019) showed that the BDNF genotype is associated with a bias in non-veridical preferences, and that Val/Val and Val/Met subjects responded differently to right DLPFC rTMS stimulation, further enhancing their preexisting selection biases. Thus, it is possible that genetic variance dependent efficacy of NIBS may be moderated by style of cognitive preferences and sensitivity to environmental cues. The latter is an important factor in the development of depression. Treatment resistance has been linked to insufficient brain plasticity and chronic inflammation; in a study encompassing the analysis of neurotrophic and inflammatory factors in psychiatric patients undergoing rTMS and ECT in order to refine the selection of patients and predict clinical outcomes, Valiuliene and colleagues (2021) showed that depressive patient treatment with rTMS had increased BDNF concentration, while a lower initial pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) concentration could be a marker for treatment success in depressed patients undergoing rTMS. Future research in the domain of combined utilization of NIBS and genotyping should help shed more light on the theoretical standing of the organic *versus* reactive hypothesis on the causes of PD in general, and its TRD-associated variety in particular, also supporting treatment optimization.

5. GENERAL SUMMARY AND CONCLUDING REMARKS

5.1. General summary

The research questions posed at the beginning of this thesis were:

1. What is the current understanding of the neural circuitry of affective processing in depression related to PD?
2. How does depression influence the overall disease trajectory and quality of life of PD patients?
3. Can a NIBS method such as rTMS effectively, safely, and tolerably be applied to treat depression related to PD? In addition to treating depression, is there evidence regarding the treatment of other common neuropsychiatric problems associated with PD using rTMS?
4. What are the known obstacles and emerging questions to be mindful of when using rTMS to treat PD patients with treatment-resistant depression? How can the treatment process be optimized to achieve better outcomes?

The thesis summarized and expanded the knowledge and expertise regarding the therapeutic use of rTMS to treat depression related to PD, while also looking at possible implications for other neuropsychiatric symptoms and the patients' health-related quality of life. To summarize the theoretical analysis-based and empirical findings of the three studies included in this dissertation, the following statements can be made:

1. Depressive symptom severity is an important factor modulating various clinical aspects of PD, and quality of life of PD patients, tying into the notion that neuroanatomical alterations of the brainstem raphe nuclei are involved in the pathogenesis of depressive disorders and underlining the growing importance and utility of brain-based biomarkers of depression in PD.
2. It is likely that treatment with rTMS, adhering to an evidence-based selection of stimulation parameters, can give a rapid therapeutic response comparable to an effective regimen of antidepressants in a majority of patients with depression related to PD. Targeting the DLPFC by rTMS is a viable treatment strategy for depression related to PD, and possibly other associated neuropsychiatric phenomena (e.g. cognitive impairment, anxiety, apathy), the latter pending on further research.
3. Patients with PD-related TRD represent a heterogeneous clinical sample with many complex, often inadequately met needs, emphasizing the interindividual variability in both clinical status and characteristics of treatment response, thus warranting personalized intervention approaches that also include NIBS.

Prospective, longitudinal studies have demonstrated that the cumulative prevalence of most psychiatric complications related to PD is higher than earlier cross-sectional studies suggested, with many disorders having a cumulative frequency over 50%, often beginning as early as the prodromal or *de novo* state (Chaudhuri et al., 2020). As summarized by Weintraub (2020), the neural substrate of NMS in PD is a complex interaction of PD pathology, treatment

effects, changes in multiple neurotransmitter systems and neural circuitry, and genetic influences. Non-motor complications related to PD are associated with excess disability, worse quality of life, poorer outcomes (including morbidity and mortality), and greater caregiver burden. Current treatment options for NMS in PD remain quite limited in their potentially beneficial effect. For multiple major neuropsychiatric disorders (e.g., depression, cognitive impairment, and psychosis), there remains evidence for under-recognition and undertreatment (Shulman et al., 2002; Chaudhuri et al., 2020). PD and its comorbidities are no different in this respect.

There is no consensus as to whether the etiology of depression associated with PD is organic, reactive, or both (Leentjens, 2004). There is a greater degeneration of dopaminergic neurons in the ventral mesencephalon in PD patients who are depressed than in those who are not (Mann & Kapur, 1995). Although levodopa is helpful in treating depression in a minority of PD patients, most do not exhibit a brisk response to this therapy alone. Depression is linked to changes in the activity of various neurotransmitters, including serotonin. As indicated in the results of **Study I** of this dissertation, serotonergic projections from the brainstem raphe nuclei undergo degeneration in PD, which may be a key abnormality in the etiology of depression associated with PD (Okun & Watts, 2002). Structural brainstem midline alterations have also been detected in both magnetic resonance images and transcranial sonograms in patients with primary depression and in those with depression associated with PD, supporting an important role of the median raphe nuclei in mood disorders (Berg et al., 2001; Toomsoo et al., 2017).

Depression is a long-term, relapsing condition with a tendency towards chronicity. Unfortunately, many patients do not achieve full remission for various reasons which include poor compliance, premature ending of treatment, the use of inadequate treatment options, and other factors. Despite the substantial number on studies on PD-related depression, its precise role in PD and respective treatment methods are insufficiently understood and underdeveloped. Repetitive transcranial magnetic stimulation is an established way to non-invasively modulate brain excitability and to induce brain plasticity. However, studies incorporating rTMS to alleviate neuropsychiatric symptoms associated with PD are quite scarce. The precise combination of stimulation parameters suitable for depressed PD patients was up until recently yet to be determined. **Study II** set out to pool the available scientific literature on the therapeutic usage of rTMS on neuropsychiatric symptoms of PD specifically associated with the dorsolateral prefrontal cortex (i.e., depression and cognitive impairment). The goal was to gain practical knowledge on using rTMS in the context of common neuropsychiatric symptoms of PD. One of the critical implications drawn out of this line of research is that the treatment outcome in NIBS depends on multiple factors, and the interactions between them.

Previous studies have identified multiple factors, including female sex, older age, single status, education level, physical disease, family history of depression, cognitive disorders, smoking status, alcohol use, early childhood

adversity, personality traits, and recent positive and negative life events, that can affect the progression of depression in PD patients (Global Parkinson's Disease Survey Steering Committee, 2002; Schrag, 2006; Reijnders et al., 2008; Leentjens et al., 2013). A recent meta-analysis indicated that the 5-HTTLPR genotype (S/S-Allele) is correlated with an increased depression risk in PD, and this highlights the needs for these people to take effective approaches in prevention of depression of PD before its onset (Cheng et al., 2020). **Study III** provided preliminary evidence on applying rTMS that could suit clinically complex PD patients, i.e., those with treatment-resistant depression and/or other neuropsychiatric and somatic comorbidities. As implicated by the aforementioned study, difficulties concerning subject recruitment, strict inclusion criteria, difficulties complying to the study protocol, natural fluctuations in the disease course as well as patients' motor and ADL difficulties along with the overall burden of the disease illustrate the challenges of conducting clinical research on subjects with advanced PD and comorbid neuropsychiatric and somatic problems.

The identification of the factors related to the development and course of depression in PD patients could aid in the identification of preventive measures for this condition (Sagna et al., 2014). This dissertation has contributed to identifying influential factors and distilling optimal brain stimulation parameters for improving the treatment efficacy of PD-related depression, while argumentatively proposing an approach that synthesizes the newest clinical evidence with traditional practices of applying NIBS. Many clinical trials applying rTMS have taken place in an inpatient setting, where treatments can be administered in consecutive days while maintaining the highest possible quality of life, thus minimizing subject attrition. While a robust clinical improvement is sometimes difficult to accomplish, the increase in HR-QoL metrics has been noted with growing frequency. This raises the need to keep incorporating measures on HR-QoL into clinical studies that seek to treat neuropsychiatric symptoms related to neurodegeneration using NIBS methods. An empirical investigation illustrating this was done in **Study III**. Large-scale, innovative, neuroscience-informed protocols are recommended to elucidate the potential utility of rTMS for the complex neuropsychiatric symptoms associated with PD. Stimulating multiple targets on various cortical layers, varying stimulation techniques and protocols, as well as combining NIBS with cognitive training and other pharmacological and non-pharmacological interventions warrant further investigation in future studies to better elucidate main effects and interactions.

5.2. Concluding remarks

The research carried out during the proceedings of this dissertation has unearthed a multifaceted and complex system of interacting symptoms, comorbidity ranges, and treatment pathways, also bringing forward various outstanding issues that challenge developing safe, efficient, and tolerable neuromodulation interventions for depression and related neuropsychiatric phenomena in PD. It has also further stressed the growing importance of personalized medicine. The etiology of the neuropsychiatric manifestations of PD is complex, and there is evidence to support multiple influential factors, including the psychological reaction to a serious, progressive diagnosis, a consequence of treatment of the disease, and the pathological process of PD (Dhingra et al., 2021). Problems with managing PD-related NPS include the need for early recognition, timely assessment and diagnosis using suitable measures, personalized planning of interventions (while being mindful of treatment resistance), and challenges related to maintaining the highest possible HR-QoL during the disease course. Refining, unifying and streamlining treatment protocols (including those applying NIBS) in both typical and more complex cases of PD is important to maximize the beneficial response and overcome treatment resistance whenever possible. Combining various treatment methods to achieve maximal success is both realistic and crucial to consider. Thankfully, the brain stimulation revolution is unfolding around us as we speak. This area is fertile, expanding, and accelerating. Each month, we have novel brain stimulation methods obtaining clinical approval and improving society's health by treating our diseases. The brain stimulation methods are not only powerful therapies, they are also in the midst of unlocking one of the last great frontiers in science – how the human brain works (George, 2020).

ACKNOWLEDGEMENTS

Parts of this work were supported by the Estonian Research Council grant IUT20-40 (sub-grant TSVPH14140I, awarded to Talis Bachmann) and the project ASTRA PER ASPERA (financed by the EU Regional Development Fund and administered by the University of Tartu). The dissertation author received no additional renumeration apart from the national doctoral stipend (2013–2017) as well as monthly wages (2017–2019). The TMS sessions were performed at the Cognition & Consciousness Lab of the University of Tartu, under the supervision of professor Talis Bachmann.

I would like to thank my doctoral supervisor professor Talis Bachmann for various support during the production of this doctoral dissertation throughout the years. Concerning the lab's research staff and students, my gratitude goes to Jaan Tulviste, Renate Rutiku, Inga Karton, Anu Einberg, and Jaan Aru for their helpful advice on experimental design and TMS methodology. Toomas Toomsoo and Inna Rubanovits from the Neurology Center of East Tallinn Central Hospital are to be thanked for sparking a deeper interest in PD in the first place, as well as the neurological assessment of the reasearch subjects. I'm thankful to Külli Davel, also from the Neurology Center of East Tallinn Central Hospital, who provided medical oversight during the TMS sessions. I would like to acknowledge professors Daniela Berg (University of Tuebingen, Department of Neurology), and professors Pille Taba and Toomas Asser (University of Tartu, Tartu University Hospital) and their research groups for their support. Grigori Joffe from the Helsinki University Central Hospital and Marika Tammaru from the Research & Development Center of East Tallinn Central Hospital are to be thanked for experimental study design related advice. Thanks also to Katrin Kõdar from the Radiology Clinic of East Tallinn Central Hospital for neuroradiological consultations. The staff at the Institute of Psychology have been more than helpful in dealing with administrative tasks regarding the doctoral curriculum, and the Doctoral School for Behavioral, Social and Health Sciences has provided an educationally and socially stimulating environment in which to thrive.

I owe heartfelt gratitude to my life partner Merle and our three daughters who have been kind and supportive at home throughout the years. I'd like to dedicate this dissertation to the memory of my grandfather Vova who passed away in 2019. Curiosity, the drive to explore the unknown, bring order to chaos, and tackle problems head on − no matter the complexity – were characteristics I have tried to adopt directly from him.

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SUMMARY IN ESTONIAN

Parkinsoni tõbi ja depressioon: ajumehhanismid ja mitteinvasiivse ajustimulatsiooni põhised ravistrateegiad

Parkinsoni tõbi (PT) on teine kõige sagedamini esinev neurodegeneratiivne haigus, mis puudutab 2–3% üle 65-aastaseid inimesi (Poewe et al., 2017). Neuroloogilised haigused on nüüdseks kujunenud juhtivaks puudeallikaks maailmas, mille puhul Parkinsoni tõvele omistatud kasvu hinnatakse kiireimaks. PT-d iseloomustavad motoorsed ja mittemotoorsed tunnused, viimaste hulka kuuluvad ka neuropsühhiaatrilised häired. Neuropsühhiaatrilised sümptomid (näiteks emotsionaalsed, käitumuslikud ja kognitiivsed probleemid) on PT kontekstis olulised mittemotoorsed tunnused, mis esinevad sageli ja millel on märkimisväärselt pärssiv mõju inimese elukvaliteedile. Depressioon on väga levinud neuropsühhiaatriline häire, mille eluaegne haigestumisrisk on ligi 20% ning mida seostatakse kõrgenenud suremusega (Palazidou, 2012). Uuringud on näidanud üldpopulatsiooniga võrreldes depressiooni suurenenud levikut PT-ga inimestel − raskete depressioonivormide esinemissagedus on nende puhul 5–20%, kusjuures kergemaid vorme esineb täiendavalt 10–30% PT-ga inimestest (Weintraub & Burn, 2011). Üle maailma esineb seega kuni pooltel PT patsientidest kliiniliselt olulisi depressioonisümptomeid, mis on levimuse poolest tunduvalt kõrgem tase kui üldpopulatsioonis (13,5%)(Beekman et al., 1999; Hely jt., 2005; Dissanayaka jt., 2011; Marsh, 2013; Pachana jt., 2013). Depressioon on PT-ga inimeste tervisega seotud elukvaliteedi (ingl. k. *health-related quality of life*) peamine mõjutegur (Jones jt., 2015), mis on ühtlasi seotud motoorsete ja kognitiivsete funktsioonide kiirenenud häirumisega (Ng jt., 2015; Santangelo jt., 2009). Longituuduuringud on näidanud, et depressioon on oma olemuselt pikaajaline ja episoodiline haigus, millel on kalduvus kroonilisusele ning kordumise oht suureneb iga uue episoodiga (Palazidou, 2012). Kolm neljandikku depressiooniga inimestest kogeb rohkem kui ühte depressiooni-episoodi ning kordumise oht on suurem, kui esimene episood esineb nooremas eas ning kui depressiooni on esinenud ka teistel perekonnas (Hollon jt., 2006). Lisaks episoodide arvule mõjutab depressiooni prognoosi ka ravimata jäänud haiguse kestus; mida pikemaks see venib, seda halvem on võimalik ravivastus ja väiksem on remissiooni saavutamise tõenäosus (Okuda jt., 2010). Suur osa patsientidest ei saavuta täielikku remissiooni erinevatel põhjustel, mille hulka kuuluvad ka ravi ebasobivus, ravi kõrvaltoimed, ravi enneaegne lõpetamine jpt. Suhteliselt tavapärane on pikaajaline depressioon (kestvusega üle 2 aasta), mis on kliiniliselt raskem kui episoodiline depressioon ning sellega kaasneb enam igapäevase toimetuleku langust ning kõrvalabivajadust. Kuna depressiooni sümptomid suurenevad kooskõlas PT progresseerumisega, suurendavad need ka otseseid tervishoiukulusid, (sh uuringud ja ravi) ning kaudseid kulusid (sh puudega tekkega seotud töökohakaotus, suurenenud hoolduskoormus) (Huse et

al., 2005; Johnson et al., 2013). Neid järeldusi arvestades on kriitilise tähtsusega tagada efektiivne ravi alates depressiooni esimesest episoodist. Nagu Weintraub (2020) kokku võttis, on mittemotoorsete sümptomite neuraalseks substraadiks PT-s haiguse patoloogia, raviefektide, mitmete neurotransmittersüsteemide ja närviringetes esinevate muutuste ning geneetiliste mõjude keerukas ja mitmetahuline koostoime. PT-ga seotud mittemotoorsed probleemid on seotud liigse puude, halvema elukvaliteedi, kehvemate näitajate (sh haigestumus ja suremus) ning suurema hoolduskoormusega. PT mittemotoorsete sümptomite praegused ravivõimalused on endiselt oma potentsiaalselt kasuliku mõju osas üsna piiratud. Paljude peamiste neuropsühhiaatriliste häirete (nt depressioon, kognitiivsed häired ja psühhoos) korral on tõendeid nende puuduliku äratundmise ja käsitluse kohta (Shulman et al., 2002; Chaudhuri et al., 2020).

Kuigi PT-d peetakse endiselt liigutushäireks ja seda diagnoositakse peamiselt motoorsete tunnuste ja sümptomite põhjal (Postuma et al., 2015), viitab neuropsühhiaatriliste sümptomite suur levimus sellele, et seda võib klassifitseerida ka neuropsühhiaatrilise häirena (Weintraub & Burn, 2011). Nagu on kirjeldanud Gallagher ja Schrag (2012), on neuropsühhiaatriliste sümptomite patofüsioloogia keeruline, kajastades PT-s laialt levinud ajutüve ja ajukoore patoloogiat, mis hõlmab mitmeid neurotransmittereid (sh dopamiinergilisi, serotonergilisi, noradrenergilisi ja kolinergilisi süsteeme). Psühhiaatriliste seisundite, eriti emotsionaalsete häirete diagnoosimine on keeruline, kuna psühhiaatriliste häirete somaatilised tunnused võivad osaliselt kattuda aluseks oleva liigutushäirega. PT ja depressiooniga patsientide abistamiseks on arendatud mitu raviviisi, teiste hulgas farmakoteraapia, psühhoteraapia ja ajustimulatsioon. Multimorbiidsed, mitut ravimit samaaegselt kasutavad PT patsiendid kujutavad endast olulist väljakutset terapeutilise ohutuse ja ravivastuse saavutamisel (Chen & Cheng, 2008). Kõige tavapärasem depressiooniravi kujutab endast farmakoloogilist sekkumist, samuti kasutatakse ka psühhoteraapiat. Uuem lähenemine depressiooni etioloogias postuleerib, et neuropsühhiaatrilised sümptomid tulenevad konkreetsete ajupiirkondade ja/või -võrgustike elektrilise aktiivsuse häiritusest (Holtzheimer jt., 2018). Kortikaalset düsfunktsiooni on PT puhul dokumenteeritud neurokuvamuslike ja -füsioloogiliste uuringutega, mis on viidanud erinevate ajupiirkondade hüpo- või hüperaktivatsioonile (Lefaucheur, 2006; Lefaucheur, 2009). Üks võimalus aju elektrilise aktiivsuse moduleerimiseks on kasutada ajustimulatsiooni. Nii invasiivsed kui ka mitteinvasiivsed ajustimulatsioonimeetodid võivad neurofüsioloogiliste omaduste tasakaalutust korrigeerida. Mitteinvasiivsed ajustimulatsioonimeetodid nagu korduv transkraniaalne magnetiline stimulatsioon (rTMS) ja transkraniaalne alalisvoolustimulatsioon (tDCS) on näidanud võimekust mõjutada frontostriaatalse närvivõrgustiku tööd dorsolateraalse prefrontaalkoore (DLPFK) stimuleerimise kaudu (Kanno et al., 2004; Marcolin & Padberg, 2007), leevendades seeläbi nii nii emotsionaalseid kui kognitiivseid sümptomeid (Schulz et al., 2013). Transkraniaalse magnetstimulatsiooni (TMS) tööprintsiibiks on lühikeste magnetimpulsside suunamine läbi peanaha ja kolju eesmärgiga indutseerida huvipakkuva ajupiirkonna kortikaalsete neuronite laenglemist; rTMS on see-

juures magnetimpulsside kogumite järjestikune kiire esitamine. Nüüdseks on juba suur hulk uuringuid analüüsinud rTMS-i kui uurimisvahendit ning mitmesuguste neuroloogiliste ja psühhiaatriliste häirete potentsiaalset ravi (Kamble et al., 2014). Alates USA Toidu- ja Ravimiameti loaandmisest raviresistentse (unipolaarse) depressiooni raviks 2008. aastal on rTMSi aktiivselt rakendatud erinevate neuropsühhiaatriliste häirete, sealhulgas PT-ga seotud sümptomite leevendamiseks.

Käesoleva doktoritöö peamine eesmärk oli koondada ja laiendada teadmisi tõhusa rTMS ravi kohaldamise kohta patsientidel, kellel on diagnoositud nii PT kui ka depressioon, hõlmates potentsiaalseid mõjutusi ka väljaspool meeleoluhäiret (näiteks kognitiivsed probleemid ja ärevushäired) ning kaardistada seeläbi võimalikke efekte inimese elukvaliteedile. Protseduur oli kolmeetapiline: a) analüüsiti saadaolevaid teadmisi depressiooni närviringide kohta ning valideeriti need PT kontekstis, b) analüüsiti rTMSi kasutatavust ja rakenduslikke parameetreid depressiooni ravis PT patsientidel ja c) rakendati kahes eelmises punktis saadud teadmisi kliiniliselt keeruka PT-ga patsiendivalimi peal (hõlmates inimesi, kel on muu hulgas diagnoositud raviresistentne depressioon), eesmärgiga hinnata individuaalsete erinevuste rolli ravivastuses ja koguda andmeid praktiliste probleemide kohta ravimeetodi kasutamisel eelkirjeldatud kliinilises kontekstis. Eksperimentaalset uuringuprotokolli käsitleti pilootmudelina, mida saaks hiljem aluseks võtta optimaalse raviprotokolli väljatöötamisel PT-ga seotud raviresistentse depressiooni leevendamiseks.

Doktoritöös käsitletavateks uurimisküsimusteks olid:

1. Milline on praegune teaduslik arusaam depressiooni olulisemarest närvivõrgustikest PT kontekstis?
2. Kuidas mõjutab depressioon PT-ga patsientide üldist haiguse trajektoori ja elukvaliteeti?
3. Kuidas rTMSi efektiivselt, turvaliselt ning patsiendile talutavalt rakendada depressiooni raviks PT kontekstis? Kas lisaks depressiooni ravile on tõendeid ka teiste PT-ga seotud neuropsühhiaatriliste probleemide ravimise kohta rTMS-i abil?
4. Mida silmas pidada, kui kasutada rTMSi raviresistentse depressiooni ravis PT kontekstis? Kuidas saab raviprotsessi parimate võimalike tulemuste saavutamiseks optimeerida?

Küsimustele vastamiseks planeeriti ja viidi läbi uuringud. Doktoritöö **I uuringu eesmärk** oli kirjeldada depressioonisümptomite levimust ja raskusastet PT patsientidel ning analüüsida võimalikke seoseid konkreetsete ajupõhiste biomarkerite − antud juhul ajutüve raphe-tuumade sonograafiliste uuringute tulemuste − ja depressioonisümptomite vahel. Peamine ootus uurimistööle oli leida kinnitus, et raphe-tuumade neuroanatoomilised muutused (väljendatud ehhogeensuse tasemetena transkraniaalses ultrahelis) on seotud PD-ga seotud depressiooni patogeneesiga ning eelmainitud muutuste määr on otseselt seotud depressiooni sümptomite raskusastmega. Arvestades, et depressioonisümptomite raskusaste on oluline PD kliiniliste aspektide mõjutegur, rõhutab see vajadust uute tõhusate ravimeetodite järele (eriti raviresistentse depressiooniga

PT patsiente silmas pidades). Dorsolateraalse prefrontaalkoore (DLPFK) hüpoaktiivsust depressioonis on leidnud mitmed varasemad uuringud ja seda peetakse nüüdseks depressiooni oluliseks neurofüsioloogiliseks tunnuseks (Ring jt., 1994; Dragaševic jt., 2002; Mottaghy jt., 2002; Fregni jt., 2006; Cardoso jt., 2008; Bench jt., 2009; Koenings ja Grafman, 2009). DLPFK-d kui stimuleeritavat ajupiirkonda peetakse rTMS-i ravis kõige ligipääsetavamaks (Wassermann & Lisanby, 2001). **II uuringu eesmärk** oligi koondada olemasolev teaduskirjandus rTMS terapeutilise kasutamise kohta PD neuropsühhiaatriliste sümptomite ravi kontekstis, mis on eelkõige seotud DLPFK'ga (s.t. depressioon ja kognitiivsed häired). I ja II uuringu käigus saadud teadmistele tuginedes oli **III uuringu eesmärgiks** disainida esialgne, maksimaalselt efektiivne, ohutu ja inimesele talutav rTMS-protokoll raviresistentse depressiooniga PT patsientidele. Vastav patsiendigrupp kujutab endast keerukat kliinilist valimit, keda iseloomustab suur individuaalne variatiivsus nii kliinilises seisundis kui ka võimalikus ravivastuses. Uuringuprotokolli kirjeldamisel püüti võtta neid omadusi arvesse, et see saaks olla võimaliku raviviivisi aluseks PT-ga seotud raviresistentse depressiooni käsitlemisel edaspidi.

Kuigi levodopast on abi depressiooni ravimisel väikesele osale PT-patsientidest, ei näita enamik neist ainuüksi sellele ravile kiiret vastust. Depressioon on seotud erinevate neurotransmitterite, sealhulgas serotoniini aktiivsusmustriga. Nagu on näidatud selle väitekirja **I uuringu** tulemustes, hävivad PT puhul ajutüve raphe-tuumade serotonergilised projektsioonid neurodegeneratsiooni tõttu, mis võib olla PT-ga seotud depressiooni etioloogias üks olulisi põhjuslikke tegureid (Okun & Watts, 2002). Nii primaarse kui ka PT-ga seotud depressiooniga patsientidel on neuroanatoomilisi muutusi ajütüve piirkonnas (aju keskjoone tasemel) tuvastatud nii magnetresonantstomograafias kui ka transkraniaalses sonograafias, toetades meeleoluhäirete korral arusaama raphe tuumade olulisust (Berg jt., 2001; Toomsoo jt., 2017). Depressioon on pikaajaline ja episoodilise iseloomuga seisund, millel on kalduvus kroonilisusele. Kahjuks ei saavuta paljud patsiendid täielikku remissiooni ja seda erinevatel põhjustel, mida käesolevas doktoritöös lähemalt ka analüüsitakse. Vaatamata PT-ga seotud depressiooni uuringute märkimisväärsele arvule ei ole selle haiguse täpne roll PT kontekstis piisavalt mõistetud ega sellele vastavad ravimeetodid rahuldavalt välja arendatud. Tavapärane antidepressantravi ei pruugi aidata saavutada ootuspäraseid tulemusi. rTMS on väljakujunenud viis aju elektrilise aktiivsuse mitteinvasiivseks mõjutamiseks. Uuringud, mis hõlmavad rTMS-i PT-ga seotud neuropsühhiaatriliste sümptomite leevendamiseks, on üsna napid. Depressiooniga PT patsientidele sobivate stimulatsiooniparameetrite täpne kombinatsioon oli alles hiljuti kindlaks tegemata. **II uuringu tulemusel** koguti ja süstematiseeriti praktilisi teadmisi rTMS-i kasutamise kohta PT puhul sagedamini esinevate neuropsühhiaatriliste probleemide ravis. Üks tõekspidamisi oli see, et ravi tulemus sõltub mitmetest teguritest ja nende omavahelisest vastasmõjust. Varasemad uuringud on tuvastanud mitu tegurit, sealhulgas naissugu, vanem vanus, üksielamine, madalam haridustase, füüsilised (somaatilised) haigused, depressioon perekonnas, kognitiivsed häired,

suitsetamine, alkoholi liigtarvitamine, varase lapseea raskused, isiksuseomadused ning hiljutised elusündmused, mis võivad mõjutada depressiooni kulgu PT-ga inimestel (Global Parkinson Disease Survey Steering Committee, 2002; Schrag, 2006; Reijnders jt., 2008; Leentjens jt., 2013). **III uuring** esitas esialgsed tõendid rTMS-i rakendamise kohta, mis võiksid sobida kliiniliselt väga keerukatele PT-ga patsientidele, sh neile, kellel on raviresistentne depressioon ja/või muud neuropsühhiaatrilised ja kaasuvad somaatilised haigused.

PT-ga patsientide depressiooni kuluga seotud tegurite kindlakstegemine võib aidata luua haiguse süvenemist ennetavaid sekkumisi (Sagna et al., 2014). Käesolev doktoritöö on aidanud kaasa sedalaadi mõjutavate riskifaktorite väljaselgitamisele ja optimaalsete ajustimulatsiooniparameetrite tuvastamisele PT-ga seotud depressiooni ravi efektiivsuse parendamiseks ja raviresistentsuse ületamiseks, pakkudes teaduslikult argumenteeritult lähenemisviisi, mis sünteesib uusimaid kliinilisi tõendeid mitteinvasiivse ajustimulatsiooni rakendamisest ja seostamisest traditsioonilisemate sekkumistega. Kuigi objektiivsete kliiniliste näitajate märkimisväärset paranemist on sageli keeruline saavutada, on elukvaliteedialaste näitajate suurenemist täheldatud üha enamates kliinilistes uuringutes. See tekitab vajaduse jätkata elukvaliteedialaste näitajate mõõtmist uuringutes, mille eesmärgiks on ravida neurodegeneratsiooniga seotud neuropsühhiaatrilisi sümptomeid ajustimulatsioonimeetodite abil. Sellist lähenemist illustreerivat empiirilist uurimist püüti rakendada ka käesoleva doktoritöö eksperimentaalses osas. rTMSi potentsiaalse kasulikkuse täpsustamiseks PD-ga seotud neuropsühhiaatriliste sümptomite korral on soovitatav lähtuda teaduspõhistest alustest. Erinevate ajupiirkondade stimuleerimine erinevates kortikaalsetes kihtides, erinevad stimulatsiooniparameetrid ajustimulatsiooni kombineerimine teiste (farmakoloogiliste ja mittefarmakoloogiliste) sekkumistega jm metodoloogilised aspektid nõuavad edasisi pikaajalisi mahukaid kliinilisi uuringuid, et täpsustada sekkumiste mõjusid ja koostoimeid ning neid optimeerida. Väitekirjas sisalduvate uuringute kokkuvõttena saab esitada järgnevad väited:

1. Depressioonisümptomite raskusaste on oluline PT kliinilisi aspekte ja patsientide elukvaliteeti mõjutav tegur. Ajutüve raphe-tuumade neuroanatoomilised muutused on otseselt seotud depressioonihäirete patogeneesiga ning rõhutavad depressiooni neurokuvamuslike biomarkerite kasvavat tähtsust ja diagnostilist rakendatavust PT kontekstis.
2. DLPFK stimuleerimine rTMS-ga on efektiivne PT-ga seotud depressiooni ravistrateegia, kusjuures võimalik on ka positiivne mõju teistele neuropsühhiaatrilistele probleemidele (nt kognitiivsed häired, ärevushäired, apaatsus) − viimaste osas on vajalikud kinnitused edaspidistes kliinilistes uuringutes.
3. Raviresistentse depressiooniga PT patsiendid kujutavad endast keerukat kliinilist valimit, millel on palju, sageli ebapiisavalt kaetud ravivajadusi. See rõhutab vajadust arvesse võtta individuaalset varieeruvust nii kliinilises seisundis kui ka võimalikus ravivastuses ja õigustab seeläbi isikupärastatavaid ravialaseid sekkumisviise, mille hulka sobib nii eraldivõetuna kui ka teiste meetoditega kombinatsioonis mitteinvasiivne ajustimulatsioon (sh rTMS).

PUBLICATIONS

CURRICULUM VITAE

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Education:

2013–2021	University of Tartu – Psychology (PhD)
2009–2011	University of Maastricht, Netherlands – Neuropsychology (MSc)
2009	University of Melbourne, Australia (one semester)
2008–2011	University of Tartu – Biomedical Sciences (MSc)
2005–2008	University of Tartu – Psychology (BA)
1999–2002	Tallinn Nõmme Gymnasium (science focus area) – secondary education

Professional experience:

2013–	Neura – CEO and Clinical Neuropsychologist
2021–2021	Estonian Health Insurance Fund, Dept. of Innovation – Project Manager
2020–2021	MinuDoc – Mental Health Service Manager
2019–2021	SENSUS Psychiatry and Psychotherapy Center – Clinical Neuropsychologist
2018–2020	Ministry of Social Affairs, Dept. of Social Welfare – Adviser
2018–2018	4 Clinic, Psychiatry Center and Sleep Center – Clinical Neuropsychologist
2017–2019	University of Tartu, Institute of Psychology – Junior Research Fellow
2013–2016	Cognuse – Consultant and Member of the Scientific Advisory Board
2011–2018	East Tallinn Central Hospital, Neurology Center – Clinical Neuropsychologist

Professional certifications:

- Clinical Psychologist, Clinical Neuropsychologist – Union of Estonian Psychologists
- European Certificate in Psychology (field: clinical and health psychology) – European Federation of Psychologists' Associations

Membership in professional organizations:

2014–	Estonian Association of Gerontology and Geriatrics
2013–	American Psychological Association, Society for Clinical Neuropsychology
2013–	International Neuropsychological Society
2018–2020	Alzheimer Europe Group of Governmental Experts on Dementia National Representative (Estonia)
2013–2021	Doctoral School of Behavioural, Social and Health Sciences

Volunteering:

2017–	NGO Life with Dementia – Member
2016–2016	Estonian Dementia Special Interest Group – Co-founder
2015–2019	International Neuroopsychological Society – Local Representative in Estonia
2010–2011	AIESEC Estonia, Tartu Office – Public Relations Officer Project "World at Home"

Publications:

1. Toomsoo, T., Randver, R., Liepelt-Scarfone, I., Kadastik-Eerme, L., Asser, T., Rubanovits, I., ... & Taba, P. (2017). Prevalence of depressive symptoms and their association with brainstem raphe echogenicity in patients with Parkinson's disease and non-PD controls. *Psychiatry Research: Neuro-imaging, 268*, 45–49. https://www.sciencedirect.com/science/article/abs/pii/S092549271730032X
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2009	Melbourne'i Ülikool, Austraalia (vahetussemester)
2008–2011	Tartu Ülikool, biomeditsiin, magistrikraad (MSc)
2005–2008	Tartu Ülikool, psühholoogia, bakalaureusekraad (BA)
1999–2002	Tallinna Nõmme Gümnaasium (reaalharu), keskharidus

Teenistuskäik:

2013–	Neura – Tegevjuht, neuropsühholoog
2021–2021	Eesti Haigekassa, Innovatsiooniosakond – Projektijuht
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2019–2021	Psühhiaatria ja Psühhoteraapiakeskus SENSUS – Neuropsühholoog
2018–2020	Sotsiaalministeerium, Hoolekande osakond – Nõunik
2018–2018	4 Kliinik, Psühhiaatriakeskus, Hea Une Keskus – Neuropsühholoog
2017–2019	Tartu Ülikool, Psühholoogia Instituut – Nooremteadur
2013–2016	Cognuse – Konsultant, teadusnõukoja liige
2011–2018	Ida-Tallinna Keskhaigla, Neuroloogiakeskus – Neuropsühholoog

Erialasertifikaadid:

- Kliiniline psühholoog, tase 7 ja neuropsühholoog, tase 7 – Eesti Psühholoogide Liit
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Liikmelisus erialastes organisatsioonides:

2014–	Eesti Gerontoloogia ja Geriaatria Assotsiatsioon (EGGA)
2013–	Ameerika Psühholoogiaassotsiatsioon (APA), Kliinilise neuropsühholoogia ühing (SCN)
2013–	Rahvusvaheline Neuropsühholoogiaühing (INS)
2018–2020	Alzheimer Europe riiklike dementsuse ekspertide töögrupp
2013–2021	Käitumis-, sotsiaal- ja terviseteaduste doktorikool

Vabatahtlik töö:

2017–	MTÜ Elu dementsusega – liige
2016/03–2016/09	Dementsuse töögrupp – kaasasutaja
2015–2019	Rahvusvaheline Neuropsühholoogiaühing (INS) – Eesti esindaja
2010–2011	AIESEC Eesti, Tartu osakond – Avalike suhete korraldaja Projekt "World at Home"

Publikatsioonid:

1. Toomsoo, T., Randver, R., Liepelt-Scarfone, I., Kadastik-Eerme, L., Asser, T., Rubanovits, I., ... & Taba, P. (2017). Prevalence of depressive symptoms and their association with brainstem raphe echogenicity in patients with Parkinson's disease and non-PD controls. *Psychiatry Research: Neuroimaging, 268*, 45–49. https://www.sciencedirect.com/science/article/abs/pii/S092549271730032X
2. Randver, R. (2018). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex to alleviate depression and cognitive impairment associated with Parkinson's disease: A review and clinical implications. *Journal of the Neurological Sciences, 393*, 88–99. https://www.sciencedirect.com/science/article/abs/pii/S0022510X18303356
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4. Randver, R., Vahter, L., & Ennok, M. (2015). Neuropsychological Services in Estonia: A Survey Study. *Baltic Journal of Psychology*, *16*(1, 2), 72–82. https://dspace.lu.lv/dspace/bitstream/handle/7/37237/Baltics_Psychology_Journal_2015.pdf#page=72

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