Aus der Klinik und Poliklinik für Neurologie

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der Universitätsmedizin der Universität Greifswald

The Effect of Non-Invasive Brain Stimulation with Cognitive Training or alone on Cognition in Individuals with Parkinson’s Disease: A Systematic Review and Meta-Analysis

Inaugural - Dissertation

zur

Erlangung des akademischen

Grades

Doktor der Medizin

(Dr. med.)

der

Universitätsmedizin

der

Universität Greifswald

2024

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Tag der Disputation: 10. April 2025

Dedicated to My Family

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List of Abbreviations or Acronyms

A. M.	Anna Mäder
AD	Alzheimer's disease
ADHD	Attention-Deficit/ Hyperactivity Disorder
ANT	Attention Network Test
BDI-II	Beck Depression Inventory II
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
CT	Cognitive Training
DLPFC	Dorsolateral Prefrontal Cortex
DR	Delayed Recall
GABA	Gamma- Aminobutric Acid
HRDS	Hamilton Rating Scale for Depression
HVLT	Hopkins Verbal Learning test
HVLT-R	HVLT-Revised
i.e.	id est (that is)
IPNP	International Picture Naming Project
IR	Immediate Recall
iTBS	intermittent Theta Burst Stimulation
J.E.	Julia Engel
LNS	Letter-Number Sequencing test
LTD	Long-Term Depression
LTP	Long-Term Potentiation
M	Mean
M. M.	Marcus Meinzer, Prof. Dr.
M.R.	Mandy Roheger, Prof. Dr.
mA	Milliamperes
MAO-B	Monoamine Oxidase Type B Inhibitor
MCI	Mild Cognitive Impairement
MMP	Mini-Mental Parkinson
MMSE	Mini-Mental-Status-Test
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NIBS	Non-Invasive Brain Stimulation
NMDA	N-Methyl-D-Aspartate
NMSQ	Non-Motor Symptoms Questionnaire
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PD	Parkinson's disease
PD-CRS	Parkinson's Disease-Cognitive Rating Scale, Parkinson's Disease-Cognitive Rating Scale
PDD	Parkinson's Disease with Dementia
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
PDQ-39	Parkinson's Disease Questionnaire
PICOT	Participants, Intervention, Comparison, Outcome, Time
PPC	Posterior Parietal Cortex
PRISMA	Preferred Report Items of Systematic Review and Meta-analysis
QoL	Quality of Life
R.M.	Rashed Mshael
RAVLT	Rey Auditory Verbal Learning test
RBANS	Repeatable Battery of Assessment of Neuropsychological Status
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RS-tDCS	Remotely Supervised- tDCS
rTMS	repetitive Transcranial Magnetic Stimulation
S	*Siehe* Standard Deviation
SMD	Standardized Mean Deviation
SOC	Stocking of Cambridge test
tCS	transcranial Current Stimulation
tDCS	transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
WCST	Wisconsin Card Sorting Test
WM	Working Memory

1. Introduction

1.1. Parkinson’s Disease

Parkinson's disease (PD) is a prevalent movement disorder and the second most common neurodegenerative disease. Typically, the onset occurs between the ages of 65 and 70. It was first described by James Parkinson in his "Essay on the Shaking Palsy". The disease encompasses both motor and non-motor symptoms, including mental symptoms. The primary motor signs, considered hallmarks of the disease, are bradykinesia, rigidity, and tremor. Neuropathologically, the presence of alpha-synuclein in the substantia nigra and the loss of dopaminergic neurons in the pars compacta of the same region are notable features (Tysnes and Storstein, 2017).

The prevalence of the disease is approximately 100 to 200 per 100,000 people in the population of Europe, with an incidence of around 10 to 20 per 100,000 per year (von Campenhausen *et al.*, 2005). Previously study investigating the prevalence of PD among gender have observed, that within specific timeframe, the risk of developing Parkinson’s disease is higher for men than for women (Elbaz *et al.*, 2002). On the other hand, a new observation suggests, that prevalence of PD with respect gender may be lower than previously thought (Zirra *et al.*, 2022). Furthermore, another observation emphasizes a prevalence of female with specific mutation, correlating it with the risk of developing PD (Chen *et al.*, 2020).

An intriguing review examining protective and risk factors for the development of PD reported several protective factors. These include smoking, caffeine consumption, physical activity, and the use of anti-inflammatory drugs such as NSAIDs. Conversely, the review identified dairy consumption, traumatic brain injury, and exposure to pesticides as risk factors for developing of PD. Additionally, the review found no significant association between body mass index (BMI) and the risk of PD (Ascherio and Schwarzschild, 2016). Furthermore, a recent study found, for the first time, an association between religiosity and the risk of developing PD. The study reported a potential higher risk of PD among individuals with low religiosity in adulthood within populations in England and the USA (Otaiku, 2023). An association between PD and genetic factors has also been described in the literature, resulting in the early onset of the disease (Lücking Christoph B. *et al.*, 2000).

The clinical diagnosis of Parkinson's disease is based on the cardinal symptoms, including bradykinesia, rigidity, rest tremor and postural instability (Postuma *et al.*, 2015; Gibb and Lees, 1988; for an overview see Figure 1). Motor symptoms in PD typically begin on one side of the body and this asymmetry tends to continue throughout the course of the illness. The average age at which symptoms first appear is in the late fifties, but onset can occur as early as under 40 years old or as late as over 80 years old (Poewe *et al.*, 2017).

Alongside the primary motor symptoms, most patients with PD also experience a range of non-motor symptoms. These non-motor symptoms encompass various functions and include disturbances in circadian rhythm regulation, cognitive function (such as difficulties with executive functions, memory, dementia, and hallucinations), autonomic dysfunction, mood and affect disorders, as well as sensory symptoms (particularly reduced sense of smell) and pain (Chaudhuri and Schapira, 2009; Poewe, 2008; see Figure 1). A review discussed that non-motor symptoms often precede the motor symptoms of PD and can serve as biomarkers for earlier diagnosis of the disease (Bang, Lim and Choi, 2021).

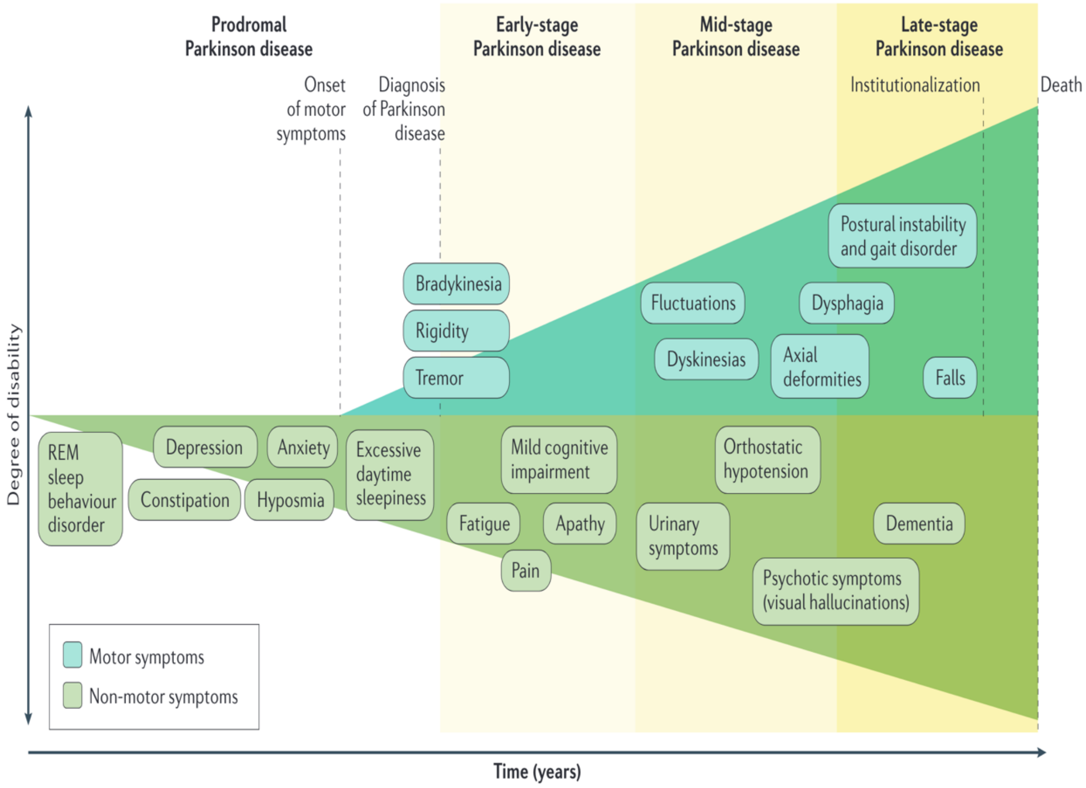


***Figure 1**: Motor and non-motor symptoms of Parkinson's disease (PD)*
Prodromal PD is characterized by non-motor symptoms, which can precede the onset of motor symptoms. The appearance of motor symptoms typically marks the clinical diagnosis of PD, often occurring at an early stage of the disease. Subsequently, the disease progresses through intermediate and advanced stages, with both motor and non-motor symptoms evolving over time. Source: (Poewe et al., 2017).

Dopamine replacement therapies remain the gold standard for treating dopamine-related motor symptoms in PD. However, non-motor symptoms generally do not improve with dopamine replacement therapy, which is primarily targeted at alleviating motor deficits (Ray Chaudhuri, Poewe and Brooks, 2018). Neglecting the treatment of non-motor symptoms can lead to a deteriorating disease prognosis and markedly diminish the quality of life in patients with PD (Sauerbier *et al.*, 2016).

Cognitive changes are increasingly recognized as a fundamental non-motor aspect of PD, having a major impact on the patient's quality of life, the strain on caregivers, healthcare usage, and mortality rates (Bock and Tanner, 2022). Individuals with Parkinson's disease face up to a sixfold higher risk of cognitive impairment compared to the general population (Aarsland *et al.*, 2001).

There are various approaches to therapy aimed at enhancing cognition in Parkinson's disease with mild cognitive impairment (PD-MCI) or Parkinson's disease with dementia (PDD), including both pharmacological and non-pharmacological strategies. Non-pharmacological interventions include techniques such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and cognitive training. However, the efficacy of these non-pharmacological therapies in treating PD-MCI remains under investigation (Sun and Armstrong, 2021; Zhang *et al.*, 2020).

Therefore, further research is needed to evaluate the effects of these approaches, as well as their potential synergistic benefits when combined with cognitive training, on cognitive function in individuals with PD.

1. 2. Parkinson and Cognition

i. Epidemiology

Cognitive decline is a prevalent non-motor symptom in Parkinson's disease (PD). This symptom often manifests as an intermediate stage between normal cognition and dementia. Recent studies have demonstrated that cognitive deficits can be detected during the prodromal phase of the disease, preceding the onset of motor symptoms (Weil, Costantini and Schrag, 2018). In the literature, it has been reported that the risk of developing dementia is 2.5 to 6 times higher in patients with PD compared to individuals of similar age without PD (Aarsland *et al.*, 2001; Perez *et al.*, 2012). In recent years, mild cognitive impairment (MCI) has been increasingly acknowledged as a significant prodromal stage of dementia in PD (Pan *et al.*, 2021). A longitudinal study estimated that approximately half of PD patients with normal cognition developed MCI within six years. Subsequently, these individuals progressed to Parkinson's disease dementia (PDD) within an additional five years (Pigott *et al.*, 2015). Early mild cognitive impairment in Parkinson's disease, whether it persists or reverts to normal cognition, holds prognostic significance for predicting the development of dementia in PD patients (Pedersen *et al.*, 2017). The same study reported that approximately 40% of patients with PD-MCI converted to PDD within five years. Therefore, MCI is increasingly recognized as a significant precursor stage of dementia in individuals with PD.

ii. Pathophysiology

The primary neuropathological features of Parkinson's disease (PD) include the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of alpha-synuclein in Lewy bodies, which initially affects cholinergic and monoaminergic neurons as well as the olfactory system (Poewe *et al.*, 2017). Cognitive decline in PD is associated with neurodegenerative brain changes, including the degeneration of neurotransmitter systems, abnormal accumulation of alpha-synuclein, and other genetic factors that may influence cognitive function (Aarsland *et al.*, 2021). Subsequently, the different aspects of the aforementioned changes in brain regions and their functions will be discussed in further detail.

Patients with Parkinson's disease (PD) experience a loss of dopaminergic neurons in the nigrostriatal pathway. Individuals with PD and mild cognitive impairment (PD-MCI) have a more widespread loss of dopaminergic neurons, particularly in the striatum, compared to PD patients without cognitive impairment (Sasikumar and Strafella, 2020; Aarsland *et al.*, 2021). When comparing PD-MCI to Parkinson's disease dementia (PDD), the dopaminergic neuron loss in PDD is even more extensive, affecting additional brain regions such as the temporal, frontal, and parietal lobes (Sasikumar and Strafella, 2020; see Figure 2). In healthy individuals, cortical dopamine modulation enhances working memory, visuospatial processing, and attentional processing, while also promoting cognitive effort (Ranganath and Jacob, 2016; Westbrook *et al.*, 2020). These indicate that dopamine plays a crucial role in cognitive function.

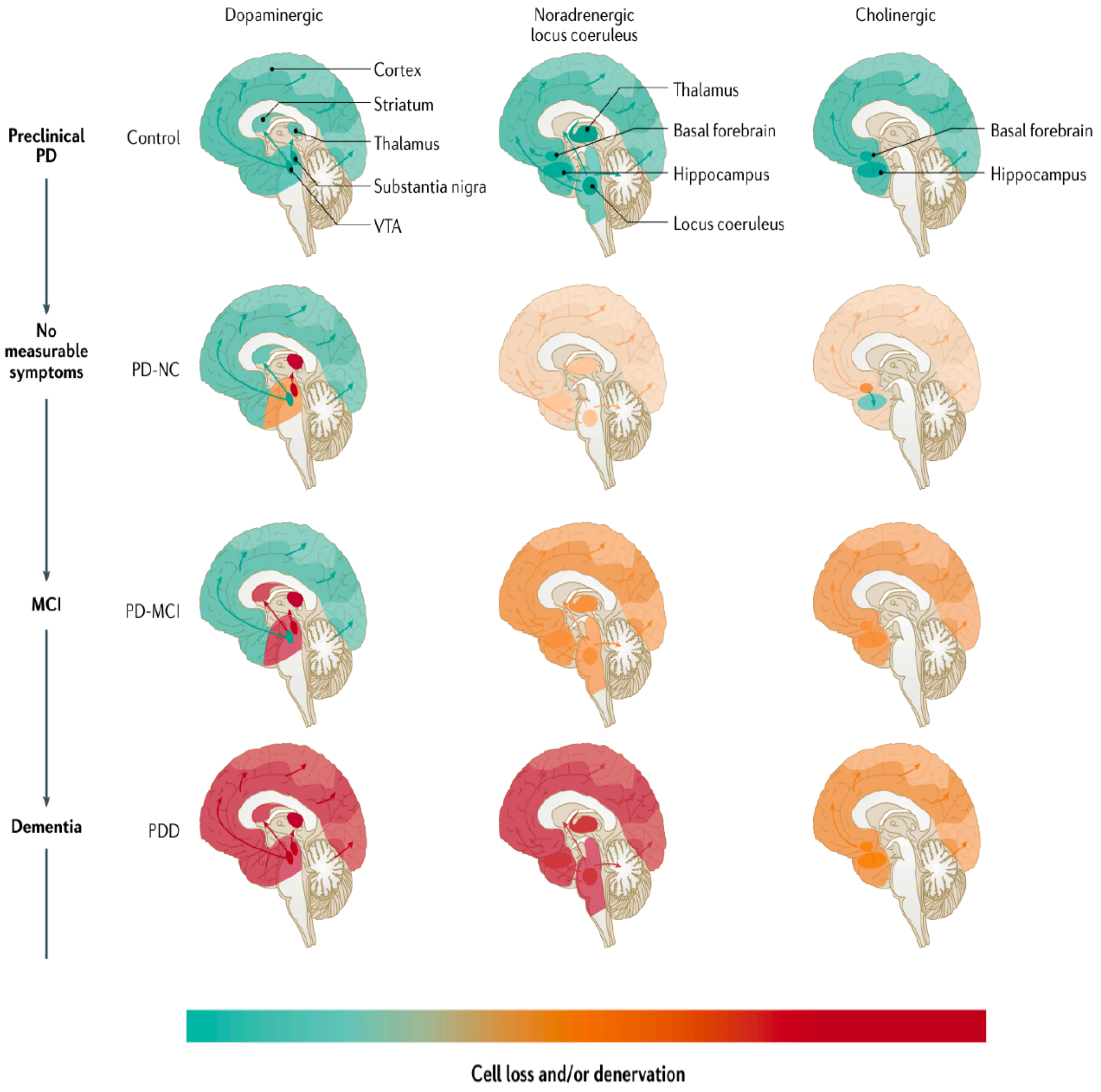


***Figure 2**: Association between neurotransmitter deficits and cognitive decline in PD*
In PD with mild cognitive impairment (PD-MCI), dopaminergic deficits initially manifest in the nucleus caudatus and later extend to the limbic and neocortical brain regions as the disease progresses to Parkinson's disease dementia (PDD). Similarly, noradrenergic and cholinergic deficits are present in the brains of individuals with PD, with these deficits becoming more widespread and severe as cognitive impairment increases. Source: (Aarsland et al., 2021).

Noradrenaline-synthesizing neurons located in the locus coeruleus contribute to various aspects of cognition, including working memory, attention, and behavioral flexibility (Borodovitsyna, Flamini and Chandler, 2017). Deficit in noradrenergic neurons in the locus coeruleus contribute to the pathophysiology of cognitive decline in patients with PD (Aarsland *et al.*, 2021). An association between the reduction of the MRI signal of the locus and the presence cognitive decline was found, furthermore the signal reduction was associated with orthostatic hypotension (Sommerauer *et al.*, 2018). Based on a previous review, a hypothesis suggests that cognitive decline in PD may be caused by cerebral hypotension, resulting from orthostatic hypotension in PD patients (McDonald, Newton and Burn, 2016).

The basal forebrain cholinergic system regulates brain circuits related to various aspects of cognition, such as attention, executive function, and memory (Ballinger *et al.*, 2016). Targeting the cholinergic system may also play a crucial role in causing cognitive decline in PD patients. The degeneration of the basal forebrain nuclei and the cortical cholinergic system is associated with the development of cognitive decline and other neuropsychiatric symptoms (Pasquini, Brooks and Pavese, 2021). While cholinergic degeneration independently contributes to the progression of cognitive impairment in PD patients, it also interacts with dopaminergic degeneration, resulting in a more pronounced cognitive decline (Bohnen *et al.*, 2015).

The aggregates of alpha-synuclein protein across various brain regions may have a fundamental impact on cognition (Smith *et al.*, 2020). A previous study suggested that plasma alpha-synuclein levels correlate with cognitive decline in PD patients, highlighting the underlying pathophysiology of alpha-synuclein (Lin *et al.*, 2017). Additionally, there is evidence that alpha-synuclein can transmit from affected neurons to neurons in other brain regions, leading to the progression of alpha-synuclein pathology throughout the brain (Henderson, Trojanowski and Lee, 2019).

Finally, the pathophysiology of cognitive decline in individuals with PD is multifactorial. It includes neurodegenerative changes in brain regions affecting neurotransmitter systems, the pathology of alpha-synuclein aggregates, and other genetic factors, all of which may contribute to cognitive impairment in PD patients.

1. 2. 1. Pharmacological Therapy

To address cognitive decline in patients with Parkinson's disease (PD), researchers have evaluated the effects of various pharmacological treatments on Parkinson's disease with mild cognitive impairment (PD-MCI) to determine their efficacy in improving cognitive function. This chapter discusses three drugs—rivastigmine, rasagiline, and atomoxetine—that target different neurotransmitter systems in the brain in an attempt to enhance cognition (Poewe *et al.*, 2017).

Rasagiline, a selective monoamine oxidase type B (MAO-B) inhibitor, enhances dopaminergic level in the brain, thereby exerting a beneficial effect in the treatment of PD (Oldfield, Keating and Perry, 2007). In a randomized controlled trial (RCT), significant improvements in digit span and verbal fluency total scores were reported in the group receiving 1 mg/day of rasagiline over a three-month period compared to the placebo group (Hanagasi *et al.*, 2011). In contrast, another RCT involving 151 participants did not find improvements in cognition when comparing the group receiving 1 mg/day of rasagiline with the placebo group (Weintraub *et al.*, 2016).

In a 24-weeks randomized, placebo-controlled study evaluating the efficacy of the rivastigmine transdermal patch, a cholinesterase inhibitor, in patients diagnosed with MCI, a total of 28 participants were enrolled. The study results indicated that treatment with rivastigmine did not demonstrate statistically significant improvements in cognitive function compared to the placebo group (Mamikonyan *et al.*, 2015). Another RCT study noted a delay in the progression of cognitive decline with rivastigmine treatment (Li *et al.*, 2015).

Atomoxetine, a selective norepinephrine reuptake inhibitor, is utilized in the treatment of attention deficit hyperactivity disorder (ADHD) (Kratochvil *et al.*, 2003). In a RCT assessing the effects of atomoxetine on cognition in patients with PD-MCI, no significant improvement was observed on cognitive tests. It is important to note that the study had a small sample size (n=30) (Hinson *et al.*, 2017). Additionally, a meta-analysis of three studies reported no significant improvement in complex attention and other cognitive domains following treatment with atomoxetine (Ghosh *et al.*, 2020).

Considering the aforementioned studies and their results, the pharmacological approach cannot be regarded as the therapy of choice for treating cognitive decline in PD-MCI. While a few studies have reported significant improvements, these findings are not consistent across all research. Therefore, alternative approaches should be assessed to determine their effects on cognition in PD.

1. 2. 2. Non-Pharmacological Therapy

As a non-pharmacological therapy, this section explores two prevalent non-invasive brain stimulation techniques utilized in the treatment or modulation of neurodegenerative diseases: transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) (Sanches *et al.*, 2021). These approaches will be further explained in detail, focusing on their mechanisms and impacts on the brain.

i. tDCS: transcranial direct current Stimulation

The transcranial direct current stimulation (tDCS) involves the application of a constant, low current (1-2 mA) between two electrodes placed on the scalp (Filmer, Dux, and Mattingley, 2014; Nitsche and Paulus, 2000; see Figure 3). The primary objective of this stimulation is to induce cortical polarization by modulating the membrane resting potential, thereby making neurons more or less likely to generate an action potential (Paulus, Peterchev and Ridding, 2013). Animal studies have demonstrated that anodal stimulation of the cortex induces depolarization of the membrane resting potential, whereas cathodal stimulation results in hyperpolarization of the membrane (Bindman, Lippold and Redfearn, 1964; Purpura and Mcmurtry, 1965; see Figure 3). In a human study examining the interaction of tDCS stimulation and drugs, it has been reported that channel blockers such as carbamazepine and flunarizine reduce cortical excitability following anodal stimulation (Nitsche *et al.*, 2003). Conversely, these drugs have no effect after cathodal stimulation (hyperpolarization) (Nitsche *et al.*, 2003). This lack of effect may be attributed to the hyperpolarization induced by cathodal stimulation, which inactivates the channels. These findings underscore the modulating effect of tDCS on the neural membrane.

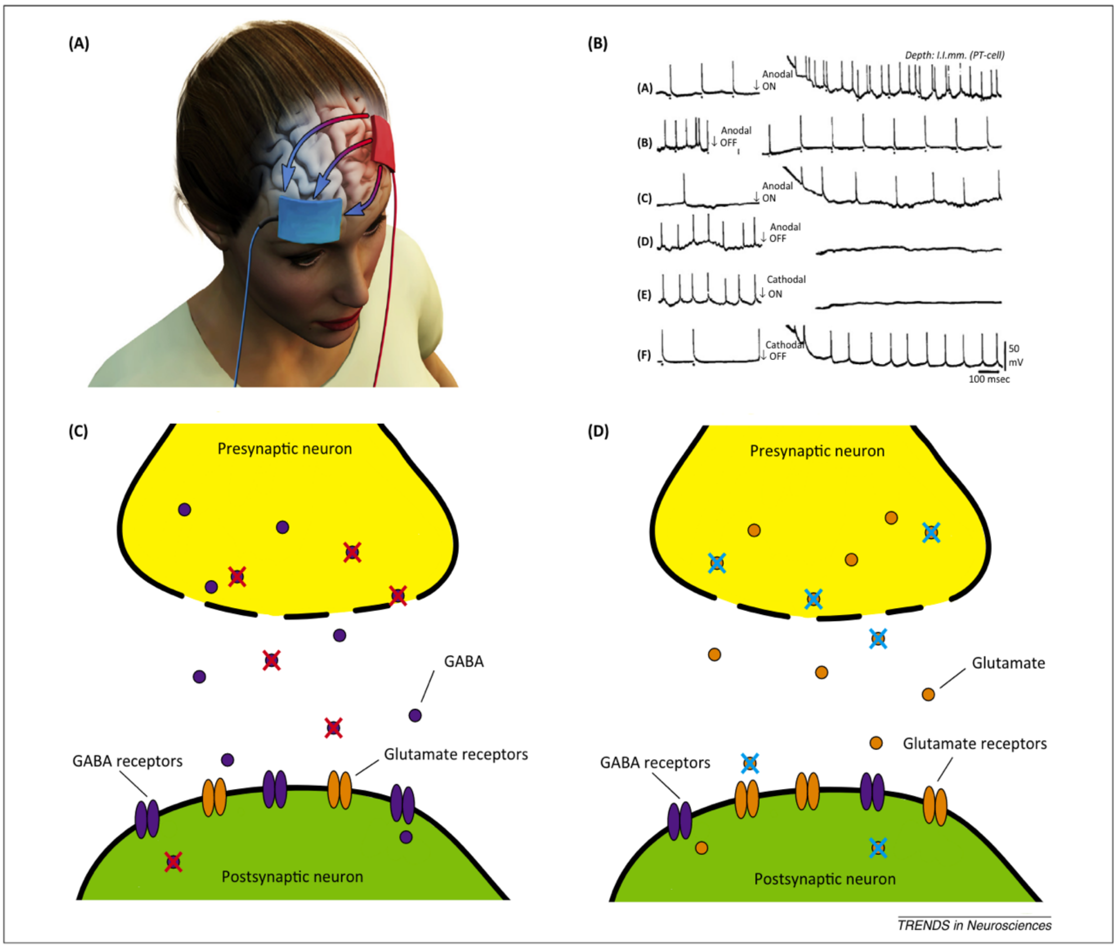


***Figure 3**: The neurobiological mechanism and effect of tDCS*

A) Electrode Placement: Electrodes for tDCS are placed on the cortex. The anode is positioned over the prefrontal cortex (red), while the cathode is placed on the orbitofrontal region. Current flows between the electrodes from the anode to the cathode. B) Neuronal Firing Rates: Neuronal firing rates vary under different electrodes. The anode increases the firing rate of neurons, whereas the cathode decreases it. C) GABAergic Synaptic System: Anodal stimulation via tDCS inhibits GABA transmission (reproduced from Purpura and Mcmurty 1965). D) Glutamatergic Synaptic System: Cathodal stimulation via tDCS inhibits glutamate transmission. Source: (Filmer, Dux and Mattingley, 2014).

Furthermore, the literature describes a decrease in GABA transmission after anodal stimulation (Stagg *et al.*, 2009; Medeiros *et al.*, 2012). Additionally, cathodal stimulation inhibits the glutamate transmission (Liebetanz *et al.*, 2002; Medeiros *et al.*, 2012; see Figure 3). By altering neurotransmitter systems, tDCS play a role in modulating neuroplasticity, which is an important factor in clinical treatment (Filmer, Dux and Mattingley, 2014). In summary, the effects of tDCS on neuronal cells in the brain extend beyond modulating the resting membrane potential. tDCS also influences synaptic transmission, which in turn affects the plasticity of neuronal structures.

The neurobiological mechanisms and the endogenous induction processes of synaptic neuroplasticity through tDCS remain largely unexplored. Therefore, investigations will be carried out using animal models. A study conducted by Kronberg et al. (2017) described the role of tDCS as a modulator of Long-Term Potentiation (LTP) and Long-Term Depression (LTD), as a possible elucidation of the modulation of endogenous synaptic induction. Specifically, tDCS was shown to enhance LTP and reduce LTD (Kronberg *et al.*, 2017). A systematic review also examined the mechanisms by which tDCS enhances neuroplasticity and cognition in animal models. The enhancement is attributed to LTP, the upregulation of brain proteins such as N-Methyl-D-Aspartate (NMDA) receptors and Brain-Derived Neurotrophic Factor (BDNF) (Cavaleiro *et al.*, 2020). The literature reports the crucial role of BDNF in learning, memory, and synaptic plasticity (Kowiański *et al.*, 2018)

Regarding cognition, there is a body of literature describing the application of tDCS to affect cognition. An improvement in executive function and delayed recall was reported in a RCT involving individuals with PD-MCI (n=26) after 5 days of tDCS administration over the dorsolateral prefrontal cortex (DLPFC) (Aksu *et al.*, 2022). Another RCT also reported enhanced executive function in individuals with PD without dementia after applying tDCS over the prefrontal cortex (Doruk *et al.*, 2014). A single-session tDCS over the prefrontal cortex did not result in significant cognitive improvement in non-demented individuals with PD (Lau *et al.*, 2019). These findings may underscore the impact of the parameters included in the tDCS protocol on the effectiveness of this method. Furthermore, attentional function was not improved after a single session of tDCS applied over the left prefrontal cortex in a study involving demented individuals with PD (Elder *et al.*, 2017).

ii. TMS: Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive method, developed in the mid-1980s by Anthony Barker (Barker, Jalinous and Freeston, 1985). It used to stimulate specific regions of the brain. A magnetic coil generates a brief, high-intensity magnetic field over a targeted brain area, altering the excitability of the affected region. Repetitive stimulation of brain areas can influence their function, making TMS valuable for various clinical and therapeutic purposes (Hallett, 2007).

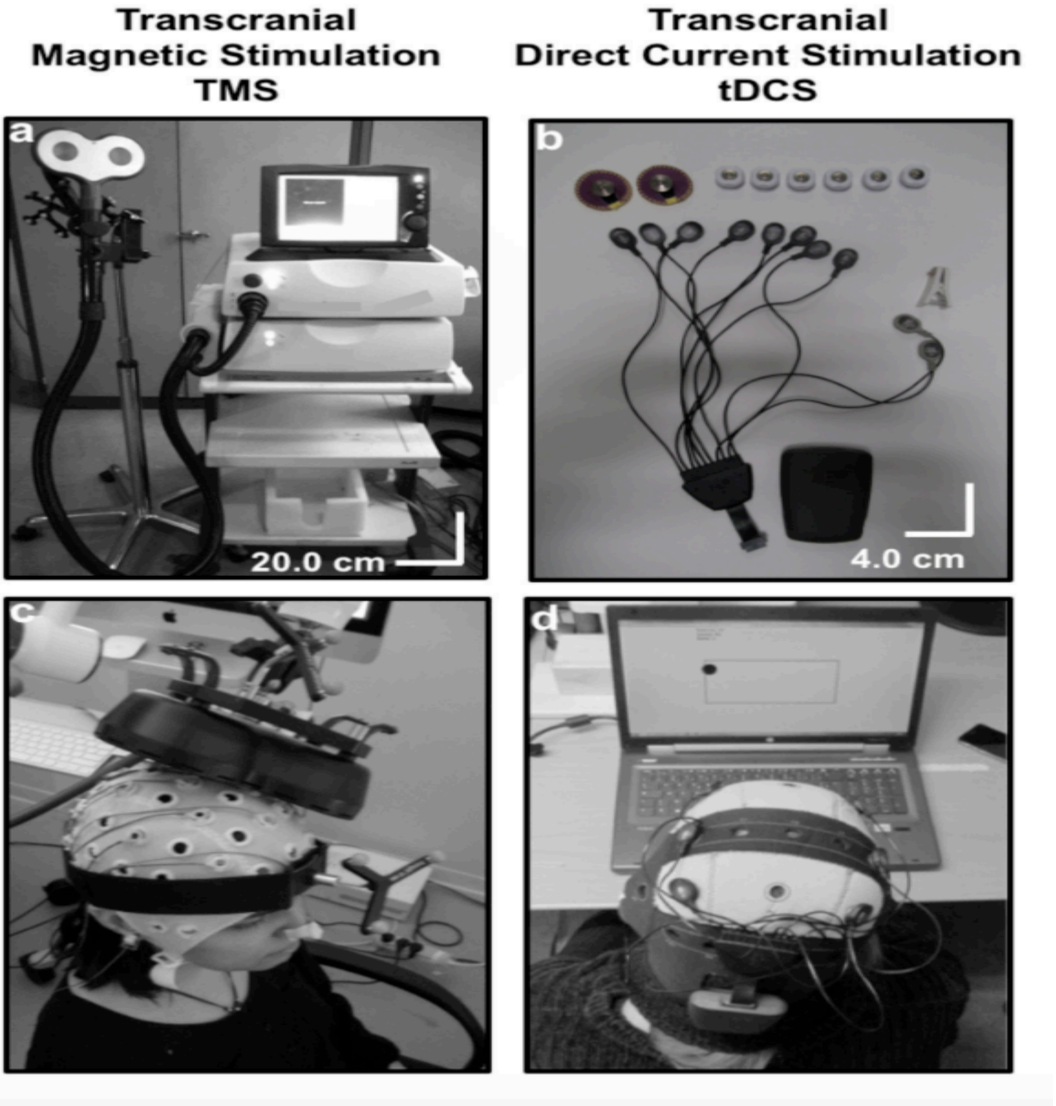


***Figure 4**: Equipment and use procedures for TMS and tDCS*
a+c) Upper image: TMS equipment, which is heavy and non-portable, delivers electrical currents through a coil (e.g., a 70 mm butterfly-shaped coil, as depicted in the image). The design of the coil and the pulse intensity, determine both the penetrability and the current density achieved at the targeted cortical area. Bottom image: A TMS coil is positioned on the targeted area of the scalp. Participants must remain still to ensure accurate and consistent stimulation. b+d) Upper image: The tCS device, which is portable and powered by a battery system, is controlled via a computer or control device. It typically involves at least two leads—one for the cathode and one for the anode—placed on the scalp to deliver current. Bottom image: The tDCS device is mounted using a cap worn by the participant. Unlike TMS, tDCS can be controlled wirelessly and is compatible with patient movement. Source: (Sanches et al., 2021).

TMS involves passing a short-lasting electrical current through a coil placed on the head. This generates a magnetic field perpendicular to the coil, which in turn induces an electrical current in the stimulated area. This electrical current depolarizes the membranes of neurons. If the threshold for firing an action potential is reached, the neuron generates an action potential. This is the basic concept of TMS at the neuronal level (Siebner *et al.*, 2022), which differs from the basic concept of tDCS (see Figure 4).

To understand the effect of TMS in modulating synapses and synaptic proteins, various studies have been conducted. An animal study describes the association between the increase of synaptic proteins, such as BDNF, following rTMS stimulation and the enhanced spatial cognition and synaptic plasticity (Shang *et al.*, 2016).

Changes in the brain caused by rTMS have been found to be related to the frequency of the stimulation. rTMS with higher frequencies (>5 Hz) is more likely to produce cortical excitability, whereas frequencies around 1 Hz decrease the excitability of the cortex (Hoogendam, Ramakers and Di Lazzaro, 2010). A systematic review describes that high-frequency rTMS (10-20 Hz) over the DLPFC is more likely to significantly improve cognitive function in patients with neurological or psychiatric diseases (Guse, Falkai and Wobrock, 2010). On the other hand, no significant effects on cognition were found with low-frequency rTMS (≤1 Hz) applied to various brain regions, including the DLPFC (Lage *et al.*, 2016). An alleviation of cognitive impairment was also observed in aged mice after the application of high-frequency rTMS (Ma *et al.*, 2019).

The effect of TMS on cognition in individuals with PD-MCI is controversial in the literature. A RCT involving individuals with PD-MCI (n=46) was conducted to evaluate the impact of rTMS on cognitive function. The trial did not demonstrate a significant improvement in overall cognition in the intervention group, which received 20 Hz rTMS over the bilateral DLPFC for two weeks (Buard *et al.*, 2018). In contrast, another study investigated the effects of intermittent theta-burst stimulation (iTBS) on individuals with PD-MCI (n=24). Participants received stimulation of the left DLPFC for three days (twice a day), resulting in an enhancement of overall cognition that lasted up to one month (Trung *et al.*, 2019). In recent literature, differences in the efficacy of various TMS modalities in enhancing cognitive function in PD patients have been reported. High-frequency TMS demonstrated significantly superior efficacy in improving cognition compared to low-frequency TMS and intermittent Theta Burst Stimulation (iTBS) in individuals with PD (Yang *et al.*, 2024). Furthermore, the number of sessions of rTMS may influence cognitive function and produce superior effects on cognition, as mentioned in a meta-analysis conducted on patients with Alzheimer's disease (AD) (Wang *et al.*, 2020). Additionally, the cortical region targeted for stimulation, specifically the right or left DLPFC, may exert differential effects on cognitive function (Turriziani, 2012)

These findings underscore the impact of the parameters included in the TMS protocol on the effectiveness of this method, such as the frequency modality, the number of sessions, and the site of brain stimulation. Nonetheless, the method could play a crucial role as a therapy for PD-MCI or at least as an adjunctive effect. Therefore, further research is needed to better determine its effects.

1. 3. Combining of NIBS and Cognitive Training: Add-on-Effect

Non-invasive brain stimulation (NIBS) methods have recently been widely used to determine their effect on cognition in individual with cognitive decline. Many studies in the literature describe a potential positive effect on the improvement of cognition and the potential use of NIBS as a therapeutic tool (refer to Section 1. 2. 2.). Research has also explored the additive effect of combining NIBS with cognitive training by individuals with neurological disease or psychiatric disorder, which appears to have a greater effect than either method alone (Lawrence *et al.*, 2018; Manenti *et al.*, 2018; Rodella *et al.*, 2022).

A RCT involving individuals with PD-MCI (n=42) compared the effects of different approaches (standard cognitive training, tailored cognitive training, tDCS, tDCS combined with standard or tailored cognitive training, and a control group) on cognitive function. Cognitive function was statistically improved after the interventions compared to the control group, with the most significant improvement observed in the groups combining tDCS with cognitive training (standard or tailored) (Lawrence *et al.*, 2018). Another RCT conducted by Manenti et al. (2018) reported an additional significant effect of computerized cognitive training alongside tDCS (over the left DLPFC) on cognitive performance and mood disturbances in individuals with PD (n=22). Compared with sham tDCS combined with computerized cognitive training, the cognitive functions related to the prefrontal cortex -such as language, attention, and executive function- were enhanced after active tDCS (Manenti *et al.*, 2018).

A meta-analysis conducted to determine the effect of combining cognitive training and tDCS in neuropsychiatric disorder populations observed a small but significant positive effect on measures of attention and working memory when comparing post-treatment to pre-treatment results. Conversely, tasks assessing global cognition and language did not reveal a statistically significant effect (Burton *et al.*, 2023). Another meta-analysis evaluating the efficacy of NIBS (tDCS or TMS) on global cognition in individuals with AD and MCI, compared to sham stimulation, found improvement in global cognition after administering active NIBS in the AD population. The effect on global cognition being greater after active rTMS than in the tDCS group, where the improvement was non-significant. The same study found no beneficial effects on global cognition after cognitive training as adjunctive therapy to the NIBS (Teselink *et al.*, 2021).

The potential synergistic effects of Non-Invasive Brain Stimulation (NIBS) combined with cognitive training may yield greater positive outcomes for individuals with PD and cognitive dysfunction, compared to either of the methods alone. Consequently, this question constitutes a primary focus of this thesis, which is extensively addressed herein.

1. 4. **The aim of the research**

Cognitive changes are now widely acknowledged as a crucial non-motor feature of Parkinson's disease, affecting the patient's quality of life, increasing the burden on caregivers, influencing healthcare utilization, and impacting mortality rates (Bock and Tanner, 2022). Individuals with PD face up to a sixfold higher risk of cognitive impairment compared to the general population (Aarsland *et al.*, 2001).

Various therapeutic approaches are being explored to enhance cognition in individuals with PD and cognitive decline, encompassing both pharmacological and non-pharmacological strategies. Non-pharmacological interventions include methods such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and cognitive training. Nevertheless, the effectiveness of these non-pharmacological treatments for cognitive dysfunction in PD patients is still under investigation (Sun and Armstrong, 2021; Zhang *et al.*, 2020).

Research has also examined the synergistic effects of combining NIBS with cognitive training in individuals with neurological diseases or psychiatric disorders. Findings indicate that this combined approach may be more effective than using either method alone (Lawrence *et al.*, 2018; Manenti *et al.*, 2018; Rodella *et al.*, 2022). Therefore, the aim of this thesis was to conduct a systematic review and meta-analysis to investigate the effects of NIBS, as well as its synergistic effect when combined with cognitive training, on cognition in individuals diagnosed with PD.

This thesis will address the following research questions:

i. What is the impact of non-invasive brain stimulation (NIBS), specifically transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS), on cognitive function in individuals with Parkinson's disease and cognitive impairment?

ii. Does the integration of NIBS with cognitive training produce a superior effect on cognitive function compared to NIBS alone in individuals diagnosed with Parkinson's disease and cognitive impairment?

iii. What are the effects of these interventions on mood and quality of life in individuals with Parkinson's disease, considered as secondary outcomes?

2. Methods

The current study is a systematic review and meta-analysis, conducted to examine the efficacy of non-invasive Brain Stimulation (NIBS) when combined with cognitive training or administered alone in patients diagnosed with Parkinson's disease (PD). The systematic review and meta-analysis were conducted in accordance with the Preferred Report Items of Systematic Review and Meta-analysis (PRISMA) (Moher *et al.*, 2009).

The Study was divided to tow research sections. Each research section was conducted by R.M. or J.E., each addressing a specific research question. The specific research section reported in this thesis was conducted by R.M.

2. 1. Study design

2. 1. 1. Eligibility criteria

PICOT criteria were employed to define the participants, intervention, comparison, outcomes, and timing involved in the systematic review. Only studies that aligned with the specified PICOT criteria were considered for inclusion (refer to PICOT Table 4 in Appendices).

- **Study Types:** The systematic review included only randomized controlled trials with both intervention and control arms. Multi-arm studies containing relevant information regarding the research question of the systematic review were also considered. On the other side, consensus studies, cross-over studies, prospective observational cohort studies or another type of studies with lower evidence than randomized controlled trials were excluded.
- **Participants**: The study included individuals diagnosed with idiopathic PD, either with normal cognition with mild cognitive impairment (MCI), aged 50 years or older. Individuals with other neurodegenerative and psychiatric diseases were excluded. No restrictions were applied regarding sex, education level or disease duration. To investigate the effect of the intervention on the participants, it was important to ensure that the cognition of the participants was either normal or with mild cognitive impairment. The study didn't include patients in the late stage of Parkinson's disease.
- **Intervention:** The studies involved Non-Invasive Brain Stimulation (NIBS) combined with cognitive training (CT) or administered alone as intervention. The NIBS methods included in the systematic review were as follows:
    - Transcranial direct current stimulation
    - Transcranial magnetic stimulation
    - Transcranial alternating current stimulation

  The cognitive training (CT) consisted of either standard cognitive training with various tasks or computerized cognitive training.
- **Comparator:** The intervention group was compared with a control group that received either cognitive training alone or sham NIBS alone or combination of

cognitive training with sham NIBS (refer to PICOT Table 4 in Appendices for more details).

- **Outcomes:** The primary outcome considered was the effect of the intervention on cognition in patients diagnosed with PD. Cognition was measured either with cognitive tests such as, the Mini-Mental-Status-Test (MMSE), the Parkinson's Disease-Cognitive Rating Scale (PD-CRS), the Montreal Cognitive Assessment (MoCA), or with study-specific tests. Both types of measures were included and further examined for equivalence.

  Quality of Life, mood and adverse events were included as secondary outcomes.
- **Timing:** The outcomes were assessed both pre- and postintervention. Follow-up assessments were also included.

The purpose of this systematic review and meta-analysis was to search published articles among the database and to select the studies, that investigate the effect of NIBS or cognitive training, or NIBS combined with cognitive training on the cognition in patients with PD.

2. 1. 2. Search strategy

At the first, synonyms were researched to create a search string. This step was conducted by R.M. and M.R. (refer to Table 5 in Appendices).

The search in the databases was performed without restricting the year until 05.02.2022. The following databases were searched: PubMed, MEDLINE, and EMBASE. The search strategy was performed and proved by M.R. Below is an example for the search string:

((Parkinson OR Parkinson's OR PDD OR PD-MCI) AND (non-invasive brain stimulation OR tDCS OR rTMS OR t-DCS OR cognitive training OR brain training OR training)).

2. 2. Study selection

The identified studies were exported for screening into Abstrackr. (Byron C. Wallace, 2012). Two reviewers (R. M. and A. M.) screened the titles and abstracts of the studies. If a study met the criteria for inclusion based on title and abstract, it proceeded to the next stage of screening of the full text, otherwise, it was excluded. The studies were independently screened by the two reviewers (R. M. and A. M.). The total number of identified studies was 1856.

After Screening we summarized the included studies in an excel table to assess consensus between the two researchers. If a study matched in the two independent screenings, it proceeded to the next stage involving a full text review. In case of mismatch in the two independent screenings, the study was excluded. If disagreements arose between the reviewers, a discussion regarding the study's suitability was initiated, and if further disagreements persisted, M. M. was involved in resolution of disagreements.

We totally screened 1856 studies in Abstrackr. (Byron C. Wallace, 2012). After assessing consensus and discussing mismatched assessments, as well as resolving the disagreements by M. M., 128 studies were included in the next level involving full-text review.

At the end, we searched for the full text of the 128 studies in the database and downloaded the corresponding PDF file. We observed that 27 studies were duplicates and other were excluded due to different criteria (refer to section 2. 1. 1.). Consequently, the final number of studies included in the full-text review was 83.

2. 3. Data extraction

For this systematic review, 1865 titles and abstracts for suitability regarding the PICOT and eligibility criteria were screened. Out of this total, 128 studies were assessed as reaching consensus among the reviewers (R.M., A.M.). After searching the full-text of these 128 studies and eliminating duplicates and unsuitable studies, the final number of studies proceeding to the full-text review was 83. These 83 studies were divided into two parts (part 1 included 42 studies, part2 included 41 studies). Part 1 was reviewed by R.M., and part 2 by J.E.

During the full-text review, the studies were meticulously examined by the reviewers, and their eligibility was assessed based on the predefined PICOT criteria. For a study to be included in the data extraction stage of the systematic review, the participants, intervention, comparison, outcomes, and timing had to align with the abovementioned criteria. Only the studies meeting these criteria were included in the systematic review and subsequent meta-analysis.

The studies that met the PICOT criteria after a full-text review were included in the data extraction. Various data from each study were then extracted and compiled into an word table. The extracted data included the following:

- Study name, year of publication
- Study design
- Behavioral training details (Intervention and Control group)
- NIBS training details (Intervention and Control group)
- Population information (Overall number of participants, participants' number per arm, age, gender, dropped-out participants)
- Timepoints (pre- and postintervention measurements, Follow-up)
- Outcomes (primary, secondary)
- Results (assessment of outcomes, significance)

To elucidate the method and the data extraction process used in this systematic review and meta-analysis, a Data Extraction Table was created, encompassing various data and detailed description (see Table 1).

***Table 1**: Description of Data Extracted from Full Texts*

Study	The study name and year of publication were extracted to identify the large number of studies
Design	Describing the study type, such as Randomized Controlled Trials (RCT), and providing an in-depth exploration of the study design approach, specifically whether it adopts a single or double-blind design, and assessing their respective impacts one the overall study
Behavioral training	Encompassing the approach of the cognitive training (standardized, individualized) and detailing the intensity/ duration per session, per week and over the therapy period for both intervention and control groups
NIBS training	Encompassing the method of NIBS used (tDCS, TMS, tACS), the stimulated side of the head, the stimulated brain region and detailing the intensity/ duration per session, per week and over the therapy period, including the applied current if mentioned for both intervention and control groups
Population	Mentioning the overall number of participants in the study, the number of participants per arm/ group (intervention/ control), and the dropped-out participants. Additionally, other details such as age, and gender (gender ratio) are included to assess their impact on the overall study
Timepoints	Elucidating the timepoints of outcome measurements, including pre- and postintervention, and further follow-ups conducted in the study
Outcomes	Extracting the primary and secondary outcomes of the study aligned with the PICOT criteria. The main outcome is cognition, and the secondary outcomes include quality of life and mood (depression)

Results	Evaluating the extracted outcomes, assessing the effect, and determining the significance of the intervention

After undergoing a thorough full-text review by R.M. and J.E., and in alignment with the PICOT criteria, N=42 of studies was included in the systematic review (see Figure 5). At this juncture of the study, each reviewer focused on different aspects of the overall systematic review and the primary research question. The present thesis was specifically concerned with the efficacy of NIBS combined with cognitive training or administered alone, to enhance cognitive outcomes in patients with PD. The methods and outcomes will be described in subsequent sections (Systematic Review and Meta Analysis).

2. 4. Systematic Review and Meta-Analysis

In addition to the Systematic Review, a meta-analysis was undertaken to empirically assess the research question pertaining to the effectiveness of combining of Non-Invasive Brain Stimulation (NIBS) with cognitive training or NIBS alone in the enhancement of cognitive functions among patients diagnosed with Parkinson's disease.

A total of 12 studies were identified and included in the analyses. These studies were meticulously organized into a tabular format, considering the outcomes measured as well as the specific tests employed to assess these outcomes.

To conduct a comprehensive meta-analysis, it was imperative to identify a minimum of three studies employing identical interventions and measuring similar or analogous outcomes through comparable tests. In instances where measurements or information about the used tests were absent in a study, efforts were made to obtain the missing information from the respective authors within a14-days period. In the absence of the requisite information within this timeframe, the study was excluded from further consideration in the meta-analysis. Following the exclusion of inappropriate studies and those lacking detailed descriptive information on outcomes six studies were eliminated from the initial pool of N=12 (refer to Figure 6). The ensuing meta-analysis comprised six studies. Of these, three studies used Transcranial Direct Current Stimulation (tDCS) in conjunction with cognitive training, while the remaining three studies employed Transcranial Magnetic Stimulation (TMS) as the sole intervention. The following studies were included in the meta-analysis: (Manenti *et al.*, 2018; Lawrence *et al.*, 2018; Biundo *et al.*, 2015; He, Wang and Tsai, 2021; Zhuang *et al.*, 2020; Wei *et al.*, 2022).

The NIBS modality employed in the studies conducted by (Manenti *et al.*, 2018; Lawrence *et al.*, 2018; Biundo *et al.*, 2015), was tDCS. TMS was utilized in other investigations, specifically (He, Wang and Tsai, 2021; Zhuang *et al.*, 2020; Wei *et al.*, 2022).

In this segment of the study, four meta-analyses were conducted to explore the effects of the intervention involving tDCS combined with cognitive training as compared to cognitive training alone on cognition of individuals diagnosed with PD. The investigation focused on five distinct domains of cognition in patients with PD: global cognition, attention & working memory, immediate memory and delayed memory, and an additional meta-analysis was performed to assess impact of the same intervention on Quality of Life (refer to section 3. 3. 1).

Examining the effect of TMS as the exclusive intervention against sham TMS, a meta-analysis was executed to investigate its impact on global cognition in patients with PD (refer to section 3. 3. 2.).

2. 3. Statistical Analysis

The meta-analyses were conducted using the program RStudio (Posit team, 2024). The extracted data for each included study in a meta-analysis was entered into RStudio. These data involved the sample size, the mean difference, and the mean difference of the standard deviation for both intervention and control groups. The required data were extracted from the included studies, the calculation of the mean difference or the standard deviation were done as follow:

For the Intervention group:

- Me (Mean; intervention) =Me postintervention-Me preintervention
- Se (Standard deviation; intervention) =Se postintervention-Se preintervention

For the control group:

- Mc (Mean; control) =Mc postintervention-Mc preintervention
- Sc (Standard deviation; control) =Sc postintervention-Sc preintervention

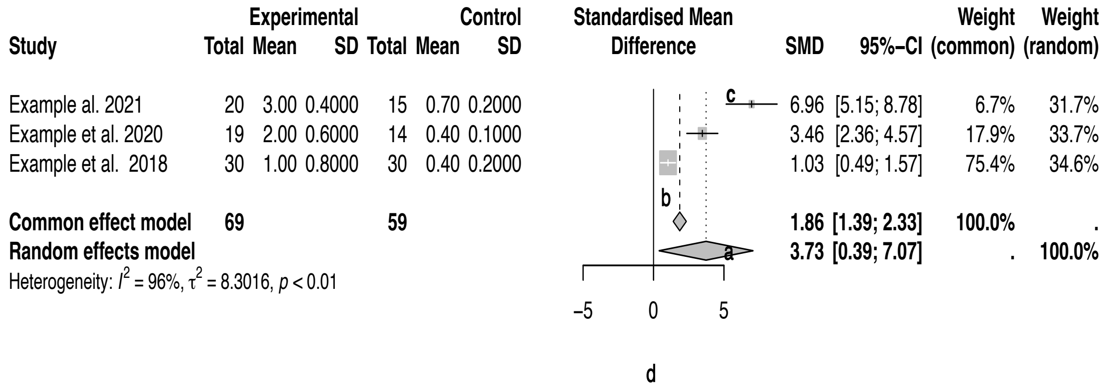
In the studies where the statistical data wasn't available or clarified, a request was sent to the author requiring the full statistical data within 2 weeks. In the case of Trung et al. 2019, the author was sent a request but without answer. Due to the missing data, the study was excluded.

The meta-analyses were computed using the "meta" package in RStudio. To quantify the effect size of the intervention used in the studies as compared with the control group, on the respective cognitive domains, the standardized mean difference was calculated. This approach allows comparison of finding across studies while evaluating a common outcome, despite using distinct methodologies for its measurement. It gauges the difference in mean of outcomes between groups, normalized in relative to the standard deviation of these outcomes (Deeks, Higgins and Altman, 2008). To interpreted the effect size of the standardized mean deviation (SMD) following guidelines were used (Cohen, 1988): small (*SMD=0.2*), medium (*SMD=0.5*) and large magnitude (*SMD=0.8*) . A random-model effect as well a fixed-model effect were calculated for each meta-analysis. To conduct a meta-analysis with a random-effect model, the inverse-variance method was employed, incorporating studies that assess different yet related intervention effects (Deeks, Higgins and Altman, 2008). This methodology, which integrates the heterogeneous intervention effects of different studies into an overall intervention effect, is recognized as the DerSimonian and Laird method (DerSimonian and Laird, 1986). Fixed-effect meta-analyses ignore the heterogeneity of intervention effects, estimating a single intervention effect. Furthermore, the overall effect of the fixed-effect model meta-analyses does not incorporate the disparity of the intervention effects across the studies. Due to this fact, it is merely mentioned but not interpreted (Deeks, Higgins and Altman, 2008). It is assumed that heterogeneity across studies is unavoidable due to differences in the clinical diversity and methodologies (Higgins *et al.*, 2003). To assess the impact of the heterogeneity across the studies in the meta-analyses, a statistical test I^2 ,with a confidence interval and p value was used, and interpreted as follows (Deeks, Higgins and Altman, 2008):

- I^2 *=0%-40%*: might not be important
- I^2 *=30%-60%*: moderate heterogeneity
- I^2 *=50%-90%*: substantial moderate heterogeneity
- I^2 *=75%-100%*: considerable heterogeneity

Findings are displayed as forest-plots, a graphical display describing the results of the meta-analyses clear and concise.

A forest plot presents the results of studies both numerically and graphically. It includes the study name, number of participants, mean difference, standard deviation, and the calculated standardized mean difference for both control and intervention groups. Furthermore, it displays the weight of each study; generally, studies with a large number of participants provides more information and thus have a greater weight in the analysis. This weighting reflects the degree of influence each study has on the overall pooled estimate of the effect size. The graphic representation consists of horizontal lines, boxes, a vertical line of no effect, and a diamond. Furthermore, it provides estimates effect of the single studies, the overall pooled estimate effect of all studies and test of heterogeneity (Dettori, Norvell and Chapman, 2021). Below is an example of a forest plot with accompanying details (see Figure 5).



Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight (common)	Weight (random)
Example al. 2021	20	3.00	0.4000	15	0.70	0.2000	6.96	[5.15; 8.78]	6.7%	31.7%
Example et al. 2020	19	2.00	0.6000	14	0.40	0.1000	3.46	[2.36; 4.57]	17.9%	33.7%
Example et al. 2018	30	1.00	0.8000	30	0.40	0.2000	1.03	[0.49; 1.57]	75.4%	34.6%
Common effect model	**69**			**59**			**1.86**	**[1.39; 2.33]**	**100.0%**	**.**
Random effects model							**3.73**	**[0.39; 7.07]**	**.**	**100.0%**

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 8.3016$, $p < 0.01$

***Figure 5**: Forest Plot*

Positioned on the right side of the diagram is a comprehensive numerical description of the studies encompassed within the meta-analysis. This section features three primary columns including the study name, the intervention group (experimental), and the control group. Within each group, there are further three additional columns providing the number of participants, measurements of mean difference and standard deviation respectively denoted as Total, Mean and SD. Moreover, the standardized mean difference, confidence interval and the weight of each study are prominently displayed. At the conclusion of the diagram, the assessment of the random and fixed model effect is presented. The overall pooled effect size of all studies together is presented with a diamond (a). The squares represent the estimate effect of size of each study (b). The width line extending through the square corresponding to a study represent the confidence interval, which is the range within which the effect size of the intervention could lie with

95% certainty (c). The null line denoted by a letter (d) representing the no effect line. Crossing the line would indicate no significant effect of the intervention, while lying on the right of the line without crossing it would signify a significant effect of the intervention. In the lower-left corner of the diagram, the assessment of the heterogeneity test (I^2) is prominently displayed (Explanation reproduced from (Dettori, Norvell and Chapman, 2021)).

2.4. Risk of bias

To assess the risk of bias within the studies, the RoB 2.0 tool was employed, which represents a revised framework for evaluating bias in randomized trials (Sterne *et al.*, 2019). Utilizing the provided word templates and comprehensive guidance accompanying the tool, each study was systematically evaluated across five specific domains. The domains encompassed bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported results pertaining to the effect of assignment to intervention. Each domain was scrutinized through a series of signaling questions, to which responses were categorized as ‘yes’, ‘probably yes’, ‘no’, ‘probably no’ or ‘no information’. The determination of the bias judgment of each specific domain followed predefined algorithm delineated in the guidance. Three potential choices were available for the bias judgment, namely low risk, some concerns or high risk (Higgins *et al.*, 2023).

At the end, the various bias judgments of the specific domains within a study were synthesized to determine the overall bias of the study. To present the overall risk of bias of a specific study the following categorization was employed (Higgins *et al.*, 2023):

- **Low risk**: This designation was assigned when all domains were judged to present a low risk of bias
- **Some concerns**: This classification was attributed when at least one domain was deemed to present some concerns
- **High risk**: This categorization was applied when at least one domain was assessed to present high risk of bias, or when multiple domains were determined to present some concerns

Different colors are utilized to represent varying levels of bias, as well the overall bias of the studies. The assessment was conducted by (R. M.). To the detailed assessment refer to (Table 3).

3. Results

The systematic review commenced with an exhaustive search within scientific databases, yielding a total of 1865 studies. The initial screening process involved the assessment of titles and abstracts for alignment with the PICOT (Population, Intervention, Comparison, Outcome, Time) criteria and eligibility standards. Subsequently, 1737 studies were excluded during this phase due to a variety of reasons, failing to meet the specified criteria. Upon completion of the initial screening, 128 studies remained. After eliminating duplicates and the exclusion of studies lacking accessible content or presenting a different study design, as predetermined, 83 studies proceeded to the subsequent level of examination of the full text articles. From the remaining pool of 83 studies encompassed within the systematic review, a total of 12 studies were subjected to the meta-analysis conducted within the confines of this study. After assessment of the full-text articles by the reviewers, a subset of 6 studies was deemed ineligible, resulting in their exclusion from the final analysis due to non-compliance with predetermined eligibility criteria (refer to PRISMA diagram; Figure 6).

To document the progression of the study selection leading to those included in the meta-analysis, a visual representation in the form of follow diagram, as Preferred Reporting Items for Systematic Reviews an Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009), was employed (see Figure 6).

3. 1. Systematic Review: Description of the included studies

In this meta-analysis, a total of 12 studies were considered, with Non-Invasive-Brain-Stimulation (NIBS) as the intervention modality in Parkinson's disease patients. Six studies met the inclusion criteria. The following six studies were excluded: (Trung *et al.*, 2019; Aksu *et al.*, 2022; Suárez-García *et al.*, 2021; Doruk *et al.*, 2014; Hill *et al.*, 2020; Khedr, Mohamed, *et al.*, 2020; Trung *et al.* 2019) was eliminated due to insufficient required for conducting a meta-analysis. The studies conducted by, Suárez-García et al. (2021), Aksu et al. (2022), Doruk et al. (2014), were excluded due to lacking comparable test, concerning cognition through the studies. While the study conducted by Khedr et al. (2020) stimulated the motor cortex, the study conducted by Hill et al. (2020) didn't meet the inclusion criteria outlined above (refer to section 2. 1. 1.).

3. 1. 1. Study design

All the studies incorporated into the systematic review were limited to randomized controlled trials, each accompanied by pre- and postintervention assessments and, in most cases, follow-up assessments. All other studies design with non-randomized trial formats were explicitly excluded.

3. 1. 2. Study participants

All individuals who participated in the meta-analysis were patients diagnosed with Parkinson's disease. The participants in the studies, involving in the meta-analysis had an average age of 60 years or older. They may have exhibited cognitive impairment, but without dementia or any other diagnosed psychoneurological diseases. The overall sample size across all included studies for both NIBS (tDCS and TMS) was 213 participants, with 112 involved in the intervention group and 101 in the control group. The participants in the meta-analysis included both men as women, with a notably higher representation of men in most of the included studies, it is noteworthy that in the study by Lawrence et al. (2018) and Wei et al. (2022), the rate of women was higher (or equal) than that of men rate.

3. 1. 3. Intervention

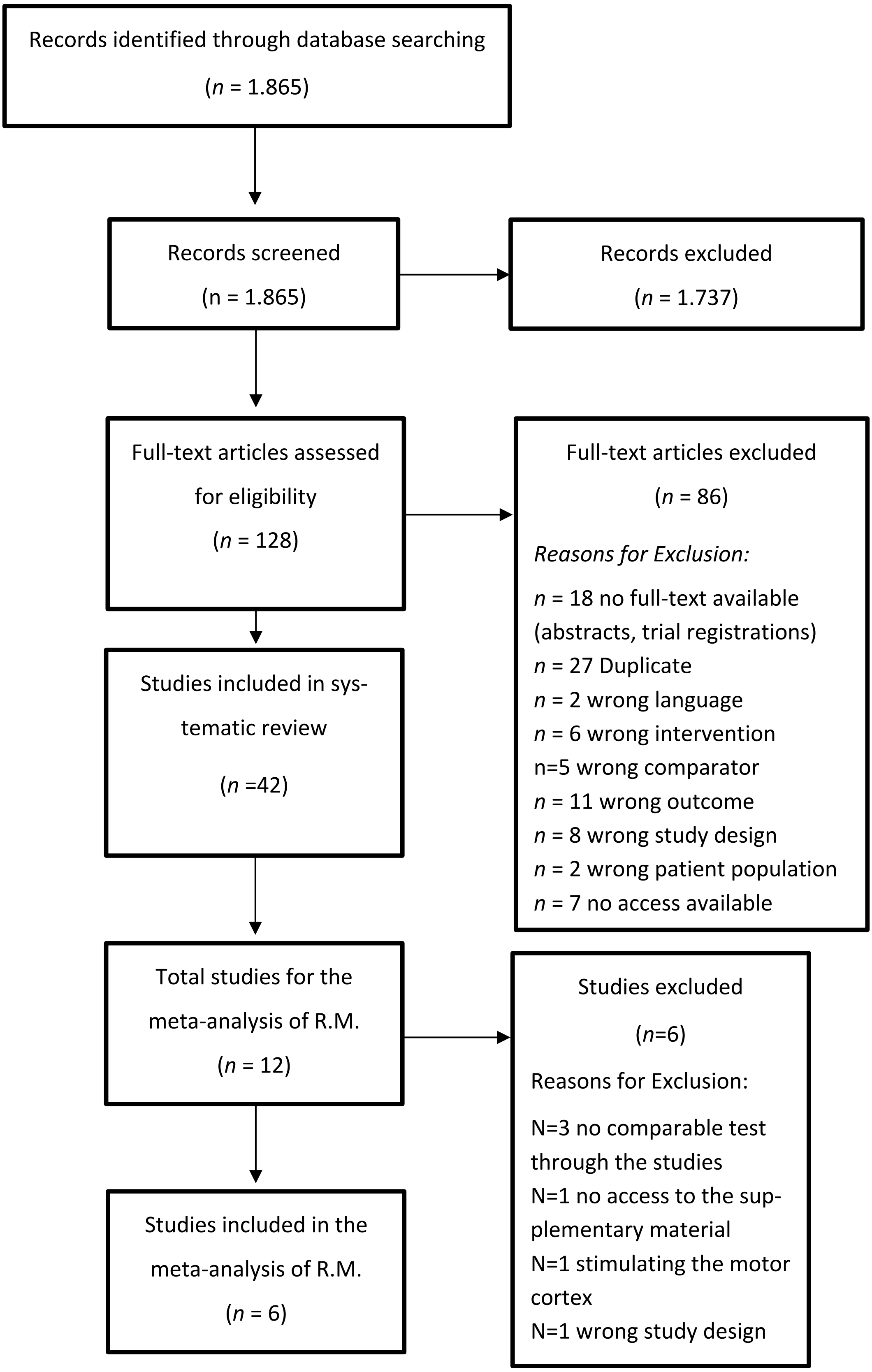
i. tDCS plus cognitive training

A meta-analysis was conducted, comprising three studies that investigated potential add-on effects of transcranial direct current stimulation (tDCS) in conjunction with cognitive training, as compared to cognitive training (CT) alone, on cognition in PD patients. The meta-analysis involved a total sample size of 52 participants, with 25 individuals undergoing the Intervention (NIBS+ CT), while the remaining individuals served as the control group, receiving CT alone. In the three studies conducted by Manenti et al. (2018), Lawerence et al. (2018) and Biundo et al. (2015), the stimulated area of the brain was the left dorsolateral prefrontal cortex (DLPFC). The duration of the intervention was 4 weeks by the studies conducted by Lawerence et al. (2018) and Biundo et al. (2015), while the study conducted by Manenti et al. (2018) had an intervention duration of 2 weeks (see Table 2 in Appendices).

ii. TMS

A meta-analysis was conducted, comprising three studies that investigated the effect of NIBS, specifically utilizing transcranial magnetic stimulation (TMS) alone, as compared to sham TMS stimulation, on cognition in PD patients. The studies involved in the meta-analysis were the following: (Wei *et al.*, 2022; He, Wang and Tsai, 2021; Zhuang *et al.*, 2020). The meta-analysis involved a total sample size of 128 participants, with 69 individuals undergoing the Intervention (TMS), while the remaining individuals served as the control group, receiving sham TMS. In the investigations conducted by Wei et al. (2022) and He et al. (2021), the targeted region of the brain was the left DLPFC. Notably, the former employed TMS as the chosen modality, while the latter utilized intermittent Theta Brust Stimulation (iTBS) for the stimulation of the left DLPFC. In contrast Zhuang et al. (2020) stimulated the right DLPFC using TMS as the selected modality. The intervention period in the investigations conducted by Wei et al. (2022), He et al. (2021) and Zhuang et al. (2020) spanned a duration of 2 weeks (see Table 2 in Appendices for more details).

***Figure 6**: PRISMA Diagram of the study selection process*
The diagram illustrates the flow of the studies through the different phases of the systematic review, including the identification, screening, eligibility, inclusion and exclusion phases.



3. 1. 4. Outcomes

3. 1. 4. 1. tDCS plus cognitive training

i. Lawrence et al. (2018)

The study conducted by Lawrence et al. (2018) reported statistically significant results after tDCS combined with tailored cognitive training when comparing postintervention to baseline measurements. The improvements were observed in the following cognitive domains: executive function assessed with the Stocking of Cambridge test (SOC), attention and working memory assessed with the Letter-Number Sequencing test (LNS), memory assessed with Paragraph Recall, and language assessed with the Similarities test. However, global cognition, measured with the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) and the Mini-Mental State Examination (MMSE), did not show statistically significant improvements post-intervention. Conversely, tailored cognitive training alone did not result in significant improvements in the cognitive domain tests when comparing post-intervention and baseline measurements. Notably, there was a significant improvement in Quality of Life (QoL), assessed with the Parkinson's Disease Questionnaire (PDQ-39) (refer to Table 2).

ii. Manenti et al. (2018)

The study conducted by Manenti et al. (2018) reported statistically significant results in both the intervention group, which received active tDCS combined with computerized cognitive training, and the control group, which received sham tDCS combined with the same cognitive training, when comparing post-intervention to baseline measurements. Improvements were observed in the following cognitive domains: global cognition assessed with the PD-CRS, attention and executive function assessed with the Stroop test, and language assessed with the International Picture Naming Project (IPNP) test. However, phonemic verbal fluency assessed with the IPNP and depression assessed with the Beck Depression Inventory II (BDI-II) showed significant improvements in the intervention group compared to the control group. Conversely, no significant improvements were observed in Quality of Life (QoL), assessed with the PDQ-39 (refer to Tale 2).

iii. Biundo et al. (2015)

The study conducted by Biundo et al. (2015) reported statistically significant results in the intervention group, which received active transcranial direct current stimulation (tDCS) combined with cognitive training as compared with, the control group, which received sham tDCS combined with the same cognitive training. Deterioration was observed in the following cognitive domains: attention assessed with the written coding test and the delayed memory (refer to Table 2).

3. 1. 4. 2. TMS

i. Wei et al. (2022)

The study conducted by Wei et al. (2022) reported statistically significant results after transcranial magnetic stimulation (TMS) when comparing post-intervention to baseline measurements. Improvements were observed in the following cognitive domains: executive function assessed with the Wisconsin Card Sorting Test (WCST) and the Stroop test. Additionally, statistically significant results were observed in the intervention group, which received active TMS, compared to the control group, which received sham TMS, when comparing post-intervention to baseline measurements. Improvements were observed in the cognitive domain of attention, assessed with the Attention Network Test (ANT). No other significant results were observed (refer to Table 2).

ii. He et al. (2021)

The study conducted by He et al. (2021) reported statistically significant results in the intervention group, which received active intermittent theta-burst stimulation (iTBS), compared to the control group, which received sham iTBS, when comparing post-intervention to baseline measurements. Improvements were observed in global cognition, measured with the Repeatable Battery of Assessment of Neuropsychological Status (RBANS) and the Montreal Cognitive Assessment (MoCA) tests, as well as in some subtests of these batteries. No significant improvement in depression was observed (refer to Table 2).

iii. Zhuang et al. (2020)

The study conducted by Zhuang et al. (2020) reported statistically significant results in the intervention group, which received active TMS, compared to the control group, which received sham TMS, when comparing post-intervention to baseline measurements. Improvements were observed in the cognitive domain of global cognition, assessed with the MoCA test. Additionally, an improvement in depression, measured with the Hamilton Rating Scale for Depression (HRDS), was observed. Statistically significant results were also observed in the Non-Motor Symptoms Questionnaire (NMSQ) in the intervention group (refer to Table 2).

3. 2. Cognition tests and comparison

In each meta-analysis we compared outcomes related to a cognition domain among all studies that involved in the corresponding meta-analysis and utilized the same intervention. The included cognitive domains in the study, along the corresponding measurement test used for each domain, which were subsequently compared, were as follow:

- Global cognition: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Mini-Mental Parkinson (MMP).
- Working memory: Digit-Span Test and Letter-Number Sequencing test (LNS).
- Memory (immediate recall): Hopkins Verbal Learning test (HVLT), Rey Auditory Verbal Learning test (RAVLT) and List learning test.
- Memory (delayed recall): Rey Auditory Verbal Learning test (RAVLT), Paragraph recall and Story recall tests.
- Quality of Life (QoL): Parkinson's Disease Questionnaire (PDQ-39/ -8).

To investigate the combined effect of tDCS in conjunction with cognitive training, in individuals with PD the following three studies were compared in the metanalysis: (Manenti *et al.*, 2018), (Lawrence *et al.*, 2018) and (Biundo *et al.*, 2015). Six meta-analyses were conducted, each pertaining to a specific cognitive domain, comparing the corresponding tests used to measure each domain.

In the meta-analysis conducted on the cognitive domain of global cognition, several tests were compared. Specifically, the MMP, MMSE, and MoCA were utilized, as referenced in the studies by Manenti et al. (2018), Lawrence et al. (2018), and Biundo et al. (2015) respectively. For the cognitive domain of working memory, the meta-analysis compared the Digit-Span test and the LNS test. The Digit-Span test was employed in both the studies by Manenti et al. (2018) and Biundo et al. (2015), whereas the LNS test was utilized in the study conducted by Lawrence et al. (2018). Within the Memory subtest immediate recall, the meta-analysis examined the RAVLT, HVLT, and List learning test. These tests were respectively employed in the studies by Manenti *et al.* (2018), Lawrence et al. (2018), and Biundo et al. (2015). Similarly, within the same cognitive domain, the subtest delayed recall was analyzed using the RAVLT, Paragraph story, and story recall tests. These tests were respectively utilized in the studies conducted by Manenti et al. (2018), Lawrence et al. (2018), and Biundo et al. (2015). Regarding the secondary outcome of Quality of Life (QoL), the meta-analysis compared the PDQ-39 and PDQ-8 questionnaires. The PDQ-39 was administered in both the studies by Manenti et al. (2018) and Lawrence et al. (2018), while the PDQ-8 was utilized in the study conducted by Biundo et al. (2015).

On the other hand, to examine the effect of TMS alone on cognition in individuals with PD, a metanalysis pertaining to global cognition was conducted. This meta-analysis compared the findings of the following three studies: (Wei *et al.*, 2022; He, Wang and Tsai, 2021; Zhuang *et al.*, 2020). The MoCA was the test used for comparison across these studies.

Observations confirmed that MoCA test demonstrated superior discriminative validity compared to other screening tests for the detection of mild cognitive impairment (MCI) (Mazancova *et al.*, 2020). Furthermore the test achieved greater accuracy in the differentiation of MCI among Parkinson's individuals (Mazancova *et al.*, 2020). A study conducted by Scheffels et al. (2020) discussed a concordance between MoCA and MMSE in differentiating between normal cognition and MCI was observed to be 57.3% (Scheffels *et al.*, 2020). Another observations confirmed that MMSE and MoCA are comparable cognitive assessment tools, a suggested conversion between the two tests is deemed reliable and valid (Lawton *et al.*, 2016). Although, MoCA has superior specifity than other tests, with lower risk of false positivity and a suggested sensitivity of at least 80% (Mazancova *et al.*, 2020). The working memory was assessed, using the Digit-Span test or LNS test. The LNS is suitable for assessing working memory (WM) and attention (Crowe, 2000). Furthermore, it can measure visuospatial functions effectively (Crowe, 2000). Other study confirmed the distinctive significance of Digit Span test in assessing MCI in PD (Biundo *et al.*, 2013). Additionally, the observation conducted by Warden et al. (2016) suggests that Digit Span Backward is an appropriate screening tool for WM, furthermore, the Digit Span Backward demonstrated better sensitivity than the Forward version for cognitive classification (Warden *et al.*, 2016). An interesting observation from the same study was that dopaminergic medication could significantly impact the Digit Span Backward by PD individuals (Warden *et al.*, 2016). In a new observation has been suggested that the sensitivity of span tests, encompassing both verbal and visual-spatial span, in detecting MCI in individuals appears to vary depending on the specific test utilized, and relies on distinct components of the WM system (De Tollis *et al.*, 2021). Other tests were compared to assess memory (immediate recall), included the HVLT, RAVLT and List learning test. For memory (delayed recall), the comparison involved the RAVLT with the subtest (delayed recall) as well as the paragraph recall and story recall tests. The distinctive significance of RAVLT immediate recall in assessing MCI in PD was previously reported (Biundo *et al.*, 2013). Other observations confirmed the reliability and the internal consistency of the RAVLT (Paula *et al.*, 2012). Furthermore, a similar discrimination ability of both short-time delayed recall and long-term delayed recall of the RAVLT to differentiate between individuals with MCI and those with normal cognitive function individuals was reported (Zhao *et al.*, 2012). Despite the inclusion of HVLT immediate recall subtest in assessing memory in this study, a study conducted by Webb et al. 2022 to examine the test-retest reliability of cognitive assessments, suggest that the HVLT-R (Revised) delayed recall exhibited a high level of reliability (Webb *et al.*, 2022). An acceptable reliability of HVLT-R, measuring delayed recall was also reported in a previous study (Benedict *et al.*, 1998).

3. 3. Meta-analysis

3. 3. 1. Effect of tDCS combined with Cognitive Training (CT)

i. Global cognition

For the comprehensive assessment of the impact of transcranial direct current stimulation (tDCS) coupled with cognitive training (CT) as compared to cognitive training in isolation on global cognition in individuals with PD, a meta-analysis was conducted, incorporating three studies encompassing a total of 25 participants in the intervention group (tDCS +CT) and 27 patients in the control group (CT). The overall effect size (SMD=1.75, 95% CI: -1.77-5.28), did not attain statistical significant (p=0.33), manifesting a substantial confidence interval that fails to demonstrate a noteworthy distinction between the intervention and control group. Furthermore, the heterogeneity (I^2=93%, 95% CI: 0.82-0.97, p<0,01) was markedly high (see Figure 7).

In summarizing the results of this meta-analysis concerning the global cognition of PD patients, the overall size effect of the intervention (tDCS+CT) across the three studies didn't reach statistical significance. A notable solitary effect was observed in the study conducted by Manenti et al. (2018), as depicted in the forest plot; however, it was accompanied by a relatively substantial confidence interval (SMD=5.52, CI: 3.61-7.44).

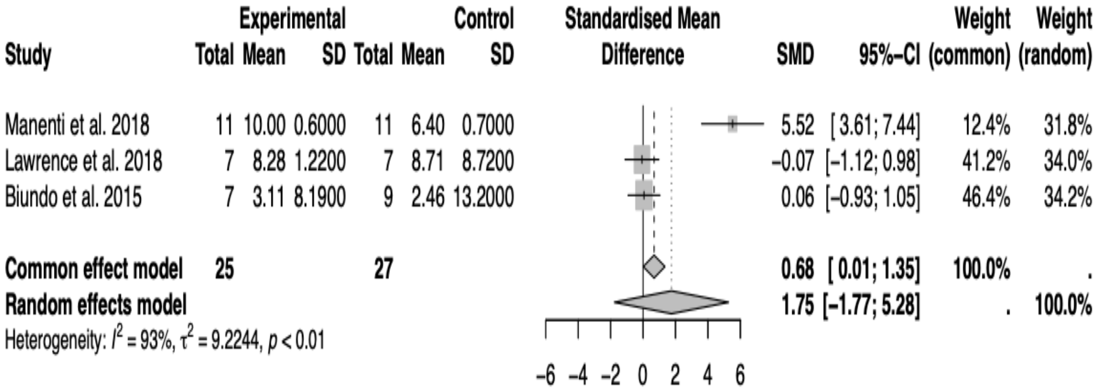


***Figure** 7: Forest Plot: Effect of (tDCS+CT) on global cognition*

The results of the meta-analysis evaluating the effect of tDCS combined with cognitive training (tDCS+CT) versus CT alone on global cognition in PD patients. The analysis found no significant difference in global cognition between the two interventions.

ii. Working memory

For the comprehensive assessment of the impact of tDCS coupled with cognitive training as compared to CT in isolation on WM in individuals with PD, a meta-analysis was conducted, incorporating three studies encompassing a total of 25 participants in the intervention group (tDCS+CT) and 27 patients in the control group (CT). The overall effect size (SMD=0.62, 95% CI: -1.04-2.29) did not attain statistical significant (p=0.46), manifesting a substantial confidence interval that fails to demonstrate a noteworthy distinction between the intervention and control group. Furthermore, the heterogeneity (I^2=86%, 95% CI: 0.60-0.95, p<0,01) was markedly high (see Figure 8).

In summarizing the results of this meta-analysis concerning the working memory of PD patients, the overall size effect of the intervention (tDSC+CT) across the three studies didn't reach statistical significance. A notable solitary effect was observed in the study conducted by Manenti et al. (2018), as depicted in the forest plot; albeit accompanied by a substantial confidence interval (SMD=2.12, CI: 1.06-3.19).

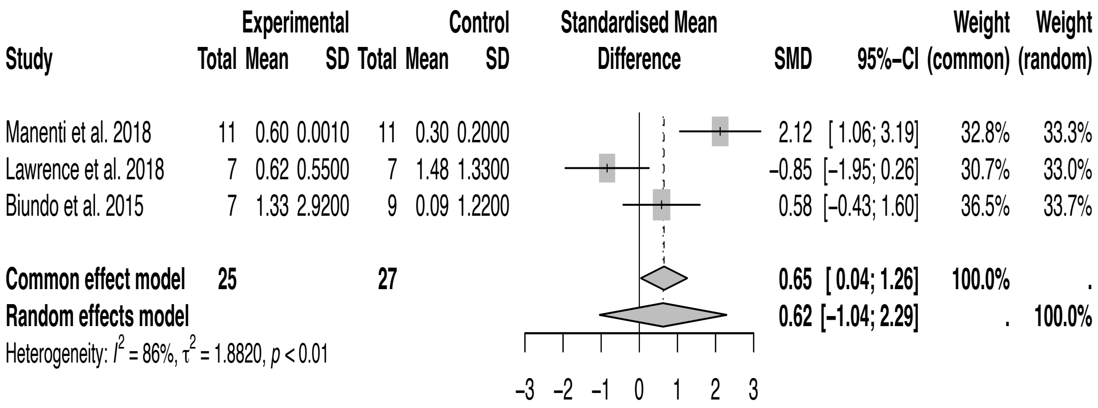


Figure 8: Forest Plot: Effect of (tDCS+CT) on WM

The results of the meta-analysis evaluating the effect of tDCS combined with cognitive training (tDCS+CT) versus CT alone on working memory in PD patients. The analysis found no significant difference in working memory between the two interventions.

iii. Memory: Immediate recall

For the comprehensive evaluation of the impact of tDCS in conjunction with CT in comparison to isolated CT on immediate recall in individuals with PD, a meta-analysis was conducted, incorporating three studies with a total of 25 participants in the intervention group (tDCS+CT) and 27 patients in the control group (CT). The overall effect size (SMD=0,22, 95% CI: -1.67-2.11) did not attain statistical significant (p=0.81), revealing a considerable confidence interval that fails to demonstrate a notable distinction between the intervention and control groups. Additionally, the heterogeneity (I^2=87%, 95% CI: 0.62-0.95, p<0,01) was notably high (see Figure 9).

In summarizing the outcomes of this meta-analysis pertaining to the immediate recall of individuals with PD, the overall size effect of the intervention (tDCS+CT) across the three studies didn't reach statistical significance. A noteworthy individual effect was observed in the study conducted by Lawrence et al. (2018), as illustrated in the forest plot; albeit accompanied by a substantial confidence interval (SMD=2.24, CI: 0.85-3.62).

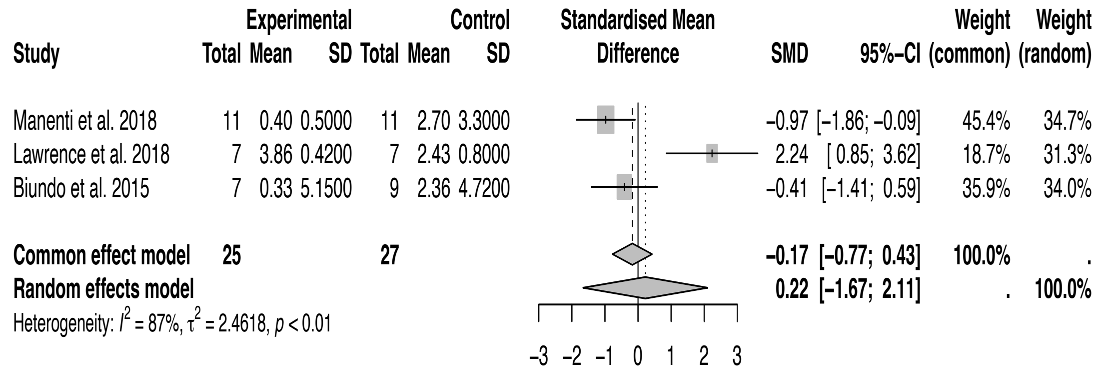


Figure 9: *Forest Plot: Effect of (tDCS+CT) on immediate recall*
The results of the meta-analysis evaluating the effect of tDCS combined with cognitive training (tDCS+CT) versus CT alone on immediate recall in PD patients. The analysis found no significant difference in immediate recall between the two interventions.

iv. Memory: Delayed recall

For the comprehensive evaluation of the impact of tDCS in conjunction with CT in comparison to isolated CT on delayed recall in individuals with PD, a meta-analysis was conducted, incorporating three studies with a total of 25 participants in the intervention group (tDCS+CT) and 27 patients in the control group (CT). The overall effect size (SMD=-0,11, 95% CI: -1.75-1.53) did not attain statistical significant (p=0.89), revealing a considerable confidence interval that fails to demonstrate a notable distinction between the intervention and control groups. Additionally, the heterogeneity (I^2=87%, 95% CI: 0.63-0.95, p<0,01) was notably high (see Figure 10).

In summarizing the outcomes of this meta-analysis pertaining to the delayed recall of individuals with PD, the overall size effect of the intervention (tDCS+CT) across the three studies didn’t reach statistical significance.

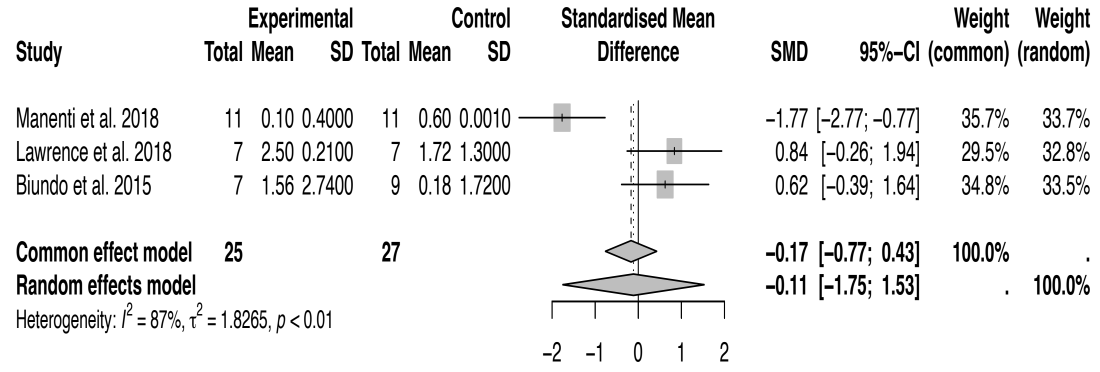
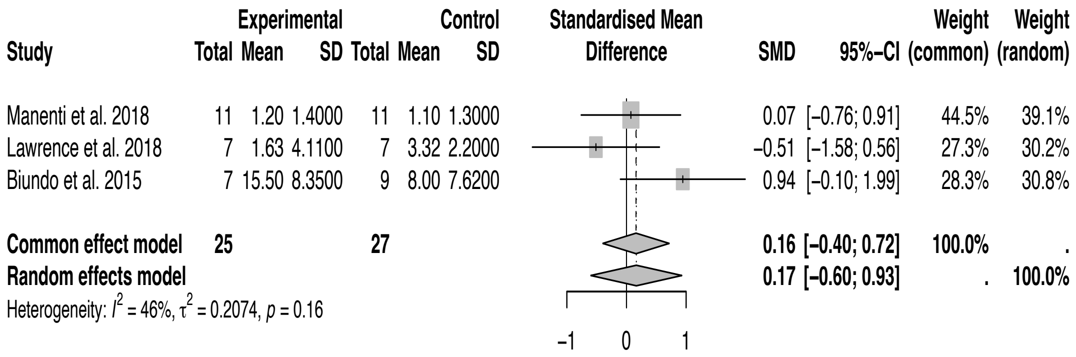


Figure 10: *Forest Plot: Effect of (tDCS+CT) on delayed recall*
The results of the meta-analysis evaluating the effect of tDCS combined with cognitive training (tDCS+CT) versus CT alone on delayed recall in PD patients. The analysis found no significant difference in delayed recall between the two interventions.

v. Quality of Life

For the comprehensive evaluation of the impact of tDCS in conjunction with CT in comparison to isolated CT on Quality of Life (QoL) in individuals with PD, a meta-analysis was conducted, incorporating three studies with a total of 25 participants in the intervention group (tDCS+CT) and 27 patients in the control group (CT). The overall effect size (SMD=0,17, 95% CI: -0.60-0.93) did not attain statistical significant (p=0.67), revealing a considerable confidence interval that fails to demonstrate a notable distinction between the intervention and control groups. Furthermore, the heterogeneity (I^2=46%, 95% CI: 0-0.84, p=0.16) was moderate but statistically not significant (see Figure 11).

In summarizing the outcomes of this meta-analysis pertaining to the QoL of individuals with PD, the overall size effect of the intervention (tDCS+CT) across the three studies didn't reach statistical significance.



Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight (common)	Weight (random)
Manenti et al. 2018	11	1.20	1.4000	11	1.10	1.3000	0.07	[-0.76; 0.91]	44.5%	39.1%
Lawrence et al. 2018	7	1.63	4.1100	7	3.32	2.2000	-0.51	[-1.58; 0.56]	27.3%	30.2%
Biundo et al. 2015	7	15.50	8.3500	9	8.00	7.6200	0.94	[-0.10; 1.99]	28.3%	30.8%
Common effect model	**25**			**27**			**0.16**	**[-0.40; 0.72]**	**100.0%**	**.**
Random effects model							**0.17**	**[-0.60; 0.93]**	**.**	**100.0%**

Heterogeneity: $I^2 = 46\%$, $\tau^2 = 0.2074$, $p = 0.16$

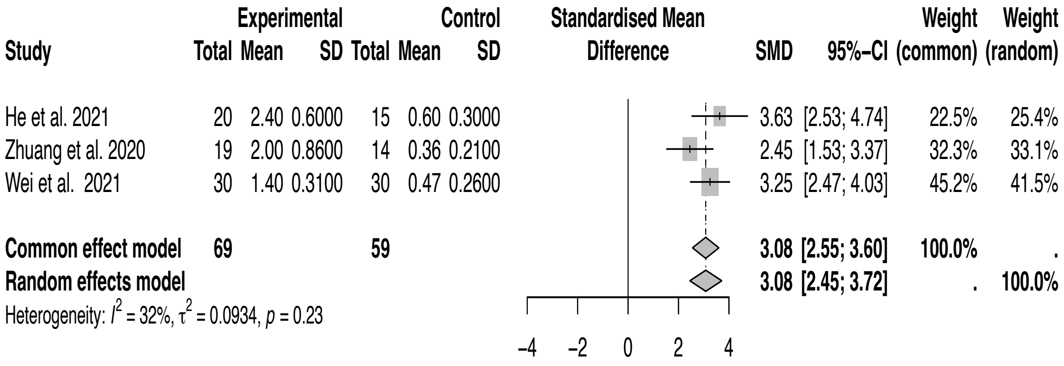
***Figure 11**: Forest Plot: Effect of (tDCS+CT) on QoL*
The results of the meta-analysis evaluating the effect of tDCS combined with cognitive training (tDCS+CT) versus CT alone on Quality of Life (QoL) in PD patients. The analysis found no significant difference in QoL between the two interventions.

3. 3. 2. Effect of TMS

TMS: global cognition

For the comprehensive evaluation of the impact of transcranial magnetic stimulation (TMS) administered alone, in comparison to sham TMS on global cognition in individuals with Parkinson's disease, a meta-analysis was conducted, incorporating three studies with a total of 69 participants in the intervention group (TMS alone) and 59 patients in the control group (sham TMS). The overall effect size (SMD=3.08, 95% CI: 2.45-3.72) was notably statistically significant (p= 1.429301e-21) accompanied by relatively small confidence interval. Furthermore, the heterogeneity (I^2=32%, 95% CI: 0-0.93, p=0.23) might not be important, with statistically non-significance (see Figure 12).

In summarizing the outcomes of this meta-analysis concerning the global cognition of individuals with PD, the overall size effect of the intervention (TMS alone) across the three studies achieved statistical significance, revealing a distinction between the intervention and control group pertaining the global cognition following the implantation of TMS. It is important to note that the observed statistical significance is accompanied by non-significant heterogeneity among the studies, emphasizing the homogeneity within the collected data.



Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight (common)	Weight (random)
He et al. 2021	20	2.40	0.6000	15	0.60	0.3000	3.63	[2.53; 4.74]	22.5%	25.4%
Zhuang et al. 2020	19	2.00	0.8600	14	0.36	0.2100	2.45	[1.53; 3.37]	32.3%	33.1%
Wei et al. 2021	30	1.40	0.3100	30	0.47	0.2600	3.25	[2.47; 4.03]	45.2%	41.5%
Common effect model	**69**			**59**			**3.08**	**[2.55; 3.60]**	**100.0%**	**.**
Random effects model							**3.08**	**[2.45; 3.72]**	**.**	**100.0%**

Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.0934$, $p = 0.23$

***Figure 12**: Forest Plot: Effect of TMS on global cognition*
The results of the meta-analysis evaluating the effect of active TMS versus sham TMS on global cognition in PD patients. The analysis found a significant distinction between the intervention und the control group pertaining global cognition following active TMS.

4. Discussion

4. 1. Discussion of findings

This thesis comprises a systematic research and meta-analysis of non-pharmacological interventions in individuals with PD, with a specific focus on Non-Invasive Brain Stimulation (NIBS) combined with cognitive training (CT) or NIBS alone. A total of 42 publications were included in the systematic review, with 12 publications meeting the criteria for inclusion in the meta-analysis. Following the exclusion of publications lacking detailed descriptive data or that could not be included in the meta-analysis comparison, a total of 6 studies remained and were subsequently analyzed. Three studies were included into the meta-analysis involving transcranial direct current stimulation (tDCS) (Manenti et al. 2018; Lawrence et al. 2018; Biundo et al. 2015). These studies investigated the effect of tDCS combined with CT on cognition functions in individuals with PD. No significant effect was found across the considered cognitive domains, namely global cognition, working memory, immediate and delayed recall. Furthermore, the effect of the abovementioned intervention on the secondary outcome, Quality of Life, didn't reach a statistical significance. Three studies investigated potential effects of TMS as standalone treatment in PD (He et al. 2021; Zhuang et al. 2020; Wei et al. 2021). A significant positive effect on global cognition was detected following the administration of TMS.

In the following sections, we will discuss the outcomes of the effects of NIBS in details, whether aligned with CT or not, on cognition, QoL and mood and affect in patients diagnosed with PD.

4. 1. 1. tDCS to enhance cognitive training effects in PD

In a pioneering study, Fregni et al. (2005) investigated the impact of tDCS on working memory (WM) performance in healthy individuals. Their findings suggested an enhancement of WM performance following tDCS stimulation of the DLPFC (Fregni *et al.*, 2005). Research indicates a potential synergistic effect in enhancing cognition by combining tDCS with CT in healthy adults, compared to CT alone. This combined approach appears to produce more significant improvements in cognitive performance, particularly in areas such as WM, underscoring the value of integrating tDCS with traditional cognitive training methods (Martin *et al.*, 2013).

On the other hand, another study found that there was no significant difference in the effect tDCS administered alone versus tDCS combined with CT in patients diagnosed with MCI (Cruz Gonzalez *et al.*, 2018).

Although the systematic review and meta-analyses were conducted according to high standards, and the methodology employed was based on RCTs, which provide high scientific evidence (Burns, Rohrich and Chung, 2011), we were not be able to confirm beneficial add-on effects of tDCS in combination with CT. These findings contradict the hypothesis of this research, which proposed that aligning tDCS with CT could have a potential positive effect on cognitive functions in individuals with PD. This lack of tDCS effects was consistent across all investigated cognitive domains. A detailed discussion of the findings and limitations for each cognitive domain is provided below.

I. Global cognition

The meta-analysis conducted to evaluate the effect of tDCS combined with CT on global cognition, compared with CT alone could not confirm significant add-on effects on global cognition in patients with PD. The analysis utilized the MMSE and MoCA tests to assess global cognition (refer to section 3. 3. 1.). Specifically, Manenti et al. (2018) and Lawrence et al. (2018) used the MMSE test or a similar test (Lawrence et al. (2018) used the MMP), whereas Biundo et al. (2015) used the MoCA test.

A potential limitation of the meta-analysis relates to the suitability of the assessment tools (MMSE, MMP, MoCA) their comparability (refer to 3.2.). The MMSE is a widely used cognitive screening tool, primarily for assessing Mild Cognitive Impairment (MCI). However, the MoCA has been shown to have superior sensitivity and specificity in detecting MCI among individuals over 60 years of age (Sokołowska *et al.*, 2016). The concordance rate between MoCA and MMSE in differentiating between normal cognition and MCI is relatively low at 57.3% (Scheffels *et al.*, 2020). Furthermore, the MMSE's ceiling effect may limit its ability to detect subtle performance changes when comparing pre- and post-intervention scores, particularly in MCI patients (Spencer *et al.*, 2013). A recent study suggests also that the MMSE test reflects not only cognitive decline but also the individual's education level (Cardoso *et al.*, 2022). The MMSE serves more as a cognitive screening, despite its common use as a cognitive test. However, it is not sufficiently accurate as a standalone tool for detecting cognitive deficits or changes due to treatment, especially for early dementia and MCI (Mitchell, 2013).

Furthermore, the timing of tDCS may impact the effectiveness of the intervention on global cognition. Agrawal et al. (2018) observed that Remotely Supervised-Transcranial Direct Current Stimulation (RS-tDCS) combined with CT in individuals with PD yielded superior results when administered in the afternoon rather than the morning, a finding attributed to circadian rhythmicity affecting cortical plasticity (Agarwal *et al.*, 2018). While the timing of stimulation was not a primary focus in the studies analyzed, it remains a relevant factor that could influence the outcomes and could be investigated in the future.

II. Working memory

Referring to Section (3.3.1.), there was no significant add-on effect on working memory (WM) after combining tDCS (administered to the left DLPFC) and CT, compared with CT alone. In the metanalysis, the following tests, measuring the cognitive domain WM were compared: Manenti et al. (2018) and Biundo et al. (2015) used the Digit Span test, while Lawrence at al. (2018) used the Letter-Number Sequencing test (LNS) (refer to section 3. 2.).

Beyond our findings, a systematic review and meta-analysis conducted by Burton et al. (2023) reported, a small significant positive effect favoring the combination of CT and tDCS on measures of attention and working memory, comparing post and pretreatment, in neuropsychiatric disorders' studies (Burton *et al.*, 2023). Another study provided evidence for improvement of WM and attention after CT plus tDCS in patients with earlier stage of neurodegenerative disease (Rodella *et al.*, 2022). Furthermore, the aforementioned intervention maintained the MMSE score stable compared to the sham group, where the score worsened in the follow-up measurements (Rodella *et al.*, 2022). Additionally, a meta-analysis conducted by Byeon et al. (2020) demonstrated a notable enhancement in the naming ability of individuals with dementia following the combination of tDCS and language/cognitive training. Conversely, the effect on naming ability in these individuals was found to be non-significant after tDCS alone, further the small size of studies under investigation was discussed as a constraint (BYEON, 2020).

Several factors may influence the effect of the investigated intervention on WM. One potential limitation is the variability in the tDCS protocols, particularly with regard to online or offline application. Manenti et al. (2018) and Lawrence et al. (2018) investigated online tDCS interventions (i.e. during cognitive training), Biundo et al. (2015) did not report specifics regarding the protocol utilized in their study. The timing/ type of tDCS application can influence WM outcomes differently. A study aimed at investigating the effects of single-session offline and online anodal tDCS over the left DLPFC on WM in healthy adults demonstrated enhanced performance in terms of both response time and accuracy following offline anodal tDCS compared to online anodal tDCS (Friehs and Frings, 2019). This underscores the significance of tDCS stimulation timing as a critical factor in the tDCS protocol for realizing effects on WM(Friehs and Frings, 2019). The offline anodal tDCS stimulation may impact the neurotransmission of the GABAergic neurons (Friehs and Frings, 2019). Previously conducted studies have demonstrated that reducing the synthesis of GABA in GABAergic neurons in the dorsolateral prefrontal cortex could lead to impairments in specific cognitive functions, notably working memory, due to this fact, altering the transmission of GABAergic neurons could potentially enhance cognitive functions in patients with depression and neuropsychiatric disorders (Lewis, Hashimoto and Volk, 2005; Prévot and Sibille, 2021; Friehs and Frings, 2019). This is because the pathology underlying GABAergic inhibitory neurotransmission is closely linked to cognitive functions (Lewis, Hashimoto and Volk, 2005; Prévot and Sibille, 2021).

Another potentially relevant factor is the administered intensity of tDCS. Manenti et al. (2018) and Biundo et al. (2015) applied 2 mA of anodal tDCS over the DLPFC, while Biundo et al. (2015) used 1.5 mA (refer to Appendices; Table 2). Initial observations provided a significant correlation between the intensity of current utilized in anodal tDCS stimulation over the DLPFC and the enhancement of WM in PD (Boggio *et al.*, 2006). Significant improvement was achieved with a current intensity of 2 mA, whereas no significant improvement was observed with a current intensity of 1 mA (Boggio *et al.*, 2006). In contrast, additionally observation found no significant effect of tDCS intensity, whether at 1 mA or 2 mA, on WM performance (Papazova *et al.*, 2020). It is also suggested that cognitive load and task difficulty may have a more substantial impact than current intensity (Papazova *et al.*, 2020).

Although all studies in the meta-analysis targeted the left DLPFC, research indicates that the stimulation site could influence WM outcomes. Živanović *et al.*, (2021) observed improvements in WM following tDCS stimulation of the right DLPFC (Živanović *et al.*, 2021). Moreover, the same study noticed a potential impact on WM after tDCS over the posterior parietal cortex (PPC). These suggests that WM performance may involve interactions among multiple brain regions. In summary, it remains unclear whether tDCS combined with CT can improve WM in PD, underscoring the need for further research.

III. Memory (immediate, delayed)

Combining tDCS and CT does not result in significant add-on-effects on memory (refer to section 3. 3. 1.). To measure the cognitive domain of memory (immediate recall/ delayed recall), the studies involved in the meta-analysis used different tests. The following tests were compared: Lawrence et al. (2018) used the Hopkins Verbal Learning Test (HVLT) and Paragraph recall for measuring immediate and delayed recall respectively. Manenti et al. (2018) used the Rey Auditory Verbal Learning Test (RAVLT), assessing both immediate recall (RAVLT-IR) and delayed recall (RAVLT-DR). Biundo et al. (2015) used the List Learning test and story recall for measuring immediate and delayed recall respectively.

Such outcomes may be attributed to a multitude of limitations inherent in the study, which warrant careful consideration and further exploration. First, the heterogeneity of tests used to measure episodic memory presents a challenge in making direct comparisons (refer to 3.2.). For example, while Manenti et al. (2018) utilized the RAVLT to assess both immediate and delayed recall, Lawrence et al. (2018) employed the HVLT to evaluate immediate recall and Paragraph Recall for delayed recall. Additionally, Biundo et al. (2015) utilized List Learning for immediate recall and Story Recall for delayed recall. The methodological differences likely introduced variability, which may have obscured of significant improvements following the combination of tDCS with CT (refer to section 4. 2.).

Second, variations in tDCS protocols may have also impacted the results. Neither Lawrence et al. (2018) nor Biundo et al. (2015) provided detailed information on whether their protocols involved online or offline stimulation. In contrast, Manenti et al. (2018) likely applied tDCS during cognitive training, indicating an online tDCS stimulation protocol. This Aspect was discussed in detail in the previous section with examples from the literature (refer to section 4. 1. 1.; Working Memory).

Third, it is notable that in the study conducted by Lawrence et al. (2018), there was a significant improvement in the Paragraph Recall test, assessing memory (delayed recall), in the group receiving tDCS combined with tailored (individualized) CT, while a non-significant effect was observed in the group receiving tDCS combined with standard CT. These findings may be elucidated by the varying modalities of cognitive training and their impact on the investigated intervention within this meta-analysis. After this observation, we suggest that the modality of CT, particularly when individualized to address specific cognitive impairments in PD, may be more effective than a standardized approach.

Additionally, it's possible that the stimulated brain areas in the studies included in this meta-analysis may not have corresponded precisely to the regions crucial for memory function. The brain area consistently targeted across the included three studies was the left DLPFC. Highlighting the significance of the stimulated brain area, an improvement was noted subsequent to bilateral tDCS directed at the temporal lobes when contrasted with bilateral tDCS applied to the bifrontal lobes (DLPFC) in individuals diagnosed with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) (Liu *et al.*, 2020). Recent observations underscore the aforementioned notion, revealing an enhancement of episodic memory subsequent to tDCS targeting the left temporal region in individuals diagnosed with Mild Cognitive Impairment (MCI) (Gu *et al.*, 2022). Therefore, the stimulated brain area could potentially influence the outcomes, and this factor should be considered when interpreting the results of this meta-analysis.

IV. Quality of Life

A significant improvement in Quality of Life (QoL) for individuals with PD was not found after combining tDCS with CT. The meta-analysis evaluated data from three studies measuring QoL in PD patients: Lawrence et al. (2018) and Manenti et al. (2018) used the Parkinson’s Disease Questionnaire (PDQ-39), while Biundo et al. (2015) used the PDQ-8 (refer to section 3. 3. 1.).

An explanation for these findings may lie in the complexity of daily activities, which encompass a combination of various capabilities including motor, cognitive, and functional skills. The multifaceted nature of these activities could make it challenging for an intervention, such as tDCS, to have a significant impact on overall QoL in PD patients (Liu *et al.*, 2021). A systematic review and meta-analysis comprising four studies, aimed at assessing the effect of tDCS on improving self-care ability in patients with PD, utilized the PDQ-39 as a measure of QoL. In line with our findings, this study also failed to demonstrate a significant enhancement in QoL attributed to tDCS stimulation (Liu *et al.*, 2021). Furthermore, it's important to note that the construct of QoL is inherently subjective. Individuals may perceive and prioritize different aspects of their life differently, which could influence their responses to measures such as the PDQ-39.

In conclusion, combining tDCS with CT did not produce a significant additive effect on cognition in PD patients. No improvements were observed in global cognition, working memory, recall, or Quality of Life. This suggests that the combination of these non-pharmacological interventions may not be beneficial for cognitive impairments in PD.

Despite the rigorous design of this study, limitations such as tDCS protocols, test comparability, stimulation site, CT modality, and small sample sizes (included patients, number of studies) should be considered when interpreting these results. Future research should address these variables through systematic reviews and further studies combining these interventions.

4. 1. 2. TMS as Intervention

In a meta-analysis that included studies by He et al. (2021), Zhuang et al. (2020) and Wei et al. (2021), the impact of transcranial magnetic stimulation (TMS) on cognition in individuals with PD was evaluated. All three studies utilized the Montreal Cognitive Assessment (MoCA) test to measure global cognition in PD patients. The cumulative findings from this meta-analysis demonstrated a statistically significant improvement in global cognition following TMS , as detailed in section 3.2.2.

These findings support our hypothesis that TMS improves cognition in patients with PD and cognitive dysfunction (refer to 1. 4.). Several studies in individuals with PD have corroborated our findings (Trung *et al.*, 2019; Jiang *et al.*, 2020; He, Wang and Tsai, 2021). Conversely, other studies in the same population have reported no effect of TMS on cognition (He *et al.*, 2022; Hai-jiao *et al.*, 2020).

An Explanation for the improvement in cognitive performance may be indirectly linked to mood enhancement (Boggio *et al.*, 2005), rather than directly impacting cognitive functions following TMS. It is well-known that TMS is utilized as a treatment for depression in PD patients, showing no discernible difference compared to antidepressant medications (Chen *et al.*, 2021). Both depression and anxiety exhibit relatively high prevalence rates among individuals with PD (Khedr, Abdelrahman, *et al.*, 2020). Cognitive function in PD patients was enhanced following TMS stimulation of the DLPFC or fluoxetine treatment; hence TMS demonstrates comparable efficacy to fluoxetine, an antidepressant medication (Boggio *et al.*, 2005).

A systematic review reported, a positive effect of rTMS on cognitive function, as measured by the MMSE (Jiang *et al.*, 2020). However, other cognitive domains such as memory, language, and attention did not reveal a significant enhancement following rTMS of the DLPFC (Jiang *et al.*, 2020). Another notable finding was the improvement in global cognition observed after administering different modalities of active NIBS in patients with AD. The effect on global cognition was greater after active rTMS compared to the tDCS group, where the improvement was non-significant (Teselink *et al.*, 2021). This phenomenon might explain a superior effect of TMS on cognition compared to tDCS, particularly concerning the stimulation modality. The differences in the effects of both NIBS techniques (TMS and tDCS) on cognition by PD warrant further exploration.

The stimulation protocols in the studies included in our meta-analysis varied. In the study conducted by Zhuang et al. (2020), the right DLPFC was stimulated, while both studies conducted by He et al. (2021) and Wei et al. (2021) used the left DLPFC as the stimulation site. The importance of the stimulated brain site was underscored in a meta-analysis of randomized controlled trials (RCTs), which failed to reveal significance in cognitive improvement following rTMS in patients with PD (He *et al.*, 2022). A possible explanation could be related to the specific brain regions stimulated, considering that cognitive impairment is complex and could involve various circuit mechanisms (He *et al.*, 2022). This notion was supported by a meta-analysis conducted in Alzheimer's patients, where multiple-site stimulation with rTMS was found to be superior to single-site stimulation (Wang *et al.*, 2020). However, the cortical region targeted for stimulation, specifically the right or left DLPFC, may exert differential effects on cognitive function (Turriziani, 2012). Considering that the studies included in our meta-analysis targeted different cortical regions, this could be viewed as a source of methodological heterogeneity. However, the overall heterogeneity in this meta-analysis was not significant.

Additionally, there were differences in the utilized frequency among the aforementioned studies. Moreover, the study conducted by He et al. (2021) employed intermittent Theta Burst Stimulation (iTBS) as a from of TMS in the stimulation protocol, while the studies by Wei et al. (2021) and Zhuang et al. (2020) used rTMS. Recent literature has reported differences in the efficacy of various TMS modalities in enhancing cognitive function in PD patients. High-frequency TMS demonstrated significantly superior efficacy in improving cognition compared to low-frequency TMS and iTBS in individuals with PD (Yang *et al.*, 2024). Furthermore, the number of rTMS sessions, coupling with cognitive training, and the frequency utilized in the stimulation may influence cognitive outcomes and produce superior effects on cognition (Wang *et al.*, 2020).

The findings suggest that TMS could serve as a potential non-pharmacological tool in treating cognitive decline or enhancing cognitive functions in patients with PD. Future research should explore the additive effect of combining CT with TMS on cognitive enhancement in individuals with PD.

In summary, despite the high standards maintained in conducting this meta-analysis, it is important to note that several concerns could influence the significant outcomes. These concerns include the variation of the stimulation sites of the DLPFC among the studies, the differing frequencies and session durations applied, and the different TMS modalities used. These factors could potentially compromise the robustness of the results obtained in the meta-analysis.

4. 2. Discussion of methods

The methodological aspects employed in different studies can significantly influence the outcomes and overall effectiveness of the investigated interventions in our meta-analyses. There are a few limitations in this study, which may impact the outcomes and prevent a significant result.

First, referring to the chapter results (refer to section 3.), considering the heterogeneity across the studies included in each meta-analysis, notably high heterogeneity was observed in the meta-analyses examining the effect of transcranial direct current stimulation (tDCS) combined with cognitive training (CT) on global cognition, working memory, delayed, and immediate recall memory (refer to section 3. 3. 1.). However, concerning Quality of Life, moderate heterogeneity was observed but it wasn’t significant. In contrast, the effect of transcranial magnetic stimulation (TMS) on global cognition, which reached a significant effect, exhibited a non-significant heterogeneity of of the involved studies (refer to section 3. 3. 2.). The heterogeneity served as a limiting factor, making a robustly evaluation of the effect of NIBS on cognition insufficient. An explanation for the high heterogeneity among the studies could be the use of different scales to measure various domains of cognition. Furthermore, the use of different cognitive training strategies in the studies, such as standard versus tailored or computerized cognitive training, may contribute to high heterogeneity. These strategies target different cognitive domains or stimulate different brain areas, potentially leading to varying outcomes.

Secondly, the small sample size served as a limiting factor affecting the outcomes of this study. Each meta-analysis involved only three studies, which may compromise the robustness of evaluating the effect of the intervention or to determine the significance of an effect investigated in a meta-analysis. Furthermore, a study conducted by Lin at al. (2018) reported, that a small sample size can substantially bias the overall estimates of the Standardized Mean Difference (SMD). However, no bias was observed regarding the overall Mean Difference (MD) (Lin, 2018). Additionally, the SMD may also be less biased when using Cohen's d compared to Hedges' g (Lin, 2018). In this study, we used the Cohen’s d to calculate the SMD.

Third, the assessment of bias across the different studies included in the meta-analyses revealed that not all studies had low bias. In Wei et al. (2021), Zhuang et al. (2020), and Lawrence et al. (2018), some concerns were noted regarding the overall bias estimation, particularly related to the randomization process and outcome measurement. The study conducted by Biundo et al. (2015) indicated substantial overall bias, suggesting a high risk of bias. The quality assessment revealed concerns about overall bias, indicating deviations from standard methodology in some studies included in the meta-analyses (refer to Table 3 in Appendices). This factor should be addressed in further studies.

Additionally, the protocol of NIBS, especially the stimulated brain site and the timing of stimulation in relation to cognitive training, can be seen as another limitation factor. The stimulation protocol was not standardized across the studies included in each meta-analysis, which could have impacted the ability to detect a potential effect of the intervention (tDCS+CT).

In summary, the aforementioned limitations in the original studies may have affected the validity and generalizability of the outcomes reported in this thesis. To better understand the impact of NIBS alone or in combination with cognitive training on cognition in PD patients, further research is needed.

5. Conclusion

This thesis evaluated the effectiveness of transcranial direct current stimulation (tDCS) combined with cognitive training in improving cognitive function in Parkinson's disease (PD) patients. The results showed no significant enhancements in overall cognition or specific cognitive domains such as global cognition, working memory, immediate/ delayed recall or Quality of Life (QoL) with this combination.

Conversely, the investigation of non-invasive brain stimulation (NIBS), specifically transcranial magnetic stimulation (TMS), compared to sham TMS, demonstrated a significant improvement in global cognition.

The study faced several limitations, including variability in NIBS protocols and the limited number of studies included in the meta-analysis. These factors might have obscured the detection of significant additive effects of NIBS on cognitive training.

Identifying limiting factors may guide future research in this field, which requires more methodologically sound and coordinated studies to determine whether NIBS alone or in combination with cognitive training are suitable for enhancing cognition, Quality of Life (QoL), and affect in individuals with Parkinson's disease (PD).

6. Abstract

Background: Cognitive decline is increasingly recognized as a significant non-motor symptom of Parkinson's disease (PD), affecting patients' Quality of Life, imposing a greater burden on caregivers, influencing the utilization of healthcare resources, and impacting mortality rates. To address cognitive deficits in PD, various therapeutic strategies are being investigated, including both pharmacological and non-pharmacological approaches. Non-pharmacological interventions encompass techniques such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and cognitive training. Additionally, research has explored the combined effects of non-invasive brain stimulation (NIBS) with cognitive training (CT) in individuals with neurological and psychiatric disorders, investigating the potential synergistic effects.

Objective: This study aimed to conduct a systematic review and meta-analysis to assess the impact of NIBS, both independently and in conjunction with cognitive training, primarily on cognitive function and secondarily on Quality of Life (QoL) and mood in individuals with PD.

Methods: The systematic review and meta-analysis adhered to PRISMA guidelines. We screened 1865 titles and abstracts based on PICOT criteria, resulting in 128 studies being assessed. After full-text review and elimination of duplicates and unsuitable studies, 83 studies were examined in detail. Ultimately, 42 studies were included in the systematic review. Twelve studies were initially selected for the meta-analysis of NIBS alone or combined with CT. Following further scrutiny, six studies met the PICOT criteria and were included in the final meta-analysis. Moreover, the Risk of Bias within the studies was assessed using the RoB 2.0 tool.

Results: The meta-analysis of three studies involving 52 PD patients receiving tDCS combined with cognitive training did not show significant effects on cognitive domains, including global cognition, working memory, immediate/ delayed recall, or QoL. In contrast, a separate meta-analysis of three studies involving 128 PD patients showed a statistically significant improvement in global cognition following active TMS compared to sham TMS.

Conclusion: While the combination of tDCS and cognitive training did not demonstrate significant cognitive benefits, active TMS showed promise in improving global cognition in PD patients. These findings suggest that TMS may be a more effective intervention for enhancing cognitive function in PD compared to tDCS combined with cognitive training. Further research is needed to explore the potential benefits of combining different non-invasive brain stimulation methods with cognitive training to optimize cognitive outcomes in PD patients.

7. Zusammenfassung

Hintergrund: Kognitive Beeinträchtigungen sind ein bedeutendes nicht-motorisches Symptom der Parkinson-Krankheit (PD). Sie beeinflussen die Lebensqualität, belasten Pflegepersonen, erhöhen die Gesundheitskosten und wirken sich auf die Sterblichkeitsrate aus. Zur Behandlung kognitiver Defizite bei PD werden sowohl pharmakologische als auch nicht-pharmakologische Methoden untersucht. Dazu gehören transkranielle Gleichstromstimulation (tDCS), transkranielle Magnetstimulation (TMS) und kognitives Training. Es wurde auch erforscht, wie die Kombination von nicht-invasiver Gehirnstimulation (NIBS) und kognitivem Training (CT) bei neurologischen und psychiatrischen Störungen wirkt.

Ziel: Diese Studie zielte darauf ab, eine systematische Übersicht und Meta-Analyse durchzuführen, um die Auswirkungen von NIBS, sowohl allein als auch kombiniert mit kognitivem Training, auf die kognitive Funktion, Lebensqualität (QoL) und Stimmung bei PD-Patienten zu bewerten.

Methoden: Die Studie folgte den PRISMA-Richtlinien. Von 1865 gesichteten Titeln und Abstracts wurden 128 Studien näher bewertet. Nach Volltextprüfung und Ausschluss von Duplikaten und ungeeigneten Studien blieben 83 Studien übrig. 42 Studien wurden in die systematische Übersicht aufgenommen. Für die Meta-Analyse von NIBS allein oder in Kombination mit CT wurden 12 Studien ausgewählt; nach weiterer Prüfung erfüllten 6 Studien die PICOT-Kriterien und wurden in die endgültige Meta-Analyse aufgenommen. Das Risiko von Bias wurde mit dem RoB 2.0-Tool bewertet.

Ergebnisse: Die Meta-Analyse von drei Studien mit 52 PD-Patienten, die tDCS und kognitives Training erhielten, zeigte keine signifikanten Effekte auf globale Kognition, Arbeitsgedächtnis, Erinnerungsvermögen oder QoL. Im Gegensatz dazu zeigte eine separate Meta-Analyse von drei Studien mit 128 PD-Patienten eine signifikante Verbesserung der globalen Kognition nach aktiver TMS im Vergleich zu Placebo-TMS.

Fazit: Die Kombination von tDCS und kognitivem Training zeigte keine signifikanten kognitiven Vorteile. Im Gegensatz dazu verbesserte aktive TMS die globale Kognition bei PD-Patienten signifikant. Diese Ergebnisse legen nahe, dass TMS möglicherweise eine effektivere Methode zur Verbesserung der kognitiven Funktion bei PD ist als die Kombination von tDCS und kognitivem Training. Weitere Forschung ist nötig, um die potenziellen Vorteile verschiedener nicht-invasiver Gehirnstimulationstechniken zusammen mit kognitivem Training genauer zu untersuchen.

8. References

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9. Appendices

***Table 2:** Summary of Data Extraction from Included Studies*
This table summarizes the data extraction from the studies included in the meta-analyses involved in this thesis. It includes the study name, the interventions (cognitive training and NIBS), the population, the timepoints, the outcomes and results for each study.

Study	Design	Behavioral training	NIBS	Population (N= Overall population; n per arm; Age: Mean (± SD), d-o=drop-out)	Timepoints (T0=baseline, T1=post Intervention, T2=follow-up, T3…)	Outcomes	Results
Wei et al. 2022	parallel groups	n/a	**TMS** **Group 1:** left DLPFC rTMS twice daily, for 2 weeks 5 Hz, 24 trains of 50 pulses, 1200 total pulses/session, intensity 110 % resting motor threshold, 6 hours between the two sessions/day **Group 2:** left DLPFC sham rTMS twice daily, for 2 weeks, same parameters as above	N=60 PD **Group 1:** n=30 Age=61.73 (±8.02) 18 w d-o=0 **Group 2:** n=30 Age=64.67 (±9.96) 15 w d-o=0	T0=baseline T1=2 weeks	**Cognitive outcomes:** -executive function (TMT A, B, word fluency, DS-T for-/backward, WCST, Stroop test) -attention (ANT: RT, accuracy)	**Referring to TimexGroup:** ↑ CC of WCST after (T1-T0): active rTMS>sham rTMS ↑ Part 3 of Stroop (T1-T0): active rTMS> sham rTMS ↑ RT for Stroop (T1-T0): active rTMS> sham rTMS <-> in the other Tests or after sham rTMS **Referring to Group-difference:** ↑ RT after active rTMS at T1 relative to sham rTMS ↑ executive part at T1 relative to sham <-> alerting, orienting parts

							<-> sham rTMS ↑ RT (Congruent/ Incongruent) after active rTMS at T1 relative to sham rTMS (in the tasks: no cue, double cue, centre cue, spatial cue) ↑ RT (Neutral) after active rTMS at T1 relative to sham rTMS (in the tasks: no cue, double cue) ↑ Accuracy (Congruent/Incongruent) after active rTMS at T1 relative to sham rTMS (in the tasks: centre cue, spatial cue) <-> RT, Accuracy after sham rTMS at T1
He et al. 2021	double-blind RCT, parallel groups	n/a	**iTBS** **Group 1:** left DLPFC iTBS 1/weekday, for 2 weeks 10 sessions **Group 2** sham Stimulation (placebo coil) 1/weekday, for 2 weeks 10 sessions	N=40 PD-MCI **Group 1:** n=20 Age=70.0 (±6.30) 7 w d-o=0 **Group 2:**	T0=baseline T1=2 weeks T2= 3 months	**Primary outcomes:** - RBANS total score (immediate memory, delayed memory, visuospatial and constructional abilities, language, attention) -MoCA total score (visuospatial/ execution, naming, attention, language,	**Referring to Time (intragroup):** ↑ RBANS total score after iTBS (T1-T0/ T2-T0) ↑ RBANs total score in sham group (T2-T1) ↑ MOCA total score after iTBS (T1-T0/ T2-T0)

				n=20 Age=74.80 (±6.90) 5 w d-o=5 at T0		abstraction, DR, orientation) **Secondary outcomes:** -depression (BDI)	RBANS subtests: ↑ immediate, delayed memory and visuospatial ability after iTBS: (T2/T1-T0) MoCa subtests: ↑ language, delayed recall after iTBS (T1-T0) <-> BDI (T1-T0/ T2-T0) **Referring to Group-differences:** ↑ RBANS total score at T1, T2: iTBS>sham ↑ MOCA total score at T1, T2: iTBS>sham RBANS subtests: ↑ immediate, delayed memory at T1, T2: iTBS>sham MoCa subtests ↑language, delayed recall at T1: iTBS>sham ↑ language at T2: iTBS>sham No time x group interaction tested

Zhuang et al. 2020	single-blind, sham-controlled RCT, parallel groups	**n/a**	**rTMS** **Group 1:** right DLPFC (5 cm anterior of M1) rTMS 20 min/ day, 10 days 1 Hz, intensity: 110 % resting motor threshold **Group 2:** sham rTMS 20 min/ day, 10 days	N=33 PD non demented **Group 1:** n=19 Age=60.58 (± 9.21) 8 w d-o=0 **Group 2:** n=14 Age=61.57 (±13.25) 7 w d-o=0	T0=baseline T1=10 days T2= 1 month T3= 3 months T4= 6 months	**Primary outcomes:** -nonmotor symptoms questionnaire (NMSQ) **Secondary outcomes:** -cognition (MoCA) -depression (HRSD)	**Referring to Timepoint:** ↑ NMSQ (T2-T0/ T1-T0) ↑ MoCA after active rTMS (T4-T0/ T3-T0/ T2-T0/ T1-T0) ↑ HRSD after active rTMS (T3-T0/ T2-T0/ T1-T0) <-> sham rTMS in NMSQ/ MoCA/ HRDS Referring to Group-difference: ↑ NMSQ at T1-T3: active rTMS>sham ↑ MoCA at T1-T4: active rTMS>sham ↑ HRDS at T1-T2: active rTMS>sham **Referring to TimexGroup:** ↑ NMSQ after active rTMS, but not sham (T1-T0) ↑ HRSD after active rTMS

Manenti et al. 2018	double-blind RCT, parallel groups	computerized CT During active or sham tDCS	**tDCS** **Group1:** left DLPFC atDCS (over F3)+ computerized CT 2 mA for 25min/ day, 5 days/ week, for 2 weeks cathode over right supraorbital area **Group2:** left DLPFC sham tDCS (F3)+ computerized CT current just for 10 sec at Begin, 25min/ d, 5d/ week, for 2 weeks cathode over right supraorbital area	N=22 PD-MCI **Group 1:** n=11 Age=65.50 (±6.40) 6 w d-o= 0 **Group 2:** n=11 Age=63.8 (±7.10) 4 w d-o= 0	T0= baseline T1= 2 weeks T2= 3 months	**Primary outcomes:** -global cognitive abilities (PD-CRS) -language; phonemic/ semantic verbal fluency (IPNP) -attention and executive function (TMT A, B; Test of attentional Performance, SI-T, FAB) -Depression (BDI-II) **Secondary outcomes:** -memory (Rey Auditory Verbal Learning; IR/ DR; DS-T Forward, Backward) -QoL (PDQ-39)	**Referring to Timepoint:** ↑ PD-CRS total score/ subcortical score (T2-T0/ T1-T0) in both groups ↑ BDI-II (T1-T0) after active tDCS + CT ↑ phonemic verbal fluency (T1-T0) in both groups ↑ semantic verbal fluency (T2-T0) both groups ↑ actions naming abilities (T2-T0, T1-T0) (IPNP) in both groups ↑ SI-T; RT (T2-T1, T1-T0) in both groups **Referring to Group-difference:** ↑ BDI-II (reduction in Depression) in active group compared with sham group ↑ phonemic verbal fluency, especially (T2-T0), in active group compared with sham group <-> secondary outcomes

Lawrence et al. 2018	Not blinded, RCT, parallel groups	**Group 1:** computerized standard cognitive training 45min/ 3 times per week, for 4 weeks **Group 2:** computerized tailored cognitive training 45min/ 3 times per week, for 4 weeks	**tDCS** **Group 3:** left DLPFC (F3 electrode) atDCS 1.5 mA for 20min/ once a week, for 4 weeks cathode placed above left eye **Group 4:** left DLPFC (F3 electrode) atDCS + computerized standard cognitive training 2 mA for 25min/ d, 5d/ 1.5 mA for 20min/ once a week, for 4 weeks+ SCT 45min/ 3 times per week for 4 weeks **Group 5:** left DLPFC (F3 electrode) atDCS + computerized tailored cognitive training 2 mA for 25min/ d, 5d/ 1.5 mA for 20min/ once a week, for 4 weeks+ tailored CT	N=42 PD-MCI **Group1:** n=7 Age=68.14 (±8.69) 3 w d-o= 2 at T2 **Group 2:** n=7 Age=65.57 (±5.20) 4 w d-o= 1 at T2 **Group 3:** n=7 Age=72.0 (±6.45) 5 w d-o= 0 **Group 4:** n=7 Age=63.57 (±5.68) 5 w d-o= 0	T0= baseline T1= 5 weeks T2= 12 weeks	-executive function (SOC, COWAT) -attention/WM (LNS, Stroop) -memory (HVLT-R, paragraph recall test) -visuospatial abilities (JLO, HVOT) -language (BNT, Similarities test) -global cognition (PD-CRS, MMSE) -ADL (UPDRS II) -QoL (PDQ-39) -depression (DASS-21)	**Referring to Group (Group, TimexGroup effect):** **Group 1:** SCT: ↑ paragraph recall (T2-T0), ↑JLO (T2-T0) ↑PDQ-39 & UPDRS II (T1-T0) **Group 2:** tailored CT: ↑ LNS (T2-T0), ↑PDQ-39 (T2-T0/ T1-T0) **Group 3:** tDCS: ↑ Stroop (T2-T0/ T1-T0), ↑paragraph recall (T1-T0) **Group 4:** SCT+tDCS: ↑ SOC (T2-T0/ T1-T0) ↑ Stroop (T2-T0/ T1-T0) ↑ similarities (T1-T0) ↑ UPDRS II (T1-T0) **Group 5:** tailored CT+tDCS: ↑ SOC (T1-T0/ T2-T0) ↑LNS (T2-T0) ↑ paragraph recall (T2-T0/ T1-T0) ↑ similarities (T2-T0/ T1-T0) **Group 6:** control group <-> all non-sigificant

			45min/ 3 times per week for 4 weeks **Group 6:** Control group No intervention	**Group 5:** n=7 Age=67.43 (±6.37) 5 w d-o= 0 **Group 6:** n=7 Age=72.29 (±6.21) 4 w d-o= 1 at T2			
Biundo et al. 2015 **(Extracted by J.E.)**	Pilot-RCT, double-blinded	**Group 1:** Cognitive training + real tDCS **Both groups**: 30 min-sessions, 4 days a week for 4 weeks (16 sessions CT in total) **Group 2**:Cognitive training + sham tDCS	**tDCS** **Group 1**: atDCS over the left DLPFC, cathode over right supraorbital region, 2 mA, 20 min/session **Group 2**: Sham tDCS	N=24 PD with MCI **Group 1**: n=7 Age:69.1(7.6) 1w. **Group 2**: n=9 Age: 72.3(4.1) 1w. d-o=8	T0=baseline T1= 4 weeks after T0 T2= 16 weeks after T0	Neuropsychological outcomes: -cognitive functions (MoCa, RBANS) -immediate memory index (list learning; story learning) - visuospatial index (complex figure copy; orientation line) -language index (naming; semantic fluency)	**Group differences at T0-T1** ↓ decreased performance of tDCS group vs. sham group in: attention (written coding test) at T0-T1 ↓ decreased performance of tDCS group vs. sham group in: delayed memory index (list recall, delayed memory index) at T0-T1 ➔ None of these effects remain in the follow-up after 16 weeks **Group differences at T0-T2** ↑ increased performance of tDCS vs. sham group in: immediate memory index (story learning,) (strong trend, p = 0.07)

						-attention (digit span; written coding test) -delayed memory index (list recall; list recognition; story recall; figure recall) Secondary outcomes: -motor functions (UPDRS-III)	

Legend: ADL= impaired activities of daily living; atDCS=active transcranial direct current stimulation BDI=beck depression inventory; BNT=boston naming test; CC=categories completed; COWAT=controlled word association test; CT=cognitive training group; DLPFC=dorsolateral prefrontal cortex; DR=delayed recall; DS-T=digit span test; FAB=frontal assessment battery; HRSD=hamilton rating scale for depression-24 item ; HVLT-R=hopkins verbal learning test-revised; HVOT= hooper visual organization test; IR=immediate recall; iTBS=intermittent theta burst stimulation; LNS= letter-number sequencing, M1=primary motor cortex; MMSE=mini mental state examination; MoCA=montreal cognitive assessment; NMSQ=nonmotor symptom questionnaire; PDQ-39=parkinson's disease questionnaire 39; QoL=quality of life; RBANS=repearable battery for assessment of neuropsychological status; RCT=randomized controlled trial; SOC=stocking of Cambridge, subtest from CANTAB; TMT A, B=trail making test A, B time; WCST=wisconsin card sorting test; PD-CRS= parkinson disease- cognitive rating scale; PD-MCI=parkinson's disease- mild cognitive impairment; rTMS=repetitive transcranial magnetic stimulation; SCT= standard cognitive training; SD=standard deviation; UPDRS= unified parkinson's disease rating scale; WM=working memory;

Acronyms: d-o=drop-outs; f-u=follow up; h=hour; i.e.=(Latin: „id est")- meaning: that is to say; min=minute; n/a=not applicable; s=second; ↑: indicates a significant improvement/ increase, ↓: indicates a significant deterioration/ decrease after intervention compared with control group/ sham group/ baseline; <->=non-significant effects after interventions compared with control group/ sham group/ baseline; △=delta score, x>y= x better than y.

***Table 3**: Assessment the Risk of Bias*
The assessed risk of bias across the five specific domains within each study, included in the metal-analyses. In the final column, the overall bias judgments are summarized. A low risk of bias is depicted in green. If some concerns were identified, the yellow color was applied, while a high risk of bias is indicated by the color red.

Study/Domain	Bias arising from the randomization process	Bias due to deviations from intended intervention	Bia due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall bias
Wei et al .2021	🟨	🟩	🟩	🟨	🟩	🟨
He et al. 2021	🟩	🟩	🟩	🟩	🟩	🟩
Zhuang et al. 2020	🟩	🟩	🟩	🟨	🟩	🟨
Manenti et al. 2018	🟩	🟩	🟩	🟩	🟩	🟩
Lawrence et al. 2018	🟩	🟩	🟩	🟨	🟩	🟨
Biundo et al. 2015	🟨	🟨	🟩	🟩	🟨	🟥

***Table 4:** PICOT*
Displaying participants, intervention, comparator, outcome and timing. A systematic review: Comparing the efficacy of non-invasive Brain Stimulation and cognitive Training in Patients with Parkinson disease.

P (Participants)	- Participants of all genders with Parkinson disease, aged >=50 years - Participants with PD and PD-MCI will also be included
I (Intervention)	- non-invasive brain stimulation, NIBS such as: • transcranial direct current stimulation • transcranial magnetic stimulation • transcranial alternating current stimulation - cognitive training studies - non-invasive brain stimulation combined with cognitive Training
C (Comparator)	- cognitive training + sham NIBS as control group - sham NIBS as stand-alone treatment

	- cognitive training + inhibitory NIBS (tDCS, TMS) or other frequency (tACS) over the target region - cognitive training + active (excitatory or inhibitory) NIBS administered over a control site (targeting non-relevant brain region) - active (excitatory or inhibitory) NIBS as stand-alone treatment administered over a control site (targeting non-relevant brain region) - cognitive training alone
O (Outcome)	Primary outcome - **Cognition**, assessed with standardized or study specific outcomes Secondary outcomes: ○ Mood ○ Quality of life ○ Adverse events
T (Timing)	- Outcomes have to be assessed pre- and postintervention - Follow-up Assessments will be included

***Table 5**: Synonyms and Word Combinations*
This table serves as a resource for generating search strings by compiling synonyms and word combinations from three specific domains: Parkinson's Disease, Cognitive Training, and Non-Invasive Brain Stimulation (NIBS). The goal is to facilitate the creation a comprehensive search string database.

Parkinson	**Cognitive Training**	**NIBS**
Parkinson’s disease (PD)	Frontostriatal Pathway	Non-invasive brain stimulation/NIBS
Parkinson/Parkinson‘s	Executive functions	tDCS/t-DCS
PD-MCI (mild cognitive impairment)	Attention	rTMS
PDD (dementia)	Visuospatial abilities/skills	Transcranial direct current stimulation
	Working memory	Transcranial alternating current stimulation
	Language	Repetitive transcranial magnetic stimulation
	Verbal fluency	
	Semantic verbal fluency	
	Phonemic verbal fluency	
	Trial making	
	Processing speed	
	Mild cognitive impairment	
	Dementia	
	Cognitive improvement	

10. Curriculum Vitae (CV)

11. Acknowledgements

I would like to express my heartfelt gratitude to my doctoral advisor, Prof. Dr. Marcus Meinzer, Director of the Cognition, Aging, and Brain Stimulation Lab in the Department of Neurology at the University of Greifswald, for providing the topic of this dissertation. Additionally, I am thankful for his continuous support throughout its realization. He was always accessible, offering extremely valuable advice, experience, and assistance, as well as his prompt feedback and tireless responses to questions.

I am deeply grateful to Prof. Dr. Mandy Roeheger for her ongoing help and guidance. She accompanied the thesis from the beginning, was always accessible, and provided prompt assistance whenever needed. I thank her for her patience, valuable advice, and perseverance in addressing my numerous questions.

I also extend my thanks to my dear wife and my entire family, who have always stood by my side and alleviated my stress during challenging times. I dedicate this dissertation to my wife out of love. I apologize for any stress and nervousness this journey may have caused.

Furthermore, I would like to thank my beloved parents, who enabled me to pursue my studies and supported me throughout. Without their support, this achievement would not have been possible.

Lastly, I want to thank my wonderful team, with whom I had the privilege of working. I am grateful for their trust and for sharing both beautiful and challenging times together. Special thanks to Anna Rysop, Julia Engel, and Anna Mäder. I wish you all the best.

12. Declaration of Personal Contribution

The dissertation topic was assigned by Prof. Dr. Marcus Meinzer, with supervision provided by both Prof. Dr. Marcus Meinzer and Prof. Dr. Mandy Roheger. The development of the search strategy was conducted by Prof. Dr. Mandy Roheger and Rashed Mshael, while the creation of the search string and the collection of relevant studies from the database were carried out by Prof. Dr. Mandy Roheger.

Rashed Mshael and Anna Mäder assessed the studies for eligibility and included the relevant primary studies in the systematic review. In cases of disagreement regarding study selection and inclusion, Prof. Dr. Marcus Meinzer was consulted to resolve the issues. Subsequently, Rashed Mshael and Julia Engel conducted a full-text review to ensure the final inclusion of appropriate studies according to the PICOT criteria. Data extraction was performed by Rashed Mshael and Julia Engel, who organized the data into a Word table. The table was then reviewed by Anna Rysop and Prof. Dr. Marcus Meinzer.

The meta-analyses in this dissertation were conducted by Rashed Mshael, including all calculations and statistical analyses, with the review carried out by Prof. Dr. Mandy Roheger and Prof. Dr. Marcus Meinzer.

The manuscript, including tables, figures, and citations, was written by Rashed Mshael, with corrections and final review provided by Prof. Dr. Marcus Meinzer.

13. Declaration of Authorship (Eidesstattliche Erklärung)

I hereby declare that I have written this dissertation independently and have not used any aids other than those specified.

The dissertation has not been submitted to any other faculty or scientific institution.

I declare that I have not previously failed any doctoral procedures and that there is no revocation of an already acquired doctoral degree

Translation to German:

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät, keiner anderen wissenschaftlichen Einrichtung vorgelegt worden.

Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

Datum 04.09.2024 Unterschrift