EFFECTS AND MECHANISMS OF WORKING MEMORY TRAINING IN PATIENTS WITH PARKINSON'S DISEASE

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I often say now I don't have any choice whether or not I have Parkinson's, but surrounding that non-choice is a million other choices that I can make.

MICHAEL J. FOX

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ABSTRACT

Objective: Cognitive decline is a common, debilitating non-motor symptom of patients with Parkinson's Disease (PD), the second most frequent neurodegenerative disorder of older age. Non-pharmacological interventions including cognitive training are increasingly recognized to possibly prevent or delay the onset and/or slow down the progression of cognitive decline in patients with PD. In this context, targeted working memory training (WMT) is especially promising, considering (i) the vulnerability of working memory and executive functions in patients with PD, (ii) reliable short- and long-term near-transfer training effects following WMT in the working memory domain and potential far-transfer effects to other cognitive domains in healthy older adults, and (iii) overlapping neural correlates of working memory, WMT induced neural changes, and the pathophysiology of PD. The present thesis project aims to investigate the effects of targeted WMT in patients with PD. Furthermore, the understanding of mechanisms underlying WMT responsiveness should be promoted. Answering the question "who benefits most?" in terms of individual (e.g., sociodemographic, neuropsychological, biological) characteristics would perspectively help to match an individual participant to a specific form of cognitive intervention and, thereby, to maximize treatment outcomes against the debilitating cognitive decline associated with PD.

Methods: The present thesis project comprises three studies. Study I evaluates a randomized controlled trial investigating the effects of a 5-week home-based computerized WMT in n = 76 patients with PD without cognitive impairment at posttest and 3-months follow-up. Study II constitutes a systematic review of n = 16 studies on predictors of WMT responsiveness in healthy older adults. Study III analyzes data of the randomized controlled trial reported in Study I with a structural equation modelling approach to investigate predictors of WMT responsiveness in patients with PD.

Results: In Study I, WMT was feasible in patients with PD without cognitive impairment and evidence for positive near-transfer training effects in the working memory domain was found. No cognitive and clinical far-transfer effects were observed. Variability of training effects was large across participants. Study II revealed several methodological shortcomings of prognostic research in the field. Nevertheless, a pattern emerged according to which lower baseline

performance and better hardware (e.g., younger age, higher intelligence) predict positive WMT responsiveness in healthy older adults. Study III revealed a similar pattern for patients with PD without clinically relevant cognitive decline. Lower baseline performance, younger age, higher fluid intelligence, higher education, and higher self-efficacy expectancy predicted larger positive WMT responsiveness in this patient group.

Conclusion: Summarizing, the findings of the present thesis substantially contribute to the research area of evidence-based cognitive interventions against the debilitating cognitive decline associated with PD. Furthermore, the findings promote the implementation of precision medicine approaches in the context of cognitive interventions in general. The potential of non-pharmacological interventions against the debilitating age- and PD-associated cognitive decline is enormous and prognostic research may unlock the possibilities for modern healthcare on the road to precision medicine. High-quality research adhering to high methodological standards on the original-study-level as well as the synthesizing meta-level will be able to close the research gaps within the next years.

STUDIES INCLUDED IN THE CUMULATIVE THESIS

This cumulative thesis comprises three key publications, referred to as Study I, Study II, and Study III. Table 1 comprises an overview of the authors' individual contributions to these publications. Based on a randomized controlled trial on working memory training in patients with Parkinson's Disease, which constitutes the basis of Study I and Study III, two further publications focusing on an explorative neuropsychological module as well as the neuroimaging module were published. These publications are not included as key publications of the cumulative thesis, but they are inherently linked to its rationale and will be discussed accordingly.

STUDY I

Ophey, A., Giehl, K., Rehberg, S., Eggers, C., Reker, P., van Eimeren, T., & Kalbe, E. (2020). Effects of working memory training in patients with Parkinson's Disease without cognitive impairment: A randomized controlled trial. *Parkinsonism & Related Disorders*, *72*, 13-22. https://doi.org/10.1016/j.parkreldis.2020.02.002

STUDY II

Ophey, A., Roheger, M., Folkerts, A.-K., Skoetz, N., Kalbe, E. (2020). A Systematic Review on Predictors of working memory training responsiveness in healthy older adults: Methodological challenges and future directions. *Frontiers in Aging Neuroscience, 12,* 1-23. https://doi.org/10.3389/fnagi.2020.575804

STUDY III

Ophey, A., Rehberg, S., Giehl, K., Eggers, C., Reker, P., van Eimeren, T., & Kalbe, E. (2021). Predicting working memory training responsiveness in Parkinson's Disease: Both "system hardware" and room for improvement are needed. *Neurorehabilitation and Neural Repair*, *35*(2), 117-130. https://doi.org/10.1177/1545968320981956

RELATED PUBLICATIONS

Giehl, K., **Ophey, A.**, Reker, P., Rehberg, S., Hammes, J., Barbe, M. T., Zokaei, N., Eggers, C., Husain, M., Kalbe, E., & van Eimeren, T. (2020). Effects of home-based working memory training on visuo-spatial working memory in Parkinson's Disease: A randomized controlled trial. *Journal of Central Nervous System Disease*, *12*, 1-9. https://doi.org/10.1177/1179573519899469

Giehl, K., **Ophey, A.**, Hammes, J., Rehberg, S., Lichtenstein, T., Reker, P., Eggers, C., Kalbe, E., & van Eimeren, T. (2020). Working memory training increases neural efficiency in Parkinson's Disease: a randomized controlled trial. *Brain Communications*, *2*(2), 1-16. https://doi.org/10.1093/braincomms/fcaa115

Table 1. Overview of the Scientific Contributions

	Study Design	Data Collection	Data Analysis	Data Interpretation	Manuscript Preparation	Manuscript Revision	Submission Process
Study I	Giehl, K. Rehberg, S. van Eimeren, T. Kalbe, E.	**Ophey, A.** Giehl, K. Rehberg, S. Eggers, C. Reker, P.	**Ophey, A.**	**Ophey, A.** Kalbe, E.	**Ophey, A.**	all authors	**Ophey, A.** Kalbe, E.
Study II	**Ophey, A.** Roheger, M. Kalbe, E.	**Ophey, A.** Roheger, M. Folkerts, A.-K. Skoetz, N.	**Ophey, A.** Roheger, M.	**Ophey, A.** Kalbe E.	**Ophey, A.**	all authors	**Ophey, A.** Kalbe, E.
Study III*	---	---	**Ophey, A.**	**Ophey, A.** Kalbe E.	**Ophey, A.**	all authors	**Ophey, A.** Kalbe, E.

Note. For detailed information on the authors' contributions to more specific parts of the studies, please refer to the contributorship statements of Study I, Study II, and Study III, respectively.
* Study III is based on data of the randomized controlled trial reported in Study I

LIST OF ABBREVIATIONS

apoE-4	Apolipoprotein-E-4
BDNF	Brain-derived neurotrophic factor
BOLD	Blood oxygen level dependent
CERAD-Plus	Consortium to Establish a Registry for Alzheimer's Disease Plus
CFI	Comparative fit index
CG	Control group
CHARMS	Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRUNCH	Compensation Related Utilization of Neural Circuits Hypothesis
FOG	Freezing of gait
fMRI	Functional magnetic resonance imaging
GDS	Geriatric Depression Scale
H&Y	Hoehn & Yahr
IPD	Individual participant data
LEDD	Levodopa equivalent daily dose
LDSM	Latent difference score model
LME	Linear mixed-effects
LPS-4	Leistungsprüfsystem subtest 4 (reasoning)
MCI	Mild cognitive impairment
MDS	Movement Disorder Society
PD	Parkinson’s Disease
PD-D	Dementia associated with Parkinson’s Disease
PD-MCI	Mild cognitive impairment associated with Parkinson’s Disease
PICOTS	Population, index prognostic factor, comparator prognostic factors, outcome, timing, setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROGRESS	Prognosis Research Strategy
PROSPERO	International Prospective Register of Systematic Reviews
RBD	Rapid eye movement (REM) sleep behavior disorder
RCT	Randomized controlled trial
SNpc	Substantia nigra pars compacta
SRMR	Standardized root-mean-square residual
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
UPDRS-III	Unified Parkinson’s Disease Rating Scale
WMT	Working memory training

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INTRODUCTION

PARKINSON'S DISEASE

Parkinson's Disease (PD) is the second most frequent neurodegenerative disorder of older age, pathologically characterized by a degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy bodies (composed of misfolded α-synuclein protein) in the surviving neurons (Przedborski, 2017). According to the *Global Burden of Disease* (GBD) *Study*, 6.1 million individuals worldwide had PD in 2016, an overall number of affected people that was already 2.4 times larger than in 1990 (GBD 2016 Parkinson's Disease Collaborators, 2018). The prevalence of PD especially increases after 60 years of age, peaking between 85 and 89 years of age (GBD 2016 Parkinson's Disease Collaborators, 2018). Due to population aging and increasing life expectancy, the number of individuals with PD is projected to more than double again within the next three decades (Bach et al., 2011; GBD 2016 Parkinson's Disease Collaborators, 2018; Rocca, 2018). Since its first elaborated description in 1817 by James Parkinson in *An Essay on the Shaking Palsy* (republished in 2002), important milestones have been made in the past more than 200 years of PD research. Those milestones revealed discoveries of clinical characteristics, pathophysiological mechanisms, disease-modifying environmental and genetic factors, as well as advances in diagnostic and therapeutic approaches, promoting the understanding of PD as a multisystem disorder (Li & Le, 2017; Marsili et al., 2018; Przedborski, 2017).

The upcoming chapter aims to establish a solid basis for the understanding of the rationale of the present thesis project, which will be extended in the subsequent ones. Before focusing on the nature of cognitive decline in patients with PD and its treatment approaches including cognitive training, a brief summary of clinical characteristics and the development of diagnostic criteria for PD will be given.

CLINICAL CHARACTERISTICS AND THE DIAGNOSIS OF PARKINSON'S DISEASE

The diagnosis of PD today is widely based on clinical features that were already described by James Parkinson in the early 19th century, and refined by Jean-Martin Charcot a few decades later (Marsili et al., 2018). According to the established *United Kingdom Parkinson's Disease Society Brain Bank* clinical diagnostic criteria (Gibb & Lees, 1988), the clinical motor syndrome of PD is defined as bradykinesia (i.e., slowness of movements) plus at least one of three other

cardinal motor symptoms, namely rest tremor, muscular rigidity, or postural instability (Figure 1, adapted from Kalia & Lang, 2015).

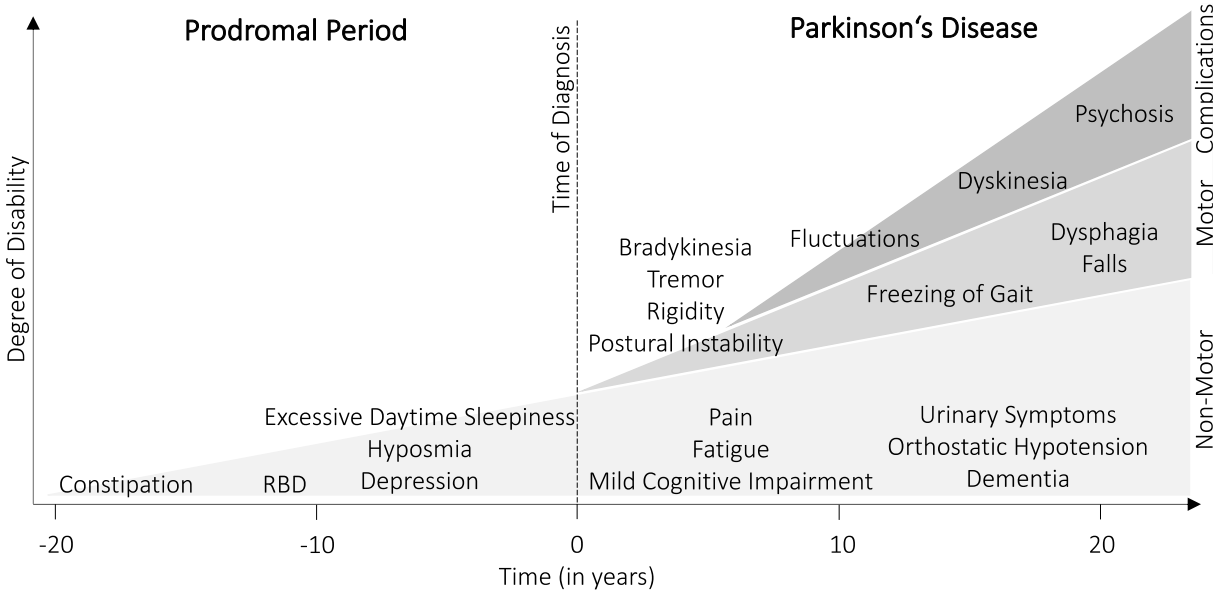


Figure 1. Clinical Symptoms and Time Course of Parkinson's Disease

Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterized by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability. RBD, rapid eye-movement (REM) sleep behavior disorder. Adapted from Kalia and Lang (2015).

Until today, the etiology of PD remains a matter of ongoing debate. Most likely, there seems to be a complex interplay among general aging processes, genetic susceptibility, and environmental factors (Bandres-Ciga et al., 2020; Pang et al., 2019). Oxidative stress, neuroinflammation, and mitochondrial dysfunctions then seem to be associated with the accumulation and spread of misfolded α-synuclein proteins and neurodegeneration in the course of PD (Pang et al., 2019; Trist et al., 2019). The extensive α-synuclein and Lewy body pathology probably leading to substantial cell loss especially in the substantia nigra pars compacta (SNpc) and following dopaminergic depletion in its main projection area, the dorsal striatum, remains the pathological hallmark of PD (Gibb & Lees, 1988; Volpicelli-Daley et al., 2011). First evidence for the striatal dopamine deficiency due to the cell los in the substantia nigra leading to the cardinal motor symptoms was reported in the mid 1900s (Ehringer & Hornykiewicz, 1960). Only shortly thereafter, levodopa, a precursor of the neurotransmitter dopamine, emerged as the premier symptomatic agent for treating the motor symptoms

associated with PD (Fahn, 2015). Besides the impressive therapeutic effects of levodopa and other dopaminergic medication, the intraindividual responses during chronic dopaminergic medication change dramatically over time. The symptomatic benefit declines progressively and medication-related complications such as dyskinesias (i.e., unintended, involuntary, and uncontrollable movements) and uncontrolled fluctuations between on- and off-phases are highly prevalent (Fabbrini et al., 2007; Rajput et al., 2002; Stacy & Galbreath, 2008).

Although still considered as a paradigmatic movement disorder, PD is associated with a broad spectrum of non-motor symptoms as well (Figure 1, adapted from Kalia & Lang, 2015), including, for example, autonomic dysfunctions, olfactory loss, depressive symptoms, sleep disorders, and cognitive dysfunctions (Chaudhuri et al., 2006; Pfeiffer, 2016; Schapira et al., 2017). Especially with disease progression, these non-motor symptoms dominate the clinical picture of PD and might be the predominant determinant of the patients' health-related quality of life across all disease stages (Duncan et al., 2014; Martinez-Martin et al., 2011; Müller et al., 2013; Ophey et al., 2018; Prakash et al., 2016). Strikingly, some of these non-motor symptoms even precede the manifestation of motor symptoms and, thus, often PD diagnosis (Chaudhuri et al., 2006; Kalia & Lang, 2015; Pfeiffer, 2016; Schapira et al., 2017). In this context, a task force of the *Movement Disorder Society* (MDS) introduced the new MDS clinical diagnostic criteria for PD, which were specifically designed for research purposes, but aim to find their way into clinical routines as well (Postuma et al., 2015). The MDS criteria were the first ones incorporating non-motor symptoms such as olfactory loss into the diagnostic workflow for clinical PD. Furthermore, a new diagnostic category, namely prodromal PD, was acknowledged as a true initial stage of PD (Marsili et al., 2018; Postuma et al., 2015).

In the early 21st century, Braak et al. (2003) already systematically described robust evidence for a slowly progressing neurodegenerative process starting long before the appearance of motor dysfunctions, suggesting preclinical and prodromal disease stages. Strikingly, at the time PD motor symptoms allow the clinical diagnosis of PD, 40% to 60% of dopaminergic neurons in the substantia nigra have already degenerated (DeKosky & Marek, 2003; Fearnley & Lees, 1991; Hu et al., 2001; Morrish et al., 1998). Evidence for the *Six-Stage Model of PD* introduced by Braak et al. (2003) suggests a mechanism by which the α-synuclein pathology systematically spreads from the olfactory bulb and the dorsal motor nucleus of the vagus nerve towards cortical areas. This might also explain the occurrence of autonomic dysfunctions and olfactory loss as early non-motor symptoms of PD (Braak & Del Tredici, 2017;

Braak et al., 2003). Furthermore, the idea that the initial route of α-synuclein pathology might arise from outside the central nervous system, for example, through the gut-brain axis, gained recognition (Hawkes et al., 2007; Klingelhoefer & Reichmann, 2015). This raises the possibility and further strengthened the hypothesis that environmental factors might trigger the pathogenesis of PD, as both the olfactory and gastrointestinal system can be considered as gateways to the environment (Klingelhoefer & Reichmann, 2015).

Taking these considerations into account, the MDS introduced the MDS research criteria for prodromal PD in 2015 (Berg et al., 2015), which were updated in 2019 (Heinzel et al., 2019). So far, these criteria (Berg et al., 2015; Heinzel et al., 2019), include rapid eye movement (REM) sleep behavior disorder (RBD), olfactory loss, autonomic dysfunctions (e.g., constipation, orthostatic hypotension, urinary dysfunctions), excessive daytime sleepiness, depressive symptoms, and global cognitive impairment as non-motor markers for prodromal PD. Each of these prodromal markers adds a positive or negative likelihood ratio to a baseline age-adjusted prevalence estimate of prodromal PD (Berg et al., 2015; Heinzel et al., 2019). This takes into account that each of these markers may be common when considered individually, however, their co-occurrence is rather specific for individuals with prodromal PD (Marsili et al., 2018).

In the following chapter, a special focus on cognitive impairment as a common non-motor symptom of PD will be set (Aarsland et al., 2017). Cognitive impairment can be regarded as one of the most debilitating non-motor symptoms, as it interferes with the patients' quality of life (Lawson et al., 2014b; Leroi et al., 2012; Reginold et al., 2013) and increases the burden on caregivers, care providers, and the public healthcare system (Mosley et al., 2017; Vossius et al., 2011).

COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

Regarding stages of cognitive impairment in patients with PD, one can distinguish the stages without cognitive impairment, mild cognitive impairment (MCI) in PD (PD-MCI), and PD dementia (PD-D). The recent diagnostic criteria for PD-MCI were published by Litvan et al. (2012). Next to a diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Gibb & Lees, 1988), the PD-MCI diagnosis requires cognitive deficits on a scale of global cognitive abilities (Level-I diagnosis) or in a comprehensive neuropsychological assessment (Level-II diagnosis). For a Level-II diagnosis of PD-MCI,

impairment on at least two neuropsychological tests (either from one cognitive domain or across two cognitive domains, referring to single-domain PD-MCI and multi-domain PD-MCI, respectively) operationalized by performance 1 to 2 *SD* below appropriate normative data is required. The applied neuropsychological test battery should include two tests within the following five cognitive domains: executive functions, attention and working memory, memory, visuospatial functions, and language (Litvan et al., 2012). The cognitive deficits should not significantly interfere with the patient's functional independence in the PD-MCI stage, which constitutes the main distinguishing criterion to the diagnosis of PD dementia (PD-D) according to the criteria proposed by Emre (2003). Beyond these objective cognitive impairment stages, subjective cognitive decline (SCD) defined as a self-perceived, subjective deterioration in potentially different cognitive domains in the absence of objective cognitive impairment (Jessen et al., 2020; Jessen et al., 2014) is increasingly discussed as a precursor of objective cognitive impairment in patients with PD (Erro et al., 2014; Galtier et al., 2019; Hong et al., 2014).

Prevalence and Epidemiological Characteristics

Prevalence rates of PD-MCI reported in newly diagnosed, drug-naïve patients with PD range from 10% to 32.9% (Muslimović et al., 2005; Poletti et al., 2012; Santangelo et al., 2015; Weintraub et al., 2015). Imposingly, a recent meta-analysis across *n* = 7053 patients with PD (Baiano et al., 2020) revealed a pooled prevalence of PD-MCI diagnosed according to the criteria of Litvan et al. (2012) of even 40% [95% confidence interval (CI): 36% – 44%]. Prevalence rates increased with disease progression assessed by the *Hoehn and Yahr* (H&Y) scale (Hoehn & Yahr, 1967). Furthermore, several demographic, disease-related, and neuropsychiatric differences between patients with PD without cognitive impairment and patients with PD-MCI were found: patients with PD-MCI were significantly older, reported less years of education, longer disease durations, higher levodopa equivalent daily doses (LEDD), more severe motor symptoms, higher levels of depression and anxiety, as well as a poorer quality of life than patients with PD without cognitive impairment (Baiano et al., 2020). In a meta-analysis on the trajectories of cognitive decline in patients with PD, PD-MCI was identified as a risk factor for the progression to PD-D, with 20% [95% CI: 13% – 30%] of patients with PD-MCI converting to PD-D within 3 years (Saredakis et al., 2019). In general, it has been reported that up to 80% of patients with PD develop PD-D during the course of their disease (Hely et al., 2008).

The seemingly inevitability of cognitive decline associated with PD and its severe consequences reveal the urgency for early diagnosis, prevention, and intervention against this debilitating non-motor symptom. In the past years, increasing scientific interest has been devoted to the development of a deeper understanding of the heterogeneous neuropsychological, neuropathological, and neurochemical nature of cognitive deficits in patients with PD (Biundo et al., 2016; Kehagia et al., 2010, 2013; Robbins & Cools, 2014).

Profiles of Cognitive Impairment in Parkinson's Disease

Executive functions, working memory, and attentional functions are among the earliest and most frequently impaired cognitive domains across various disease stages (Kalbe et al., 2016; Kudlicka et al., 2011; Litvan et al., 2011), including newly diagnosed, drug-naïve patients with PD (Lawson et al., 2014a; Muslimović et al., 2005) and even patients with prodromal PD (Fengler et al., 2017). Executive functions comprise a set of effortful, top-down cognitive processes such as inhibition, set shifting, reasoning, problem solving, and planning (Chan et al., 2008; Diamond, 2013). For example, in the influential Norman and Shallice (1986) model, executive functions are integrated as the supervisory attentional system that is needed, whenever novel situations require a deliberate planning of actions without relying on previously learned schemata, and habitual responses have to be overcome. Executive components were also integrated in several working memory models, for example, the *Multicomponent Model of Working Memory* by Baddeley and Hitch (1974) and the *Embedded-Processes Model of Working Memory* by Cowan (1999, 2005). The concept of working memory integrates both aspects of memory (maintenance of information) and executive functions (manipulation of information), which will be further discussed under "Working Memory from the Neuropsychological Perspective". In general, executive functions are an essential skill for everyday functioning, as they might predict health, wealth, and quality of life (Diamond, 2013). Therefore, it is particularly alarming that those functions are considered to be among the most vulnerable cognitive functions in the course of PD (Kudlicka et al., 2011).

Cognitive impairment in patients with PD is, however, not limited to impairments in executive functions, working memory, and attentional functions (Litvan et al., 2011). Memory, visuo-cognitive (including visuo-spatial and visuo-constructive) functions, and language impairments are frequently observed as well (Bastiaanse & Leenders, 2009; Bocanegra et al., 2015; Cronin-Golomb & Braun, 1997; Montse et al., 2001; Weintraub et al., 2004).

Neural Correlates of Cognitive Impairment in Parkinson's Disease

Kehagia et al. (2010, 2013) synthesized evidence on cognitive impairment patterns in patients with PD into the *Dual Syndrome Hypothesis* (Figure 2). The Dual Syndrome Hypothesis postulates the existence of two independent, but partially overlapping syndromes: one reflecting dopamine- and probably norepinephrine-modulated fronto-striatal dysfunctions, and the other reflecting more posterior cortical and temporal lobe dysfunctions mainly associated with cholinergic loss.

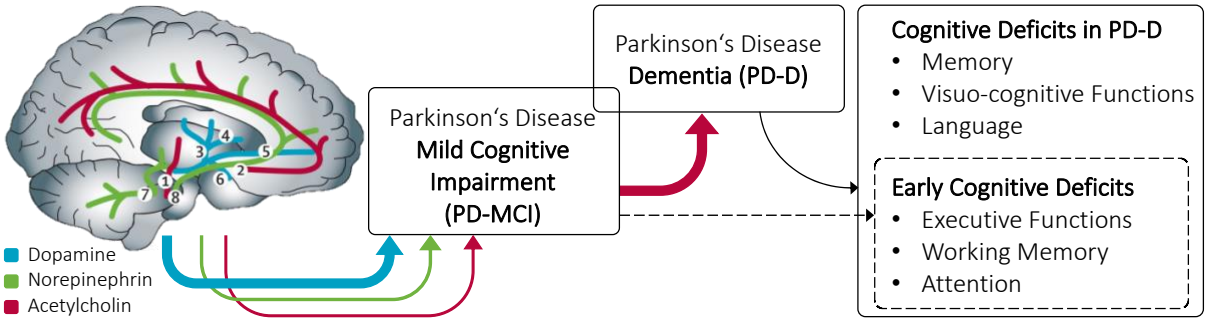


Figure 2. Cognitive Impairment in Parkinson's Disease: The Dual Syndrome Hypothesis

Cognitive Impairment in Parkinson's Disease is highly heterogeneous. Early cognitive deficits (e.g., executive functions, working memory, attention) observed in mild cognitive impairment associated with Parkinson's Disease (PD-MCI) might reflect fronto-striatal dopaminergic dysfunctions (4, 5, 6, blue). Noradrenergic dysfunctions (7, 8, green) probably contribute to these early cognitive deficits, as well as a frontal cholinergic deficit (2, red). Cognitive deficits in Parkinson's Disease Dementia (PD-D) might share features with the early frontal dysexecutive syndrome, but are mainly characterized by memory, visuo-cognitive, and language dysfunctions indicating a strong cholinergic involvement (1, 2, red). Cholinergic modulation probably has a key role in the progression from PD-MCI to PD-D (bold red arrow). Adapted from Kehagia et al. (2010, 2013).

The fronto-striatal dysfunctions, for example, in executive functions, working memory, and attentional functions, might be especially present in patients with PD-MCI, amenable to dopamine replacement therapy but also susceptible to dopamine overdosing effects, and modulated by genetic risk factors (Kehagia et al., 2010, 2013). The more posterior and temporal lobe dysfunctions, for example, in memory, visuo-cognition, and language, are especially frequent in patients exhibiting a rapid cognitive decline to PD-D, for whom cholinergic treatment may offer some clinical benefit (Kehagia et al., 2010, 2013). However, PD-D should not be understood isolated from dopaminergic dysfunctions, not least because the degeneration of nigrostriatal dopaminergic neurons constitutes the pathological hallmark of PD itself. On a neuropsychological level, cognitive dysfunctions in patients with PD-D might, but do not necessarily, share features with the early fronto-striatal syndrome. This is why Kehagia et al. (2010, 2013) speak of two independent, but partially overlapping syndromes.

Despite the popularity of the Dual Syndrome Hypothesis, results of functional neuroimaging studies investigating the neural correlates of early cognitive dysfunctions (i.e., in executive functions, working memory, and attentional functions) in patients with PD compared to healthy controls are rather inconsistent and heterogeneous. Several studies report increased task-related neural activation patterns in fronto-striatal regions in patients with PD compared to healthy controls (e.g., Boord et al., 2017; Caminiti et al., 2015; Trujillo et al., 2015). These correlates have been interpreted as a compensatory mechanism for decreased functional connectivity between those regions due to PD-related striatal dopamine depletion. Following this rationale, patients with PD have to expand more neural resources for successful task execution compared to healthy controls. However, these studies were recently synthesized within an activation likelihood estimation meta-analysis, which surprisingly did not reveal significant converging aberrant activation patterns between patients with PD and healthy controls during the performance of tasks on executive functions and working memory (Giehl et al., 2019). The authors list methodological shortcomings of the included studies as well as methodological heterogeneities as potential explanations, but also acknowledge the possibility of an overestimation of the anticipated diverging (fronto-striatal) activation patterns between patients with PD and healthy controls (Giehl et al., 2019).

TREATMENT OF COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

For the treatment of cognitive impairment in patients with PD we can differentiate between pharmacological and non-pharmacological approaches. Until today, pharmacological approaches for treating cognitive impairment in patients with PD are rare and even fully lacking for early disease stages and PD-MCI.

Pharmacological Treatment Options

Licensed, evidence-based pharmacological treatment for cognitive impairment in patients with PD is only available for patients with PD-D. Recent meta-analyses revealed beneficial effects of the two cholinesterase inhibitors rivastigmine and donepezil on a broad spectrum of cognitive domains but less evidence for memantine (Meng et al., 2019; Wang et al., 2015). Note, however, that comparable to the dopaminergic treatment against motor symptoms of PD, these pharmacological treatments for cognitive dysfunctions in patients with PD-D are symptomatic rather than curative or slowing. Additionally, frequently observed adverse events

of cholinesterase inhibitors and memantine include nausea, vomiting, and an aggravation of neuropsychiatric symptoms such as hallucinations and sleep disturbances (Meng et al., 2019; Wang et al., 2015).

Dopaminergic treatments used for the symptomatic treatment of the motor symptoms associated with PD might bear the potential to ameliorate fronto-striatal cognitive dysfunctions as well. However, as stated in the *Dopamine Overdose Hypothesis*, evidence on the beneficial effects of dopaminergic treatments for cognitive functions is mixed (Cools et al., 2001; Gotham et al., 1988; Swainson et al., 2000). Both dopamine depletion as well as dopamine overdoses might lead to adverse effects in cognitive tasks, resulting in an inverted U-shaped relationship between dopamine levels and performance (Cools et al., 2001; Gotham et al., 1988; Swainson et al., 2000; Vaillancourt et al., 2013). Furthermore, dopaminergic treatment may foster dopamine depleted neural circuits but at the same time overdose relatively intact circuits. This in turn sets dopaminergic treatment effects on cognitive functions as a function of disease progression, as PD affects different parts of the SNpc and the striatum along a gradient of degeneration (Vaillancourt et al., 2013). Whereas the ventral part of the SNpc projecting to the dorsal striatum is affected in early disease stages, therefore leading to dopaminergic depletion in this projection area and connected neural circuits, the dorsal part of the SNpc projecting to the ventral striatum remains relatively intact and would only be affected in later disease stages. In sum, the effect of dopaminergic treatment on cognitive functions in patients with PD is dependent on several complex factors such as disease progression, genetic variation influencing the individual innate baseline dopamine level, and the nature of the investigated cognitive function with its underlying brain networks (Vaillancourt et al., 2013).

Non-Pharmacological Treatment Options

Given the lack of convincing pharmacological treatment options for preventing and treating cognitive impairment in patients with PD, non-pharmacological treatment approaches focusing on the modulation of cognitive abilities gained increasing scientific interest (for systematic reviews, see Hindle et al., 2013; Lawrence et al., 2017; Pupíková & Rektorová, 2019). The spectrum of non-pharmacological treatment options is broad, including cognitive interventions, physical activity, non-invasive brain stimulation, and combinations among them.

In their recent systematic review, Pupíková and Rektorová (2019) evaluated the scientific evidence to modulate cognitive abilities in patients with PD for several non-

pharmacological approaches by classifying each study into a class of evidence and deducing one of three levels of recommendation for the investigated intervention (A: definitely effective or ineffective, B: probably effective or ineffective, C: possibly effective or ineffective) by applying established rating criteria of the *European Federation of Neurological Societies for the Preparation of Neurological Guidelines* (Brainin et al., 2004; Lefaucheur et al., 2014). None of the included studies reached the highest possible class of evidence and following none of the non-pharmacological approaches reached level A of recommendation. Cognitive training approaches reached the highest level of recommendation among the assessed interventions (level B, Pupíková & Rektorová, 2019). Level C recommendation was reached for physical interventions, and no recommendations could be gathered for non-invasive brain stimulation and multimodal interventions due to large heterogeneity and a lack of passive control conditions in combinatory trials (Pupíková & Rektorová, 2019). Before reviewing further evidence on cognitive training in patients with PD, a broader introduction to the concept of cognitive training and its general neuropsychological an neural effects in the aging population on a neuropsychological and neural level will be given.

Cognitive interventions comprise an umbrella term referring to several treatment approaches which apply a range of techniques to engage cognition with varying intensities and foci (Gavelin et al., 2020). The terms cognitive training, cognitive rehabilitation, and cognitive stimulation have been used interchangeably for a long period of time, tending to obscure important differences in concept and application (Clare & Woods, 2004; Gavelin et al., 2020). The two latter approaches pursue a functional focus to improve cognitive and social functioning in everyday life, either by targeted individualized approaches (cognitive rehabilitation) or rather global, non-specific stimulation (cognitive stimulation). In contrast, cognitive training focuses on restoring specific cognitive abilities by involving guided, repeated practice on a set of standardized, theoretically driven tasks designed to target specific cognitive functions such as memory, executive functions, working memory, attention, and visuo-cognition (Clare & Woods, 2004; Gavelin et al., 2020; Walton et al., 2017). Cognitive trainings may target multiple cognitive domains or focus on one domain only. They may be implemented computerized or in paper-pencil scenarios. The cognitive training regimes may employ a strategy-based approach or be process-based on drill and practice. They may be conducted in individual or group settings, home-based or in clinical/educational settings, supervised or unsupervised. Furthermore, cognitive trainings may be designed adaptive or non-adaptive to user

performance and they may be created on a spectrum from one-training-fits-all to highly individualized approaches (Lustig et al., 2009; Walton et al., 2017). These different properties regarding training setting and conceptualization of the training may also be combined within mixed approaches. A framework of cognitive training approaches is visualized in Figure 3.

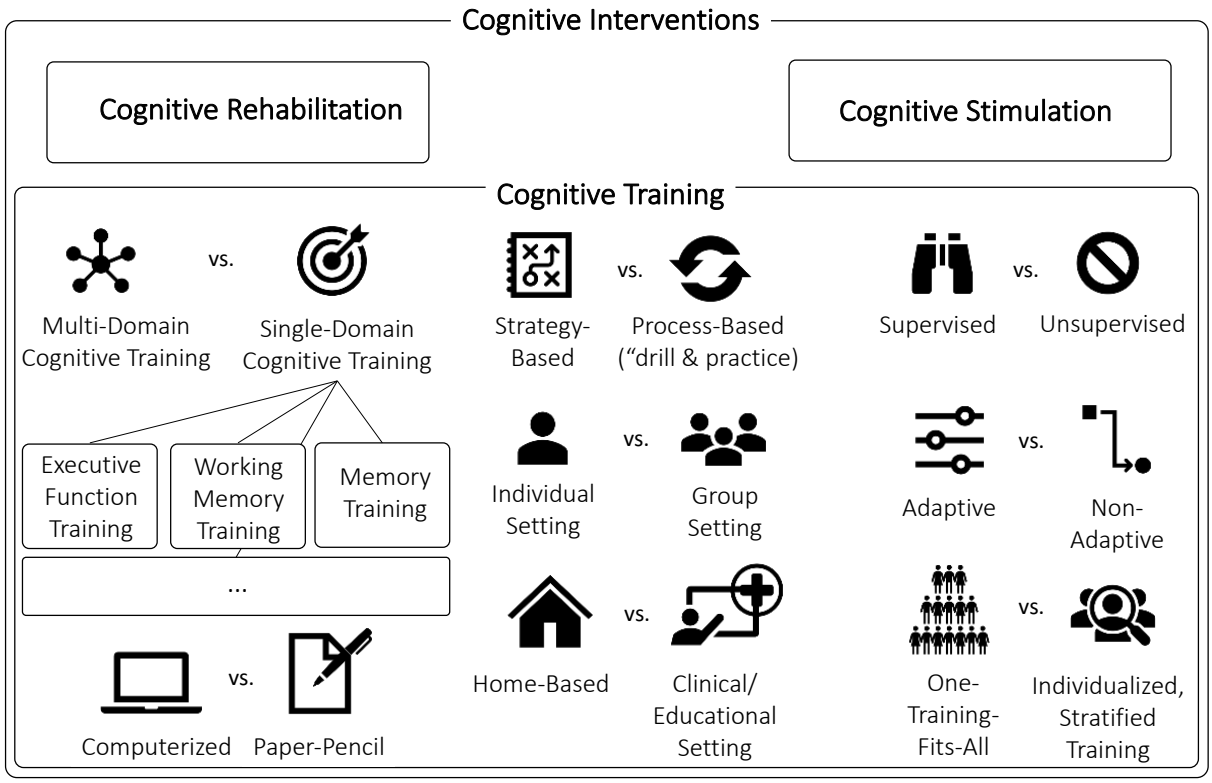


Figure 3. A Framework of Cognitive Training

Cognitive Training is next to cognitive rehabilitation and cognitive stimulation, one approach within a broad spectrum of cognitive interventions. Moreover, cognitive training itself can be subdivided into either multi-domain or targeted single-domain (e.g., executive function training, working memory training, memory training) cognitive training. Each of those cognitive training approaches in turn, is characterized by different properties regarding the training setting and conceptualization of the training.

Cognitive training and cognitive intervention approaches in general bear an enormous potential to maintain and improve cognitive functioning in the aging population. In their systematic overview, Gavelin et al. (2020) synthesized the large body of evidence from 46 meta-analyses on the efficacy of cognitive interventions to improve cognitive and non-cognitive outcomes for older adults on the spectrum from healthy aging to neurodegenerative diseases and dementia. The available evidence consistently supports the efficacy of cognitive training to improve cognitive performance in healthy older adults, MCI, and PD with small pooled effect sizes (Gavelin et al., 2020). Only limited evidence was available for cognitive rehabilitation and cognitive stimulation. Furthermore, the authors identified several shortcomings regarding a

lack of high-quality evidence, large heterogeneity among the applied methods, inconsistencies regarding the assessment of non-cognitive outcomes, and ambiguity among the clinical value of the reported effects.

Next to neuropsychological effects, the neural mechanisms underlying cognitive training approaches in healthy older adults have been summarized in several recent meta-analyses. Common neural mechanisms of different cognitive training approaches including both multi-domain cognitive training and targeted single-domain training approaches in healthy older adults revealed both increased and decreased task-related neural activation patterns, especially within the fronto-parietal network and subcortical regions involved in higher-order cognitive functions (Duda & Sweet, 2019; Nguyen et al., 2019; van Balkom et al., 2020). Furthermore, a reorganization of functional connectivity patterns counteracting age-related dysfunctional neural connectivity patterns was observed (van Balkom et al., 2020).

As previously outlined, cognitive trainings constitute the most promising approach among non-pharmacological interventions to modulate cognitive functioning in patients with PD (Hindle et al., 2013; Pupíková & Rektorová, 2019). Three meta-analyses (Lawrence et al., 2017; Leung et al., 2015; Orgeta et al., 2020) and several systematic reviews (Couture et al., 2018; Hindle et al., 2013; Nousia et al., 2020; Pupíková & Rektorová, 2019) investigating the effects of cognitive training on cognitive outcomes in patients with PD exist so far.

Whereas the recent meta-analysis by Orgeta et al. (2020) on cognitive training in patients with PD-MCI and PD-D did not find reliable evidence for significant positive training effects, evidence for the therapeutic potential of cognitive training in patients with PD in earlier disease stages seems more convincing (Lawrence et al., 2017; Leung et al., 2015). The two meta-analyses by Leung et al. (2015) and Lawrence et al. (2017) revealed significant positive cognitive training effects in executive functions with small (5 studies, Hedges' g = 0.30, Leung et al., 2015) to medium (8 studies, Hedges' g = 0.42, Lawrence et al., 2017) pooled effect sizes. For working memory and attention, Lawrence et al. (2017) reported a significant small pooled effect size (10 studies, Hedges' g = 0.23), whereas Leung et al. (2015) reported a significant medium effect size for working memory (4 studies, Hedges' g = 0.74) and a non-significant small negative effect size for attention. Furthermore, Leung et al. (2015) found a significant small positive cognitive training effect on processing speed (4 studies, Hedges' g = 0.31) and Lawrence et al. (2017) on memory (6 studies, Hedges' g = 0.33). Just recently, the first systematic review focusing on computerized cognitive training in patients with PD was

published (Nousia et al., 2020), confirming the results of the previously published meta-analyses encompassing both computerized and paper-pencil cognitive training approaches (Lawrence et al., 2017; Leung et al., 2015). Therefore, computerized and potentially home-based cognitive training approaches constitute an easily accessible, flexible, cost-efficient intervention option against debilitating cognitive decline in the course of PD.

The majority of studies within the two meta-analyses included patients with PD in rather early disease stages without cognitive impairment (i.e., without PD-MCI or PD-D). Therefore, the reported small to medium effects for cognitive functions could also reflect ceiling effects of the therapeutic potential of cognitive training in cognitively unimpaired patients with PD (Lawrence et al., 2017), as improvements from a well-functioning baseline may be limited per se. For this group of patients, the true potential of cognitive training might only be examinable with longer follow-up periods that would allow to investigate preventive effects of cognitive training in terms of delaying the onset and/or slowing down the rate of cognitive decline in patients with PD (Couture et al., 2018).

Importantly, the reported effects across cognitive training approaches seem to be concentrated on cognitive functions that are especially vulnerable in patients with PD, namely executive functions, working memory, and attentional functions (Fengler et al., 2017; Kalbe et al., 2016; Kudlicka et al., 2011; Lawson et al., 2014a; Litvan et al., 2011; Muslimović et al., 2005). Although most studies applying cognitive training in patients with PD focused on more than one cognitive domain, targeting one specific cognitive domain, namely working memory, might bear a special potential for patients with PD. The potential of targeting working memory in cognitive training approaches will further be outlined in the next chapter of the present thesis.

Regarding non-cognitive outcomes, the meta-analysis by Leung et al. (2015) revealed non-significant close-to-zero effect sizes for depressive symptoms, activities of daily living, and quality of life following cognitive training in patients with PD. The recent meta-analysis by Orgeta et al. (2020) showed similar results. So far, the meta-analytical results do not support the evidence on the single-study level, where some original studies showed positive effects on depressive symptoms, activities of daily living, and quality of life (e.g., Folkerts et al., 2018; Lawrence et al., 2018; Petrelli et al., 2014). As reported in the general aging context (Gavelin et al., 2020), evidence on the effects of cognitive training in patients with PD on non-cognitive outcomes may be limited due to a non-consistent assessment of them across studies.

WORKING MEMORY TRAINING

Working memory has already become a main target for cognitive training in healthy older adults. Before introducing the rationale behind working memory training (WMT) in patients with PD, however, it is essential to gain an overview of the concept of working memory from a broad neuropsychological perspective.

WORKING MEMORY FROM A NEUROPSYCHOLOGICAL PERSPECTIVE

This chapter aims to introduce the most influential psychological working memory models, to summarize the current consensus regarding the concept of working memory, and to present the most common neuropsychological tasks to operationalize working memory in clinical and research settings.

Working Memory Models and a Definition Approach

The term working memory was first introduced by Miller et al. (1960) and became prominent after Baddeley and Hitch (1974) introduced the Multicomponent Model of Working Memory. According to the model, working memory refers to a multicomponent system that manipulates information beyond the pure maintenance and storage of information in short-term memory for more complex cognitive tasks (Baddeley, 2000, 2010; Baddeley & Hitch, 1974). Initially, the model consisted of three subcomponents, the central executive, the phonological loop, and the visuo-spatial sketchpad (Baddeley & Hitch, 1974) and was later extended by the episodic buffer (Baddeley, 2000). The central executive controls and manages maintenance and manipulation of information in the phonological loop (verbal working memory) and the visuo-spatial sketchpad (non-verbal working memory) for higher-order functions such as decision making, problem solving, or even thesis writing (Baddeley & Hitch, 1974; Chai et al., 2018). Hence, the episodic buffer can be regarded as a temporary storage system modulating and integrating information from different sensory systems (Baddeley, 2000, 2010; Chai et al., 2018). Cowan (1999, 2005) strengthened the role of long-term memory and central executive processes such as attentional control for working memory in the Embedded-Processes Model of Working Memory. According to this model, working memory could be conceptualized as a capacity limited short-term storage component, reflecting a subset of activated long-term memory that is in the focus of attention, which in turn is controlled by central executive processes (Chai et al., 2018; Cowan, 1999, 2005).

Despite the ongoing scientific debate around the definition of working memory, a consensus emerged according to which working memory integrates both the maintenance and manipulation of verbal and/or non-verbal information (Figure 4). Whereas working memory maintenance refers to the pure capacity limited storage of information linking it to both long- and short-term memory, working memory manipulation additionally requires executive control processes to serve more complex cognitive tasks (Chai et al., 2018).

The dissociation of working memory maintenance and manipulation was further supported by the available neuroimaging evidence from studies investigating neural correlates of working memory. Despite a general fronto-parietal working memory network involving the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the parietal cortex (Chai et al., 2018; Suzuki et al., 2018), working memory manipulation additionally recruits subcortical regions, namely nuclei of the basal ganglia, reflecting a fronto-striatal working memory network (Lewis et al., 2004; McNab & Klingberg, 2008; Murty et al., 2011). Within these networks, dopamine emerges as the critical neurotransmitter, which supports the hypothesis of working memory performance being heavily dopamine-dependent (Bäckman et al., 2010; Bäckman & Nyberg, 2013).

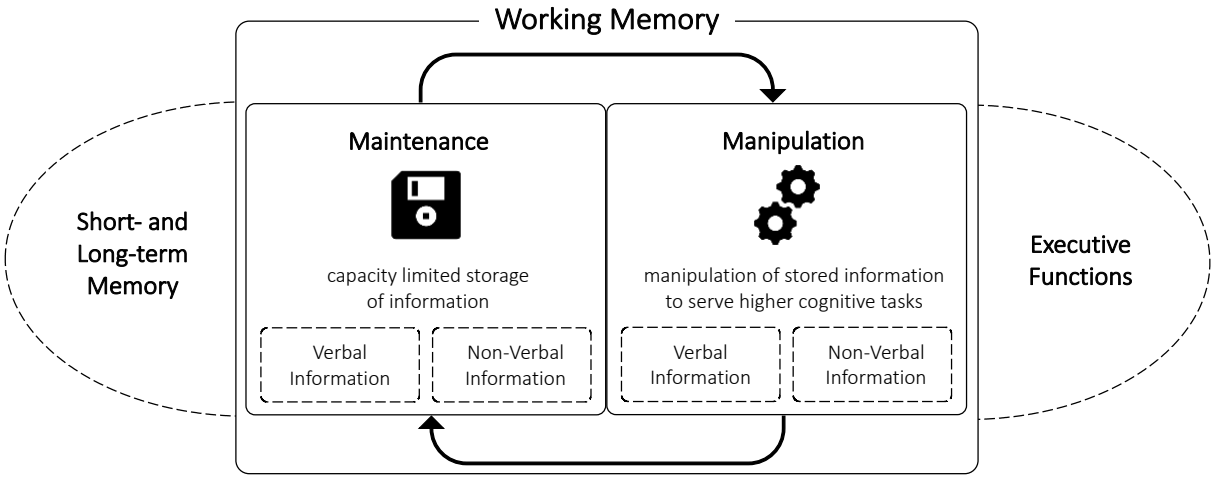


Figure 4. Working Memory: Maintenance and Manipulation

Working memory integrates both the maintenance and manipulation of verbal and/or non-verbal information. Working memory maintenance refers to the pure capacity limited storage of information (linking it to both long- and short-term memory). Working memory manipulation additionally requires executive control processes to serve more complex cognitive tasks.

The Operationalization of Working Memory

Working memory and its components have been operationalized with a variety of neuropsychological tasks (Figure 5). Popular working memory paradigms include so-called

simple and complex span tasks, as well as the n-back paradigm (Colom et al., 2006; Kessels et al., 2008; Redick & Lindsey, 2013; Schmiedek et al., 2014).

Simple span tasks such as verbal digit span tasks or non-verbal block-tapping span tasks require the maintenance of information with subsequent recall of the information in the same (forward) or reversed (backward) order (Figure 5a). The forward versions of simple span tasks, however, are discussed to reflect short-term memory rather than working memory, as the executive, manipulating component of working memory is lacking. By contrast, the maintenance component of working memory could also be regarded as a shared component of working memory and short-term memory (Colom et al., 2006). The backward versions of simple span tasks explicitly add the manipulation component of working memory for successful task completion. Complex span tasks (Figure 5b) combine the maintenance and recall of items (e.g., letters, words) with the simultaneous performance of a secondary processing task (e.g., math operations). To successfully perform these tasks, information needs to be maintained, interference from task-irrelevant, simultaneously presented information needs to be prevented, and currently task-relevant information needs to be recalled and may additionally require updating and manipulation (Redick & Lindsey, 2013). The n-back paradigm (Figure 5c) addresses similar aspects of working memory. Within the paradigm, a sequence of stimuli (e.g., numbers, letters, symbols) is presented. The task is to decide whether the current stimulus matches the stimulus n steps back (Kirchner, 1958), which requires the permanent updating and manipulation of information to constantly maintain the last n elements (Redick & Lindsey, 2013; Schmiedek et al., 2014).

Interestingly, research on the relationship of these different neuropsychological working memory tasks revealed mixed evidence regarding their construct validity. The findings were synthesized in a meta-analysis on the correlation of simple and complex span tasks with n-back paradigms (Redick & Lindsey, 2013). The results revealed low correlations among both simple span and n-back tasks (r = 0.25, 95% CI 0.21 – 0.30) and complex span and n-back tasks (r = 0.20, 95% CI 0.16 – 0.24), seemingly revealing evidence for low concurrent validity of the different working memory tasks. In contrast, the results reported by Schmiedek et al. (2014), indicate substantially higher latent correlations (e.g., complex span with n-back tasks r = 0.69), when analyses account for measurement error and content-specific sources of variance. In this context, the authors stress the importance of measuring working memory (and any other broader cognitive domain) with a heterogeneous battery of tasks and to use average

performance or latent factor scores instead of single test scores when evaluating inter- and intraindividual differences (Schmiedek et al., 2014).

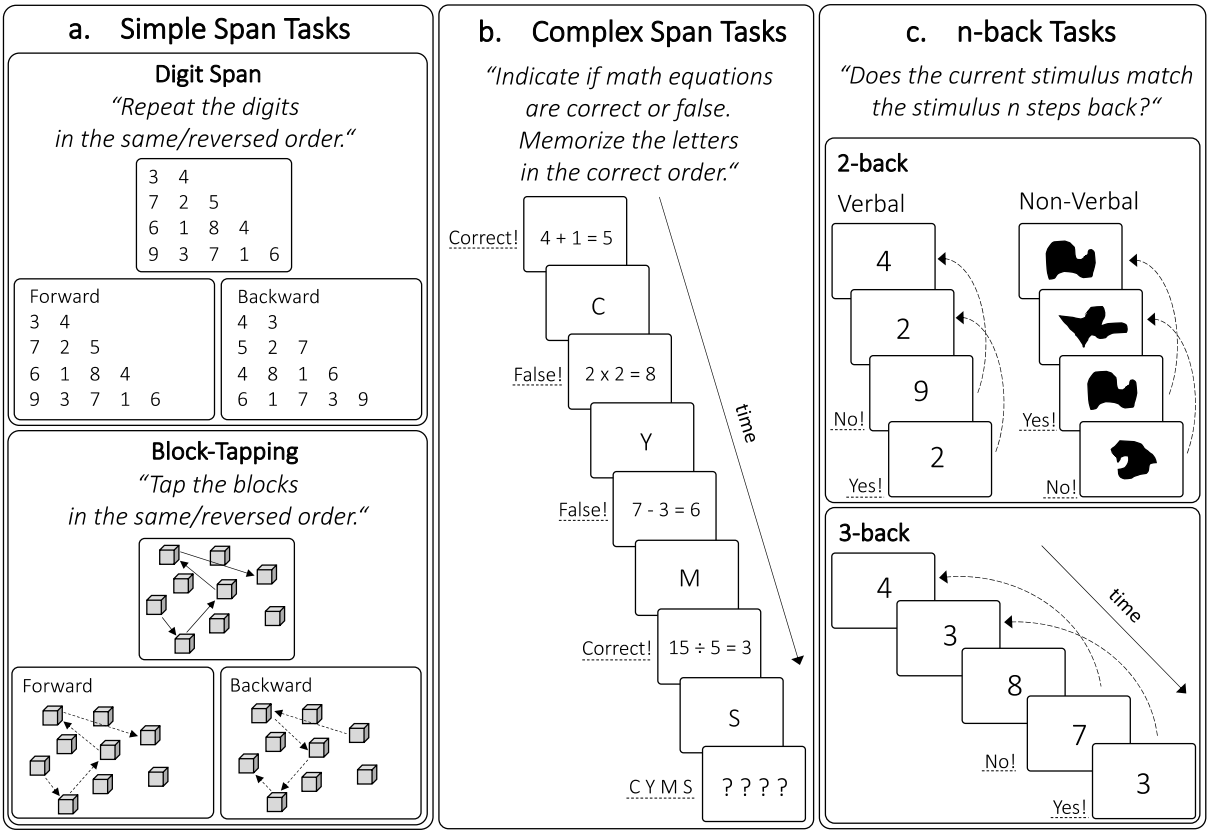


Figure 5. Operationalization of Working Memory

a. Simple span tasks (e.g., a digit span in the verbal version or a block-tapping sequence in the non-verbal version) require the recall of previously presented information in the same (forward) or reversed (backward) order. b. Complex span tasks combine the maintenance and recall of items (e.g., letters) with the simultaneous performance of a secondary processing task (e.g., math operations). c. n-back tasks require the continuous comparison of a current stimulus (e.g., a digit in the verbal version or an abstract figure in the non-verbal version) with the stimulus n (e.g., 2 or 3) steps back. If the two stimuli match, a reaction is required.

THE RATIONALE OF WORKING MEMORY TRAINING

Working memory capacity has been seen as a static entity for a long time (Miller, 1956) and was found to be strongly linked to fluid intelligence (Conway et al., 2003; Engle et al., 1999; Schmiedek et al., 2014), executive control functions (Engle, 2002; Shipstead et al., 2010), mathematic abilities (Bull & Scerif, 2001), and general achievements in school (St Clair-Thompson & Gathercole, 2006). This association of working memory with higher-order cognitive abilities and everyday functions motivated the question whether working memory functioning might be modifiable by means of systematic, targeted WMT. If working memory would indeed function as a processing resource for higher-order cognitive abilities, plastic

changes in working memory functioning should then transfer to untrained tasks and other cognitive functions (Klingberg, 2010). As a consequence, targeted WMT became one of the most extensively empirically investigated cognitive training approaches across the lifespan. The spectrum of employed WMT regimes is broad, including commercially available training programs (e.g., *Cogmed*, www.cogmed.com), pure n-back trainings, complex span trainings, and mixed approaches combining a variety of working memory tasks.

When evaluating scientific evidence on the effectiveness of targeted single-domain cognitive training approaches (e.g., WMT) the most critical issue, theoretically and practically, is the degree of transfer produced by the training. Therefore, it is common to differentiate between direct training effects, near-transfer effects, and far-transfer effects (Figure 6). Whereas direct training effects refer to effects in trained tasks over the course of training, near-transfer effects refer to effects in untrained tasks within the trained cognitive domain (e.g., untrained working memory tasks), and far transfer-effects refer to effects in untrained tasks from untrained cognitive domains (e.g., executive functions, memory, visuo-cognition) and effects in non-cognitive outcomes (e.g., depressive symptoms, quality of life, motor functioning, activities of daily living).

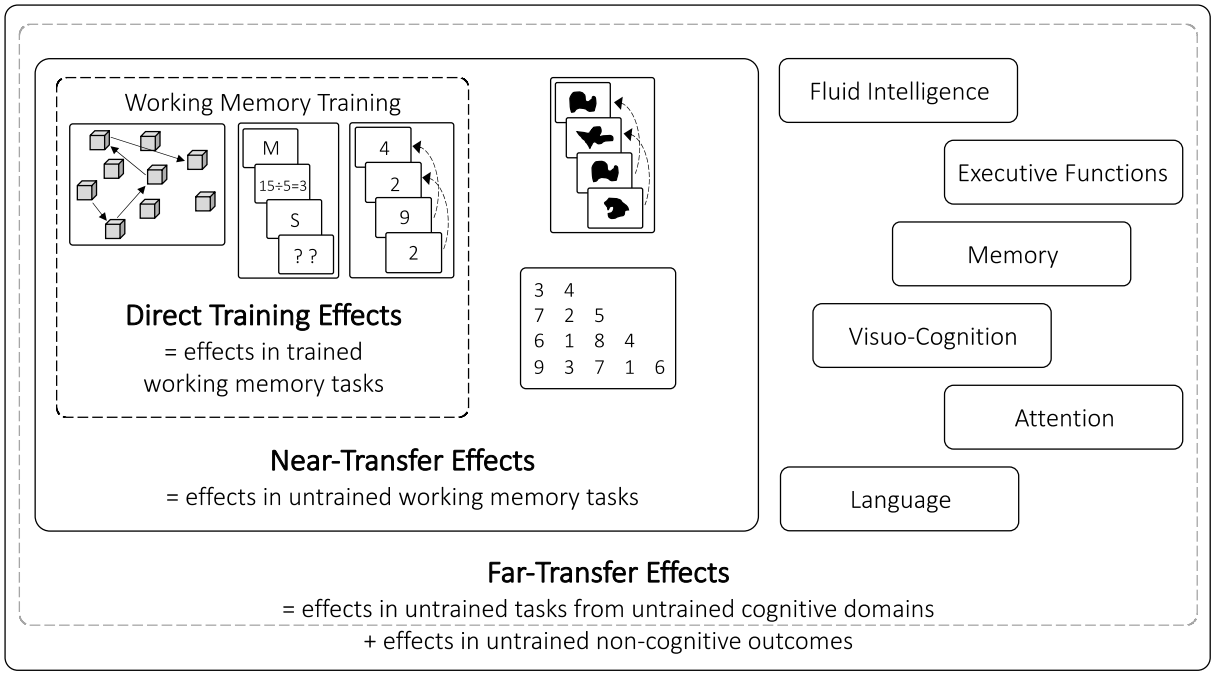


Figure 6. Effects of Working Memory Training: The Degree of Transfer

For working memory training, direct training effects refer to effects in trained working memory tasks over the course of training. Near-transfer effects then refer to effects in untrained working memory tasks and far transfer-effects refer to effects in untrained tasks from untrained cognitive domains and effects in non-cognitive outcomes (e.g., depressive symptoms, quality of life, motor functioning, activities of daily living).

The effects of WMT have been extensively investigated in empirical research and several systematic reviews and meta-analyses exist. Indeed, first WMT studies suggested promising positive effects not only in trained tasks, but also in near- and far-transfer measures (Jaeggi et al., 2008; Klingberg, 2010; Klingberg et al., 2002). Several meta-analyses across various populations (e.g., children, younger adults, older adults, patients with brain injuries) confirm evidence for positive direct training and near-transfer effects, however, evidence for reliable far-transfer effects remains a matter of ongoing debate (Au et al., 2016; Au et al., 2014; Karbach & Verhaeghen, 2014; Melby-Lervåg & Hulme, 2016; Melby-Lervåg et al., 2016; Sala et al., 2019; Soveri et al., 2017; Teixeira-Santos et al., 2019; Weicker et al., 2016). Details on the effects of WMT in healthy older adults and patients with PD will be reviewed under "Working Memory Training in Healthy Older Adults" and "Working Memory Training in Patients with Parkinson's Disease".

Next to neuropsychological effects of WMT, substantial efforts have been made to investigate neural correlates of WMT. WMT seems to induce long-lasting effects in working memory related neural circuits and the dopaminergic system (Bäckman & Nyberg, 2013; Bäckman et al., 2011; Brooks et al., 2020; Clark et al., 2017; Constantinidis & Klingberg, 2016; Dahlin et al., 2008; Iordan et al., 2020; McNab et al., 2009; Salmi et al., 2018; Takeuchi et al., 2015). Following WMT, the earliest works investigating the neural correlates of WMT found increased striatal dopamine release and decreased densities of post-synaptic dopamine receptors (e.g., Bäckman & Nyberg, 2013; Bäckman et al., 2011; McNab et al., 2009), which were referred to as "boosts in striatal activity and dopamine release" (Bäckman & Nyberg, 2013). Dahlin et al. (2008) already discussed the pivotal role of the striatum in mediating transfer to other cognitive domains following WMT. Improvements in working memory functioning on a neural and behavioral level may transfer to untrained tasks and cognitive functions due to overlapping neural systems (e.g., including dopamine-modulated striatal circuits) between working memory and other cognitive functions (Bäckman & Nyberg, 2013; Brooks et al., 2020; Constantinidis & Klingberg, 2016; Dahlin et al., 2008; Klingberg, 2010; Salmi et al., 2018). The review by Brooks et al. (2020) further emphasized the role of broad neural effects following WMT for enduring behavioral transfer effects.

After WMT completion, several studies suggest decreased neural activation patterns (Clark et al., 2017; Takeuchi et al., 2015) reflecting increased neural efficiency (Neubauer & Fink, 2009). Just recently, Brooks et al. (2020) accredited the increased neural efficiency to

functional connectivity changes in the underlying neural networks and increased myelination on a cellular level in their systematic review synthesizing findings on neural effects following WMT across several imaging modalities and populations. Changes in neural activation might, however, be dependent on working memory load (Iordan et al., 2020). As reviewed by Constantinidis and Klingberg (2016), the most consistent loci of neural activation changes associated with WMT can be found within frontal and parietal regions. This finding was confirmed and extended in a meta-analysis on task-related brain activation changes following WMT (Salmi et al., 2018), which indicated higher activation patterns within the fronto-striatal system, but lower activation patterns in the dorsolateral prefrontal cortex and parietal cortex.

WORKING MEMORY TRAINING IN HEALTHY OLDER ADULTS

The following paragraphs summarize the available evidence on neuropsychological effects of WMT in healthy older adults and outline neural correlates of working memory and WMT effects in this population.

Neuropsychological Effects of Working Memory Training in Healthy Older Adults

The neuropsychological effects of WMT in healthy older adults have been synthesized in several meta-analyses with different methodological approaches. Whereas one of the earlier meta-analyses differentiating between younger and older adults revealed significant positive near- and far-transfer effects for healthy older adults (Karbach & Verhaeghen, 2014), these results were challenged in a re-analysis controlling for baseline differences and using active control conditions by Melby-Lervåg and Hulme (2016), constituting the kickoff for a heated debate (Au et al., 2016). In a subsequent meta-analysis including a broad range of WMT types and age groups, Melby-Lervåg et al. (2016) did not find evidence for reliable far-transfer effects either, and age was not found to explain any variability of the results.

In the same year, another meta-analysis on the effects of WMT was published. Weicker et al. (2016) pursued a rather clinical approach by conducting several sub-analyses for different target groups to answer the question if WMT responsiveness might be dependent on sample characteristics. For healthy older adults, direct training effects were large (17 studies, Hedge's g = 1.49, 95% CI 1.22 – 1.77) and near-transfer effects were moderate (20 studies, Hedge's g = 0.60, 95% CI 0.34 – 0.86). Significant pooled albeit small effect sizes in far-transfer measures were reported for reasoning and intelligence (17 studies, Hedge's g = 0.35, 95% CI 0.16 – 0.54),

attention and processing speed (11 studies, Hedge's *g* = 0.39, 95% CI 0.08 – 0.70), and executive functions (14 studies, Hedge's *g* = 0.41, 95% CI 0.19 – 0.62, Weicker et al., 2016). Even though subgroup comparisons did not always reach statistical significance, effect sizes for healthy older adults, adults with acquired brain injuries (e.g., stroke, traumatic brain injuries), and adolescents with working memory deficits were descriptively larger than effect sizes for healthy children and adolescents (Weicker et al., 2016).

The more recent meta-analyses on the effects of WMT in healthy older adults, however, only partially confirm the results of Weicker et al. (2016). The finding of a large pooled effect size for direct training effects was confirmed by Sala et al. (2019; 28 studies, Hedge's *g* = 0.88, 95% CI 0.69 – 1.06). For near-transfer effects though, two recent meta-analyses report similar small (rather than medium) pooled effect sizes: For overall working memory, Sala et al. (2019) indicate a pooled Hedge's *g* of 0.27 [95% CI 0.19 – 0.36] across 39 studies. Meta-analyzing 24 studies, Teixeira-Santos et al. (2019) reported small pooled effect sizes separately for verbal working memory (Hedge's *g* = 0.23, 95% CI 0.01 – 0.46) and visuo-spatial working memory (Hedge's *g* = 0.23, 95% CI 0.03 – 0.43). The largely differing number of studies included in the two meta-analyses was due to variably strict inclusion criteria, for example, controlled trials versus randomized controlled trials (RCTs) only and working memory tasks constituting at least 50% of the training versus pure WMT (Sala et al., 2019; Teixeira-Santos et al., 2019). Despite these differences, both meta-analyses report small or close to zero far-transfer effect sizes, with the more conservative meta-analysis by Teixeira-Santos et al. (2019) only revealing a marginally significant effect for the reasoning and intelligence outcome (Hedge's *g* 0.10, 95% CI 0.01 – 0.46).

The reviewed results so far encompass immediate training effects assessed at posttest directly following the training period. Follow-up training effects were secondarily investigated in most meta-analyses, but Hou et al. (2020) were the first ones focusing on the long-term efficacy of WMT in healthy older adults. They included 22 RCTs with baseline to follow-up periods ranging from 3 to 18 months in their meta-analysis. Long-term near-transfer effects for the investigated working memory components (maintenance, updating, shifting, and inhibition) were small to moderate and robust, with Hedge's *g* for studies including less than 6 months follow-ups ranging from 0.25 to 0.52 and for studies including more than 6 months follow-ups ranging from 0.45 to 0.54 (Hou et al., 2020). Importantly, this meta-analysis also revealed small but statistically significant long-term far-transfer effects for the reasoning and

intelligence outcome (19 studies, Hedge's *g* = 0.15, 95% CI 0.01 – 0.29), as well as processing speed (11 studies, Hedge's *g* = 0.24, 95% CI 0.07 – 0.42).

Summarizing, the scientific evidence on the effectiveness of WMT in healthy older adults reveals reliable effects in trained tasks as well as near-transfer measures within the working memory domain. The evidence for reliable far-transfer effects is less conclusive. Given the considerable amount of heterogeneous results, especially regarding far-transfer effects, it seems reasonable to investigate the underlying mechanisms of the observed between and within study variance. This branch of research is further discussed under "Prognostic Research Contributing to a Precision Medicine Approach".

Neural Correlates of Working Memory (Training) in Healthy Older Adults

A decline in executive functions, working memory, processing speed, and memory are among the most prominent cognitive alterations in healthy older adults (Paraskevoudi et al., 2018). These neuropsychological changes on a functional level correlate with alterations in neural circuits. For example, healthy older adults have frequently been observed to expand more neural resources for successful working memory task execution compared to younger adults (Li et al., 2015; Suzuki et al., 2018), which has been interpreted as a compensatory mechanism to counteract age-related declines in neural efficiency and accompanying working memory performance. This compensatory mechanism, however, might be only one part of the story. The *Compensation Related Utilization of Neural Circuits Hypothesis* (CRUNCH; Reuter-Lorenz & Cappell, 2008) states that age-related decline in neural efficiency would lead to over-recruitment of neural resources under lower task demands, but a neural activation decrease under higher task demands, as neural resource availability rapidly outstrips with increasing task demands. According to CRUNCH, training should then reduce neural activation patterns under low task demands, as the need for compensatory activation would be reduced with training. Under higher demand, neural activation patterns might increase, as due to increased efficiency with lower demands more resources would be available to meet higher demands (Iordan et al., 2020; Kennedy et al., 2017).

The general neural effects of WMT across the lifespan have briefly been summarized under "The Rationale of Working Memory Training". The coexistence of neural activation decreases and increases after WMT as reported by the meta-analysis by Salmi et al. (2018) has been observed for the subgroup of healthy older adults as well. More specifically, decreased

activation patterns were observed in widespread fronto-parietal, temporal, and occipital neocortical areas and increased activation patterns were observed in subcortical regions, including nuclei of the striatum (e.g., Brehmer et al., 2011; Heinzel et al., 2014). This is in line with the recent meta-analyses on the neural effects of both multi-domain and targeted single-domain cognitive training approaches in healthy older adults (Duda & Sweet, 2019; Nguyen et al., 2019; van Balkom et al., 2020). Next to the general coexistence of neural activation decreases and increases after WMT, Iordan et al. (2020) recently confirmed the predictions of CRUNCH regarding the load-dependency of neural correlates of WMT in healthy older adults. Whereas activation decreases could be observed for working memory tasks with lower demands, the free resources led to an activation peak shift towards higher loads and enabled activation increases (i.e., more compensatory activation) for working memory tasks with higher demands (Iordan et al., 2020).

WORKING MEMORY TRAINING IN PATIENTS WITH PARKINSON'S DISEASE

The information compiled in the previous chapters converge in the present one, which summarizes the rationale for WMT in patients with PD. In the first chapters of the present thesis, we learned about the broad symptomatology of PD, encompassing both motor and non-motor symptoms. The majority of patients with PD will face at least some degree of cognitive decline in the course of their disease, for which, so far, no convincing pharmacological treatments exist. In this context, non-pharmacological interventions and above all cognitive training approaches gained increased scientific interest, as they might be able to prevent or delay the onset and/or slow down the rate of cognitive decline in patients with PD. WMT as a targeted form of cognitive training might bear a special potential for patients with PD:

(i) Working memory and executive functions are considered as the most vulnerable cognitive domains within cognitive decline associated with PD (Kalbe et al., 2016; Kudlicka et al., 2011; Lawson et al., 2014a; Litvan et al., 2011; Muslimović et al., 2005), with deficits in these domains even occurring in prodromal disease stages (Fengler et al., 2017).

(ii) Working memory is of fundamental importance for executive functions and other higher order cognitive functions with central contributions to every-day functions (Chai et al., 2018).

(iii) Meta-analyses on WMT efficacy in healthy older adults reveal reliable short- and long-term near-transfer training effects in the working memory domain (Hou et al., 2020; Sala et al., 2019; Teixeira-Santos et al., 2019). Reliable far-transfer effects are a matter of ongoing scientific debate. Compared to healthy individuals, both near- and far-transfer effects of WMT might be larger for vulnerable subgroups and subgroups already showing working memory impairments (Weicker et al., 2016).

(iv) Targeted WMT seems to enhance neural working memory network efficacy (Brooks et al., 2020; Constantinidis & Klingberg, 2016; Iordan et al., 2020; Salmi et al., 2018) and may induce alterations in the dopamine-modulated fronto-striatal system (Bäckman & Nyberg, 2013; Bäckman et al., 2011; Dahlin et al., 2008; McNab et al., 2009) - brain networks and neurotransmitter systems also relevant in the pathophysiology of PD (Przedborski, 2017). Following, WMT may potentially not only induce positive effects on cognitive functions in patients with PD but bears the potential to improve motor functioning as well.

Despite these promising links, WMT in patients with PD is largely under-investigated. This research gap motivated the question which neuropsychological, clinical, and neural effects of targeted WMT in patients with PD could be observed. Next to the RCT further described under "The Randomized Controlled Trial", which constitutes the center of the present thesis project, to the author's best knowledge only one further trial evaluated a targeted WMT regime in patients with PD so far (Fellman et al., 2018). This study revealed the general feasibility of a 5-week home-based computerized adaptive WMT regime in n = 26 patients with PD as indicated by high adherence rates, high motivation, and positive feedback. Compared to an active control group (CG, n = 26), Fellman et al. (2018) reported statistically significant positive direct training effects with moderate to large effect sizes (0.69 ≤ Hedge's g ≤ 0.98) and statistically significant positive near-transfer effects to untrained working memory tasks with a small effect size (Hedge's g = 0.49). Neither for verbal episodic memory nor executive functions and attention statistically significant far-transfer effects were observed (Fellman et al., 2018). According to a comparison with age- and education-matched healthy controls, the authors characterized their patients as cognitively well-preserved. However, no established diagnostic criteria to exclude the presence of clinically relevant cognitive decline in patients with PD (PD-D: Emre, 2003; PD-MCI: Litvan et al., 2012) were applied. Furthermore, the lack of a follow-up assessment and

accompanying neuroimaging impedes encompassing conclusions regarding the effects and mechanisms of WMT in patients with PD (Fellman et al., 2018).

Summarizing, important questions regarding the effects and mechanisms of WMT in patients with PD remain open. So far, the scientific evidence mirrors the meta-analytical evidence regarding effects of WMT in healthy older adults. Whereas reliable moderate to large direct training effects could be observed in trained tasks, near-transfer effects were rather small, and far-transfer effects have not convincingly been shown at all. For all degrees of transfer, a considerable amount of heterogeneity could be observed, which is why it seems reasonable to investigate the underlying mechanisms of the observed variance, leading to the considerations outlined in the following chapter.

PREDICTORS OF TRAINING RESPONSIVENESS

In the context of WMT and multi-domain cognitive training, both between- and within-study variance regarding the participants' intervention responsiveness can be observed. This variance might be due to systematic relationships between individual characteristics (e.g., sociodemographic, neuropsychological, biological) and training-related characteristics (e.g., type of training, training dose and length, number of sessions). These characteristics can be referred to as predictors for training responsiveness. Before reviewing the scientific evidence on such predictors in healthy older adults and patients with PD, the importance of prognostic research for modern healthcare and the rationale for prognostic research with regard to cognitive interventions will be outlined.

PROGNOSTIC RESEARCH CONTRIBUTING TO A PRECISION MEDICINE APPROACH

According to the *Prognosis Research Strategy* (PROGRESS) framework (Hemingway et al., 2013; Hingorani et al., 2013; Riley et al., 2013; Steyerberg et al., 2013), the term prognostic research refers to "the investigation of the relations between future outcomes among people with a given baseline health state in order to improve health" (Hemingway et al., 2013). Identifying characteristics that predict training responsiveness would not only contribute to the understanding of mechanisms underlying cognitive training approaches, but would also promote the movement away from a one-treatment-fits-all-approach to the development of personalized, stratified or precision medicine approaches (Hingorani et al., 2013). The three terms are frequently used interchangeably, as the visions of future healthcare associated with

each of them are largely overlapping, while their precise definitions remain a matter of debate (Erikainen & Chan, 2019). All three concepts aim to use baseline information about a patient's likely treatment responsiveness to tailor treatment decisions – in other words, to better match a patient (or a subgroup of patients) with a specific treatment (Hingorani et al., 2013; Trusheim et al., 2007), which is visualized in Figure 7.

Critique on the term personalized medicine emerged, as it may be misinterpreted and possibly overly optimistic regarding unique, individualized treatment approaches on a single-person-level (Erikainen & Chan, 2019). The term stratified medicine rather reflects the realistic effects of medicine on a population level, where treatments are tailored to subgroups of individuals sharing demographic, neuropsychological, and biological characteristics. However, the term stratified medicine may evoke associations in terms of racial profiling and should therefore be avoided. The term precision medicine was introduced as a compromise between the two: on the one hand avoiding overambitious promises, on the other hand reframing the more realistic stratification approach to an ethically neutral background (Erikainen & Chan, 2019).

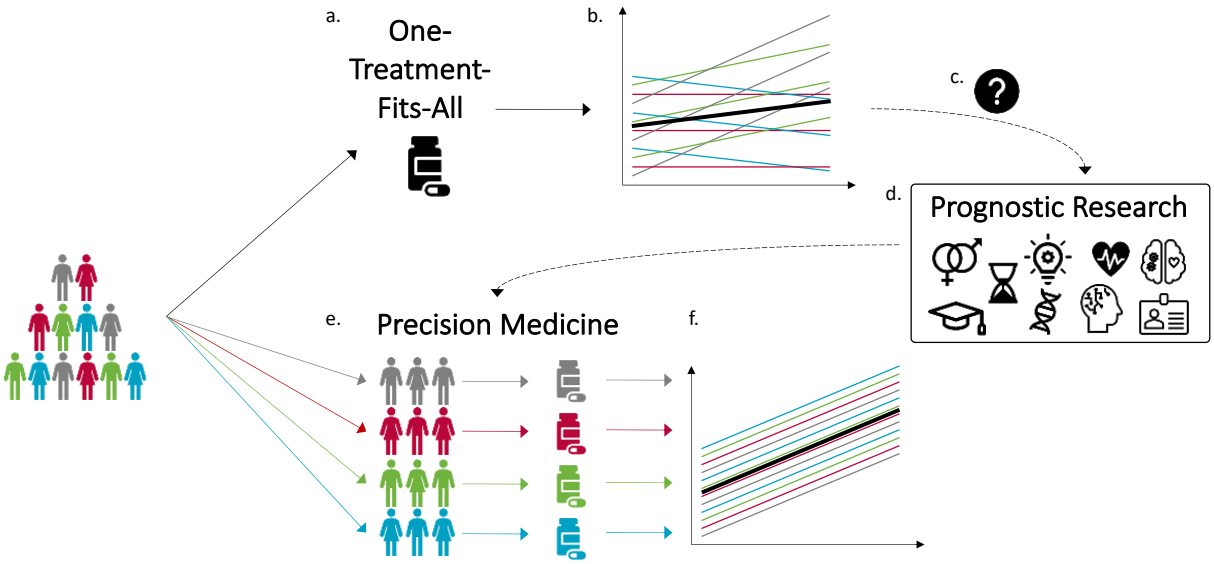


Figure 7. Prognostic Research Contributing to a Precision Medicine Approach

a. Until today, treatment decisions usually follow a one-treatment-fits-all approach, even though b. treatment responsiveness might be highly heterogeneous across patients. c. This leads to the question, whether there are certain characteristics explaining this variability in treatment responsiveness. d. To answer this question, prognostic research aims to investigate variables that are potentially associated with treatment responsiveness (e.g., sociodemographic, neuropsychological, and biological parameters). Furthermore, these variables might predict a patient's likely treatment responsiveness. e. Precision medicine uses this information to tailor treatment decisions according to a patient's (or subgroup of patients') profile, f. resulting in overall better treatment outcomes.

From a patient's perspective, precision medicine approaches would result in better treatment adherence and compliance due to greater certainty of desired outcomes (better health, less harm). At the same time, from an economic perspective, precision medicine approaches bear the potential to save enormous expenses for ineffective treatments, while offering numerous possibilities to develop new products (Trusheim et al., 2007). Taking into account the patient's likely treatment responsiveness would thereby increase healthcare outcomes regarding both effectiveness and efficiency, which is why answering the question "who benefits most?" is of high clinical importance (Hingorani et al., 2013; Riley, van der Windt, et al., 2019; Trusheim et al., 2007). Information about a patient's likely treatment responsiveness can be obtained from prognostic research investigating the relationships between individual characteristics (e.g., sociodemographic, neuropsychological, biological) and responsiveness to certain treatment types (Hemingway et al., 2013; Moons et al., 2009).

The potential clinical impact of prognostic research in general and for precision medicine in particular has been highlighted by the PROGRESS framework (Hemingway et al., 2013; Hingorani et al., 2013; Riley et al., 2013; Steyerberg et al., 2013). Since common methodological and statistical challenges of prognostic research for precision medicine have been identified in this framework (Hingorani et al., 2013), some progress regarding core methods and emerging fields of application have been made (Riley, van der Windt, et al., 2019). For example, guidelines such as the *Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis* (TRIPOD) statement (Collins et al., 2015; Moons et al., 2015) and the *Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies* (CHARMS; Moons et al., 2014; Riley, Moons, et al., 2019) for developing, testing, reporting, and summarizing prognostic research were published. However, there is still a considerable gap between the potential and actual impact of prognostic research on health (Riley, van der Windt, et al., 2019).

PROGNOSTIC RESEARCH FOR COGNITIVE INTERVENTIONS

So far, cognitive intervention approaches in general and WMT in particular are usually prescribed following a one-treatment-fits-all approach and empirical evidence from RCTs and meta-analyses focuses on the overall effectiveness of a given treatment approach. However, as visioned by Kalbe, Aarsland, et al. (2018) in the PD context, but transferable to the general aging context, cognitive interventions would progress from empirical medicine to precision

medicine interventions within the next two decades, as they would be tailored to the individual (e.g., sociodemographic, neuropsychological, biological) profile and preferences (e.g., computerized or paper-pencil, individual or group setting). A precision medicine approach in this context would, thereby, match an individual participant to a specific form of cognitive intervention, also taking into account the large heterogeneity of cognitive intervention approaches characterized by different rationales, varying intensities, and foci (Clare & Woods, 2004; Gavelin et al., 2020; Lustig et al., 2009; Walton et al., 2017).

Consequently, it is important to consider both individual characteristics as well as training-related characteristics as predictors for participants' responsiveness to cognitive interventions. In this context, one can additionally differentiate between predictors for between- and within-study variance. Between-study variance refers to heterogeneous results across studies, with some studies showing larger training effects than others or some studies not finding any training effect at all. Both diverging study population characteristics (e.g., sociodemographic, neuropsychological, biological) and training-related characteristics (e.g., type of training, training dose and length, number of sessions) might contribute to this variance. As further reviewed below, those study population and intervention-related characteristics have been taken into account in various meta-analyses as aggregated moderator variables on a study-wide level. However, considerable variance can also be observed within single studies. This within-study variance refers to heterogeneous results across participants within one study, with some participants improving stronger than others, some participants maintaining, and others even decreasing their performance. Individual differences in cognitive plasticity as a result of a complex interplay between sociodemographic, neuropsychological, and biological factors might be able to explain this variance (Baltes & Lindenberger, 1988; Bürki et al., 2014; Noack et al., 2009).

Importantly, prognostic research might be especially reasonable in the context of large heterogeneity among treatment effects, as observed for cognitive training in general and transfer effects of WMT in particular: This heterogeneity could lead to very small insignificant and even null effects reported in single trials as well as meta-analyses, as effects in opposite directions between participants might eliminate overall reported effects. Prognostic research then bears the potential to identify predictors of treatment responsiveness to answer the question if there are systematic relationships between individual characteristics and treatment response. The identification of individual- and training-related characteristics predicting

training responsiveness to understand the mechanisms underlying cognitive training in general and WMT in particular has occupied researchers in the past decades. In the following, evidence for predictors of cognitive training responsiveness in healthy older adults and patients with PD is reviewed. Summarizing the mechanisms underlying cognitive training responsiveness in healthy older adults may promote the understanding of mechanisms underlying cognitive training responsiveness in patients with PD.

Predictors of Cognitive Training Responsiveness in Healthy Older Adults

For healthy older adults, several predictors for cognitive training responsiveness are under debate. As outlined above, due to the heterogeneity of cognitive training approaches, it seems appropriate to differentiate between the different cognitive training approaches, when summarizing the available evidence.

For multi-domain cognitive training in healthy older adults, several meta-analyses included moderator analyses to identify predictors explaining between-study variability (e.g., Chiu et al., 2017; Lampit et al., 2014). These moderator analyses were focused on training-related characteristics only, revealing, for example, a superiority of group settings compared to individual training and influences of training dose and length that were, however, heterogeneous between meta-analyses (e.g., Chiu et al., 2017; Lampit et al., 2014). On a single-study-level (i.e., explaining within-study variability), inconclusive, heterogeneous, and partly conflicting results, for example, regarding the prognostic value of age, sex, education, cognitive baseline level, physical activity, genetic variation in Apolipoprotein-E-(apoE)4, a well-known risk factor for Alzheimer's Disease (Liu et al., 2013), and Brain-derived neurotrophic factor (BDNF) levels, which are discussed to regulate synaptic plasticity (Kuipers & Bramham, 2006), exist so far (Roheger et al., 2019). The systematic review and meta-analysis on prognostic factors and models of multi-domain cognitive training responsiveness in healthy older adults pre-registered in the *International Prospective Register of Systematic Reviews* (PROSPERO, ID: CRD42020-147531) might be able to synthesize those findings.

Just recently, a systematic review on prognostic factors of training responsiveness after targeted memory training has been published (Roheger et al., 2020). The systematically summarized findings indicate that more vulnerable individuals (i.e., with higher age, lower cognitive baseline performance, positive apoE4 status) benefit most from targeted memory training. However, due to large heterogeneity and low methodological quality of the included

studies, results should be treated cautiously (Roheger et al., 2020). Next to the already mentioned demographic, neuropsychological, and biological characteristics, motivational factors such as self-efficacy expectancy and personality traits are discussed to play a significant role in predicting responsiveness to cognitive interventions in general (Chiaburu & Lindsay, 2008; Double & Birney, 2016; Kalbe, Bintener, et al., 2018; West et al., 2008).

For targeted WMT in healthy older adults, several meta-analyses included moderator analyses to identify predictors explaining between-study variability as well (e.g., Hou et al., 2020; Sala et al., 2019; Teixeira-Santos et al., 2019). The meta-analysis by Teixeira-Santos et al. (2019) investigated both training-related variables (e.g., training dose and length, number of sessions, training type) and study population characteristics (e.g., mean age, mean years of formal education, general cognitive ability, baseline performance) as moderating variables. Except for lower baseline scores correlating with larger effect sizes, only training-related characteristics were found to significantly moderate WMT effects. For example, higher training doses and lengths were associated with smaller effect sizes across studies (Teixeira-Santos et al., 2019), which is in line with findings of another recent meta-analysis (Hou et al., 2020), but opposed to findings by Weicker et al. (2016), who identified training dose and length to be positively correlated with WMT effects (i.e., the higher/longer, the better).

On a single-study level, therefore explaining within-study variance, a broad spectrum of individual characteristics is discussed to potentially predict WMT responsiveness in healthy older adults. However, as for the previously discussed multi-domain cognitive training, data are inconclusive yet, as findings are highly heterogeneous and inconsistent. Two of the most frequently investigated prognostic factors for WMT responsiveness are baseline performance in working memory or the respective cognitive outcome and general cognitive ability (e.g., Borella et al., 2017; Matysiak et al., 2019; Zinke et al., 2014). For both, inconsistent findings exist, which can be discussed within the compensation versus magnification framework (Lövdén et al., 2010; Lövdén et al., 2012). Following the compensation account, individuals with lower baseline performance would show higher training benefits, because they have more room for improvement. On the contrary, the magnification hypothesis constitutes that individuals with higher abilities would benefit most, as they have more resources “to acquire, implement, and sharpen effortful cognitive strategies” (Lövdén et al., 2012).

Similar inconsistent evidence exists, for example, for demographic factors such as age, education, and sex (e.g., Borella et al., 2017; Borella et al., 2014; Borella et al., 2013; Matysiak

et al., 2019; Simon et al., 2018; Zinke et al., 2014). Furthermore, genetic variation (Bäckman & Nyberg, 2013; Bellander et al., 2011; Brehmer et al., 2009) and neuroimaging parameters (Heinzel et al., 2014) might reflect meaningful proxies for the potential to engage in cognitive plasticity following WMT. So far, no systematic review on predictors of WMT responsiveness in healthy older adults exists.

Predictors of Cognitive Training Responsiveness in Parkinson's Disease

So far, prognostic research in the context of cognitive training in patients with PD is limited to the single-study level. None of the three meta-analyses on the effects of cognitive training approaches in patients with PD conducted moderator analyses to investigate the influence of training-related variables and study population characteristics on between-study variability (Lawrence et al., 2017; Leung et al., 2015; Orgeta et al., 2020).

For multi-domain cognitive training, lower baseline performance (Zimmermann et al., 2014), the diagnosis of PD-MCI (París et al., 2011), and longer disease durations (Nguyen et al., 2020) were found to be associated with higher training responsiveness. These findings were recently confirmed with data of an RCT investigating multi-domain cognitive training in patients with PD-MCI, revealing a tendency for higher training responsiveness in patients with PD-MCI with lower baseline performance, less education, advanced disease progression in terms of higher LEDD doses (and correspondingly better motor functioning), and a positive apoE4 carrier status (Kalbe et al., 2020). For speed of processing training, Edwards et al. (2013) also identified longer disease duration and, additionally, a younger age at PD diagnosis to be associated with higher training responsiveness. These findings can be interpreted in terms of the compensation account, indicating that more vulnerable individuals might benefit most from cognitive training approaches in patients with PD (Lövdén et al., 2010; Lövdén et al., 2012). For WMT, however, the findings of Fellman et al. (2018) rather point to the magnification account: According to their results, trained task improvement over the course of WMT was positively predicted by higher baseline general cognitive abilities, higher education, and shorter disease duration.

Overall, the available evidence from prognostic research on predictors of cognitive training responsiveness in patients with PD is scarce, as the majority of studies conducting cognitive training approaches in patients with PD focuses on general effectiveness evaluations only. Furthermore, the applied statistical methods were highly heterogeneous ranging from simple correlational approaches and group comparisons to advanced methods such as growth

curve analyses. This mirrors methodological shortcomings and statistical challenges that were already identified for prognostic research in healthy older adults (Roheger et al., 2020). Given the large heterogeneity among cognitive training approaches, cognitive training effects, and cognitive impairment in patients with PD, research contributing to precision medicine approaches in the context of cognitive decline associated with PD following high methodological standards (Collins et al., 2015; Moons et al., 2015; Moons et al., 2014; Riley, Moons, et al., 2019) should be promoted (Kalbe, Aarsland, et al., 2018).

THE PRESENT THESIS PROJECT

AIM OF THE PRESENT THESIS PROJECT

The present thesis project aims to investigate the effects and mechanisms of targeted WMT in patients with PD without cognitive impairment. Therefore, this promising non-pharmacological treatment approach and specific form of cognitive training will be evaluated in a detailly characterized sample of patients with PD. Firstly, this will contribute to the development and implementation of evidence-based cognitive interventions against the debilitating cognitive decline associated with PD. Secondly, the investigation of underlying mechanisms will contribute to precision medicine approaches for cognitive interventions in patients with PD, which aim to match an individual patient to a specific form of cognitive intervention.

For these purposes, a single-blind RCT evaluating a 5-week home-based computerized WMT was conducted. Posttest and 3-months follow-up effects are investigated for neuropsychological and clinical outcomes (Study I). Before investigating the underlying mechanisms of WMT in patients with PD and answering the question which individual characteristics predict training responsiveness at posttest and 3-months follow-up (Study III), a systematic review on predictors of WMT responsiveness in healthy older adults was executed (Study II). As WMT constitutes a common cognitive training approach for healthy older adults and several studies investigated predictors of WMT responsiveness in this population with partly conflicting results, systematically summarizing this evidence seems reasonable. Furthermore, this systematic review gives the opportunity to identify general shortcomings of prognostic research in the field (Study II) and to apply a best practice approach to the data of the RCT for evaluating predictors of WMT responsiveness in patients with PD (Study III).

Hereafter, the main research questions and hypotheses of the present thesis project are stated, followed by a general introduction to the RCT, its study design, inclusion and exclusion criteria for participants, the neuropsychological and clinical test battery, and the conceptualization of the applied WMT regime. Finally, the three studies included in this cumulative thesis will be presented and for each of them information regarding its publication, the detailed scientific contributions of all authors (for an overview, see Table 1), and an elaborated abstract will be given.

RESEARCH QUESTIONS AND HYPOTHESES

(i) Is WMT feasible and effective in patients with PD without cognitive impairment? (Study I)

WMT is feasible operationalized by training completion, motivation to train, and satisfaction with the training in patients with PD without cognitive impairment and leads to positive near-transfer (i.e., verbal and non-verbal working memory) and far-transfer (i.e., other cognitive domains and clinical variables) training effects compared to a passive waiting-list CG.

(ii) Which individual characteristics predict WMT responsiveness in healthy older adults and what are methodological challenges of prognostic research on WMT responsiveness? (Study II)

Across prognostic literature on WMT responsiveness in healthy older adults, a pattern of individual (e.g., demographic, neuropsychological, biological) and training-related (e.g., training dose and length, adaptivity) parameters predicting variability in WMT responsiveness emerges. Due to heterogeneous results in existing original studies, directed hypotheses regarding specific predictors cannot be formulated.

(iii) Do individual characteristics predict WMT responsiveness in patients with PD without cognitive impairment? (Study III)

Demographic (age and education) and neuropsychological (baseline performance, fluid intelligence) characteristics, PD-related motor functioning, and self-efficacy expectancy can predict both near- and far-transfer WMT responsiveness in patients with PD without cognitive impairment. Due to inconclusive and partly heterogeneous results in existing literature, directed hypotheses regarding the specific predictors cannot be formulated.

THE RANDOMIZED CONTROLLED TRIAL

The RCT mentioned above constitutes the center of the present thesis project and provides the data base for Study I and Study III. It was designed, conducted, and evaluated at the University Hospital Cologne in collaboration of the department of Medical Psychology | Neuropsychology and Gender Studies and the Multimodal Neuroimaging Group of the department of Nuclear Medicine. The study protocol was approved by the local ethics committee of the Medical

Faculty of the University of Cologne (vote-no.16-043) and registered in the *German Clinical Trials Register* on December 13th, 2016 (ID: DRKS00009379).

STUDY DESIGN

The RCT evaluates the effects of a 5-week home-based computerized WMT via the cognitive training platform *NeuroNation* (https://www.neuronation.com, *Synaptikon GmbH*, Berlin, Germany) against a passive waiting list CG. Neuropsychological and clinical assessment took place at baseline, the week after the 5-week training/waiting period (posttest, 5.67 ± 0.58 weeks after baseline), and at 3-months follow-up (14.03 ± 0.86 weeks after posttest). The study also involved an explorative neuropsychological module on non-verbal working memory functioning (Giehl, Ophey, Reker, et al., 2020) and an optional functional magnetic resonance imaging (fMRI) neuroimaging module to investigate the neural correlates of working memory and WMT in patients with PD (Giehl, Ophey, Hammes, et al., 2020). These two publications are not included in the cumulus of the present thesis, however, briefly summarized under "The Delayed Adjustment Fractals-Task" and "The Neuroimaging Module" below and integrated into the general discussion. The study design is visualized in Figure 8.

An a-priori power analysis was conducted with *G*Power* (http://www.gpower.hhu.de; Erdfelder et al., 1996) to determine the minimum sample size for the effectiveness evaluation of the WMT. According to a meta-analysis on cognitive training in patients with PD available at the time of study set-up (Leung et al., 2015), we expected a medium effect size on working memory measures. With an a-level of .05 and 80% power, the minimum sample size comparing two groups between two points of time including a 20% dropout estimation was $N = 72$.

Data collection took place between September 2016 and July 2018. The study was single-blind with outcome assessors being blinded for group allocation. Patients were recruited via regional neurologists and PD support groups and the University Hospital of Cologne, Germany. The study was conducted in compliance with the *World Medical Association Declaration of Helsinki*. All participants gave written informed consent for participation before the baseline assessment.

PARTICIPANTS

Inclusion criteria for study participation were (i) age between 45 and 85 years, (ii) diagnosis of idiopathic PD according to the established United Kingdom Parkinson's Disease Society Brain

Bank clinical diagnostic criteria (Gibb & Lees, 1988), and (iii) normal or corrected-to-normal vision and hearing. Exclusion criteria were (i) cognitive dysfunctions according to the Level-II diagnostic criteria for PD-MCI (Litvan et al., 2012) or PD-D (Emre, 2003), (ii) severe depressive symptoms operationalized by the *Geriatric Depression Scale* (GDS, score ≥ 11; Yesavage et al., 1983), (iii) deep brain stimulation, and (iv) other reported psychiatric, neurological, and life-threatening diseases. Only if participants met those criteria at baseline assessment, they were included for further participation and randomized to either the WMT group or CG. The blocked randomized allocation sequence (block size = 10, 1:1 ratio) was generated using the online tool *ResearchRandomizer* (www.randomizer.org). Randomization was carried out by a staff member not involved in data collection. 37 patients underwent the WMT and 39 patients were randomized to the waiting list CG. Of 76 patients, 75 completed the posttest and 72 of those 75 patients completed the 3-months follow-up (Figure 8). A traditional flow chart can be viewed in the original publication of Study I.

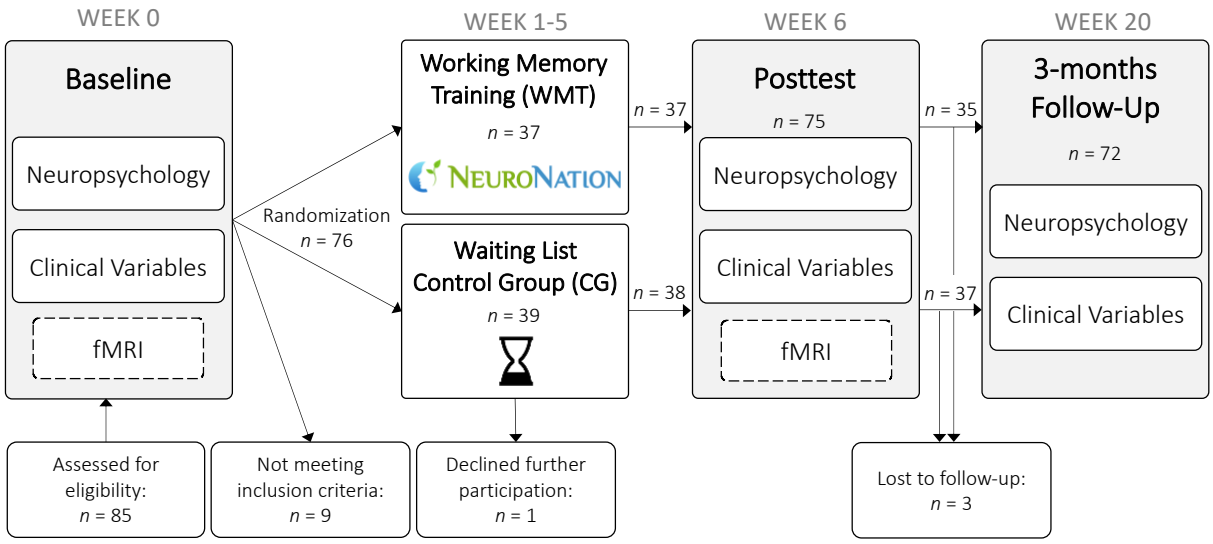


Figure 8. Study Design and Flow of Participants

The randomized controlled trial evaluates the effects of a 5-week home-based computerized working memory training via the cognitive training platform NeuroNation (https://www.neuronation.com, Synaptikon GmbH, Berlin, Germany) against a passive waiting list control group. Neuropsychological and clinical assessment took place at baseline, posttest, and at 3-months follow-up. The study also involved an optional fMRI neuroimaging module at baseline and posttest (dashed line). A traditional flow chart including further details on dropout reasons can be viewed in the original publication of Study I (Ophey, Giehl, et al., 2020).

NEUROPSYCHOLOGICAL AND CLINICAL ASSESSMENT

Neuropsychological and clinical assessment at baseline, posttest, and 3-months follow-up was administered by psychologists or trained graduate students of Psychology or Medicine. If

available, parallel test forms were used. The test sessions took 2-2.5 hours to complete, including a 30-minute break. During all assessments, patients were on their regular medication. To maintain blinding, posttest and 3-months follow-up assessments were carried out by different outcome assessors than the ones at baseline. Table 2 offers an overview over the neuropsychological and clinical assessments and their assignment to a neuropsychological or clinical domain. The explorative delayed adjustment fractals-task assessing non-verbal working memory functioning and the optional fMRI neuroimaging module are further described under "The Delayed Adjustment Fractals-Task" (Giehl, Ophey, Reker, et al., 2020) and "The Neuroimaging Module" (Giehl, Ophey, Hammes, et al., 2020).

The *Montréal Cognitive Assessment* (Nasreddine et al., 2005) was conducted as a cognitive screening instrument at baseline. Furthermore, six cognitive domains were assessed by at least two test scores for each cognitive domain derived from established cognitive tests and test batteries (Aebi, 2002; Bäumler & Stroop, 1985; Horn, 1983; Kalbe et al., 2002; Morris et al., 1989; Schretlen, 1989; Schuhfried, 1992; Sturm et al., 1993; Wechsler, 1984): working memory, executive functions, verbal memory, attention, visuo-cognition, and language. Two subtests were only included at baseline to exclude cognitive impairment according to established Level-II diagnostic criteria for PD-MCI (Litvan et al., 2012) or PD-D (Emre, 2003). If more than one test score was at least 1.5 SD below the mean of published normative data, the patient was excluded from further trial participation and not randomized to the CG or WMT group.

Additionally, patients filled out questionnaires addressing SCD (Jessen et al., 2011; Kalbe, Bintener, et al., 2018), everyday cognitive functioning (Farias et al., 2011), the presence and severity of depressive symptoms (Yesavage et al., 1983), and the quality of sleep (Buysse et al., 1989). Disease duration as the time since diagnosis and the LEDD according to the formula proposed by Tomlinson et al. (2010) to assess the amount of PD-related dopaminergic medication were recorded. Motor impairment was assessed with the *Unified Parkinson's Disease Rating Scale* (UPDRS-III; Fahn et al., 1987), the H&Y scale (Hoehn & Yahr, 1967), and the *Freezing of Gait* (FOG) *Questionnaire* (Giladi et al., 2000). The UPDRS-III motor examination was conducted and videotaped by outcome assessors and rated by a movement disorder specialist blinded for group allocation and point of study. Rigidity assessments as part of the UPDRS-III were conducted and rated during the actual test sessions. Therefore, outcome assessors were previously trained by the movement disorder specialist.

Table 2. Overview of Neuropsychological and Clinical Assessments

Domain	Subdomain	Assessment	Subtest	Base-line	Post-test	Follow-Up
Cognitive Status		Montreal Cognitive Assessment		X		
Working Memory	Verbal Working Memory	WTS	N-back Verbal	X	X	X
		WMS-R	Digit Span Forward	X	X	X
			Digit Span Backward	X	X	X
	Visual Working Memory	WTS	N-back Non-verbal	X	X	X
			Corsi Block-Tapping Forward	X	X	X
			Corsi Block-Tapping Backward	X	X	X
		Delayed Adjustment Fractals Task*		X	X	X
Executive Functions	Logical Reasoning	LPS (50+)	Subtest 4: Reasoning	X	X	X
	Mental Flexibility	CERAD-Plus	TMT-B/A	X	X	X
	Verbal Fluency	CERAD-Plus	Semantic Verbal Fluency	X	X	X
			Phonematic Verbal Fluency	X	X	X
	Inhibition	Stroop	Interference	X	X	X
Verbal Memory	Short-term	CERAD-Plus	Wordlist Learning	X	X	X
	Long-term	CERAD-Plus	Wordlist Recall	X	X	X
Attention	(Mental) Processing Speed	CERAD-Plus	TMT-A	X	X	X
		Stroop	Word Reading	X	X	X
			Color Naming	X	X	X
	Divided Attention	BTA	BTA Total	X	X	X
Visuo-Cognition	Visuo-Construction	CERAD-Plus	Figure Copying	X	X	X
			Figure Recall	X	X	X
	Spatial Rotation	LPS (50+)	Subtest 7	X		
Language	Naming	CERAD-Plus	Boston Naming Test	X	X	X
	Comprehension	ACL	Auditory Language Comprehension	X		
Subjective Cognitive Decline		Subjective Cognitive Impairment Questionnaire		X	X	X
Everyday Cognitive Functioning		Everyday Cognition Questionnaire		X	X	X
Depression		Geriatric Depression Scale		X	X	X
Quality of Sleep		Pittsburgh Sleep Quality Index		X	X	X
Parkinson's Disease Related Clinical Characteristics	Medication	Levodopa Equivalent Daily Dose		X	X	X
	Disease Duration	Time since Diagnosis		X		
	Motor Functioning	UPDRS	Part 3	X	X	X
		Hoehn & Yahr		X	X	X
	Freezing of Gait	Freezing of Gait Questionnaire		X	X	X
fMRI Neuroimaging Module⁺				(X)	(X)	

Note. A similar overview was given in the (online only) supplementary material of the original publication of Study I (Ophey, Giehl, et al., 2020). ACL, Aphasia Check List; BTA, Brief Test of Attention; CERAD-Plus, Consortium to Establish a Registry for Alzheimer Diagnosis Plus test battery; fMRI, functional magnetic resonance imaging; LPS (50+), Leistungsprüfsystem, version 50+ for patients aged ³ 50 years; TMT-A, Trial Making Test Version A; TMT-B, Trial Making Test Version B; TMT-B/A, ratio TMT-B divided by TMT-A; UPDRS, Unified Parkinson´s Disease Rating Scale; WMS-R, Wechsler Memory Scale-Revised; WTS, Wiener Test System.

*explorative neuropsychological task; for details, see "The Delayed Adjustment Fractals-Task" and Giehl, Ophey, Reker, et al. (2020)

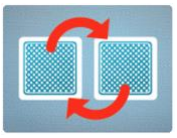
⁺ optional neuroimaging module; for details, see "The Neuroimaging Module" and Giehl, Ophey, Hammes, et al. (2020)

WORKING MEMORY TRAINING WITH NEURONATION

The WMT was compiled on the basis of the online multi-domain cognitive training program NeuroNation (https://www.neuronation.com, Synaptikon GmbH, Berlin, Germany). Out of the

broad spectrum of NeuroNation's training tasks, nine different working memory tasks (Table 3) were selected and trained according to a weekly schedule (Figure 9). The applied WMT regime can be referred to as a mixed approach combining a variety of working memory tasks, including simple span, complex span, and n-back tasks, as well as combinations among them.

Table 3. Description of the Working Memory Training Tasks Selected from NeuroNation

Task	Preview	Description
Path Finder Forward*		A sequence of dots gets connected. The sequence has to be memorized and re-clicked following that order. The sequence lengthens with progressing level of difficulty.
Path Finder Backward*		A sequence of dots gets connected. The sequence has to be memorized and re-clicked in the reverse order. The sequence lengthens with progressing level of difficulty.
Polaroid Picture*		A sequence of symbols successively appears in a grid. The positions of all the briefly shown symbols have to be remembered and indicated by clicking on the grid position. The number of symbols increases with progressing level of difficulty.
Memory interrupted#		Simple math equations have to be solved mentally. Afterwards, it has to be stated whether a shown result is correct. Meanwhile, letters and numbers are shown that have to be recalled later. The math equations get more complex and the sequence of letters and numbers lengthens with progressing level of difficulty.
Memobox#		It has to be observed how many balls leave and enter a box. After each trial, the number of balls of the same color in each box has to be entered. The number of movements increases with progressing level of difficulty.
Turnabout#		Symbols on a grid card have to be memorized. After one or more rotations, their locations have to be indicated by clicking on the grid position. The number of symbols and rotations increases with progressing level of difficulty.
Shuffler#		Symbols of the face-up cards have to be memorized. The cards will then be shuffled and the location of the memorized cards has to be determined. The number of cards and to be memorized symbols increases with progressing level of difficulty.
Memoflow+		A sequence of symbols is presented. When the current stimulus matches the symbol *n*-steps back, a button has to be pressed. The load factor *n* increases with progressing level of difficulty.
Parita#+		A sequence of symbols is presented visually and a sequence of numbers auditory. When the current symbol matches the symbol *n*-steps back, a button has to be pressed. The load factor *n* increases with progressing level of difficulty. Simultaneously, it has to be determined whether the number heard corresponds to the one memorized in the beginning.

Note. Preview pictures and task descriptions are adapted from NeuroNation (https://www.neuronation.com, Synaptikon GmbH, Berlin, Germany). A similar overview was given in the (online only) supplementary material of the original publication of Study I (Ophey, Giehl, et al., 2020). Symbols following the task name indicate the type of general working memory tasks or the combination among them: * Simple Span Task, # Complex Span Task, + n-back Task

Each training session consisted of 5 working memory tasks: Every session began with a 4-minute simple span (block-tapping) forward warm-up task, followed by four varying 6.5-minute training tasks. The WMT was administered for 30 minutes a day, 5 days a week, over 5 weeks, resulting in a maximum of 750 minutes of training distributed over 25 training sessions (Figure 9). The difficulty of training tasks adapted to user performance across training sessions. If participants completed three trials of one level of difficulty correctly in a row, they proceeded to the next level of difficulty and vice versa. The detailed descriptions of training tasks in Table 3 include a description of how the level of difficulty was modulated within each task.

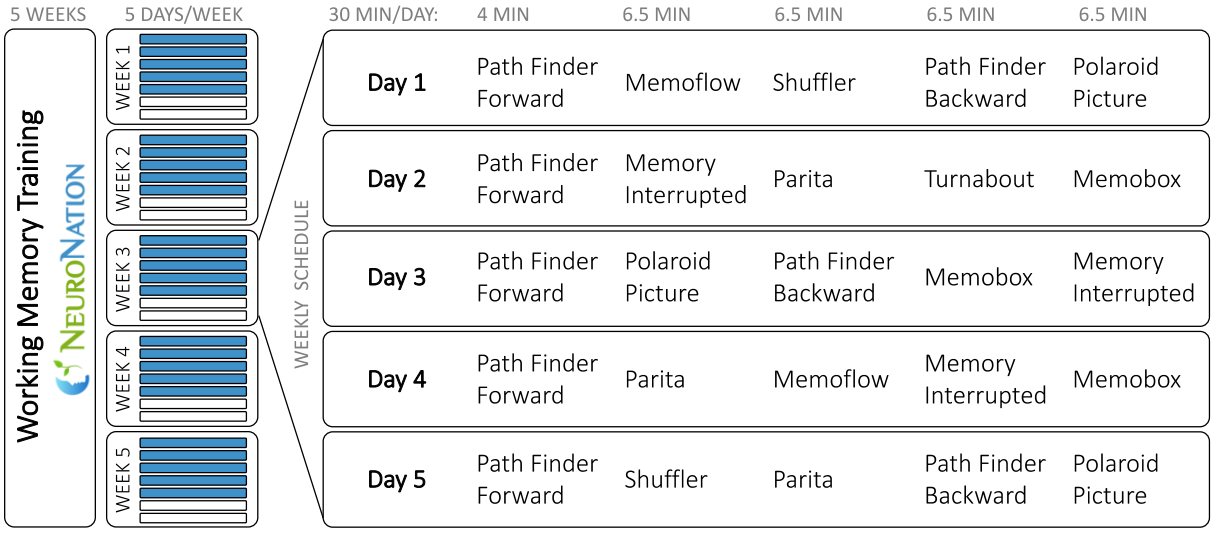


Figure 9. Training Protocol of the Working Memory Training with NeuroNation

The working memory training was administered over 5 weeks, 5 days per week, for 30 minutes a day, according to a weekly training schedule. Every training session began with the same 4-minute warm-up task, followed by four varying 6.5-minute training tasks. For detailed task descriptions, please refer to Table 3.

The WMT was administered home-based and individually accessed online. The training period was monitored on the NeuroNation website to ensure compliance with the training protocol. The training period was further accompanied by brief weekly telephone calls from the study coordinator in order to clarify potential issues with the training program. Training was regarded to be completed successfully if more than 75% of training sessions were completed. Furthermore, patients kept a training diary reporting their motivation before and their training satisfaction after each training session on a 6-point Likert-scale from 0 “not-motivated-at-all”/”not-good-at-all” to 5 “very-motivated”/”very-good”. No training was applied between posttest and 3-months follow-up. The CG was a passive waiting list CG and therefore did not receive any training nor weekly telephone calls. However, the CG was granted access to the

WMT after their last follow-up. In return for taking part in the study, both the WMT group and the CG received a free 6-months license including the full spectrum of NeuroNation's cognitive training tasks after their last follow-up.

SUMMARY OF STUDY I: OPHEY, GIEHL, ET AL. (2020)

Ophey, A., Giehl, K., Rehberg, S., Eggers, C., Reker, P., van Eimeren, T., & Kalbe, E. (2020). Effects of working memory training in patients with Parkinson's Disease without cognitive impairment: A randomized controlled trial. *Parkinsonism & Related Disorders*, *72*, 13-22. https://doi.org/10.1016/j.parkreldis.2020.02.002

GENERAL INFORMATION

The first study, which evaluates the immediate and 3-months follow-up effects of the 5-week home-based computerized WMT on neuropsychological and clinical outcomes in patients with PD (Ophey, Giehl, et al., 2020), was published in *Parkinsonism & Related Disorders*. The manuscript was initially submitted on June 24th, 2019, revised in December 2019, and accepted for publication on February 10th, 2020.

SCIENTIFIC CONTRIBUTIONS

The study is based on the previously described RCT, which was a collaboration of the department of Medical Psychology | Neuropsychology and Gender Studies and the Multimodal Neuroimaging Group of the department of Nuclear Medicine of the University Hospital Cologne. The present subproject was supervised by Elke Kalbe. Kathrin Giehl, Sarah Rehberg, Thilo van Eimeren, and Elke Kalbe conceptualized and designed the RCT including the design of the working memory training. **Anja Ophey**, Kathrin Giehl, and Sarah Rehberg had a major role in the acquisition of data and supervising data collection. Carsten Eggers supported patient recruitment. Paul Reker rated the video data of the PD motor symptom assessments. **Anja Ophey** conceptualized and conducted the data analysis. **Anja Ophey** and Elke Kalbe interpreted the results. **Anja Ophey** drafted the first version of the manuscript. All authors revised the manuscript for intellectual content and approved the final version of the manuscript. **Anja Ophey** and Elke Kalbe led the submission process and drafted the revisions until final publication.

ELABORATED ABSTRACT

Objective: Given the rationale of WMT in patients with PD as outlined under "Working Memory Training in Patients with Parkinson's Disease", targeted WMT seems a promising non-pharmacological, cognitive training approach in patients with PD for possibly preventing or delaying the onset and progression of cognitive impairment, treating early cognitive dysfunctions, and antagonizing these processes as early as possible. However, WMT in patients with PD is largely under-investigated so far (Fellman et al., 2018). Therefore, the aim of the present work was to determine the feasibility and evaluate effects of WMT in patients with PD without cognitive impairment (yet) on neuropsychological and clinical outcomes.

Hypotheses: WMT is feasible operationalized by training completion, motivation to train, and satisfaction with the training in patients with PD without cognitive impairment and leads to positive near-transfer (i.e., verbal and non-verbal working memory) and far-transfer (i.e., other cognitive domains and clinical variables) training effects compared to a passive waiting-list CG.

Methods: 76 patients with PD without cognitive impairment, who met the inclusion criteria described in detail under "Participants", were randomized to either the WMT group (n = 37), who participated in a 5-week home-based, computerized, adaptive WMT compiled on the basis of the cognitive training program NeuroNation (for details, see "Working Memory Training with NeuroNation"), or a passive waiting-list CG (n = 39). Training completion, motivation to train, and satisfaction with the training were regarded as indicators of feasibility. Patients underwent neuropsychological and clinical examination at baseline, after training, and at 3-months follow-up (for details, see "Study Design"). Outcome assessors were blinded for group allocation.

Cognitive domains were operationalized as domain composite scores computed as the average of the corresponding equally weighted single test standardized z-scores derived from established cognitive tests and test batteries (Aebi, 2002; Bäumler & Stroop, 1985; Horn, 1983; Kalbe et al., 2002; Morris et al., 1989; Schretlen, 1989; Schuhfried, 1992; Sturm et al., 1993; Wechsler, 1984). Table 2 comprises an overview of the assignments of single test scores to a cognitive domain. Verbal and non-verbal working memory were considered as near-transfer, primary outcomes. Executive functions, verbal memory, visuo-cognition, attention, and language constituted the cognitive far-transfer, secondary outcomes. Further far-transfer, secondary outcomes included SCD (Jessen et al., 2011; Kalbe, Bintener, et al., 2018), everyday

cognitive functioning (Farias et al., 2011), the presence and severity of depressive symptoms (Yesavage et al., 1983), the quality of sleep (Buysse et al., 1989), motor impairment as assessed with the UPDRS-III (Fahn et al., 1987), the H&Y scale (Hoehn & Yahr, 1967), and the FOG questionnaire (Giladi et al., 2000).

The final sample included for the statistical analyses, which were conducted in *R* (https://www.r-project.org; R Core Team, 2018), consisted of *n* = 75 patients (age: 63.99 ± 9.74 years, 46.7% female, 93% H&Y stage 2: bilateral involvement without impairment of balance). Linear mixed-effects (LME) models estimated with the *nlme*-package (Pinheiro et al., 2017) using maximum likelihood estimation were used to analyze training effects. Dependent variables were the cognitive domain composite scores, which were assessed at three points of time each. The LME models included time (baseline, posttest, and 3-months follow-up), group (WMT and CG), and the interaction between time and group (time*group) as fixed factors. Furthermore, subjects and time were included as random factors. The reporting of the RCT follows the *Consolidated Standards of Reporting Trials* (CONSORT) recommendations (Moher et al., 2010; Schulz et al., 2010).

Results: All WMT participants completed the training successfully and reported high levels of motivation for and satisfaction with the training. The repeated-measures, LME models revealed positive near-transfer training effects for the WMT group compared to the CG in verbal working memory with a small relative effect size (0.39, 95% CI 0.05 – 0.76) for the 3-months follow-up only. No other reliable near- and far-transfer training effects in neuropsychological and clinical variables were found for either point of time.

Discussion: In this RCT, WMT was feasible and led to 3-months follow-up near-transfer effects in verbal working memory for patients with PD without cognitive decline. No cognitive and clinical far-transfer effects were observed. Several factors might have contributed to limited observed training effects in this cognitively high functioning cohort. Especially for the target group of cognitively unimpaired patients with PD, one would probably not expect large training effects anyhow, as the improvement potential from a well-functioning baseline might be limited per se. Additionally, cognitive decline within the investigated timeframe without WMT is not to be expected either, which limits the informative value regarding the preventive effects of WMT. Hence, RCTs with longer follow-up periods than our 3-months follow-up are necessary

to evaluate the potential long-term preventive benefits of WMT in patients with PD. Furthermore, more sensitive assessment tools unsusceptible for ceiling effects as realized in an explorative module of our study (Giehl, Ophey, Reker, et al., 2020) might be necessary. Moreover, variability of training effects was large across participants. Therefore, follow-up analyses on predictors of training responsiveness are highly relevant to answer the question "who benefits most?" from WMT in terms of sociodemographic, neuropsychological, and clinical characteristics (see Study III).

Conclusion: This RCT provides some evidence for potentially positive WMT effects in the prevention of cognitive decline associated with PD possibly resulting in long-term benefits for the patients' cognitive health. Identifying predictors of WMT responsiveness in patients with PD is necessary to explain the observed heterogeneity of training effects and would contribute to the development of individualized, stratified cognitive intervention approaches in terms of a precision medicine approach against one of the most common and debilitating non-motor symptoms associated with PD. So far, the potential of non-pharmacological interventions is underutilized while effective treatment options against cognitive decline, especially in the subclinical stage, in patients with PD are lacking.

SUMMARY OF STUDY II: OPHEY, ROHEGER, ET AL. (2020)

Ophey, A., Roheger, M., Folkerts, A.-K., Skoetz, N., Kalbe, E. (2020). A Systematic review on predictors of working memory training responsiveness in healthy older adults: Methodological challenges and future directions. *Frontiers in Aging Neuroscience, 12,* 1-23. https://doi.org/10.3389/fnagi.2020.575804

GENERAL INFORMATION

The second study, the systematic review on predictors of WMT responsiveness in healthy older adults (Ophey, Roheger, et al., 2020), was published in *Frontiers in Aging Neuroscience*. It was pre-registered in PROSPERO (ID: CRD42019142750) on October 22nd, 2019. The manuscript was initially submitted on June 24th, 2020, revised in August 2020, and accepted for publication on August 26th, 2020.

SCIENTIFIC CONTRIBUTIONS

The systematic review was conceptualized by Anja Ophey, Mandy Roheger, and Elke Kalbe. Mandy Roheger conducted the systematic search. Nicole Skoetz gave advice regarding the systematic search. Anja Ophey, Mandy Roheger, and Ann-Kristin Folkerts conducted the title and abstract screening in a dual control principle (i.e., each title and abstract was screened by two of the three potential reviewers). Anja Ophey and Mandy Roheger conducted the full text screening, extracted the data, and conducted the risk of bias assessment in a dual control principle. Anja Ophey and Elke Kalbe interpreted the results. Elke Kalbe supervised the project during each stage of work. Anja Ophey drafted the first version of the manuscript. All authors revised the manuscript for intellectual content and approved the final version of the manuscript. Anja Ophey and Elke Kalbe led the submission process and drafted the revisions until final publication.

ELABORATED ABSTRACT

Objective: Research on predictors of WMT responsiveness is a timely topic in healthy aging, as prognostic research in this context might contribute to the development of precision medicine approaches against cognitive decline (see “Prognostic Research for Cognitive Interventions”). Perspectively, individual participants could be matched to a specific form of cognitive intervention, taking into account individual differences in their potential to engage in cognitive plasticity and the large heterogeneity of cognitive intervention. Predictors for WMT responsiveness in healthy older adults have been investigated within moderator analyses in meta-analytic approaches (assessing predictors for between-study variability) as well as on a single-study-level (assessing predictors for within-study variability). So far, findings are highly heterogeneous, reporting partly conflicting results following a broad spectrum of methodological approaches to answer the question “who benefits most?” from WMT. The present systematic review aimed to systematically investigate and summarize evidence for predictors for WMT responsiveness in healthy older adults on a single-study level.

Hypotheses: Across prognostic literature on WMT responsiveness in healthy older adults, a pattern of individual (e.g., demographic, neuropsychological, biological) and training-related (e.g., training dose and length, training adaptivity) parameters predicting variability in WMT

responsiveness emerges. Due to heterogeneous results in existing original studies, directed hypotheses regarding specific predictors cannot be formulated.

Methods: The systematic review question was defined using the six-item *PICOTS* system (population, index prognostic factor, comparator prognostic factors, outcome, timing, setting) as proposed by CHARMS (Moons et al., 2014; Riley, Moons, et al., 2019). The reporting follows the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guideline for systematic reviews and meta-analyses (Moher et al., 2009). Four online databases were searched up to October 2019 (MEDLINE Ovid, Web of Science, CENTRAL, and PsycINFO). The inclusion criteria for full texts were (i) publication in a peer-reviewed journal in English/German, (ii) inclusion of healthy older individuals aged ≥55 years without any neurological and/or psychiatric diseases including cognitive impairment, and (iii) the investigation of prognostic factors and/or models for training responsiveness after targeted working memory training in terms of direct training effects, near-transfer effects to verbal and visuospatial working memory as well as far-transfer effects to other cognitive domains and behavioral variables. The study design was not limited to RCTs. We included all studies investigating prognostic factors and/or prognostic models regardless of whether or not significant general training effects and/or significant relationships between prognostic factors and training responsiveness were found.

In general, a prognostic factor is defined as any measure that, among people with a given condition (e.g., the process of aging), is associated with a subsequent outcome (e.g., changes in cognition after certain interventions; Riley et al., 2013). The terms predictor and prognostic factor can be used interchangeably. In prognostic research, prognostic factor finding studies and prognostic model studies are distinguished: Prognostic factor finding studies aim at establishing one or several variables as independent prognostic factors associated with an outcome. In contrast, prognostic model studies identify more than one prognostic factor, assign relative weights to each prognostic factor, and estimate the model's predictive performance through calibration and discrimination (Moons et al., 2009). The *Quality in Prognosis Studies* (QUIPS) checklist (Hayden et al., 2013) was used to examine the risk of bias of the included studies across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, statistical analyses and reporting.

Results: 12,966 records were identified through the database search. After removing duplicates, titles and abstracts of 9,583 records were screened for eligibility. Finally, a total of 16 studies including *n* = 675 healthy older individuals with a mean age of 63.0 to 86.8 years were included in this review. Within these studies, five prognostic model approaches and 18 factor finding approaches were reported.

The risk of bias assessment with the QUIPS checklist, indicated that important information, especially regarding the domains study attrition, study confounding, and statistical analysis and reporting, was lacking throughout many of the investigated studies. Due to heterogeneous methods and poor reporting quality, we were not able to meta-analyze groups of similar prognostic factors. The applied analytical approaches ranged from group comparisons (e.g., ANOVAs, *t*-tests, comparisons of effect sizes) to correlational analyses (e.g., correlation coefficients, linear regression analyses) and LME models. Investigated predictors for WMT responsiveness included individual-related sociodemographic factors (e.g., age, sex, education), neuropsychological variables (e.g., baseline performance, intelligence, processing speed), and biological factors (genes, brain metabolism), as well as training-related factors (e.g., training dose, training adaptivity). Age, education, intelligence, and baseline performance in working memory or other cognitive domains were among the most frequently investigated predictors across studies. Younger age, less educational years, higher intelligence, and lower baseline performance may predict WMT responsiveness in healthy older adults.

Discussion: Several methodological considerations and implications can be derived from the present systematic review. First, the applied analytical approaches did not only differ widely per se, but have differing suitability to investigate causal relationships between prognostic factors and training responsiveness. To circumvent statistical fallacies emerging with frequently used analytical approaches (e.g., artificial dichotomization, regression to the mean effects), predictors of training responsiveness should be investigated with advanced statistical methods such as latent difference score models (LDSM) or growth curve analyses, constituting highly flexible statistical approaches from the structural equation modelling background. This would allow to explore the (statistical) properties of change through training without actually calculating change scores and with highly flexible options to model interdependencies between several variables (Smoleń et al., 2018). Furthermore, CGs and adequate sample sizes detangle

predictors of specific treatment response from general prognostic factors of retest effects such as practice effects and regression to the mean (Hingorani et al., 2013).

Despite these methodological considerations, the possible predictors for WMT responsiveness can be embedded to a contextual framework within cognitive aging literature considering the cognitive reserve framework (Stern, 2009; Stern et al., 2020) and the compensation versus magnification account (Lövdén et al., 2010; Lövdén et al., 2012). Within our systematic review, we found hints for a dualism between compensation and magnification. Whereas the findings of baseline performance as a negative predictor might rather reflect mechanisms following the compensation account, our findings regarding intelligence as a possibly positive predictor and age as a possibly negative predictor for WMT responsiveness are more interpretable in terms of the magnification account. Higher intelligence might constitute the required "hardware" to utilize the possibilities given by WMT to extend the cognitive repertoire, and, in the broadest sense, reflecting cognitive plasticity. Age might be a proxy for the course of the interplay between neural and cognitive plasticity, which yields a higher potential for plastic changes in younger age than in old-old age (Burke & Barnes, 2006; Greenwood & Parasuraman, 2010; Li, 2013). For education, we found a tendency of being a negative predictor of WMT responsiveness. A higher cognitive reserve (e.g., by more education) is commonly associated with less cognitive deficits given the same brain pathology (Hoenig et al., 2019; Wilson et al., 2013). Therefore, for individuals with less education, brain reserve might be higher, which corresponds to a better hardware to adapt training benefits.

Conclusion: Given the methodological shortcomings of the included studies, no clear conclusions can be drawn, and emerging patterns of prognostic effects will have to survive sound methodological replication in future attempts to promote precision medicine in the context of cognitive interventions in general and WMT in particular. Within the small body of evidence and despite the complex relationships between cognitive reserve, neural plasticity, and different proxies for these constructs, it seems that there has to be room for improvement (i.e., lower baseline performance) to engage in training-related cognitive flexibility, but also sufficient hardware (e.g., age, intelligence, brain metabolism, genetic variation) to engage in training-related cognitive and neural plasticity. An individual participant data (IPD) meta-analysis might be able to overcome the current research gaps regarding prognostic factors for WMT responsiveness in healthy older adults.

SUMMARY OF STUDY III: OPHEY ET AL. (IN PRESS)

Ophey, A., Rehberg, S., Giehl, K., Eggers, C., Reker, P., van Eimeren, T., & Kalbe, E. (2021). Predicting working memory training responsiveness in Parkinson's Disease: Both "system hardware" and room for improvement are needed. *Neurorehabilitation and Neural Repair*, *35*(2), 117-130. https://doi.org/10.1177/1545968320981956

GENERAL INFORMATION

The third study, which investigates predictors of WMT responsiveness in patients with PD, was published in *Neurorehabilitation and Neural Repair.* The manuscript was initially submitted on July 6th, 2020, revised in October 2020, and accepted for publication on November 11th, 2020.

SCIENTIFIC CONTRIBUTIONS

As Study I, this study is based on the previously described RCT. Therefore, the authors' contributions to design and conceptualization of the primary study, data collection, and patient recruitment are the same as for Study I. The present subproject was also supervised by Elke Kalbe. **Anja Ophey** conceptualized and conducted the data analysis. **Anja Ophey** and Elke Kalbe interpreted the results. **Anja Ophey** drafted the first version of the manuscript. All authors revised the manuscript for intellectual content and approved the final version of the manuscript. **Anja Ophey** and Elke Kalbe led the submission process and drafted the revisions until final publication.

ELABORATED ABSTRACT

Objective: So far, evidence on the effectiveness of WMT in patients with PD is limited to direct training and partial near-transfer effects and the degree of far-transfer effects is unclear (Fellman et al., 2018; Ophey, Giehl, et al., 2020). Furthermore, even within near-transfer effects, data of the RCT reported in Study I indicate responsiveness to training to be highly heterogeneous, with some patients improving stronger than others, some patients maintaining, and others even decreasing their performance (Study I, Ophey, Giehl, et al., 2020). For far-transfer effects, this heterogeneity may have led to very small insignificant or null effects, as effects in opposite directions between participants might have eliminated overall reported effects. By further analyzing this data, the aim of the present study was to investigate individual characteristics associated with WMT responsiveness in patients with PD including

both posttest and 3-months follow-up data with LDSM, a structural equation modelling technique. By applying this advanced statistical approach, we followed the recommendation by Smoleń et al. (2018) and circumvented several statistical fallacies in the context of prognostic research for WMT responsiveness (Study II, Ophey, Roheger, et al., 2020).

Hypotheses: Demographic (age and education) and neuropsychological (baseline performance, fluid intelligence) characteristics, PD-related motor functioning, and self-efficacy expectancy can predict both near- and far-transfer WMT responsiveness in patients with PD without cognitive impairment. Due to inconclusive and partly heterogeneous results in existing literature, directed hypotheses regarding the specific predictors cannot be formulated.

Methods: Data of 75 patients with PD (age: 63.99 ± 9.74 years, 46.7% female, 93% H&Y stage 2) without cognitive dysfunctions from the previously described RCT were analyzed using LDSM. LDSM were fitted in R (https://www.r-project.org; R Core Team, 2018) with the *lavaan*-package (Rosseel, 2012) with and without covariates predicting the variance of the latent change scores at posttest (Dposttest) and follow-up (Dfollow-up) and compared between the WMT group (n = 37) and the waiting-list CG (n = 38). The LDSM models are visualized in the original publication of Study III. As suggested for SEM with small samples (Krebsbach, 2014), Bollen-Stine bootstrapping with n = 1000 bootstrap replicates was performed for both model parameter estimates and fit indices (e.g., c^2-Test, standardized root-mean-square residual, SRMR, comparative fit index, CFI) using the *semTools*-package (Jorgensen et al., 2018).

We analyzed data of two cognitive domains: working memory as a near-transfer effect measure and executive functions as a far-transfer effect measure, operationalized as the domain composite scores of equally weighted single test age-, sex-, and education corrected T-scores (M = 50, SD = 10). Working memory was assessed by digit spans forward and backward (*Wechsler Memory Scale revised*; Wechsler, 1984), a verbal and a non-verbal n-back task and the CORSI block-tapping tasks forward and backward (*Wiener Testsystem*; Schuhfried, 1992). Tests for executive functions included semantic and phonemic verbal fluency (*Consortium to Establish a Registry for Alzheimer's Disease Plus*, CERAD-Plus; Aebi, 2002; Morris et al., 1989) , Trail Making Test B/A (CERAD-Plus; Aebi, 2002; Morris et al., 1989), and the interference measure of the *Stroop Color-Word-Interference* test (Bäumler & Stroop, 1985). Age in years, education in years, fluid intelligence as measured with subtest 4 (reasoning) of the

Leistungsprüfsystem (LPS-4; Horn, 1983; Sturm et al., 1993), PD motor impairment as measured with the UPDRS-III (Fahn et al., 1987), and self-efficacy expectancy as measured with the *Skala zur Allgemeinen Selbstwirksamkeitserwartung* (SWE; Jerusalem & Schwarzer, 1999) were investigated as predictors of WMT responsiveness. Furthermore, the effect of baseline performance in the outcome measure on training responsiveness was estimated via the covariance between baseline performance and the latent change scores in the LDSM.

Results: The LDSM with covariates yielded adequate model fit (χ^2-Test $p > .05$, SRMR $\leq .08$, CFI $\geq .95$). LDSM with freely estimated parameters between the WMT group and the CG fitted significantly better than LDSM with equality constraints on parameters across groups for both the near-transfer working memory composite and the far-transfer executive function composite (χ^2-Test $p > .05$).

For the near-transfer working memory composite, age was found to be a significant negative and fluid intelligence a significant positive predictor of Δposttest in the WMT group, indicating that younger individuals with higher levels of fluid intelligence show largest immediate training gains. For Δfollow-up, only for education a trend towards significance as a positive predictor was reported (i.e., the more educational years, the higher the training gains). In the WMT group, the covariances of baseline performance and both Δposttest and Δfollow-up were significantly negative, suggesting that individuals with lower baseline performance reported both larger immediate and follow-up gains through training than individuals with higher baseline performance. A comparison of standardized covariances indicated significantly stronger negative relationships between baseline performance and Δposttest and Δfollow-up in the WMT group compared to the CG. The covariates explained 28% of Δposttest variance and 18% of Δfollow-up variance in working memory. None of the covariates was found to be a significant predictor of variance in Δposttest and Δfollow-up for working memory within the CG.

For the far-transfer executive function composite, self-efficacy expectancy tended to be a significant positive predictor of variance at Δposttest in the WMT group, indicating that individuals with higher levels of self-efficacy expectancy show larger immediate training gains. No other covariate was found to be a significant predictor of variance in Δposttest and Δfollow-up within the WMT group. The covariates explained 17% of Δposttest variance and 18% of Δfollow-up variance in executive functions. The LDSM with covariates of the CG revealed age

to be a significant positive predictor of the variance in Δposttest and a trend of fluid intelligence being a positive predictor and self-efficacy expectancy being a negative predictor of the variance in Δposttest.

Discussion: The combination of demographic (age and education) and neuropsychological (baseline performance, fluid intelligence) characteristics, PD-related motor functioning, and self-efficacy expectancy was able to partly predict variability of WMT responsiveness at posttest and 3-months follow-up for both near- and far-transfer effects in patients with PD without cognitive impairment. The analytical approach of fitting LDSM that allowed to explore the (statistical) properties of change without actually calculating change scores, and the comparison of models fitted in the WMT group versus models fitted in the CG, enabled us to draw inferences on predictors specific for training responsiveness compared to regression to the mean and practice effect (Hingorani et al., 2013; Ophey, Roheger, et al., 2020; Smoleń et al., 2018). By applying a bootstrapping technique to estimate model parameters and fit indices of our LDSM, we made this modeling technique suitable even for small sample sizes (Krebsbach, 2014). However, our sample size still was fairly small to apply SEM, which is why the present findings need to be replicated by methodological high-quality research applying advanced statistical methods with larger samples or IPD meta-analytic approaches.

We identified lower baseline performance to be a significantly stronger negative predictor of latent change scores in the WMT group compared to the CG. This difference can be interpreted in terms of an increased compensation effect through training in the WMT group. Individuals with lower performance prior to training have more room for improvement than individuals already performing at or near optimal levels and, therefore, show larger training gains (Lövdén et al., 2010; Lövdén et al., 2012). Our data regarding associations of other predictors than baseline performance rather point to evidence for the magnification account: latent change score estimates were higher for individuals of the WMT group with higher intelligence, younger age, more educational years, and higher self-efficacy expectancy. These findings partly confirm hypotheses derived from the healthy aging context (Study II, Ophey, Roheger, et al., 2020), where higher intelligence and younger age might constitute the required hardware to utilize the possibilities given by WMT to extend the cognitive repertoire and engage in neural and cognitive plasticity (Greenwood & Parasuraman, 2010; Li, 2013). As in Fellman et al. (2018), education might be a proxy for cognitive reserve (Stern, 2009), which in

terms of the magnification hypothesis enables individuals to engage in processes of plasticity (Lövdén et al., 2010; Lövdén et al., 2012). The positive effects of higher self-efficacy expectancy on training responsiveness might be interpretable in terms of strong links to motivational processes and general training success (Chiaburu & Lindsay, 2008; West et al., 2008).

Conclusion: This study contributes to the examination of individual characteristics of patients with PD associated with responsiveness to WMT, a promising non-pharmacological intervention option against cognitive dysfunction in patients with PD. WMT might be especially beneficial for patients with PD of younger age, higher education, higher intelligence, and greater self-efficacy expectancy. However, there has to be room for improvement, as lower baseline performance is associated with a greater positive WMT responsiveness as well. The present findings need to be replicated by methodological high-quality research with larger samples.

SUMMARY OF PUBLICATIONS RELATED TO THE PRESENT THESIS PROJECT

Based on the RCT on working memory training in patients with Parkinson's Disease, which constitutes the basis of Study I and Study III, two further publications focusing on an explorative neuropsychological module (Giehl, Ophey, Reker, et al., 2020) and the neural effects of WMT in patients with PD (Giehl, Ophey, Hammes, et al., 2020) were published. These publications are not included as key publications of the cumulative thesis, but they are inherently linked to its rationale and will be summarized below.

THE DELAYED ADJUSTMENT FRACTALS-TASK: GIEHL, OPHEY, REKER, ET AL. (2020)

Beyond the commonly applied neuropsychological assessments of working memory summarized under "Neuropsychological and Clinical Assessments" and Table 2, an explorative neuropsychological module investigated non-verbal working memory functioning in a so-called delayed adjustment fractals-task at baseline, posttest, and 3-months follow-up (Giehl, Ophey, Reker, et al., 2020). In the conducted delayed adjustment fractals-task, participants were instructed to remember both the identity and the location of one or three abstract fractals on a black screen (depending on the load condition). Following, they had to select the/a previously shown fractal out of two fractals (one distractor) and drag it to the location, where it was

previously shown. In addition to providing a discrete measure of identification performance (i.e., if a fractal was remembered or not), this task also provides a continuous measure of object localization performance (i.e., how accurate the location of the fractal was remembered). For details on the task, please refer to Giehl, Ophey, Reker, et al. (2020). The delayed adjustment fractals-task revealed some evidence for positive near-transfer training effects to non-verbal working memory (Giehl, Ophey, Reker, et al., 2020): Following the WMT, positive training effects of medium effect size were found on discrete identification performance at posttest and 3-months follow-up, but not on the object localization performance.

THE NEUROIMAGING MODULE: GIEHL, OPHEY, HAMMES, ET AL. (2020)

The neural correlates of working memory and WMT induced effects in patients with PD were investigated in an optional fMRI imaging module. At baseline, correlates of working memory maintenance and manipulation were assessed in a subsample of *n* = 41 patients with PD with a newly developed fMRI paradigm that allowed to detangle these two subprocesses (Giehl, Ophey, Hammes, et al., 2020). While both working memory maintenance and manipulation activated an extended fronto-parietal and -cerebellar network, only working memory manipulation additionally recruited subcortical striatal areas including the bilateral anterior striatum and the right precuneus. This is in line with previously reported correlates of working memory and its subprocesses, therefore validating the applied fMRI paradigm (Chai et al., 2018; Constantinidis & Klingberg, 2016; Lewis et al., 2004; McNab & Klingberg, 2008; Murty et al., 2011; Suzuki et al., 2018).

The neural correlates of changes induced by the WMT revealed generally less blood oxygen level dependent (BOLD) signal and decreased functional connectivity mainly focused around the anterior striatum in the WMT group (*n* = 19) compared to the CG (*n* = 22). Significantly reduced BOLD signals were located in and close to the anterior striatal area as well as the right precuneus, the regions uniquely contributing to the additional activation observed for working memory manipulation compared to pure maintenance at baseline. Interestingly, BOLD signal changes in the anterior striatum correlated with behavioral change, which will be further discussed in the general discussion of the present thesis. In-depth analyses revealed decreased functional connectivity originating from the anterior striatum and dorsolateral prefrontal cortex after WMT for working memory maintenance, whereas a re-organization of functional connectivity was observed for working memory manipulation. Here, decreased

functional connectivity originating the dorsolateral prefrontal cortex and increased functional connectivity originating the anterior striatum and supplementary motor area were observed. Further details are reported in Giehl, Ophey, Hammes, et al. (2020).

GENERAL DISCUSSION

The aim of the present thesis project was to investigate the effects and mechanisms of targeted WMT in patients with PD without cognitive impairment, which, in the long run, would contribute to the implementation of evidence-based and the development of precision medicine approaches against the debilitating cognitive decline associated with PD. By conducting a single-blind RCT evaluating a 5-week home-based computerized WMT in patients with PD, we strived to answer the question if WMT might be feasible and effective in this patient group (Study I). Results and implications from a systematic review on predictors of WMT responsiveness in healthy older adults (Study II) were then used to develop the analytical approach to investigate the mechanisms underlying WMT responsiveness in patients with PD (Study III).

This general discussion will summarize the main results of the present thesis project according to the three research questions depicted under "Research Questions and Hypotheses". For a summary of the discussion of the individual studies included in this thesis, please refer to the elaborated abstracts of Study I, Study II, and Study III, respectively. Details on the mentioned methodological aspects and the contextual embedding to the cognitive training literature in healthy older adults and patients with PD, as well as the debate around the compensation versus magnification account and the cognitive and neural plasticity framework can be found in the original publications of the present thesis (Study I: Ophey, Giehl, et al., 2020; Study II: Ophey, Roheger, et al., 2020; Study III: Ophey et al., in press). This general discussion will concentrate on some of those key aspects only and will primarily address concepts introduced in the first chapters of this thesis, embed the present findings to a broader context including the findings of the exploratory delayed adjustment fractals-task (Giehl, Ophey, Reker, et al., 2020) and the neuroimaging module (Giehl, Ophey, Hammes, et al., 2020) of our RCT, and outline future directions of research against cognitive decline associated with PD.

RESEARCH QUESTION (I)

Is WMT feasible and effective in patients with PD without cognitive impairment? (Study I)

As WMT in patients with PD is largely under-investigated so far, the general feasibility and effects of WMT on clinical and neuropsychological variables were investigated in an RCT with

n = 75 patients with PD without cognitive impairment according to established diagnostic criteria. The main hypothesis was that WMT is feasible in patients with PD and leads to positive near-transfer and far-transfer training effects compared to a passive waiting-list CG. The following chapters will discuss aspects of WMT feasibility and a broad discussion around the effectiveness of WMT in patients in PD regarding near-transfer effects in the working memory domain and far-transfer effects to other cognitive and clinical domains.

FEASIBILITY OF WORKING MEMORY TRAINING IN PATIENTS WITH PARKINSON'S DISEASE

The RCT revealed a high feasibility of the conducted home-based computerized WMT via NeuroNation in patients with PD without cognitive impairment as indicated by training adherence and completion rates, reported motivation to train, and satisfaction with the training (Ophey, Giehl, et al., 2020). These findings support the hypothesis for research question (i) regarding WMT feasibility in patients with PD without cognitive impairment and are well in line with Fellman et al. (2018), who reported feasibility of home-based WMT in cognitively well-preserved (not further specified) patients with PD as well. A home-based flexible implementation of WMT and cognitive training regimes in general might bear the potential to reach patients that would otherwise not participate in cognitive trainings due to personal reservations, inconveniences associated with supervised training in a clinical setting, living in rural areas with limited healthcare infrastructure, and/or packed daily routines especially for employed patients. It remains an open question, however, whether this home-based largely unsupervised training approach might be feasible for patients with PD-MCI or even PD-D as well. With PD progression it might be necessary and beneficial to involve non-professional caregivers, for example, from the family environment to supervise the training process (Wilms, 2020).

EFFECTIVENESS OF WORKING MEMORY TRAINING IN PATIENTS WITH PARKINSON'S DISEASE

Compared to the passive waiting list CG, the conducted WMT led to near-transfer effects in verbal working memory at 3-months follow-up in patients with PD (Ophey, Giehl, et al., 2020). Near-transfer training effects in non-verbal working memory at posttest and follow-up were only observed in the explorative delayed adjustment fractals-task (Giehl, Ophey, Reker, et al.,

2020). In the next two chapters, the near-transfer effects will be critically discussed regarding task-specificity of transfer and evidence for differential training effects for working memory maintenance and manipulation, also integrating findings from the neuroimaging module of the RCT. The neuroimaging module revealed evidence for decreased task-related BOLD signals following WMT and subprocess-dependent changes in functional connectivity. No reliable far-transfer effects to other cognitive domains or clinical variables were observed (Ophey, Giehl, et al., 2020). Following, the hypothesis for research question (i) regarding WMT effectiveness in patients with PD was only partly supported by the present findings, which will be further discussed below.

Our RCT evaluating WMT in patients with PD with yet no clinically relevant cognitive impairment follows the recommendation of Weicker et al. (2016) to promote the application of WMT in clinical settings. In their meta-analysis they found evidence of positive short- and long-term near-transfer as well as far-transfer effects being especially pronounced in healthy older adults, adults with acquired brain injuries (e.g., stroke, traumatic brain injuries), and adolescents with working memory deficits. This led to the hypothesis of potentially pronounced WMT effects in patients with PD (Weicker et al., 2016), which could, however, not be supported by data of the present trial.

Nevertheless, the observed small to moderate near-transfer effects partially confirm the findings of Fellman et al. (2018) and WMT literature in healthy older adults (Hou et al., 2020; Sala et al., 2019; Teixeira-Santos et al., 2019; Weicker et al., 2016). Notably, in our cohort of patients with PD without cognitive impairment, the observed training effects were larger and more reliable at follow-up than at posttest, as they were present for both verbal and an explorative measure for non-verbal working memory at follow-up but not at posttest. Firstly, this confirms the finding of reliable follow-up effects after WMT in healthy older adults (Hou et al., 2020; Sala et al., 2019; Teixeira-Santos et al., 2019; Weicker et al., 2016). Secondly and even more importantly, the meta-analyses on WMT in healthy older adults comparing immediate posttest versus follow-up training effects revealed similar or even increased effect sizes at follow-ups. Whereas this is discussed to reflect some kind of selection bias in one of the meta-analyses (Sala et al., 2019), it could also be an indicator for recreation processes and deeper elaboration and consolidation of the WMT content beyond the training period (Ophey, Giehl, et al., 2020; Penner et al., 2012; Weicker et al., 2016).

Near-Transfer Effects versus Task-Specificity of Transfer

As briefly introduced in the original publication of Study I, our findings seem to reveal a task-specificity of transfer (Soveri et al., 2017), even though other previously discussed potential explanations for limited training effects exist (e.g., impossibility to investigate preventive effects with only 3-months follow-up, ceiling effects in the neuropsychological test battery; Ophey, Giehl, et al., 2020). Upon close inspection of the NeuroNation training tasks (Table 3) and comparison with the neuropsychological tests used to assess verbal and non-verbal working memory, we should, however, rather speak of a domain-specificity of transfer, which in turn corresponds to the popular definition of near-transfer effects (Figure 6).

Of tasks that entered the near-transfer verbal working memory composite (digit span forward and backward, i.e., two simple span tasks, and a verbal n-back task), the WMT with NeuroNation only trained other versions of verbal n-back tasks, but no verbal simple span tasks. Interestingly, no task-specific transfer was observed from the daily simple span (block-tapping) forward warm-up task in NeuroNation to the non-verbal working memory composite, which was assessed by block-tapping tasks forward and backward and a n-back non-verbal task (Ophey, Giehl, et al., 2020). This strengthens the hypothesis of domain-specificity rather than task-specificity of transfer induced by WMT in patients with PD.

Working Memory Maintenance versus Manipulation

The observed near-transfer effects following the WMT for patients with PD can be further discussed regarding differential training effects for the working memory subprocesses maintenance and manipulation (Figure 4). The verbal working memory composite, for which positive near-transfer training effects following the WMT were observed (Ophey, Giehl, et al., 2020), comprised three verbal working memory tasks. Taking into account the single-task level, it should be noted that the overall observed training effect in the verbal working memory composite score seems to be mainly driven by positive training effects in the digit span forward and verbal n-back task, i.e., one simple span task focusing on working memory maintenance (digit span forward) and one verbal n-back task relying on both working memory maintenance and manipulation. The positive training effects in the explorative delayed adjustment fractals-task revealed further evidence for WMT induced effects on working memory maintenance in patients with PD (Giehl, Ophey, Reker, et al., 2020). Summarizing, a tendency of WMT effects

being more pronounced for working memory maintenance compared to working memory manipulation could be observed for neuropsychological outcomes.

This tendency, however, might be driven by means of our neuropsychological test battery. The training with NeuroNation encompassed a broad range of working memory tasks including several variations of complex span tasks (Table 3), that more than simple span tasks and probably more excessively than n-back tasks rely on both working memory maintenance and manipulation (Figure 4). Unfortunately, our neuropsychological test battery did not include complex span tasks to assess working memory performance (Ophey, Giehl, et al., 2020). Therefore, tasks focusing on working memory manipulation might have been underrepresented in our test battery. As already outlined in a meta-analysis on the psychometric properties of working memory tasks, the construct-validity of working memory increases with more heterogeneous task selections (Schmiedek et al., 2014). Only a heterogeneous task selection would ensure that all aspects of working memory are covered. For a valid assessment of working memory, future clinical trials focusing on WMT and/or working memory as an outcome should include the full spectrum of working memory tasks, including verbal and non-verbal simple span tasks, complex span tasks, and verbal and non-verbal n-back tasks (Figure 5).

A dissociation of the two working memory subprocesses was also found with regard to neural correlates of WMT induced changes. As already summarized under “The Neuroimaging Module”, decreased functional connectivity after WMT was observed for working memory maintenance, whereas a re-organization of functional connectivity was observed for working memory manipulation (Giehl, Ophey, Hammes, et al., 2020). These correlates are in accordance with predictions of the CRUNCH (Reuter-Lorenz & Cappell, 2008), as differential neural correlates for working memory maintenance, reflecting rather lower task demands, versus working memory manipulation, reflecting rather higher task demands, were shown. Regarding BOLD signal change, several clusters of decreased activation in regions associated with working memory functioning were observed, generally supporting the neural efficiency idea, according to which trained individuals might need less neural resources for successful task completion than untrained individuals (Haier et al., 1988; Neubauer & Fink, 2009).

The near-transfer neuropsychological changes as assessed with the posttest minus baseline difference scores in the verbal working memory composite (Ophey, Giehl, et al., 2020) and the non-verbal working memory identification performance measure of the delayed

adjustment fractals-task (Giehl, Ophey, Reker, et al., 2020) were significantly positively correlated with BOLD signal change during working memory maintenance (Giehl, Ophey, Hammes, et al., 2020). Only the change score of the verbal working memory composite was significantly positively correlated with activation change during working memory manipulation. However, this correlation was not significant when pure manipulation (i.e., manipulation minus the maintenance component) was investigated. Following, the observed neural changes seem to support the specific corresponding working memory subprocesses operationalized in the neuropsychological measures (Giehl, Ophey, Hammes, et al., 2020). The correlations between the verbal working memory composite and BOLD signal change for the three mentioned contrasts are also visualized in Figure 10 and further discussed under "Brain-Behavior Correlations".

Far-Transfer Effects to Untrained Cognitive Domains and Clinical Variables

The lack of reliable far-transfer training effects to other cognitive domains in our RCT blends well into the ongoing debate around far-transfer effects following WMT in healthy older adults (for details, see "Working Memory Training in Healthy Older Adults"). If working memory would indeed function as a processing resource for higher-order cognitive abilities (Chai et al., 2018), plastic changes in working memory functioning after WMT should transfer to untrained cognitive functions (Klingberg, 2010). However, this kind of far-transfer was not observed in the present study. Beyond issues regarding the composition of neuropsychological test batteries and follow-up periods, which have already been discussed in the original publication of Study I, it may, however, also be possible that far-transfer effects following WMT do not appear for patients with PD as a whole, but only of patients with PD and a specific profile regarding demographic, neuropsychological, and biological characteristics, which was investigated in Study III and will be discussed under "Research Question (III)". The following paragraphs will discuss the absence of observed far-transfer effects following WMT regarding SCD and the investigated clinical variables, which has only partly been discussed in the original publication of Study I.

We did not find evidence for positive training effects following WMT on SCD. SCD describes a self-perceived, subjective deterioration in several cognitive domains despite the absence of objectively measurable cognitive impairment (Jessen et al., 2020; Jessen et al., 2014). SCD might constitute a precursor of objective cognitive decline in patients with PD (Erro

et al., 2014; Galtier et al., 2019; Hong et al., 2014), which is one reason why this outcome was deemed especially reasonable in our cohort of patients with PD without objective cognitive decline (yet). Despite its clinical importance, SCD is scarcely investigated in cognitive intervention research. The systematic overview on cognitive interventions for older adults in the spectrum from healthy aging to neurodegenerative diseases and dementia by Gavelin et al. (2020) found inconsistent evidence of cognitive interventions to reduce SCD, possibly due to a small number of primary trials leading to imprecise effect estimates within the included meta-analyses. Neither the meta-analyses on WMT in healthy older adults included SCD as an outcome, nor the meta-analyses on cognitive training in patients with PD (Lawrence et al., 2017; Leung et al., 2015; Orgeta et al., 2020), nor the single-trial investigating WMT in patients with PD by (Fellman et al., 2018). As further discussed below, the inclusion of outcomes beyond objective cognitive functioning in primary trials investigating the effects of cognitive interventions on cognition across several populations should be promoted.

Next to objective and subjective (far-transfer) cognitive outcomes, we assessed a broad spectrum of clinical variables within our RCT, for which no far-transfer effects were detected either. Following, we were not able to confirm the findings of Fellman et al. (2018), who reported decreased depressive symptoms following WMT in patients with PD compared to an active CG. Only one of the meta-analyses on cognitive training in patients with PD investigated effects on depressive symptoms and revealed a non-significant close-to-zero effect size (Leung et al., 2015). As discussed in the original publication of Study I (Ophey, Giehl, et al., 2020), the observed limited effect might be due to a ceiling effect, as the prevalence of depressive symptoms was generally low across participants within our study. Clinical trials investigating cognitive training approaches in patients with PD frequently exclude participants with severe depressive symptoms. The condition might constitute a confounding variable as depressive symptoms often manifest with cognitive impairment (Austin et al., 2001) and additionally may affect training adherence and motivation to train. However, depressive symptoms constitute a common non-motor symptom in patients with PD (Reijnders et al., 2008) and a meta-analysis on computerized cognitive training in patients with major depressive disorder revealed general feasibility in this patient group and significant improvements of depressive symptoms (Motter et al., 2016). Therefore, future clinical trials evaluating cognitive interventions in patients with PD should include patients with more severe depressive symptoms as well, which would increase the generalizability and external validity of the findings.

The absence of an effect on everyday functioning in the present RCT might also be due to a ceiling effect, as in our cohort of patients with PD without clinically relevant cognitive decline problems with activities of daily living are most likely very scarce and should, by definition, not be present. Unfortunately, the meta-analysis by Orgeta et al. (2020) focusing on patients with PD-MCI and PD-D neither found evidence for reliable improvements in activities of daily living following cognitive interventions. They also discuss this finding to reflect a ceiling effect, as primary studies in patients with PD-D were rare and clinically relevant impairments in activities of daily living should, by definition, neither be present in patients with PD-MCI.

We did not find evidence for far-transfer effects following WMT on the quality of sleep of patients with PD. The relationship between the quality of sleep and cognition in general is likely to be bidirectional: On the one hand, adequate sleep was found to be essential for optimal cognitive function across the lifespan (Lo et al., 2016; Scullin & Bliwise, 2015) and sleep disorders such as RBD constitute a prodromal marker of neurodegenerative disorders associated with an α-synuclein pathology (so-called α-synucleinopathies) including PD, dementia with Lewy bodies, and multiple system atrophy (Iranzo et al., 2016; Postuma et al., 2019). On the other hand, the quality of sleep in terms of subjectively experienced quality of sleep, sleep continuity, and sleep stability may be ameliorated by cognitive activity, which can be increased, for example, by cognitive training (Cerasuolo et al., 2019; Haimov & Shatil, 2013).

No significant WMT induced training effects were found on motor outcomes including general motor functioning in patients with PD as assessed with the UPDRS-III (Fahn et al., 1987) and FOG as assessed with a FOG questionnaire (Giladi et al., 2000). WMT effects on motor functioning were not investigated in the trial of Fellman et al. (2018). We hypothesized WMT to be especially promising for far-transfer effects to motor functioning: As WMT was found to boost striatal activity and corresponding dopamine release (Bäckman & Nyberg, 2013; Bäckman et al., 2011; Dahlin et al., 2008; McNab et al., 2009), WMT may bear the potential to compensate the striatal dopamine deficiency associated with PD (Przedborski, 2017). Several factors might have contributed to the absence of significant effects, for example, a ceiling effect and low variability of motor impairment in our patient cohort (Ophey, Giehl, et al., 2020), but also the usage of outcome measures with only little sensitivity to detect subtle changes in these functional measures. Perspectively, clinical trials on cognitive interventions in patients with PD may include wearable devices that collect continuous, objective data on a patient's physical activity during a longer period of time (Kalbe, Aarsland, et al., 2018). This was realized in a multi-

center RCT (German Clinical Trials Register, ID: DRKS00010186) investigating multi-domain cognitive training in patients with PD-MCI by accelerometer sensor recordings over one week prior and post training. However, only the training effects on cognitive and traditional non-cognitive outcome measures are published so far (Kalbe et al., 2020).

Especially for FOG, cognitive interventions in general and WMT in particular might bear a promising non-pharmacological treatment option (Walton et al., 2014). FOG is an important clinical symptom of PD characterized by the sudden inability to initiate a next step and the reduction of forward progression of the feet despite the intention to do so (Nutt et al., 2011). Even though FOG is commonly classified as a PD motor symptom, a close relationship to cognitive functions, especially executive functions, working memory, and attentional functions, all reflecting fronto-striatal functions, has been reported in both neuropsychological and neuroimaging studies (Walton et al., 2014). FOG is often triggered by environmental stimuli that require a flexible adaption of a gait pattern (e.g., passing through narrow doorways, crossing streets following green traffic lights), further supporting the idea of the involvement of inhibitory control, set-shifting, working memory, and attentional demands to this clinical phenomenon (Walton et al., 2014).

During our trial, I remember one patient reporting problems with FOG and talking about his own technique to overcome this symptom. When experiencing FOG, he would always imagine the picture of a flamingo, with a greater intonation on the last syllable (i.e., flamin-GO) to initiate an accentuated “flamingo-step” lifting one foot knee-high, thereby virtually overstepping an obstacle, to start or keep moving forward. This strategy can be referred to as an internal cueing strategy, relying on the internal presentation of stimuli facilitating gait initiation and/or continuation (Nieuwboer, 2008). As such internal cueing strategies require increased executive and attentional demands, it might be beneficial to train such strategies in early PD stages counteracting more severe motor impairments as early as possible (Nieuwboer, 2008).

Targeted cognitive training approaches focusing on executive functions or working memory as realized in our RCT might not only bear the potential to improve trained cognitive domains (and also untrained cognitive domains in terms of far-transfer effects), but also FOG (Walton et al., 2014). An RCT evaluating a combined executive functions and working memory training in patients with PD with self-reported FOG revealed first evidence that cognitive training approaches might indeed be able to reduce the severity of FOG in this patient group

(Walton et al., 2018). Future clinical trials evaluating such targeted cognitive interventions in patients with PD should use more objective and sensitive assessments of FOG to reliably assess effects on this debilitating symptom in the interplay of cognition and motor functions.

Despite a lack of far-transfer effects following WMT to other cognitive domains and clinical variables in the present trial, future research on cognitive interventions in patients with PD should more consistently include non-cognitive outcomes (e.g., depression, activities of daily living, quality of life, motor functioning), which was already promoted by the most recent systematic reviews, meta-analyses and systematic overviews in the field (Gavelin et al., 2020; Leung et al., 2015; Orgeta et al., 2020), as well as the vision paper on cognitive interventions in patients with PD of Kalbe, Aarsland, et al. (2018). Furthermore, truly patient-centered outcomes assessing aspects that are most important for the individual patient are increasingly recognized to constitute relevant outcomes in general intervention research (Kalbe, Aarsland, et al., 2018; O'Connell et al., 2018).

RESEARCH QUESTION (II)

Which individual characteristics predict WMT responsiveness in healthy older adults and what are methodological challenges of prognostic research on WMT responsiveness? (Study II)

Before investigating the mechanisms underlying WMT responsiveness in patients with PD (Study III), one part of the present thesis project was to systematically summarize the available evidence of prognostic research on WMT responsiveness in healthy older adults. In this population, WMT has a longer tradition and predictors of between-study variability (mainly training-related predictors) have been investigated in several meta-analyses and predictors of within-study variability (mainly individual-related predictors) in several primary studies (for an introduction, see "Prognostic Research for Cognitive Interventions"). The present systematic review constitutes the first review systematically summarizing the available evidence of prognostic research in primary studies of WMT in healthy older adults, therefore focusing on individual-related sociodemographic, neuropsychological, and biological predictors of within-study variability. We hypothesized that across prognostic literature on WMT responsiveness in healthy older adults, a pattern of individual (e.g., demographic, neuropsychological, biological) and training-related (e.g., training dose and length, adaptivity) parameters predicting variability in WMT responsiveness emerges.

PREDICTORS OF TRAINING RESPONSIVENESS IN HEALTHY OLDER ADULTS

Within 16 primary studies, a total of 23 prognostic model and prognostic factor finding approaches were reported (Ophey, Roheger, et al., 2020). In the original publication of Study II (Ophey, Roheger, et al., 2020), the possible predictors for WMT responsiveness have been extensively embedded into a contextual framework within the compensation versus magnification account (Lövdén et al., 2010; Lövdén et al., 2012), cognitive reserve, and brain reserve (Stern, 2009; Stern et al., 2020). We hypothesize that there has to be room for improvement (i.e., lower baseline performance) to engage in WMT-related cognitive flexibility, but also sufficient hardware (e.g., younger age, higher intelligence, more youth-like brain metabolism, genetic variation) to engage in WMT-related cognitive and neural plasticity. However, the body of evidence (so far) is too weak to draw clear conclusions and we were not able to reliably answer the first part of research question (ii). Future studies of high methodological quality will have to replicate the proposed framework for the interpretation of relationships between the prognostic factors and WMT responsiveness. One further possibility in this context would be to conduct an IPD meta-analysis based on already existing data, which is further discussed under “Future Directions”.

METHODOLOGICAL CHALLENGES OF PROGNOSTIC RESEARCH

One immense problem with prognostic research in the context of WMT and cognitive interventions in general is that it is often considered as an add-on analysis beyond standard effectiveness evaluations only. Hence, it is frequently lacking sufficient statistical power and, more generally speaking, methodological quality. So far, most of the existing prognostic research approaches in the field of cognitive interventions neither follow the recommendations of the PROGRESS framework (Hemingway et al., 2013; Hingorani et al., 2013; Riley et al., 2013; Steyerberg et al., 2013), nor the TRIPOD statement (Collins et al., 2015; Moons et al., 2015).

The methodological challenges and future directions identified in the conducted systematic review mainly reflect common challenges of prognostic research: from the selection of a suitable analytical approach, to an appropriate selection of candidate predictors with a proper operationalization, the inclusion of control conditions, and achieving adequate sample sizes (Hingorani et al., 2013; Ophey, Roheger, et al., 2020). Whenever possible, prognostic research should be conducted with advanced statistical methods such as LDSM or growth curve analyses. On the one hand, this would allow to circumvent several statistical fallacies from

which clinical trial data often suffer including violations of multivariate normality assumptions, non-linear change trajectories, and missing data patterns (Newsom, 2015). On the other hand, it would allow to explore the (statistical) properties of change through training without actually calculating change scores and with highly flexible options to model interdependencies between several variables (Smoleń et al., 2018). In this context, artificial dichotomization of candidate predictors should be avoided. Several studies in the systematic review used median splits to create artificial groups (e.g., high- versus low-performers, young-old versus old-old participants) from originally continuous variables (e.g., baseline performance, age). This might have resulted in a loss of information, possible misunderstandings of actual continuous relationships, and a severe loss of power (Dawson & Weiss, 2012; Fernandes et al., 2019; Moreau et al., 2016). Prognostic analyses should always include data of at least one CG, as this constitutes the only way to detangle predictors of specific treatment response from general prognostic factors of retest effects such as practice effects and regression to the mean (Hingorani et al., 2013). Finally, prognostic research should be incorporated at the study design stage to calculate adequate sample sizes to reach sufficient statistical power to detect possible relationships. Typically smaller sample sizes of cognitive intervention studies should, however, not discourage researchers from applying advanced statistical approaches (Smoleń et al., 2018), even though results need validation in other samples and/or IPD meta-analytical approaches and should be treated cautiously. The replication, confirmation, and validation of prognostic factors and models is one central claim in the PROGRESS framework, but needs to be promoted in the context of prognostic research for cognitive interventions.

RESEARCH QUESTION (III)

Which individual characteristics predict WMT responsiveness in patients with PD without cognitive impairment? (Study III)

Study I revealed large heterogeneity among WMT responsiveness across participants, which may (next to other methodological considerations) have contributed to limited observed overall effects. This highlights the importance and the potential of prognostic research on the road to precision medicine cognitive intervention approaches against the debilitating cognitive decline associated with progressing PD. Study II facilitated the implementation of high methodological standards to answer the question “who benefits most?” and provided the contextual framework to interpret predictors of WMT responsiveness in Study III. We

hypothesized demographic (age and education) and neuropsychological (baseline performance, fluid intelligence) characteristics, PD-related motor functioning, and self-efficacy expectancy to be predictive of both near- and far-transfer WMT responsiveness in patients with PD without cognitive impairment.

PREDICTORS OF TRAINING RESPONSIVENESS IN PATIENTS WITH PARKINSON'S DISEASE

Following the systematic review on predictors of WMT responsiveness in healthy older adults, we hypothesized that there has to be room for improvement to engage in WMT-related cognitive flexibility, but also sufficient hardware to engage in WMT-related cognitive and neural plasticity (Ophey, Roheger, et al., 2020). Interestingly, hints for this dualism between compensation and magnification processes were present in the analyses on WMT responsiveness in patients with PD without clinically relevant cognitive impairment as well (Ophey et al., 2021). For near-transfer working memory, lower baseline performance, younger age, and higher fluid intelligence significantly predicted higher change scores at posttest, and lower baseline performance and higher education predicted larger change scores at 3-months follow-up. For far-transfer executive functions, higher self-efficacy expectancy showed a trend to significantly predict larger positive WMT responsiveness at posttest. These relationships were present in the WMT group, but not in the CG, which points to mechanisms specific for WMT responsiveness rather than general retest effects (Ophey et al., 2021), at least partly supporting the hypothesis for research question (iii).

Lower baseline performance robustly predicted larger near-transfer WMT responsiveness beyond statistical bias regarding retest effects and especially regression to the mean (Smoleń et al., 2018). Following, „room for improvement" regarding participants' working memory abilities at baseline seems necessary, which is in line with predictions of the compensation hypothesis (Lövdén et al., 2010; Lövdén et al., 2012). As in Study II (Ophey, Roheger, et al., 2020), data regarding associations of other predictors than baseline performance rather point to evidence for the magnification account, indicating that several hardware requirements have to be met in order to utilize the possibilities given by WMT to extend the cognitive repertoire and to engage in true plasticity (Lövdén et al., 2010; Lövdén et al., 2012). Importantly, these findings support the rationale of conducting WMT in early PD stages, as in early disease stages brain reserve of these patients is higher. With disease

progression, PD related brain pathology increases (Braak & Del Tredici, 2017; Braak et al., 2003), which might reduce the possibility of the brain to engage in plastic processes.

EDUCATION, COGNITIVE RESERVE, AND BRAIN RESERVE

Only one dissociation between predictor directions was observed between the systematic review on predictors of WMT responsiveness in healthy older adults (Ophey, Roheger, et al., 2020) versus the present analyses in patients with PD (Ophey et al., 2021). While a tendency for education being a negative predictor of WMT responsiveness was observed in healthy older adults, a tendency for education being a positive predictor of WMT responsiveness was observed in our PD sample. Both can be integrated to a discussion within the framework of cognitive reserve and brain reserve (Stern, 2009; Stern et al., 2020), as education may function as a proxy for brain reserve and for cognitive reserve, respectively.

A higher cognitive reserve is commonly associated with less cognitive deficits given the same brain pathology (Hoenig et al., 2019; Wilson et al., 2013). Following, two individuals with similar cognitive functioning but different educational backgrounds might also differ in their brain pathology: the individual with higher education might already show a higher level of brain pathology compared to the individual with lower education, which in turn comes down to lower levels of brain reserve for individuals with higher levels of cognitive reserve given similar levels of cognitive functioning. In healthy older adults, individuals with less educational years, i.e., lower lifetime cognitive reserve, may show higher levels of brain reserve, which corresponds to a better hardware to adapt training benefits. Therefore, education could be interpreted as a proxy of brain reserve rather than cognitive reserve in the conducted systematic review in healthy older adults (Ophey, Roheger, et al., 2020).

In the LDSM with data of patients with PD, however, we controlled for PD motor impairment, which can be considered to reflect a proxy to the amount of PD related brain pathology or brain reserve (Braak et al., 2003). PD motor impairment did not emerge as a significant predictor or WMT responsiveness itself. Nevertheless, our analyses thereby controlled for a proxy brain reserve, which is why education might have emerged as a proxy of cognitive reserve rather than brain reserve in the LDSM (Ophey et al., 2021). Similarly, Fellman et al. (2018), who also investigated predictors of WMT responsiveness in patients with PD, found higher WMT responsiveness in individuals with higher levels of education and shorter disease durations. Comparable to PD motor impairment, disease duration could be regarded

as a proxy for PD related brain pathology and brain reserve, which is why education rather reflects a proxy for cognitive reserve in their analyses as well.

BRAIN-BEHAVIOR CORRELATIONS

Giehl, Ophey, Hammes et al. (2020) not only investigated the neural correlates of working memory and effects of WMT on BOLD activity and functional connectivity in patients with PD, they also investigated brain-behavior correlations between the WMT-induced neuropsychological change and BOLD signal change. These brain-behavior correlations were already mentioned under the general discussion of research question (i) in terms of supporting the differentiation of training effects for working memory maintenance versus manipulation. The positive correlations between neuropsychological change and BOLD signal change were observed despite the overall finding of several clusters of decreased BOLD signals following WMT (Giehl, Ophey, Hammes, et al., 2020). As can be gathered from Figure 10a, the majority of patients in the WMT group exhibited decreased BOLD signals for all three contrasts at posttest, which probably accounts for this overall finding. Notably, the majority of patients in the WMT group that participated in the neuroimaging module of our study showed positive verbal working memory change scores at posttest, indicating better performance in the neuropsychological measures at posttest compared to the baseline assessment.

Patients with decreased BOLD signals in the anterior striatum following WMT might have shown increased neural activation patterns in terms of compensatory mechanisms at baseline. Compensatory neural activation has been observed in healthy older adults when compared to younger adults (Li et al., 2015; Suzuki et al., 2018) and has also been discussed in the context of PD when compared to activation patterns in healthy older adults (e.g., Boord et al., 2017; Caminiti et al., 2015; Trujillo et al., 2015). Within the group of healthy older adults, positive correlations between task-related neural activity and neuropsychological performance have been observed for old-old adults but not for young-old adults (Suzuki et al., 2018). This indicates that task-related over-recruitment might be more pronounced in individuals experiencing age-related reduction in neural and cognitive processing resources (Paraskevoudi et al., 2018; Park & Bischof, 2013). Following WMT, these individuals might have been able to reduce this compensatory activation in line with the neural efficiency hypothesis (Haier et al., 1988; Neubauer & Fink, 2009). Moreover, for some patients the increases in efficiency were accompanied by better performance in the verbal working memory composite. These

"efficiency-gainers" (Figure 10a) were able to reduce the neural resources needed for successful task execution and simultaneously not only to maintain their neuropsychological performance level, but even improve their performance. Efficiency-gainers might be able to reverse compensatory neural activation patterns associated with both normal aging-related and pathological PD-related decreases in neural efficiency. Hypothetically, those individuals might benefit from WMT in the long run as the neural effects indicate true plastic effects in terms of reversing aberrant neural activation patterns.

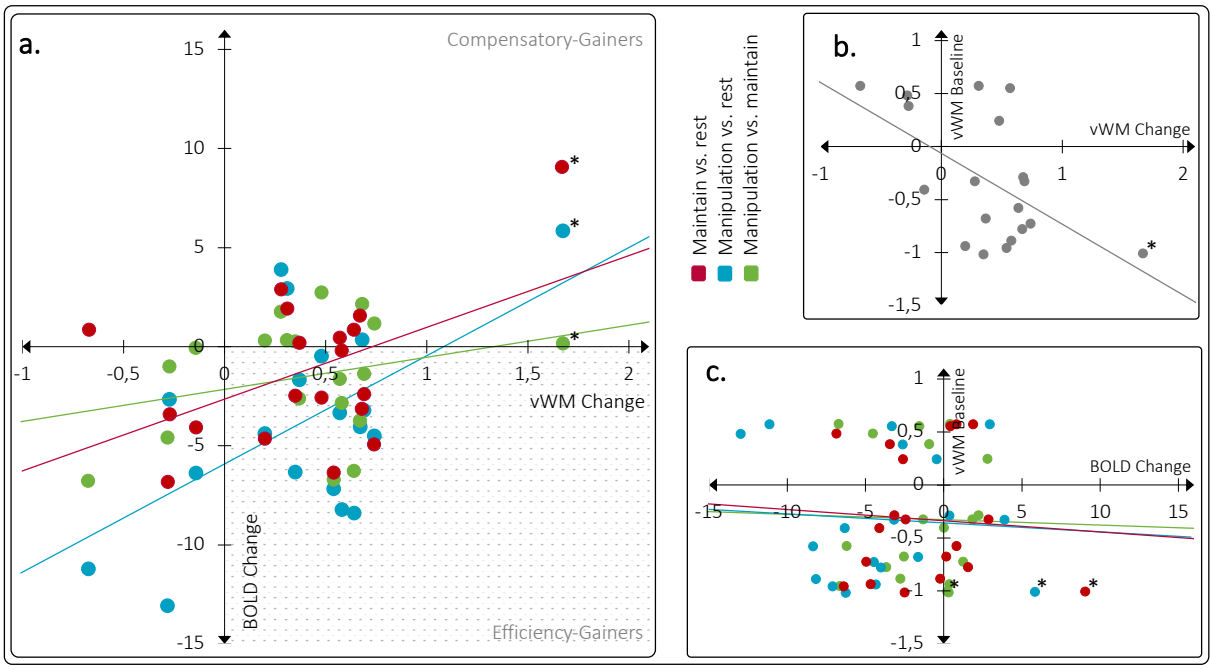


Figure 10. Brain-Behavior Correlations

a. Correlation between the BOLD signal change for each of the three fMRI contrasts (red: maintain vs. rest, blue: manipulation vs. rest, green: manipulation vs. maintain) and verbal the working memory (vWM) composite posttest minus baseline change score, adapted from Giehl, Ophey, Hammes et al. (2020). Patients with positive neuropsychological change score can be divided into compensatory- and efficiency-gainers according to increased or decreased BOLD signals following WMT. b. Correlation between the baseline verbal working memory composite and the posttest minus baseline change score. c. Correlation between the baseline verbal working memory composite and the BOLD signal change for each of the three fMRI contrasts.
* indicates one exemplary compensatory-gainer patient with low neuropsychological baseline scores and both increased neuropsychological performance and increased BOLD signal following WMT

Some patients, however, showed increased BOLD signals in the anterior striatum following WMT corresponding to larger neuropsychological gains (Figure 10a). Notably, the positive correlations between neuropsychological change and BOLD signal change seem to be largely driven by one single patient with positive BOLD signal change and the largest observed neuropsychological change in the verbal working memory composite. Interestingly, this patient additionally showed a low baseline verbal working memory composite score (Figure 10b and

c). One might hypothesize, that this patient and patients with similar patterns (i.e., low neuropsychological baseline scores, WMT induced increases in neuropsychological performance BOLD signal) could be referred to as "compensatory-gainers". These compensatory-gainers may expand more (compensatory) neural activation following WMT and simultaneously improve their neuropsychological performance.

From the healthy aging context, one could have expected increases in BOLD signal following WMT in subcortical striatal areas (e.g., Brehmer et al., 2011; Duda & Sweet, 2019; Heinzel et al., 2014; Nguyen et al., 2019; van Balkom et al., 2020), which is why those BOLD signal increases interpreted as compensatory gain could also be interpreted as "more youth-like" when considered alone (i.e., without taking into account participants' baseline information). This dissociation highlights the importance of attempts trying to understand the mechanisms leading to observed effects.

Nevertheless, neuropsychological baseline performance alone is not able to predict whether someone will exhibit more or less neural activation following WMT (Figure 10c), even though it emerged as one of the strongest predictors of neuropsychological WMT responsiveness in patients with PD in Study III and the correlation between the baseline verbal working memory composite scores and the corresponding change score at posttest showed strongly negative correlations in the fMRI subsample as well (Figure 10b). It would have been interesting to investigate the correlation between the baseline BOLD signal and BOLD signal change following WMT to gain more insights into the mechanisms of WMT responsiveness on a neural level.

Summarizing, the neuroimaging module of the present RCT indicated that WMT may induce plastic processes in the brain of patients with PD, either increasing neural efficiency or facilitating compensatory neural activation both potentially leading to improved neuropsychological performance. Future research in the field should be encouraged to further investigate these brain-behavior correlations and to try to understand the mechanisms leading to plastic processes in the brain and on a behavioral level.

GENERAL STRENGTHS AND LIMITATIONS

The main strength of the present dissertation is the application of high methodological standards to answer the three research questions depicted under "Research Questions and Hypotheses" across all stages of the scientific process from study design to statistical analyses

and reporting. The RCT (Study I) constitutes one of the first trials investigating a targeted WMT in patients with PD without cognitive impairment as excluded by established diagnostic criteria (PD-D: Emre, 2003; PD-MCI: Litvan et al., 2012). Study II and Study III posed the future-oriented question of "who benefits most?" from WMT taking important steps into the direction of precision medicine approaches to counteract age- and PD-related cognitive decline by cognitive interventions. The main limitation of the present thesis project refers to the design of the RCT regarding the short follow-up duration and the composition of the test battery, which should, perspectively, include more sensitive assessment tools. Furthermore, on a single-study level, larger sample sizes are needed to obtain reliable results with sufficient statistical power to reduce the risk of missing important effects and of reporting false alarms. A detailed discussion on strengths and limitations of the study design of the individual studies, statistical analyses, and methodological considerations beyond those already discussed in the previous chapters of the present general discussion can be found in the original publications.

The reporting of the RCT (Study I) followed the CONSORT recommendations (Moher et al., 2010; Schulz et al., 2010). The systematic review question (Study II) was defined using the PICOTS system as proposed by CHARMS (Moons et al., 2014; Riley, Moons, et al., 2019) and the reporting followed the PRISMA guidelines (Moher et al., 2009). The reporting of the prediction analyses with LDSM (Study III) included the relevant items of the CHARMS Checklist (Moons et al., 2014), allowing future research to more reliably synthesize findings from single prognostic trials. The latter is strikingly important as limitations of sample sizes in original trials necessitate the possibility to meta-analytical synthesize data across several trials.

FUTURE DIRECTIONS

Both the present general discussion and the original publications already revealed several future directions for research in the field of cognitive interventions, WMT in particular, in both healthy older adults and patients with PD. The potential of IPD meta-analytical approaches, the extension of follow-up periods and target populations, as well as the road ahead towards precision medicine intervention approaches on the continuum from healthy to pathological aging will be emphasized in the following paragraphs.

THE POTENTIAL OF INDIVIDUAL PARTICIPANT DATA META-ANALYSES

As mentioned several times, advanced meta-analytical approaches based on IPD bear an enormous potential on the road to precision medicine cognitive intervention approaches in healthy and pathological aging. IPD meta-analyses are considered to reflect the gold standard for meta-analytical approaches today (Simmonds et al., 2015; Stewart et al., 2015). Why have they not yet been carried out then in the context of cognitive intervention research? The answer to this question is as simple as it is pragmatic. The IPD approach is extremely resource intensive, as substantial time and costs are required to obtain IPD data from original study authors and to conduct adequate data management to generate a consistent data format across studies (Riley et al., 2010). Importantly, these considerations to not only apply to the authors of the IPD meta-analysis, but also to the authors of the original publication, as they need to be willing to collaborate as well (Riley et al., 2010; Rogozińska et al., 2017). Nevertheless, IPD meta-analytical approaches might be indispensable to close the gap between the potential and actual impact of prognostic research on (cognitive) health (Riley, van der Windt, et al., 2019).

A large body of data on WMT effectiveness for healthy older adults is available for post-hoc prognostic analyses, either with tiny-scale IPD meta-analyses from in-house data of comparable WMT trials (e.g., as conducted in Borella et al., 2017), or, perspectively, with the full body of WMT data. The application of an IPD meta-analytical approach would bear several advantages in synthesizing the available evidence on WMT in healthy older adults compared to common meta-analytical approaches with aggregate data (Riley et al., 2010). One could apply consistent inclusion and exclusion criteria across studies and/or account for baseline prognostic factors, which would not only allow to statistically adjust for potential confounding factors but also to investigate systematic relationships between individual-related characteristics and WMT responsiveness (Riley et al., 2010). Furthermore, it would be possible to investigate relationships between training-related and individual-related prognostic factors, taking into account the variability of WMT regimes commonly synthesized in meta-analytical approaches.

Beyond WMT in healthy older adults, a network meta-analysis comparing different cognitive intervention approaches based on IPD would be able to synthesize prognostic research findings across the broad range of cognitive interventions for different target populations to generate an encompassing view taking the road to precision medicine approaches for cognitive interventions to a whole new level. Predictors of training

responsiveness may largely differ between different cognitive intervention approaches, as different prerequisites may have to be met (Ophey, Roheger, et al., 2020; Roheger et al., 2020). The large heterogeneity of cognitive intervention approaches characterized by different rationales, varying intensities, and foci (Clare & Woods, 2004; Gavelin et al., 2020; Lustig et al., 2009; Walton et al., 2017) may lead to a different suitability of each intervention approach for an individual participant regarding the individual (e.g., sociodemographic, neuropsychological, biological) profile and personal preferences (e.g., computerized or paper-pencil, individual or group setting). In the original publication of Study II (Ophey, Roheger, et al., 2020), this is discussed for targeted memory training versus targeted WMT, constituting a common strategy-based training versus process-based training (Lustig et al., 2009). The two different approaches may implicate different levels of cognitive demands that have to be met in order to benefit from the trainings.

Recently, a preprint of a network meta-analysis on computerized cognitive training approaches in healthy older adults based on aggregated data has been published (Lampit et al., 2020). This systematic review and network meta-analysis investigates training-related predictors (e.g., type of training, training dose and length, number of sessions) of between-study variability. Individual-related differences were not considered. The authors conclude supervised multi-domain cognitive training approaches with up to 3 training sessions per week to be most efficacious (Lampit et al., 2020). In terms of a one-treatment-fits all approach this might be true, however, outcomes may be ameliorated when individual profiles and preferences are taken into account for treatment decisions (Figure 7).

FOLLOW-UP PERIODS AND TARGET POPULATIONS

As outlined in the original publication of Study I, limited training effects in the present RCT might be inherently linked to the investigated study population, i.e., patients with PD without clinically relevant cognitive decline as excluded by Level-II diagnostic criteria for PD-MCI (Litvan et al., 2012) and PD-D (Emre, 2003). One reason why WMT in patients with PD without cognitive decline seems reasonable is that executive functions, working memory, and attentional functions constitute the most vulnerable cognitive domains in patients with PD (Kalbe et al., 2016; Kudlicka et al., 2011; Lawson et al., 2014a; Litvan et al., 2011; Muslimović et al., 2005), which is also supported by the Dual Syndrome Hypothesis (Figure 2; Kehagia et al., 2010, 2013).

In terms of preventing or delaying the onset and progression of cognitive impairment and treating these early cognitive dysfunctions as early as possible, targeted WMT in patients with PD without clinically relevant cognitive decline would show its full potential only when investigated over the course of several years. Within the timeframe of the present study (20 weeks) it was not possible to evaluate the long-term effects of WMT: On the one hand, improvements of WMT group participants from a well-functioning baseline might be limited per se (also in terms of potential ceiling effects in the neuropsychological test battery). On the other hand, cognitive decline within the passive waiting-list CG is not to be expected either (Ophey, Giehl, et al., 2020). Therefore, delaying or even preventive effects for cognitive decline in our patients with PD could not be detected. One could hypothesize that the WMT led to near-transfer effects in the working memory domain as this domain was already affected by subclinical cognitive decline and near-transfer effects following WMT are generally larger than far-transfer effects. In turn, far-transfer effects in particular might show themselves in more subtle changes and could only be detected with longer follow-up periods.

Perspectively, it would also be interesting to evaluate neuroprotective effects of WMT in cohorts of individuals at-risk for conversion to PD and PD-associated cognitive decline, namely individuals with prodromal PD or idiopathic RBD. RBD does not only constitute the most predictive non-motor marker of prodromal PD (Berg et al., 2015; Heinzel et al., 2019) but in its isolated form also the prodromal phase of other α-synucleinopathies such as dementia with Lewy bodies and multiple system atrophy (Iranzo et al., 2016; Postuma et al., 2019). A broad ethical discussion around diagnosing these high-risk individuals for phenoconversion from RBD to α-synucleinopathies is present (Dommershuijsen et al., 2020), as so far neither convincing pharmacological nor non-pharmacological interventions exist. However, RBD and prodromal PD are more than clinical syndromes and may offer an early window for neuroprotective interventions (Weil & Morris, 2019).

Individuals with RBD might also show subtle deficits in motor-cognitive dual tasking (Ehgoetz Martens et al., 2020), other cognitive functions (e.g., executive functions, working memory, visuo-cognition; Galbiati et al., 2019; Génier Marchand et al., 2018), and motor functions (e.g., balance and gait). Since both motor and cognitive deficits have been identified as risk factors for phenoconversion to α-synucleinopathies, it may be reasonable to not only focus on targeted WMT but to also evaluate clinical benefits of multi-domain interventions in this context (Postuma & Berg, 2019). For Alzheimer's Disease several large prevention trials

evaluating such multi-domain interventions (e.g., targeting motor functions, cognition, and an active, healthy lifestyle in general) with promising results exist (Ngandu et al., 2015; Vellas et al., 2014). Such multi-domain intervention, however, walk on the line between a clinically oriented mindset and the urgent need to understand the basic mechanisms behind these interventions. A best practice trial design would not only include a multi-domain intervention group compared to a passive waiting-list CG, but also active CGs targeting only one single domain incorporated within the multi-domain intervention (e.g., physical therapy, cognitive training). Depending on the primary study outcome, large sample sizes are required to have sufficient power to detect potential effects and to perform subgroup analyses and prognostic analyses to identify predictors of intervention responsiveness.

PRECISION MEDICINE FOR THE CONTINUUM OF HEALTHY TO PATHOLOGICAL AGING

The present thesis project revealed similar mechanisms of WMT responsiveness in healthy older adults and patients with PD without cognitive impairment. In both target populations predictors indicate that both room for improvement and system hardware are needed to benefit from WMT, which can be interpreted in terms of processes referring to the compensation versus magnification framework (Lövdén et al., 2010; Lövdén et al., 2012). System hardware represents both an individual's brain reserve and cognitive reserve, i.e., the neurobiological capital in combination with the adaptability of cognitive processes largely influenced by innate (e.g., in utero or genetically determined) individual differences and lifetime exposures (e.g., education, occupation, physical exercise, social engagement; Stern et al., 2020). The more system hardware, the more it allows an individual to cope with the impact of pathological processes (e.g., age-or PD-related brain changes) and to maintain or even improve levels of cognitive and everyday functions. As cognitive reserve is an actively modifiable, dynamic construct and the mentioned pathological processes are (rather passively) slowly progressing, it may be beneficial for researchers and clinicians to refrain from categorizing individuals into diagnostic categories at least with regard to cognitive functioning and to strengthen the promotion of preventive approaches on the continuum from healthy to pathological aging.

A yet utopian vision could be to give every individual worldwide access to educational material regarding the prevention of cognitive decline and a healthy lifestyle in general, to strongly recommend consultations regarding lifestyle decisions at certain points in life and not

only when pathological processes already started, and to give personalized and/or stratified recommendations regarding non-pharmacological prevention and intervention approaches that fit to the individual's demographic, neuropsychological, and biological characteristics, its lifestyle, and preferences in terms of a precision medicine approach. Taking the prognosis by the *Profiles of Ageing* (United Nations, 2019) as the basis, the percentage of the population worldwide over the age of 60 will increase from 13.2% in 2019 to 21.4% in 2050. Due to this population aging and generally increasing life expectancies, the global burden of PD, Alzheimer's Disease and other dementias, as well as neurological disorders will increase, fostering the need for new knowledge to develop effective prevention and treatment strategies (GBD 2016 Dementia Collaborators, 2019; GBD 2016 Neurology Collaborators, 2019; GBD 2016 Parkinson's Disease Collaborators, 2018).

CONCLUSION

Summarizing, the present thesis project revealed some evidence for potentially long-term positive training effects of computerized, home-based WMT as an easily accessible, flexible, cost-efficient intervention option in patients with PD without clinically diagnosed cognitive impairment. Future research with longer follow-up periods and encompassing sensitive test batteries incorporating a broad range of neuropsychological, (PD-related) clinical, and patient-centered outcomes will have to prove this concept and evaluate the true preventive potential of WMT against the debilitating and seemingly inevitable cognitive decline in patients with PD. WMT effects were pronounced in patients with better system hardware (e.g., younger age, higher intelligence) in terms of both cognitive and brain reserve and more room for improvement (i.e., lower baseline scores). The investigation of neural effects and mechanisms as well as a better understanding of brain-behavior correlations may help to gain a full understanding of mechanisms underlying WMT responsiveness in patients with PD. Importantly, the present mechanisms in patients with PD seem to be similar to those in healthy older adults. The body of literature on non-pharmacological interventions including targeted WMT, other cognitive training approaches as far as broad lifestyle interventions on the continuum from healthy to pathological aging bears the potential to utilize existing data for post-hoc analyses in global research collaborations to finally unlock the full preventive and clinical potential of precision medicine approaches against cognitive decline in general.

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ORIGINAL PUBLICATIONS

STUDY I

Ophey, A., Giehl, K., Rehberg, S., Eggers, C., Reker, P., van Eimeren, T., & Kalbe, E. (2020). Effects of working memory training in patients with Parkinson's Disease without cognitive impairment: A randomized controlled trial. *Parkinsonism & Related Disorders*, *72*, 13-22. https://doi.org/10.1016/j.parkreldis.2020.02.002

STUDY II

Ophey, A., Roheger, M., Folkerts, A.-K., Skoetz, N., Kalbe, E. (2020). A Systematic Review on Predictors of working memory training responsiveness in healthy older adults: Methodological challenges and future directions. *Frontiers in Aging Neuroscience, 12,* 1-23. https://doi.org/10.3389/fnagi.2020.575804

STUDY III

Ophey, A., Rehberg, S., Giehl, K., Eggers, C., Reker, P., van Eimeren, T., & Kalbe, E. (2021). Predicting working memory training responsiveness in Parkinson's Disease: Both "system hardware" and room for improvement are needed. *Neurorehabilitation and Neural Repair*, *35*(2), 117-130. https://doi.org/10.1177/1545968320981956

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