The Effects of Working Memory Updating Training in People with Parkinson's Disease

Training Gain, Transfer, and Meaning

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Psychology

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In loving memory of Jan Kuipers

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Abstract

Cognitive deficits are common in Parkinson's disease (PD) and reduce quality of life, yet they are often overlooked in clinical practice and respond poorly to standard medication. Working memory updating (WMU) training has shown to improve WMU performance and dopaminergic availability in healthy populations. As PD is characterized by dopaminergic depletion, WMU training may represent a promising intervention. This thesis investigated the feasibility, effects, and experience of WMU training in people with PD.

A feasibility study and single-subject study (study I) indicated that WMU training is feasible, and improvements were observed in cognition, motor function, and functional brain response.

In study II, 86 people with PD were randomized to 30 sessions of WMU training or active control. Findings demonstrated improvements immediately after training for the WMU group on cognitive tests that share cognitive processes with the training tasks, and these gains were maintained four months after training. Broader cognitive improvements were observed at follow-up, suggesting delayed transfer effects to untrained domains. Self-reported psychological health remained stable.

Study III focused on the experience of cognitive training via semi-structured interviews with 18 people with PD. Three themes were identified: commitment to the training, receiving feedback during training, and inspiration to apply strategies from training to everyday life.

In sum, this thesis provides evidence that WMU training in people with PD is feasible and leads to measurable cognitive benefits. Improvements were observed on tasks that share cognitive processes with the training, and after four months in broader cognitive domains. The findings further indicate that emotional, motivational, and metacognitive processes develop during training and transfer to everyday life. Together, these results suggest that WMU training can enhance aspects of cognitive ability and cognitive efficiency in people with PD.

List of Papers

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Enkel Sammanfattning på Svenska

Kognitiva svårigheter, såsom uppmärksamhets- och minnessvårigheter, är vanliga vid Parkinsons sjukdom och kan påverka livskvalitet påtagligt. Trots detta uppmärksammas kognitiva symtom ofta för lite i vården, och svarar dessutom dåligt på de läkemedel som vanligtvis används för att behandla sjukdomen. Därför behövs nya sätt att stödja kognitiva funktioner hos personer med Parkinsons sjukdom.

En lovande möjlighet är kognitiv träning som fokuserar på att uppdatera sitt arbetsminne. Arbetsminnesuppdatering gör att vi under en kort stund kan ta in ny, relevant information och samtidigt släppa gammal, irrelevant information. Vår uppdateringsförmåga är betydelsefull i många situationer, till exempel när vi följer instruktioner, löser problem, eller är delaktig i ett samtal med flera personer samtidigt. Forskning på friska personer har visat att uppdateringsträning kan förbättra förmågan att uppdatera arbetsminnet och även höja nivåerna av signalsubstansen dopamin i hjärnan. Eftersom Parkinsons sjukdom kännetecknas av brist på dopamin har det föreslagits att denna typ av kognitiv träning skulle kunna vara särskilt användbar för personer med sjukdomen.

Denna avhandling har i tre studier undersökt om uppdateringsträning är genomförbar, vilka effekter den har på kognition och psykisk hälsa, samt hur personer med Parkinsons själva upplever träningen.

Studie I bestod av en genomförbarhetsstudie och en fallstudie där en deltagare följdes före, under och efter träningen. Resultaten visade att uppdateringsträningen var genomförbar för personer med Parkinsons och deltagaren i fallstudien visade förändringar i kognitiva testresultat, motorik och i funktionell hjärnaktivitet efter avslutad träning.

Studie II var en dubbelblind randomiserad kontrollerad studie. Här deltog 86 personer med Parkinsons sjukdom som genomförde 30 träningspass. Hälften genomförde uppdateringsträningen medan den andra hälften genomförde en aktiv kontrollträning. Deltagarna testades före träningen, direkt efter och fyra månader efter avslutad träning. Uppdateringsgruppen förbättrade sina resultat på kognitiva test som mätte uppdatering, dvs de kognitiva processer som tränades, direkt efter träningsperioden och bibehöll dessa effekter fyra månader senare. Vidare sågs mer generella kognitiva förbättringar först vid uppföljningen, vilket kan tolkas som att effekterna kan sprida sig till andra kognitiva domäner med tiden. Överlag förblev den självrapporterade psykiska hälsan stabil under studieperioden.

Studie III undersökte hur deltagarna själva upplevde den kognitiva träningen. Genom intervjuer med 18 personer med Parkinsons identifierades tre teman: ett starkt engagemang i träningen, betydelsen av att märka egna kognitiva förändringar under träningsperioden, samt inspiration att använda strategier och tankesätt från träningen i vardagen. Deltagarna beskrev också hur känslor och motivation spelade en viktig roll för att träningen skulle få betydelse i det dagliga livet.

Sammantaget visar resultaten att uppdateringsträning är genomförbar för personer med Parkinsons sjukdom. Den kan ge förbättringar i uppgifter som mäter samma kognitiva processer som träningen och även mer övergripande kognitiva förbättringar som framträder senare. Studierna visar dessutom att känslor, motivation och medvetenhet om ens egna kognition utvecklas under träningen, vilket var relaterat till att föra över träningen till vardagen. Tillsammans tyder dessa resultat på att uppdateringsträning kan förbättra aspekter av kognitiv förmåga och sättet att använda sin kognition.

Abbreviations

AC	Active control
CIS	Checklist Individual Strength
CT	Cognitive training
CWIT	Color Word Interference Test
DAT	Dopamine transporter
DRT	Dopamine replacement therapy
EOPD	Early-onset Parkinson's disease
HADS	Hospital Anxiety and Depression Scale
LOPD	Late-onset Parkinson's disease
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDQ-39	Parkinson's Disease Questionnaire
PRMQ	Prospective Retrospective Memory Questionnaire
RCT	Randomized controlled trial
TMT	Trail Making Test
WM	Working memory
WMU	Working memory updating

Introduction

When people actively monitor and code new information that is relevant for the task at hand, while letting go of old, irrelevant information, they are using the cognitive function called working memory updating (WMU; Miyake et al., 2000). Training WMU through the performance of challenging cognitive tasks that are often executed 3-5 times a week for 20-45 minutes, has shown to lead to improvements in WMU performance as well as increased dopaminergic availability and striatal activity after training (Bäckman et al., 2011; Bäckman et al., 2017; Dahlin et al., 2008; Kühn et al., 2013). These findings suggest that WMU training may represent a promising non-pharmacological intervention for supporting cognitive function in people with Parkinson's disease (PD), where a shortage of dopamine is a neurobiological characteristic (Tanner & Ostrem, 2024) and cognitive deficits are a common occurrence (Aarsland et al., 2017; Domellöf et al., 2015). On another note, dopamine also plays an important role in psychological health (Basile et al., 2021; Orth et al., 2022). For instance, in people with PD, higher levels of anxiety and depression have shown to be associated with diminished dopamine transporter (DAT) availability (Weintraub et al., 2005). Furthermore, Fellman et al. (2018) reported a decrease in depressive symptoms in people with PD after WMU training, which potentially illustrates the malleability of the dopaminergic system through WMU training.

Taken together, these findings demonstrate how dopamine is connected to WMU and psychological health, as well as how WMU training has been able to modulate neurobiological networks. The current thesis focuses on WMU training in people with PD, and aims to examine the feasibility, effects, and experience of WMU training in people with PD. Three studies form the foundation for the thesis. Study I is a feasibility and single-case study that assessed change in cognition, psychological health, functional brain response, and goal-directed movement after completion of working memory updating training. The second study examined the effects of working memory updating training on cognition and psychological health for people with PD through a randomized controlled trial. Lastly, study III investigated the experience of cognitive training for people with PD.

The thesis is organized into three sections. I will start by providing an overview of the research field. Afterwards, I will describe the designs, methodologies and results of the three empirical studies, and I will close with a discussion and synthesis of the findings.

Clinical Characteristics of Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder with a current estimation of more than 6 million patients worldwide. A twofold increase in numbers has occurred since 1990 and numbers are expected to continue rising (Dorsey & Bloem, 2018). The diagnosis of PD is based on the presence of motor symptoms, such as slowness of movement, tremor, rigidity, and postural instability (Postuma et al., 2015). Besides the characteristic motor symptoms, patients experience non-motor symptoms, such as cognitive deficits, depression, anxiety, pain and gastrointestinal disorders (Rodriguez-Blazquez et al., 2021; Schapira et al., 2017). Such symptoms can be observed during the prodromal phase of the disease, with patients often having experienced non-motor symptoms for ten years before definite diagnosis (Mahlknecht et al., 2015). Moreover, close to all people with PD report at least one non-motor symptom at time of diagnosis (Erro et al., 2012). PD is a heterogenous disorder and therefore several attempts at classifying PD into subtypes have been recorded over the years, yet to date such subtypes have shown temporal instability and an inability to be reproduced in other datasets (Mestre et al., 2018; Outeiro et al., 2023).

As PD is a progressive neurodegenerative disorder, both motor and non-motor symptoms gradually become worse over time, leading to a continuous decrease in functional mobility (Ou et al., 2021; Shulman et al., 2008). People with PD and their close relatives also report that especially non-motor symptoms have a negative effect on their quality of life (Grün et al., 2016; Martinez-Martin et al., 2011). Nevertheless, non-motor symptoms often go underrecognized in the clinic yet have started to receive more attention during the past two decades (Chaudhuri et al., 2010).

One type of non-motor symptoms are cognitive deficits, such as memory, attention, and executive functioning. Cognitive difficulties in daily life are reported by 85% of people with PD (Barbosa et al., 2019) and studies show that 25% of people with PD can be classified as having a mild cognitive impairment (MCI) (Aarsland et al., 2010). Such deficits display a progressive decline with approximately 80% of people with PD being diagnosed with Parkinson's disease dementia (PDD) after 20 years (Gallagher et al., 2024; Hely et al., 2008).

The cognitive deficits are heterogenous in people with PD and include difficulties in executive functions, processing speed, attention, episodic memory, and visuo-spatial abilities (Aarsland et al., 2021; Aarsland et al., 2017; Elgh et al., 2009; Gonzalez-Latapi et al., 2021). Cognitive symptoms in people with PD can occur early in the disease and studies highlight the presence of cognitive impairments during the prodromal phase of the disease with especially difficulties in executive functions being apparent (Fengler et al., 2017; Weintraub et al., 2017). Furthermore, the occurrence of cognitive impairments increases the likelihood of being diagnosed with Parkinson's disease dementia (PDD) later in the disease (Bäckström et al., 2022; Domellöf et al., 2015) and cognitive symptoms have a negative impact on quality of life (Kudlicka et al., 2014; Leroi et al., 2012). Hence, the investigation of interventions that target cognitive symptoms in PD is an important area for more research.

Another type of non-motor symptom that is often experienced by people with PD is symptoms of anxiety and depression. Estimates indicate that up to 35% of people with PD have clinically relevant depressive symptoms (Barone et al., 2009; Reijnders et al., 2008) and 20% of those who suffer from depressive symptoms indicate comorbid anxiety (Brown et al., 2011). Furthermore, depression can be experienced in the prodromal phase of PD and persist as the disease progresses (Aarsland et al., 2012). People with PD who experience symptoms of depression and anxiety have shown to report a lower level of quality of life (Lawrence et al., 2014; Quelhas & Costa, 2009). Connections between cognitive and affective symptoms have also been reported, whereby people with PD who experienced depressive symptoms had a faster decline in cognitive function (Andersson et al., 2021) as well as cognitive symptoms being more common in people with PD who experience affective symptoms (Alzahrani & Venneri, 2015).

Working Memory Updating

WMU is a core executive function, which is a set of higher-order cognitive functions that guide goal-directed behavior and exert supervisory control over other cognitive processes (Baddeley, 2012). Miyake's model of executive functions describes three interrelated yet distinct components (Miyake et al., 2000). These components are shifting (i.e. the ability to smoothly switch between two cognitive tasks), inhibition (i.e. the ability to inhibit automatic responses in order to stay focused on the task at hand), and working memory updating (i.e. the ability to let go of information stored in working memory and take on new information relevant for the task at hand).

Furthermore, working memory updating can be distinguished from other components of working memory, such as active and passive working memory (Adams et al., 2018; Bruyer & Scailquin, 1998; Vecchi et al., 2005; Waris et al., 2015). Passive working memory is the ability to maintain mental representations over a short period of time and can also be referred to as short-term memory. Here, the focus is on storage of information, often measured through single span tasks where a list of items is presented to a participant who recalls them immediately in the same order. Active working memory, on the other hand, refers to the manipulation of such representations, whereby information is transformed. Complex span tasks aim to measure active working memory through asking participants to immediately recall and manipulate a list of stimuli (Adams et al., 2018).

A substantial body of research shows that WMU is strongly associated with fluid intelligence, with some studies suggesting that performance on WMU tasks explains a large proportion of the variance in fluid intelligence measures (Friedman et al., 2006; Wongupparaj et al., 2015). Importantly, fluid intelligence is a robust predictor of a range of outcomes, including education achievement and various indicators of physical and mental health across the lifespan (Deary, 2012), which further highlights the central role of WMU in complex cognition. However, other studies have demonstrated that it is especially one's ability to maintain information in working memory that is correlated to fluid intelligence (Frischkorn et al., 2022).

Neurobiology of Parkinson's Disease and Dopamine's Role in Cognition and Psychological health

The pathological hallmark of Parkinson's disease is the loss of dopaminergic neurons within the substantia nigra (Kalia & Lang, 2015). However, neuroinflammation and Lewy pathology also occur in a progressive manner in people with PD (Hirsch & Standaert, 2021; Tiwari & Pal, 2017). The depletion of dopamine affects the functionality of the striatum, which is defined as the major hub of the basal ganglia and plays a role in multiple complex behaviors, such as motor control and reward learning (Prager & Plotkin, 2019). Findings suggest that the striatum can be divided into three sections based on its functionality (Basile et al., 2021; Orth et al., 2022) and projections from the midbrain (Bonelli & Cummings, 2007; Papenberg et al., 2019). First, the caudate nucleus has connections with the dorsal prefrontal cortex, receives input from the mesocortical pathway and has been described as the cognitive part of the striatum. Second, the ventral striatum is innervated by dopaminergic projections from the mesolimbic pathway and has connections to limbic areas of the brain, often defined as the affective part of the striatum. Third, the putamen has connections with the sensorimotor cortex and receives input from the nigrostriatal pathway, often described as the motor part of the striatum.

In relation to cognition, dopaminergic activity is associated with WMU. Studies in healthy participants have shown that the level of dopamine available in the striatum is correlated to performance on tests that aim to measure WMU test performance (D'Esposito & Postle, 2015; Fallon et al., 2015; Marklund et al., 2009). Moreover, working memory capacity has been associated with baseline level of dopaminergic activity within the striatum (Cools et al., 2008), whereby people with a decreased WM capacity demonstrated lower dopaminergic synthesis. Within the PD population, WMU deficits have been measured in PD patients when their dopaminergic medication has worn off and performance on WMU tasks has been suggested as a potential candidate to a cognitive marker of PD, thereby being able to differentiate between people with PD and healthy controls (Salmi et al., 2020). Taken together, these studies demonstrate that working memory and WMU in particular seem to be dependent on dopaminergic activity within the striatum.

Substantial evidence shows that dopamine also contributes to psychological health (Basile et al., 2021; Orth et al., 2022). Within the PD population, presynaptic dopamine transporter (DAT) availability has been linked to the severity of affective symptoms (Prange et al., 2022). For example, people with PD who report more anxiety, apathy, or depression often exhibit more pronounced reductions in DAT availability (Erro et al., 2012; Santangelo et al., 2015; Weintraub et al., 2005). However, the literature remains inconsistent, with some studies reporting a positive correlation between DAT density and affective symptoms in people with PD (Ceravolo et al., 2013) and others finding no association between DAT availability and affective symptoms (Park et al., 2019). These divergent findings may reflect the influence of neuroplastic processes occurring throughout disease progression, as well as the multifactorial and heterogeneous pathophysiology underlying depression in PD (Ahmad et al., 2023). For instance, dysfunction of other neurotransmitter systems, e.g. the serotonergic and noradrenergic, has also been related to depression in people with PD (Jellinger, 2022).

Lastly, dopamine plays a central role in the regulation and initiation of voluntary movement, particularly through its influence on the fronto-striatal motor network (Redgrave et al., 2010). Studies have reported shorter movement onset times following levodopa administration, which increases dopamine availability in the brain (Haslinger et al., 2001; Spay et al., 2019). This evidence supports the idea that dopamine facilitates the initiation and coordination of goal-directed motor behavior. However, resting tremor, another common motor symptom of PD, is less related to dopamine deficiency in the striatum (Dirkx et al., 2016; Moustafa et al., 2016).

Treatment for Parkinson's Disease and the Growing Interest in Non-pharmacological Interventions

To date, there is no curative treatment for PD, yet pharmacological treatments can lessen symptoms. Standard treatment for people with PD involves Dopamine Replacement Therapy (DRT) which aims to increase cerebral dopamine level (Connolly & Lang, 2014). Early in the disease, DRT has shown to have a good effect on several motor symptoms. However, with time people with PD experience side effects, such as dyskinesias, which are involuntary, often smooth movements, as well as on-off fluctuations (Huot et al., 2013).

As non-motor symptoms are diverse and thought to have different neurobiological underpinnings beyond the dopaminergic system, the picture concerning the effectiveness of pharmacological interventions becomes more complex. Some non-motor symptoms, such as mood and sleep disturbances, have shown to react positively to DRT, whilst others, of which cognitive symptoms are one, have been regarded as therapy-resistant (Vorovenci et al., 2016). Other studies have shown that DRT leads to both deleterious effects and benefits for different cognitive domains, potentially demonstrating the inverted U-shaped model of dopaminergic stimulation whereby both insufficient and excessive levels of dopamine are related to cognitive deficits (Roy et al., 2018).

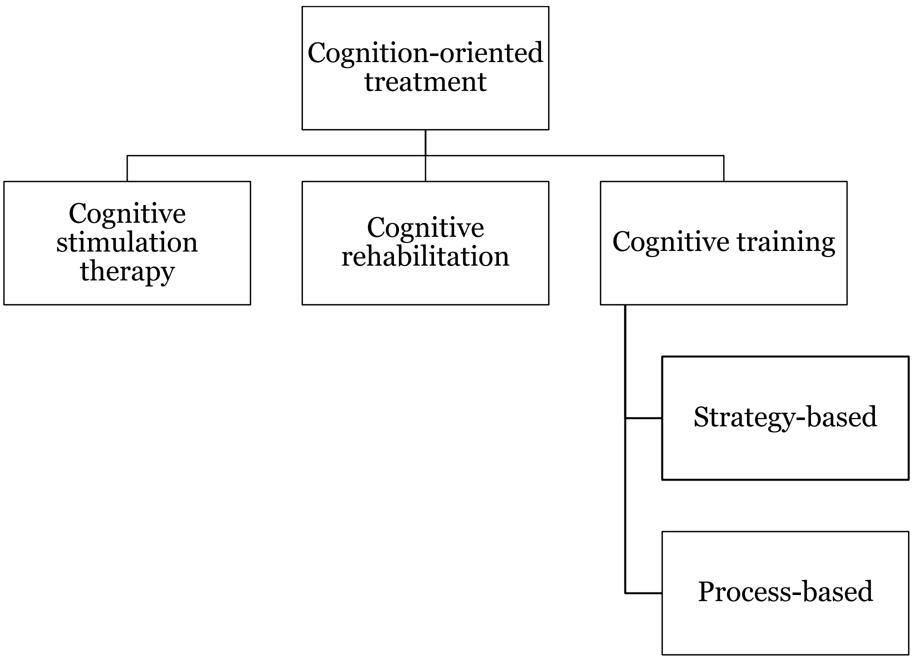
When cognitive symptoms become more advanced and start to affect one's ability to perform activities of daily life, studies have shown that acetylcholinesterase inhibitors may improve symptoms of dementia (Kalbe et al., 2024). However, for cognitive symptoms of a milder nature, there is currently no pharmacological treatment that is recommended for people with PD (Weintraub et al., 2022). Polypharmacy is furthermore common in this population, leading to unwanted drug interactions (Bhagavathula et al., 2022). Several research groups have therefore been advocating for safe, non-pharmacological interventions that are able to positively influence cognitive symptoms and improve quality of life for people with PD (Bega et al., 2014; Li et al., 2016; Sharpe et al., 2020). Non-pharmacological interventions are defined as nonmedicinal, theoretically based, replicable interventions that are either group-based or individual and address social, psychological, physical, lifestyle, or environmental factors to improve symptoms of patients, reduce disability, better manage an illness or optimize health care needs (Kooijmans et al., 2025).

Cognitive Training as a Non-pharmacological Intervention to Support Cognition

Cognition-oriented treatments are a group of non-pharmacological interventions where different techniques are used to engage cognitive functions with the goal to improve or maintain cognitive abilities in daily life (Bahar-Fuchs et al., 2019). Within this group, different types of cognition-oriented treatments can be defined, as depicted in Figure 1, with their own goals and methods of action, i.e. cognitive training, cognitive rehabilitation, and cognitive stimulation (Mowszowski et al., 2010). In cognitive stimulation therapy, participants will perform activities that aim to improve cognitive and social functioning often in group format, e.g. discussion or reminiscence. Cognitive rehabilitation focuses on identifying cognitive difficulties in daily life and learning strategies to improve or compensate for these difficulties. It can also include the third type of cognition-oriented treatment, i.e. cognitive training.

Figure 1

Overview of the Different Types of Cognition-oriented Treatments



Cognitive training is subdivided into strategy-based cognitive training and process-based cognitive training (Bahar-Fuchs et al., 2019). In strategy-based cognitive training, participants learn strategies that can support task performance during cognitive tasks, e.g. mnemonic strategies to support episodic memory. Process-based cognitive training, however, has the goal to increase the capacity of basal cognitive processes, e.g. working memory or inhibition. Here, participants repetitively execute cognitive tasks under increasing task demands over time. Nowadays process-based cognitive training is often computerized and can either focus on several cognitive functions (i.e. multi-domain training) or one specific type of cognitive function (i.e. single-domain).

The effect of cognitive training on cognitive functioning has been debated throughout the years (McCabe et al., 2016; Redick, 2019; Simons et al., 2016; Smid et al., 2020; van Heugten et al., 2016). However, a similar pattern of results has been seen across studies examining the effects of cognitive training. Studies demonstrate that cognitive training leads to improvements in the trained task and near-transfer tasks (i.e. tasks that measure the same or closely related cognitive abilities as those trained) in both healthy populations and people with cognitive impairments (Kelly et al., 2014; Mowszowski et al., 2016; Zhang et al., 2019). Often effect sizes of such near-transfer outcomes measures are small to moderate in size, ranging from 0.2 – 0.7 (Kelly et al., 2014; Melby-Lervåg et al., 2016; Rodas et al., 2024; Zhang et al., 2019). However, question marks remain linked to far-transfer effects, the long-term effects of training and its influence on everyday functioning (Kelly et al., 2014; Nguyen et al., 2019; Sala et al., 2019; Simons et al., 2016; Zhang et al., 2019). Furthermore, the research field is characterized by a range of methodological limitations, including small sample sizes, the use of passive control groups, lack of blinding among participants and researchers, and reliance on single outcome measures (McCabe et al., 2016; Redick, 2019). More research with better methodological designs is needed.

Process-based Cognitive Training for People with Parkinson's Disease

Cognitive training for people with PD has also received increased scientific attention and a wide range of training programs have been employed to assess its effects. Two recent meta-analyses examining diverse process-based cognitive training programs in people with PD concluded that there is evidence that cognitive training leads to improvements in global cognition, abstract reasoning, executive functions and short-term memory (Gavelin et al., 2022; Giustiniani et al., 2022). Furthermore, process-based cognitive training is now recommended as a possible treatment for people with PD with a mild cognitive impairment (MCI) (Kalbe et al., 2024). However, the field is also characterized by shortcomings similar to those observed in the broader cognitive training literature (Kalbe et al., 2018) and few studies have examined the long-term effects of cognitive training (Gavelin et al., 2022)

Most commonly, process-based cognitive training trials within the PD population make use of a multi-domain training regime in which participants practice various cognitive tasks for 45 minutes three times per week on average (Gavelin et al., 2022). For example, Van De Weijer et al. (2020) used a cognitive training program that focused on attention, working memory, episodic memory, psychomotor speed, and executive function. Such a design makes it difficult to determine whether the observed effects can be attributed to specific components of the training or to the program as a whole. Exceptions to these multi-domain cognitive training trials for people with PD can also be found, as RCTs have examined the effects of single-domain training of attention (Cerasa et al., 2014), speed of processing (Edwards et al., 2013), working memory (Ophey et al., 2020), and working memory updating (Fellman et al., 2018). These studies show improvements on tests that share cognitive processes with the training tasks (i.e. near-transfer, which will be further discussed in a later section), yet do not show improvements in cognitive tests on more distantly related cognitive domains (i.e. far transfer) (Cerasa et al., 2014; Edwards et al., 2013; Fellman et al., 2020; Ophey et al., 2020). One way to advance the field is to focus on the underlying mechanisms of cognitive training, for example by testing training regimes that have been shown to engage neurobiological constructs relevant to the population under study (Smid et al., 2020).

Working Memory Updating Training and its Neurobiological Underpinnings

Since WMU is modulated by dopaminergic activity in the striatum, several studies have investigated if the dopaminergic system changes in response to WMU training. Within healthy populations, studies have reported that the dopaminergic network adapts as a function of WMU training (Pappa et al., 2020; Salminen et al., 2016). For example, Dahlin et al. (2008) demonstrated improved cognitive performance and a higher degree of striatal activity during a WMU task in young and older adults after five weeks of WMU training. Bäckman et al. (2011) further investigated the same training regime and showed that WMU training also led to a higher release of dopamine after the intervention in healthy, younger participants. These findings were then replicated and extended in a similar population (Bäckman et al., 2017), where the same increase in dopamine was measured after training. Moreover, a decrease in activity in frontoparietal areas has been reported after WMU training (Dahlin et al., 2008; Pappa et al., 2020), which are areas of the associative subsystem of striatum, primarily playing a role in cognitive functions (Orth et al., 2022). Kühn et al. (2013) also reported training-related changes in striatal areas, whereby a rapid increase in striatal activity was seen after one week of WMU training, which was maintained after 50 days of training.

Taken together, these imaging studies point to the malleability of the dopaminergic system through WMU training. This suggests that WMU training could be an interesting candidate as a non-pharmacological intervention for people with PD, where dopamine depletion is a core neurobiological finding. Furthermore, dopamine has especially been related to WMU and less so to other executive functions, i.e. inhibition and shifting (Korkki et al., 2023). Adding to this, criticism of cognitive training studies has highlighted a lack of mechanistic theory underlying the observed changes (Smid et al., 2020). In response, our research team decided to examine WMU training as a single-domain, process-based cognitive intervention in individuals with PD.

To date, one randomized controlled trial has focused on WMU training in people with PD (Fellman et al., 2018), which reported improvements in cognitive performance on untrained tasks that were structurally similar to the training (i.e. task-specific near transfer), as well as reductions in depressive symptoms. Future well-designed studies are necessary to further investigate the effects of WMU in the PD population.

Transfer after Cognitive Training

The ultimate goal of cognitive training is to improve cognitive functioning in everyday life. Accordingly, both training gains and transfer effects are essential concepts to consider. First, studies are recommended to assess changes in the targeted cognitive function by including both trained and untrained tasks that measure the same cognitive function. For example, WMU training studies should incorporate a criterion task, identical or highly similar to the training tasks, to assess training gains, as well as additional tasks that measure the same cognitive function but differ from the trained tasks. This approach allows for a more robust evaluation of whether training enhances WMU as a cognitive ability, rather than merely producing task-specific improvements (Noack et al., 2014).

In addition to improvements in the trained function, it is essential to determine whether training generalizes to other cognitive domains that share limited overlap with the trained ability, commonly referred to as transfer (Greenwood & Parasuraman, 2016) and which will also be referred to as transfer in the remainder of this text. To evaluate this, studies are advised to employ a comprehensive battery of cognitive tests to determine whether improvements extend beyond the trained domain.

Transfer effects are often categorized into near, intermediate, and far transfer. Near transfer refers to improvements on untrained tasks that rely on cognitive processes similar to those engaged during training, whereas far transfer refers to improvements in more distantly related cognitive domains, often reflecting broader cognitive or functional outcomes. Intermediate transfer is often used to describe effects that fall between these two levels of similarity (Noack et al., 2009). However, these distinctions are not consistently defined, and there is no clear consensus regarding the criteria used to differentiate them (Noack et al., 2014; Pappa et al., 2021; von Bastian et al., 2022). Demonstrating far transfer is particularly important, as it provides stronger evidence that cognitive training generalizes beyond the specific tasks practiced and may have meaningful implications for everyday functioning.

Beyond defining and measuring transfer, there are differing perspectives on the mechanisms underlying transfer and the conditions necessary for such effects to occur following cognitive training. Focusing on underlying mechanisms, the neuronal overlap hypothesis proposes that transfer to untrained tasks depends on the extent to which training and transfer tasks recruit overlapping neural substrates (Noack et al., 2014). In other words, when training tasks engage specific neural networks that are also involved in untrained tasks, improvements are more likely to generalize. Empirical support for this hypothesis has been provided by Dahlin et al. (2008), who showed that transfer effects were associated with a shared, training-related increase in brain activity for both the criterion task and the near-transfer task within the striatum, which was already engaged prior to training. After training, striatal activation had increased (in both young and older participants) while frontoparietal activation had decreased (in the younger participants). Improvements after training were observed in a cognitive task that showed striatal activation at pre-test (i.e. n-back which measures WMU), whilst no improvements were seen in another task that did not rely on the same activation pattern at pretest (i.e. Stroop which measures inhibition). These findings suggest that transfer occurs when criterion and transfer tasks rely on overlapping cognitive processes and neural substrates.

Another theory on the mechanisms of transfer focuses on the degree of overlapping cognitive processes in training and transfer tests (Sprenger et al., 2013). Transfer to non-trained tasks relies upon their degree of dependency of the cognitive processes that have been trained. For example, after WMU training, one would expect to see larger improvements in tests that measure other executive functions as opposed to tests that measure cognitive domains with less overlap with the cognitive domain trained during training (e.g. language). This means that if training leads to an improved ability within a certain cognitive domain, then tasks that tap into this cognitive domain will also show improvements in a gradient fashion (Noack et al., 2014).

A third explanation for transfer to other cognitive tests following cognitive training involves the strategies used during training and test performance. Instead of an improved cognitive ability after training, this perspective focuses on a more efficient, flexible usage of one's cognitive capacity, for example via using strategies that improve cognitive performance (Lövdén et al., 2010; von Bastian et al., 2022). Studies have demonstrated how strategy use improves performance on tasks that allow the same training-related strategies to be employed (Dunning & Holmes, 2014; Laine et al., 2018), yet that such strategies will rarely transfer to untrained tasks (von Bastian et al., 2022).

Beyond identifying patterns and mechanisms of transfer, it is also important to consider the conditions under which transfer is likely to occur. First, evidence states that the cognitive training must create a mismatch between functional supply and task demands, thereby challenging the individual at a level that surpasses their current performance (Lövdén et al., 2010). For example, cognitive training may ensure such a mismatch by placing increasing demands on one's updating ability. In addition, training should be administered with sufficient frequency and duration. For instance, when comparing 24 versus eight training sessions over eight weeks, only the more intensive training schedule resulted in transfer effects (von Bastian & Oberauer, 2014).

Taken together, future studies must transparently define and measure both training gain as well as training-related transfer (i.e. near, intermediate and far transfer). Moreover, effective cognitive training programs should be of sufficient duration and incorporate adaptive difficulty levels to ensure that participants are continuously challenged.

Cognitive Training and its Effect on Psychological Health in People with Parkinson's Disease

Psychological (or mental) health is defined by the World Health Organization as "a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn and work well, and contribute to their community" (World Health Organization, 2026). Within the field of cognitive training, psychological health is most commonly measured with patient reported outcome measures (PROM), which are questionnaires or rating scales that gather subjective information regarding a certain condition (in this case psychological health) directly from the participant and transform subjective qualities into quantitative measures (Krogsgaard et al., 2021).

Evidence regarding the effects of process-based cognitive training on psychological health in PD is mixed. Several studies have assessed self-reported depression (Fellman et al., 2018; Ophey et al., 2020; París et al., 2011; Petrelli et al., 2014) as well as quality of life (Monticone et al., 2015; Ophey et al., 2020; París et al., 2011; Petrelli et al., 2014; Reuter et al., 2012). While some trials have reported reductions in depressive symptoms following cognitive training

(Fellman et al., 2018; Petrelli et al., 2014), others found no such effects (París et al., 2011). Moreover, Ophey et al. (2020) demonstrated more depressive symptoms over time in both the cognitive training group and the passive waitlist control group in their study. The authors interpreted this finding as potentially related to general study participation, whereby the participants were confronted more with their PD. Nevertheless, the above-mentioned studies all consisted of people with PD who had few depressive symptoms, with most participants scoring below the clinical cut-off for mild depression. A similar inconsistency is observed for quality of life outcomes. For instance, París et al. (2011) reported no training-related changes in a self-reported measure of quality of life, whereas Pena et al. (2014) demonstrated better functional disability after cognitive training, which is closely related to quality of life.

Two recent meta-analyses, which included self-report measures of psychological health and quality of life, concluded that cognitive training does not reliably improve these domains in PD (Gavelin et al., 2022; Giustiniani et al., 2022). Overall, few studies have incorporated psychological or quality of life outcomes. Consequently, the field emphasizes the need for future cognitive-training research in PD to include broader, non-cognitive outcome measures (Kalbe et al., 2018; van Heugten et al., 2016).

The Experience of Cognitive Training in People with PD

In the field of cognitive training, qualitative studies are few in comparison to the number of quantitative studies. Furthermore, qualitative studies foremost focus on evaluating the cognitive training program, e.g. advantages/disadvantages of the training program (Eskilsson et al., 2020), participants' opinion about the training format (Contreras et al., 2016; Haesner et al., 2015), or which changes can be made to the set-up to ensure lower drop out (Beishon et al., 2022). Moreover, a qualitative methodology is oftentimes used as an add-on to the mainly quantitative assessment of feasibility (Hoffman et al., 2023).

Such qualitative assessments of feasibility are essential to ensure cognitive training programs are accepted and meaningful for the target population, yet they do not fully grasp the experience of participants. Questions regarding if and how participating in cognitive training can enhance understanding of one's own cognitive processes, if the training is meaningful, and which emotions are connected to starting cognitive training, are often disregarded. One possible explanation is the prevailing view of cognitive training as a largely mechanistic process in which participants "simply" need to complete sufficiently challenging cognitive exercises for a specified duration for cognitive change to occur. To date, the field has shown limited interest in how participants engage and reflect on cognitive training, or how their experience of cognitive training influences people's daily life. Given that quantitative findings remain mixed and show substantial variability in measured outcomes, qualitative research may be particularly valuable for illuminating experiential aspects of cognitive training that could inspire and inform future studies.

The iPARK Trial

In summary, the scientific field of cognitive training for people with PD requires methodologically robust studies that systematically examine the effects of such interventions on both cognitive functioning and psychological health. Future research should be grounded in clear theoretical frameworks that guide the selection of cognitive training approaches and the measurement of outcomes. Additionally, incorporating qualitative methods is essential to capture participants' subjective experience of cognitive training. Collectively, these considerations informed the conceptualization of the iPARK trial.

The iPARK trial is a randomized controlled trial designed to assess the effects of WMU training in people with PD. During its development, key methodological challenges and theoretical inconsistencies in the field were carefully addressed. Accordingly, the trial incorporates an active control group, employs a double-blind procedure with a parallel-group design, and recruits a sufficiently large sample to ensure adequate statistical power. Furthermore, outcome measures were selected to capture both training-related gains and varying degrees of transfer effects. The study also includes a long-term follow-up assessment, conducted four months after training, alongside measures of psychological health. Finally, a qualitative component was integrated to explore participants' experience of cognitive training and to examine perceived transfer to everyday functioning.

Aims of the Thesis

This thesis focuses on the feasibility, the effects, and the experience of WMU training in people with PD.

More specifically, study I aims to assess the feasibility of WMU training for people with PD and measure change observed in a selection of behavioral, self-reported and brain imaging outcomes (study I) after WMU training in one person with PD. Study II aims to examine the immediate and long-term effects of WMU training on cognition and psychological health for people with PD, while study III aims to investigate how people with PD experienced cognitive training.

The studies have the following specific research questions:

1. Is WMU training feasible for people with PD to complete, and can change be observed in cognitive performance, self-reported psychological health, goal-directed upper-limb movement, and functional brain response in one individual with PD after completion of WMU training?
2. In comparison to an active control group, does working memory updating training for people with PD lead to improvements in:
   a. the trained tasks?
   b. untrained cognitive tasks (transfer effects)?
   c. self-reported everyday cognitive function and psychological health?

   Moreover, are improvements (if any) maintained four months after training?
3. How do people with PD experience a process-based cognitive training program? Here, the study focused on engagement during training as well as how the training influenced everyday life.

Method

Design

Study I had a pre-post design and included several types of outcome measures to assess change after WMU training in cognitive performance, psychological health, goal directed movement and cerebral activity. Study II is a double-blinded, randomized controlled trial with an active control group and parallel group design to assess the effects of WMU training. Study III is a qualitative study that focused on the experience of cognitive training in people with PD through individual interviews.

Participants

In study I, participants were recruited from a population-based study on idiopathic parkinsonism, i.e. the NYPUM project at Umeå University Hospital, Sweden. Inclusion criteria were: 1) definite or probable PD according to United Kingdom Parkinson's Disease Brain Bank; 2) Mini Mental State Examination above 24; and 3) no additional severe diseases or psychological disorders. Thirteen participants were invited to participate in the study of which four participants agreed. One participant did not complete the intervention due to personal reasons. One of the remaining three participants was diagnosed with MCI according to the criteria of the Movement Disorder Society (Litvan et al., 2012). The single subject (referred to as FL) is female, 47 years old, less than two years since diagnosis of PD according to the UKPDSBB-criteria, Hoehn and Yahr stage I, no other diseases in the CNS, and intact cognitive function.

In study II, all participants were recruited via the Neurology Clinic at Norrlands University Hospital. The following inclusion criteria were used in the study: 1) diagnosis of PD according to United Kingdom Parkinson's Disease Brain Bank; 2) Hoehn and Yahr stage I-III; 3) pathological dopamine transporter scan; 4) a score of 24 or higher on the Mini Mental State Examination; 5) stable medication over the past three months; and 6) access to and ability to use a home-based computer with internet connection. The exclusion criteria were: 1) unstable medication; 2) ongoing cognitive training; 3) diagnosis of Parkinson's disease dementia; 4) ongoing drug or alcohol abuse. 5) other diseases of the central nervous system or other serious medical condition. The study invited 240 individuals to participate, of whom 96 consented and completed the pre-test assessment. Ten participants were excluded at pre-test as they did not meet the inclusion/exclusion criteria. The remaining 86 participants were then randomized to one of the two arms of the study (stratified by sex and age), i.e. the WMU training intervention and an active control (AC) intervention.

In study III, all participants who had completed either the WMU or AC intervention no earlier than a year ago were invited to participate in a semi-structured interview about their experience of cognitive training. Twenty-three participants were invited to participate, of which 18 agreed and completed the interview.

Intervention

Working Memory Updating Training

In the feasibility study, the WMU training incorporated six computerized tasks that were performed on-site at Umeå university, three times a week for five weeks in total. The first task was the Letter Memory test, in which the participant was presented with ten counterbalanced lists of the letters A-D with varied lengths (5-15 letters). The letters were presented one at a time, two seconds per letter. Instructions were to recall the four last presented letters in the correct order when the list presentation ended. The participant responded on a computer keyboard using four adjacent keys with the corresponding letters taped over the keys, i.e. A=index finger, B=middle finger, C=ring finger, D=little finger. This task was not adaptive to the performance of the participant.

In four of the other tasks, the participant was presented with five lists of items and asked to recall the last four presented items, which are often referred to as running span tasks. The lists consisted of letters, colors, spatial locations, and numbers. The length of these lists varied to be sufficiently demanding throughout the training period with low (4-7 items), medium (6-11 items) and high (5-15 items) cognitive demands. All items were presented sequentially for a duration of 2 seconds per stimulus with an inter-stimulus interval of 1 second. When a participant scored over 80% correct in a certain training task, they advanced to a higher level. The participant responded on a computer keyboard using four adjacent keys with the corresponding stimuli taped over the keys or clicking on the correct stimuli on the computer screen (i.e. for the training task with spatial locations as stimuli).

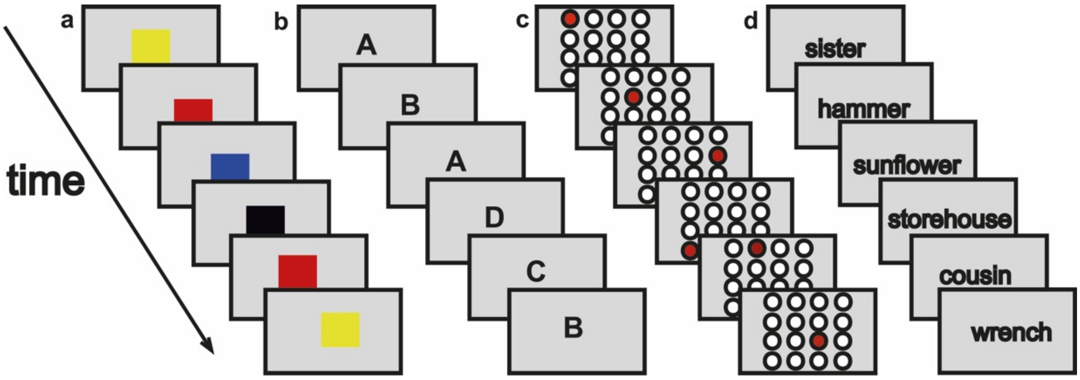
The sixth and last task differed slightly from the other training tasks as participants were instructed to mentally place a list of words into different semantic categories that were presented on the screen as boxes (i.e. animals, professions, countries, clothes, relatives and sports). After the presentation, the participant was requested to type the last presented word in each category under the matching box. Here, difficulty levels consisted of low (three target categories), medium (four target categories) and high (five target categories). Two versions of this task were used in each training session.

In the single-subject study, all training was home-based in response to feedback from the feasibility study participants. The first 16 training sessions consisted of the following tasks: the Letter Memory Test as described above and the running span training tasks with colors, spatial locations, categories and letters as stimuli. Total training time was 45 minutes. After 16 sessions, an adaptation was made to the training program in order to reduce the total time spent training per day (as proposed by the feasibility participants and FL). Thereby, the last 14 sessions consisted of a total training time of 20 minutes per day and included the four running span training tasks (colors, spatial locations, categories and letters as stimuli). Responses were provided through typing or clicking on the correct stimuli on the computer screen.

This last version of the WMU training that FL completed was subsequently used in the randomized controlled trial (study II). The training was web-based and adaptive, and consisted of 30 sessions (20 minutes per session, 4-5 times a week for 6-8 weeks). In total, the goal was to complete 30 sessions. Figure 2 provides a schematic overview of the training used in study II. Further details can be found in the study protocol of study II (Domellöf et al., 2020).

Figure 2

Schematic Overview of the Working Memory Updating Training



Low-dose Short-term Memory Training

The active control group completed a low dose short-term memory program. It was visually and structurally identical to the WMU training from study II except that only four stimuli are sequentially presented. Thereby, participants were not practicing working memory updating and the same difficulty level was maintained throughout the training. Evidence has also demonstrated that four to five stimuli can be held in the focus of attention at one time (Cowan, 2011).

Outcome Measures

Table 1 provides an overview of the different outcome measures used in the three studies.

Cognitive Measures

Study I and II used a selection of cognitive tests to assess training gain and transfer after cognitive training. First, training gains were assessed using the Letter Memory task as the criterion test. This task closely resembles the version used during training but incorporates a slightly different motor response and a time constraint on responses, making it somewhat more demanding than the training task. Both the total number of correct responses as well as the number of correctly reported 4-letter sequences were used as outcome measures from the Letter Memory criterion test.

To measure transfer, a selection of cognitive tests was used in study I and II. Based on the theory of overlapping cognitive domains, the cognitive tests were subdivided into different levels of transferability, i.e. near, intermediate, and far transfer tasks (Melby-Lervåg et al., 2016). Two near-transfer tasks, digit running span and n-back, were used to measure working memory updating and combined into a composite score. Four intermediate transfer tests were used to measure working memory and executive functions and formed two composites respectively. Digit Span and Letter-Number sequencing, both from WAIS-IV (Wechsler, 2008) to assess the ability to maintain and manipulate information in WM, while inhibition and shifting were measured with the Color-Word interference test and the Trail Making Test (TMT), both from D-KEFS (Delis et al., 2001). Far transfer tests consisted of measures of episodic memory (Buschke's Selective Reminding Test (Buschke, 1973), problem solving (Matrix Reasoning (WAIS-IV)) and mental- and psychomotor speed (CWIT part 1 and 2, Coding (WAIS-IV) and TMT part 2 (D-KEFS). Episodic memory and problem solving were assessed as separate tests, while CWIT part 1 and 2, Coding, and TMT 2 formed the mental and psychomotor speed composite.

Self-reported Psychological Health

Self-reported psychological health was assessed with the following self-report questionnaire: the Prospective Retrospective Memory Questionnaire (PRMQ; Crawford et al., 2003) which assesses everyday memory failures; the Hospital Anxiety and Depression Scale (HADS, depression and anxiety seen as separate constructs; Zigmond & Snaith, 1983) that assesses symptoms of depression and anxiety; the Parkinson's Disease Questionnaire (PDQ-39; Jenkinson et al., 1997) that assesses function and wellbeing related to PD; and the Checklist Individual Strength (CIS; Worm-Smeitink et al., 2017) that assesses fatigue.

Brain Imaging

Functional brain response was measured at pre- and post-test in the single-subject part of study I. A 3T GE Discovery MR750 scanner equipped with a 32-channel head coil was used for data acquisition. Imaging parameters were as follows: echo time = 30 ms, repetition time = 2,000 ms, flip angle = 80°, field of view = 25 × 25 cm, matrix size = 96 × 96, slice thickness = 3.4 mm, and 37 slices. The in-scanner assessment included both the Letter Memory test and the n-back task.

Goal-directed Movement

Hand tremor and goal-directed upper-limb movements were assessed at pre- and post-test in the single-subject component of study I. Postural and resting tremor were measured unilaterally and bilaterally while participants were seated with the arm either extended or flexed with elbow support. Goal-directed upper-limb function was evaluated using a task in which participants pressed three buttons sequentially with the left or right index finger (unimanual) or with both index fingers simultaneously (bimanual) (Johansson et al., 2012). Participants wore spherical passive markers on the head, shoulders, elbows, wrists, and index fingers, and movements were recorded with a six-camera optoelectronic system (ProReflex, Qualisys Inc., Gothenburg, Sweden)

Table 1
Overview of the Three Studies

	Study I	Study II	Study III
Design	Pre-post single-group and single-subject design	Double-blinded, randomized controlled trial with an active control group and parallel group design	Qualitative study using individual, semi-structured interviews
Intervention	Feasibility study: 15 sessions of on-site, computerized WMU training, 3 times a week, 45 minutes per session Single-subject study: 30 sessions of home-based, computerized WMU training, 4-5 sessions per week, 45 minutes per session at the start, which was reduced to 20 min following feedback from the participant	30 sessions of home-based, computerized WMU training or low-dose short-term memory (active control group) training, 4-5 sessions per week of 20 minutes, total of 6-8 weeks	30 sessions of home-based, computerized WMU training or low-dose short-term memory training (active control group), 4-5 sessions per week of 20 minutes, total of 6-8 weeks
Participants	Feasibility study (n = 3); single-subject study (n = 1)	86 participants (42 WMU; 44 AC)	18 participants (10 WMU; 8 AC)
Outcome Measures	**Feasibility measures**: acceptability, practicality, self-reported change in cognition, and compliance. **Cognition:** Criterion Test: Letter Memory test; Near-transfer tasks: digit memory running span and n-back; Intermediate transfer	**Cognition:** Criterion Test: Letter Memory test; Near-transfer tasks: digit memory running span task and n-back; Intermediate transfer tests: digit span (WAIS-IV), spatial span (inhouse constructed visuospatial WM task), CWIT inhibition cost (D-KEFS), TMT switching cost (D-KEFS);	Semi-structured, individual interviews

	tests: digit span (WAIS-IV), letter number sequencing, CWIT inhibition cost (D-KEFS), TMT-4 switching cost (D-KEFS); Far transfer tests: Buschke's Selective Reminding test, Matrix Reasoning (WAIS-IV), Coding (WAIS-IV) and TMT-2 (D-KEFS). **Self-reported psychological health:** PRMQ, HADS, PDQ-39, CIS **Functional brain response:** fMRI during task performance **Goal-directed movement and hand tremor:** Movement kinematics during rest and a goal-directed movement test	Far transfer tests: Buschke's Selective Remining test delayed recall, Matrix Reasoning (WAIS-IV), Coding (WAIS-IV), TMT-2 (D-KEFS), CWIT part 1 and 2. Construction of composites to reflect the assessment of cognitive abilities. **Self-reported psychological health:** PRMQ, HADS anxiety, HADS depression, PDQ-39	
Method of data analysis	**Feasibility measures and pre-post behavioral outcome measures**: visual inspection of the data **Functional brain response:** pre-processing and analysis of three contrasts with General Linear Model **Goal-directed movement:** 2 (test: pre/post) × 2 (side: right/left) × 2 (task: bi/unimanual) factorial design	Multi-level models according to Hesser et al. (2015)	Reflexive thematic analysis (Braun & Clark, 2021)
My role as PhD student	Data analysis of the feasibility and behavioral outcomes measures, manuscript writing	Creation of data analysis plan, data analysis, manuscript writing	Study planning and conceptualization, data collection, data analysis, manuscript writing

Data Analysis

In study I, the data on cognitive test performance and self-reported psychological health was examined through visual inspection of the z-score change from pre- to post-test. Pre- to post-test differences in the kinematic data were analyzed with a 2 (test: pre/post) × 2 (side: right/left) × 2 (task: bi/unimanual) factorial design. Concerning the fMRI data, a whole brain analysis was applied with a general linear model for each paradigm (i.e. Letter Memory and n-back) respectively. The contrast (updating vs rest) was used to assess the pre to post changes during the Letter Memory test. Two contrasts (2-back – 1-back) and (3-back – 1-back) were used to assess the pre to post changes during the n-back test.

Study II employed multi-level models to assess the effect of WMU over time in comparison to an AC group in terms of cognitive test performance and self-reported psychological health. Multi-level models were chosen as the data analysis method as it accounts for the correlation between repeated observations and does not exclude participants who have missing data (Hesser, 2015). Furthermore, Bayesian analyses were performed to assess robustness of the results.

In study III, reflexive thematic analysis was applied to analyze the data from semi-structured, individual interviews (Braun & Clarke, 2021).

Open Science Practices

The studies within this thesis are based within the Open Science practices to allow for more transparency in scientific procedures. First, all articles were and will be published with open access, ensuring availability of the results to all people with access to the internet. Secondly, studies II and III are pre-registered at the pre-registration website clinicaltrials.gov (identifier: NCT03680170) and the study protocol was published (Domellöf et al., 2020). Thirdly, the data analysis plan for study II was published on the Open Science Framework website osf.io prior to data analysis. Combined with this, the code from the open-licensed, statistical software R will be published in the same OSF platform.

Beyond the above actions that are related to the scientific field, I have reached out to the Swedish Parkinson's Association where I have met people with PD over coffee and cake (i.e. Swedish fika) on a regular basis. They have taught me so much about what it means to have PD and I have been able to share my research work in a more informal setting with people with PD. Furthermore, findings from the three studies have been presented at various scientific conferences as well as at the yearly gathering of the Swedish Parkinson's Association in Värmland and Umeå, ensuring dissemination to other sectors besides the research community.

Ethical Considerations

The studies that are part of this thesis were conducted in accordance with the Declaration of Helsinki and were approved by the Swedish Ethical Review Authority or the former Umeå Ethical Review Board (Dnr. 09- 049M and Dnr. 2016/110-31).

The studies adhered to the four ethical principles outlined by the Swedish Research Council (2024), namely the requirements of information, consent, confidentiality, and use for research purposes. Prior to the start of the study, all participants received both written and verbal information detailing the study’s purpose and the nature of their participation. Participants were informed that participation was voluntary, that they retained the right to access and control their data, and that they could withdraw from the study at any time without any consequences for their current or future care. They were also given the opportunity to ask questions to the research personnel before providing written informed consent. Moreover, a neurologist with expertise in PD was available throughout the study to oversee and address any medical concerns or adverse events.

Empirical Studies

Study I: The Effects of Working Memory Updating Training in Parkinson's Disease: A Feasibility and Single-Subject Study on Cognition, Movement and Functional Brain Response

Aims

Study I had the following aims: 1) to assess the feasibility of WMU training and examine change in cognitive test performance after completion of the training in individuals with PD; 2) to examine change in cognitive test performance, self-reported psychological health, goal-directed movement, and functional brain response in one individual with PD after completion of the WMU training program.

Method

This two-part study incorporated a feasibility study and a single-subject study. Both parts had an uncontrolled pre- and post-test design. The feasibility study included three individuals with PD who met on-site three times a week to perform computerized WMU training. Outcome measures consisted of the criterion tests and feasibility measures. In the single-subject study, one participant with PD aged 47 was included. Changes in cognitive test performance were captured via a neuropsychological test battery, whilst self-reported questionnaires were used to measure psychological health (Table 1). In addition, goal-directed movement and cerebral activity were measured at pre- and post-test.

Findings

Nine of the thirteen invited participants in the feasibility part declined participation. However, four out of five participants included (including the single-subject participant) completed the WMU training regime. The feasibility outcome measures showed that the WMU training program was deemed as acceptable and engaging by the participants, while cognitive improvements were seen in the criterion test.

The single-subject part of the study displayed gradient improvements in cognitive test performance, with largest changes seen in areas with strongest connections to WMU. Mixed results were observed related to psychological health, potentially due to baseline levels being within the normal range. Furthermore, increased striatal activity was seen at post-test together with smoother motor measures with faster onset times.

Conclusions

Study I demonstrated that WMU training was feasible for people with PD to complete and that changes were seen in several domains with links to WMU in one individual with PD. These findings supported the continued investigation of WMU training in people with PD and informed subsequent adaptations to the training protocol implemented in the second study.

Study II: The Effects of Working Memory Updating Training on Cognition and Psychological Health in People with PD

Aims

This study aimed to assess the immediate and long-term effects of a WMU training program for people with PD in terms of cognitive test performance and psychological health

Method

This study made use of data from the iPARK trial, a double-blind randomized controlled trial with a parallel-group design and active control group. 86 people with PD were randomized to WMU training or a low-dose, short-term memory training (i.e. active control group). The training schedule consisted of 20 minutes of cognitive training, 4-5 times a week, 6-8 weeks long, for a total of 30 sessions. Test performance as well as self-reported motivation and concentration were assessed during training. A battery of cognitive tests and self-report questionnaires were administered at pre-test (T0), post-test (T1), and follow-up (T2, i.e. four months after training), see Table 1. Data was analyzed using multi-level models. Both intention-to-treat, per protocol, and Bayesian analyses were performed and compared to each other.

Findings

Forty-two participants started WMU training of which 39 completed the training and the post-test assessment. Thirty-five participants completed at least 24 training sessions (i.e. 80% of the training sessions). Seven participants withdrew during the WMU training intervention, and three more did not complete T2. Reasons for study discontinuation during the intervention were training-related stress and self-reported pain. Two other participants who did complete T1 also indicated that they experienced the WMU training as stressful. Drop-out rates did not differ significantly between the WMU and AC group, nor were there any significant differences between dropouts and T2-completers on baseline characteristics.

There was a significant time by group interaction for motivation, whereby the WMU group showed decreased motivation over time (p = .003). This decrease was small with an average of 3.3 to 3.0 on a 5-point Likert scale (1=not motivated – 5=very motivated). For concentration, no time by group interaction effect was observed (p = .70), yet the WMU group reported lower concentration in general compared to AC (p = .02).

There was a significant group by time interaction in which the WMU improved more than the AC in trained tasks (ps < .01) and the near-transfer composite (p < .01) from T0 to T1. These improvements were maintained at T2 and a total cognition composite (consisting of all tests measuring untrained cognitive domains) showed larger improvements for the WMU compared to the AC at T2 (p < .03).

Furthermore, there was a significant group by time interaction in which the AC showed a larger decrease in depressive symptoms from T0 to T2 than the WMU (p = .02). Moreover, a main effect of time was observed for the PRMQ score from T0 to T2 (p = .003, d = 0.48), indicating an overall increase in self-reported cognitive difficulties across participants. Detailed results from the intention-to-treat analyses can be seen in Table 2.

Table 2

Immediate and Long-Term WMU Training Effects on the Cognitive Test Performance and Self-reported Psychological Health

	T0 to T1				T0 to T2			
Variables	***Beta***	***SE***	***p***	**Cohen's *d***	***Beta***	***SE***	***p***	**Cohen's *d***
Criterion test								
Letter Memory correct 4-letter sequences	0.94	0.34	.005	1.37	0.32	0.33	.33	0.47
Letter Memory total correct	1.04	0.24	<.001	1.40	0.40	0.24	.10	0.54
Near transfer								
Updating composite	0.47	0.15	.002	1.03	0.14	0.15	.34	0.31
Intermediate transfer								
Working Memory composite	0.09	0.13	.43	0.25	0.18	0.13	.15	0.47
Executive Functions composite	-0.08	0.09	.39	-0.28	-0.01	0.10	.91	-0.03
Far transfer								
Mental and Psychomotor composite	0.14	0.09	.11	0.52	0.07	0.09	.40	0.28
Selective Reminding Test delayed recall	0.02	0.19	.92	0.02	0.32	0.18	.07	0.38
Matrix Reasoning	-0.04	0.19	.84	-0.07	0.19	0.19	.32	0.34
Total cognition composite	0.07	0.06	.28	0.35	0.14	0.06	.03	0.75
Psychological Health								
Subjective Cognitive Complaints (PRMQ)	-0.15	0.16	.34	0.30	0.08	0.16	.63	0.15
HADS depression	0.20	0.14	.16	0.45	0.35	0.15	.02	0.79
HADS anxiety	0.06	0.16	.69	0.13	-0.07	0.16	.65	-0.15
Quality of life (PDQ-39)	-0.04	0.13	.74	-0.11	0.14	0.13	.29	-0.36

Note. Estimates represent the average difference in change over time between the WMU group and the STM training group; Cohen's d is calculated as the difference in mean change over time between the WMU group and the STM training group, divided by the residual standard deviation of the model (Feingold, 2009).

As both groups performed a type of cognitive training, it is of interest to assess the effect sizes per group, as seen in Table 3. A gradient pattern can be seen in the effect sizes of the WMU group, with the largest effects in the criterion tests, followed by near-transfer measures and smaller effects on far-transfer measures. The mental and psychomotor speed composite did follow this pattern, as it exhibited a large effect size. The AC group did not show such a clear gradient change, yet did show moderate effect sizes in criterion, near, and intermediate transfer measures, as well as large effect sizes at follow up for several cognitive measures. Both groups also demonstrated large effect sizes for the total cognition score at T1 and T2.

Table 3

Effect Sizes for the Two Groups Separately

	WMU		AC	
Variables	**T0 to T1**	**T0 to T2**	**T0 to T1**	**T0 to T2**
Criterion test				
Letter Memory correct 4-letter sequences	2.15	1.52	0.79	1.01
Letter Memory total correct	1.78	1.49	0.38	0.93
Near transfer				
Updating composite	1.63	1.32	0.60	1.01
Intermediate transfer				
Working Memory composite	0.77	0.80	0.52	0.34
Executive Functions composite	0.34	0.65	0.62	0.68
Far transfer				
Mental and Psychomotor composite	0.93	1.36	0.41	1.08
Selective Reminding Test delayed recall	-0.01	0.54	-0.03	0.16
Matrix Reasoning	0.29	0.54	0.35	0.20
Total cognition composite	1.15	1.73	0.80	0.98
Psychological Health				
Subjective Cognitive Complaints (PRMQ)	0.05	0.57	0.36	0.41
HADS depression	0.05	0.16	-0.40	-0.63
HADS anxiety	0.03	-0.24	-0.10	-0.08
Quality of life (PDQ-39)	0.13	-0.37	0.24	-0.02

Note. Estimates represent the average difference in change over time per group; Cohen's d is calculated as mean change over time for each group divided by the residual standard deviation of the model (Feingold, 2009).

Conclusions

WMU training produced short-term improvements on cognitive tests that were closely aligned with the trained tasks, and these immediate gains were maintained at follow-up. In addition, the WMU group demonstrated greater improvement in the total cognition score at follow-up, suggesting delayed transfer effects to cognitive domains that were not directly trained. Importantly, the pattern of improvements across cognitive measures appeared to be gradient, which is consistent with theories of cognitive overlap. This may indicate that the intervention enhanced underlying WMU abilities rather than merely increasing efficiency. In general, self-reported psychological health remained stable, yet, at T2, the AC group exhibited a reduction in depressive symptoms compared to the WMU group.

Taken together, these findings suggest that WMU training can yield both immediate benefits in trained tasks and delayed improvements in broader cognitive functioning. Thereby, WMU training may represent a promising non-pharmacological intervention for supporting cognitive functioning in people with PD.

Study III: The Experience of Process-Based Cognitive Training in People with Parkinson's Disease: A Route to Transfer to Everyday life

Aims

This study aimed to explore the experience of process-based cognitive training among individuals with PD, with particular emphasis on how participants engaged with the training and how they applied the training in their everyday lives.

Method

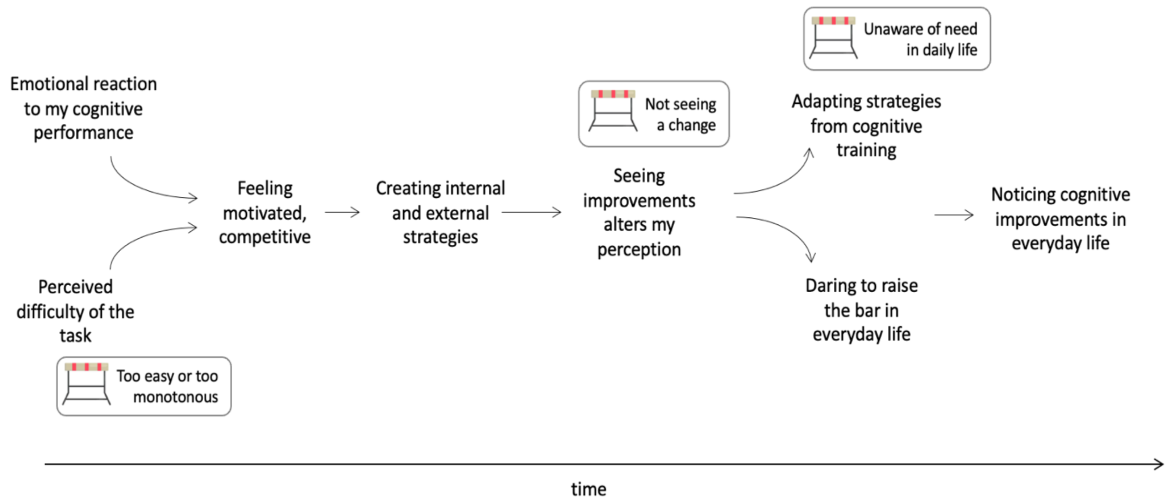
Semi-structured, individual interviews with 18 participants (WMU group = 10 participants; AC group = 8 participants) after having completed 6-8 weeks of cognitive training. Interviews were held digitally or via telephone. Data were analyzed using reflexive thematic analysis (Braun & Clarke, 2021).

Findings

Three overarching themes were conceptualized that captured the participants' active engagement with the training, the meaning of receiving proof of improvements during cognitive training, as well as the participants' integration of cognitive training into everyday life. Results demonstrated that participants who started integrating cognitive training into everyday life were those who experienced the training as more motivating, overcame emotional difficulties during training, and experienced a change in self-confidence as a result of receiving proof of improvements, as depicted in Figure 3. The experiences of participants in the WMU and AC groups were largely comparable.

Figure 3

A Visual Overview of the Time-Related Process Experienced by Participants who Started Transferring Cognitive Training into Everyday Life.



Note. Several hurdles are included in the figure that made transfer to everyday life more difficult.

Conclusions

Cognitive training is experienced as more than the passive performance of challenging cognitive tasks over time. Participants adopted an active and engaged stance, expressing a desire to integrate what they had learned into their everyday lives. Future research should explore how such reflective engagement can be fostered during training and examine whether it is associated with training outcomes

General Discussion

This thesis consists of three studies aiming to understand the effects and the experience of WMU training in people with PD. Study I focused on feasibility and measuring change in cognition, psychological health, goal-directed movement, and functional brain response. Study II examined the effects of WMU on cognition and psychological health in people with PD through an RCT, and study III explored the experience of WMU training in people with PD. Collectively, the three studies contribute to a more comprehensive understanding of WMU training in people with PD by addressing feasibility, cognitive and psychological outcomes, as well as participant experience. Below, I will summarize and reflect on the findings, as well as discuss them in relation to previous literature. Furthermore, I will address strengths and limitations of the thesis. I have chosen to organize this discussion section with the help of the research questions, thereby integrating the three studies more thoroughly.

Feasibility of WMU Training

The first research question of this thesis was if WMU training is feasible for PD patients to complete. Study I demonstrated that three of the four participants completed the on-site WMU training regime and found it acceptable. However, a web-based option was suggested to improve the accessibility of the training and facilitate more frequent training participation. Based on such participant feedback, a web-based version was developed and evaluated in a single-case study. This web-based program was regarded as feasible, although the participant perceived it as too time-consuming. Consequently, the session duration was reduced to 20–25 minutes after 15 sessions, and this revised regime was then implemented in study II.

Study II provided more robust evidence on the feasibility of WMU training, as 42 participants started WMU training of which 39 completed the training and the post-test assessment. Furthermore, most participants completed more than 80% of the training sessions. Findings from study III also demonstrate that participants were easily able to fit WMU training into their everyday life as they reported it to become part of their daily routine and expressed engagement in the cognitive training. Therefore, when looking at evidence from all three studies, it can be concluded that WMU training is feasible for people with PD to complete, which is in line with other feasibility studies on cognitive training for people with PD (Foster et al., 2018; Hoffman et al., 2023; Van De Weijer et al., 2020).

Effects of WMU Training on Cognitive Performance

Concerning the effects of WMU training on cognitive performance in people with PD, results from study 1 suggested that the single participant showed a pattern of gradient improvements with the largest gains observed in criterion and near-transfer tasks, followed by intermediate transfer tasks and limited far-transfer effects. However, these changes should be interpreted with caution, as they may also reflect practice effects or other non-specific factors due to lack of a control group.

Study II, with its stronger methodological design, is better suited to address these questions. Findings showed that WMU training led to improvements in the trained tasks as well as a near-transfer composite, yet limited gains were seen in far transfer tests. Such improvements in trained, and near-transfer tasks as well as absent far-transfer effects are in line with previous research on cognitive training in both healthy and PD populations (Costa et al., 2014; Fellman et al., 2018; Li et al., 2021; Melby-Lervåg et al., 2016; Pappa et al., 2020; Soveri et al., 2017; von Bastian et al., 2024; Waris et al., 2015). Moreover, to clarify which test drove the near-transfer effect in the composite score, a post hoc analysis revealed that the digit memory running span task was the primary contributor, while n-back performance remained stable in both groups. A lack of transfer to near transfer measures that show structural differences from the trained tasks (such as n-back in this case) have been observed after WMU training in older healthy adults and people with PD (Dahlin et al., 2008; Fellman et al., 2018) and may reflect age- and disease-related constraints on transfer.

Examining effect sizes can provide insight into the magnitude and direction of potential effects. Given that study II included a strong control group who also engaged in cognitive training, it is therefore informative to examine effect sizes within each group. In the WMU group, a gradient pattern of improvement was observed, with the largest effect sizes in the criterion composite, followed by more moderate effects sizes for the near and intermediate composites, and small effect sizes on far transfer, except for the mental speed composite. However, mental speed is closely related to working memory and executive functions, and their development and decline tend to co-vary across the lifespan (Diamond, 2013). Thus, the strong effect size for the mental speed composite is noteworthy and may suggest that WMU training influences processing speed. Within the AC groups, such a gradient pattern is not observed, yet considering the large effect sizes seen in several cognitive measures, it can be assumed that these findings are more than test-retest effects and allude to the AC training already leading to cognitive improvements for our population. Nevertheless, as the study does not have a passive control group, these results should be interpreted cautiously

As alluded to in the introduction, the cognitive training literature has long debated whether observed training gains reflect changes in underlying cognitive abilities or the adoption of task-specific strategies (Lindenberger et al., 2017; Lövdén et al., 2010; von Bastian et al., 2022). Some accounts argue that improvements primarily arise from more efficient strategies tailored to the trained tasks, while others suggest that training can induce more general changes in the targeted cognitive processes (Laine et al., 2018; Schmiedek et al., 2010; von Bastian et al., 2022). In the present study, the evidence may point to both possibilities. Findings consistent with a strategy account include the large gains observed in the digit memory running span task, alongside limited effects on n-back performance. The digit memory running span task closely resembles the criterion task, making it more amenable to the adoption of task-specific strategies learned during training. Moreover, study III, which focused on participants' experiences, indicated that participants developed greater awareness of their cognitive processes and reported applying strategies and new knowledge from cognitive training in everyday life.

Findings from this thesis that align with a change at the ability level are the clearer graded pattern of improvements after WMU training compared to the AC. Also results from the single-case study further indicate increased striatal functional brain responses as a function of training, along with smoother goal-directed movements characterized by shorter onset times. Together, these findings suggest that WMU training may influence the dopaminergic system, as has been seen in younger healthy populations (Dahlin et al., 2008; Salminen et al., 2016). In conclusion, these findings tentatively indicate that WMU training may contribute to improvements in underlying updating ability, while also fostering task-specific strategies.

The durability of cognitive training is important, as its practical value partly depends on the extent to which effects persist beyond the training period. With respect to long-term effects, improvements observed at post-training were maintained at the four-month follow-up for both the trained and near-transfer tasks, although the interaction effects were no longer significant. More intriguingly, the total cognition score, comprising tasks not primarily assessing WMU, also improved at follow-up. Such broader cognitive effects at a four month follow-up are relatively uncommon, partly because long-term outcomes of cognitive training in people with PD are less frequently examined (Gavelin et al., 2022). However, similar delayed improvements have been reported by Ophey et al. (2020) following working memory training in people with PD. The mechanism underlying this delayed effect remained unclear and the authors suggested that post-training fatigue or reduced motivation may mask immediate gains. In study II, the WMU group's self-reported motivation during training did show a larger decrease over time in comparison to the AC group whose motivation level remained stable, yet the decrease in motivation in the WMU was small. Other speculations concerning such delayed effects may include the continuing use of learned strategies, increased engagement in cognitively demanding activities, or changes in metacognition, as alluded to in study III.

Effects of WMU Training on Psychological Health

Focusing on psychological health, mixed findings were observed in study I in relation to self-reported psychological health, potentially due to baseline scores being within the normal range. Study II's findings demonstrated no significant time by group interactions in self-reported everyday memory failures, quality of life or anxiety at post-test or follow-up. However, despite neither group showing clinically elevated depressive symptoms at pre-test, participants in the AC group reported fewer depressive symptoms compared to the WMU training group four months after training.

The literature on the effects of cognitive training on psychological health is limited, and several research groups are calling for more work on this topic (Gavelin et al., 2022; Kalbe et al., 2018; van Heugten et al., 2016; Walton et al., 2017). In the PD population, some studies have observed no change in depressive symptoms after cognitive training (Ophey et al., 2020; París et al., 2011; Reuter et al., 2012), while other studies showed reduced depressive symptoms both immediately after cognitive training (Fellman et al., 2018), and even two years after training (van Balkom et al., 2023).

Notably, in study II, it was the AC group that reported reduced depressive symptoms at follow-up. As the AC group trained close to identical tasks, yet excluding the updating ability, their training can be considered less demanding. Combined with the AC group's moderate to large effects on several cognitive measures at T2 and their stable level of motivation during training, this might indicate that the AC training was sufficiently challenging and engaging for the participants. Moreover, study III showed that participants experienced both training types as meaningful and challenging, and reported increased meta-cognitive awareness and self-confidence. It can be speculated that such experiences together with the easier training of the AC might explain the decrease in depressive symptoms at follow-up.

Moreover, in terms of self-reported everyday memory failures, a main effect of time was observed indicating an overall increase in self-reported cognitive difficulties at follow-up. This may potentially be due to the progressive nature of PD, or as a consequence of being confronted with one's cognitive abilities (Ophey et al., 2020). Furthermore, self-reported cognitive difficulties have shown to have a significant, yet small association with cognitive test performance in older people (Burmester et al., 2016), potentially demonstrating that these two outcome measures are indicators of different cognitive phenomena. This may be a factor to keep in mind when interpreting the findings from study II showing overall improvements in cognitive test performance and at the same time displaying increased self-reported memory failures. Additionally, within the PD population, depressive symptoms have shown to be a predictor of subjective cognitive decline in people with PD (Ophey et al., 2022). Such patterns were, however, not seen in study II's results, as an overall increase was observed in everyday memory failures from pre-test to follow-up, whilst only the

AC group reported a larger decrease in depressive symptoms compared to the WMU group from pre-test to follow-up.

Study III also demonstrated that people with PD experienced emotional reactions such as sadness and worry, when becoming aware of their cognitive difficulties during cognitive training, which may be related to psychological health. Such emotional reactions were mostly experienced by the WMU group and thereby might have influenced self-reported depressive symptoms, as the WMU group reported stable depressive symptoms and the AC reported a decrease. Furthermore, when combining the decrease of depressive symptoms in the AC group together with their stable self-reported motivation during training and their moderate to large effect sizes on several cognitive measures at post-test and follow-up, this might indicate that the AC group already benefited from the low-dose short-term memory training sufficiently enough to improve cognitive test performance as well as serve as an encouragement to engage with cognition in one's daily life, forming an uplifting factor in relation to one's psychological health. This is in line with Diamond and Ling (2020), who concluded that effective improvement of executive functions requires interventions that both directly train and challenge executive functions and indirectly support them by reducing stress and sadness while enhancing joy, self-confidence, and social support.

The Experience of Cognitive Training in People with PD

The third research question concerned the experience of process-based cognitive training in people with PD. Study III was conceptualized to answer this research question with a specific focus on engagement during training as well as how participants made use of the training in everyday life. In general, study III demonstrated how participants were actively engaging with the cognitive training, learning more about their cognition, overcoming emotional hurdles, and transferring lessons learnt from training into everyday life. Beyond suggesting different potential moderating variables concerning the effect of cognitive training on both cognitive test performance and psychological health, study III provides evidence that the participants experienced process-based training in a much broader, reflective manner than the cognitive training field has foremost been interested in. In the following sections, I wish to highlight two especially noteworthy findings from study III.

First, the results show the importance of addressing emotional responses during cognitive training. At first, participants reported a worry concerning their cognitive functions and overall participation in cognitive training. Such negative feelings related to cognitive abilities in people with PD have also been reported by Pigott et al. (2024). Adding to this, participants in study III indicated that it took courage to take part in the study, as they were uncertain about and afraid to receive bad news concerning their cognitive abilities. Participants actively navigated such emotional reactions though and persevered in the training. Beishon et al. (2021) highlights the importance of addressing emotional responses during process-based cognitive training for people with MCI or dementia. In that study, three participants with Alzheimer's Disease dropped out due to low confidence and self-efficacy to complete the training. Similar reactions were observed in study II, as three participants reported feeling stressed during cognitive training and two of these participants decided to discontinue the WMU training. Collectively, these findings suggest that recognizing and addressing individuals' emotional responses to cognitive difficulties, while simultaneously fostering sustained engagement, is an essential component of cognitive training interventions. Strategies such as open discussion, normalization of emotional reactions, and the provision of supportive resources may facilitate continued participation, promote completion of training, and enhance the transfer of newly acquired skills and knowledge into daily life.

Second, the participants in study III reported on the importance of observing change during cognitive training. Participants reported that perceiving improvements promoted a more positive attitude toward cognitive training and strengthened their beliefs in the malleability of cognition. Such beliefs have been shown to be positively associated with training transfer (Jaeggi et al., 2014), yet contrasting evidence has also been reported in older adults (Guye et al., 2017). Relatedly, a study examining the role of feedback during the performance of a gamified cognitive task demonstrated that receiving positive, descriptive feedback was associated with greater long-term motivation to continue engaging with the task (Burgers et al., 2015). In the present work, participants reported that observing their own performance improvements during training led to a sense of increased cognitive self-efficacy and self-confidence. This finding is consistent with the review by Gibbor et al. (2021), which synthesized nine qualitative studies on cognitive stimulation therapy for people with dementia and found that participants commonly experienced enhanced self-confidence following cognitive training.

Both the emotional response during training as well as receiving feedback were furthermore highlighted by the participants as essential experiences that led them to transfer cognitive training into their everyday lives. This was done through either using strategies from cognitive training in their everyday life or using their new understanding about their cognitive functions and applying that to everyday life situations.

Theoretical Implications

The present findings have several theoretical implications. Study I offers an in-depth illustration of training-related change at the individual level. The participant not only improved on the trained tasks but also demonstrated graded improvements on tasks assessing related cognitive functions. Importantly, these cognitive improvements were accompanied by increased striatal activity following training. This finding may suggest that repeated cognitive engagement can modulate neural systems implicated in the trained cognitive function and is in line with previous studies (Dahlin et al., 2008; Kühn et al., 2013). Furthermore, the observed improvement in goal-directed movement, combined with the absence of change in tremor, may further suggest that WMU training specifically engaged the fronto-striatal network. This interpretation is consistent with evidence showing that goal-directed movement depends on the integrity of this network (Redgrave et al., 2010) and that levodopa administration is associated with reduced movement onset times (Haslinger et al., 2001; Spay et al., 2019). However, given the single-case design, these findings should be interpreted as proof-of-concept rather than evidence of generalizable neural reorganization.

As discussed earlier, studies II and III expand this perspective at the group level and suggest that the benefits of WMU training may extend beyond task-specific gains, potentially supporting broader cognitive improvements through both enhancing cognitive ability (e.g.

that the WMU showed gradient changes in the cognitive measures at T1 as well as improvements in a broader, untrained cognitive composite at T2) and efficiency (e.g. that both groups reported on creating and using strategies as well as an increased awareness of their cognitive functioning).

Clinical Implications

This thesis contributes to the clinical field through assessing the effects of an intervention focused on cognitive deficits in people with PD, an often-overlooked non-motor symptom for which standard treatment is currently insufficient. Cognitive symptoms have a strong relationship to quality of life and research has been lacking on this topic.

One important fact to highlight in relation to clinical implications is the research context of the three studies. Participants were recruited via the Neurology Clinic at Norrlands University Hospital, having been diagnosed by movement disorder-oriented neurologists, which increased diagnostic accuracy. However, all activities related to the study were performed at Umeå university and were not integrated into the participants care or the hospital department's ongoing clinical activities. This means that caution should be warranted when drawing conclusions from these studies into clinical practice, as future research is needed on the feasibility of implementing WMU training in a clinical context. Moreover, as study II did not include a treatment-as-usual group, it is not possible to determine whether WMU training is superior to the standard care received by people with PD. Furthermore, the participants in these studies indicated high motivation, had a short disease duration, high educational attainment, and low levels of anxiety and depression. Such aspects must be considered when reflecting on the generalizability of the findings.

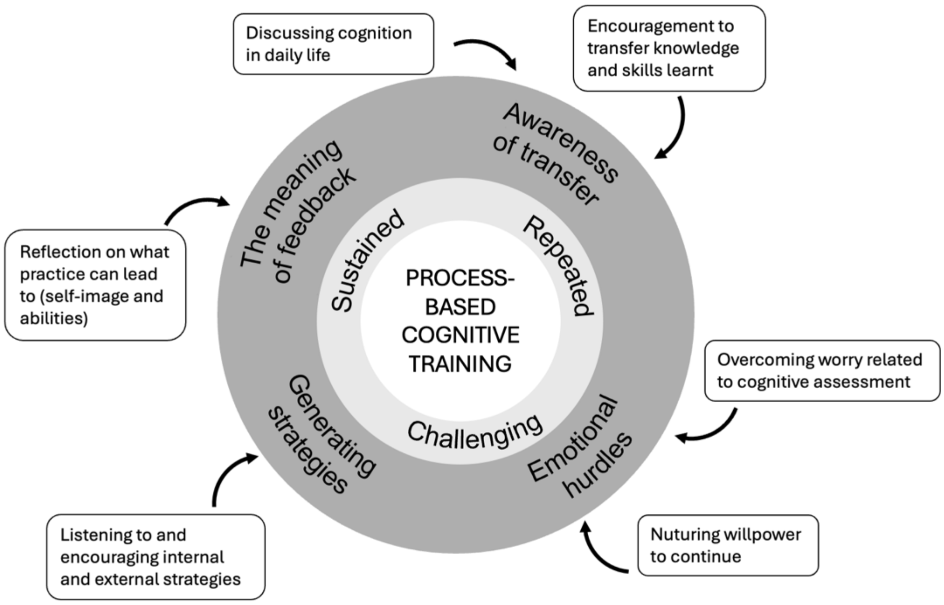
Nevertheless, the results do point out several factors that can be of interest for future clinically based studies to reflect on and hopefully be inspired by. First, the WMU group in study II demonstrated both immediate improvements in the trained tasks and long-term benefits in broader cognitive functions. These findings provide encouraging evidence that WMU training may represent a promising non-pharmacological intervention with the potential to improve cognitive abilities in individuals with PD.

Second, the level of difficulty during cognitive training comes up several times in the studies. In study II, both training groups showed performance improvements across multiple cognitive tests with gains often exceeding typical test–retest effects. In study III, participants emphasized that an appropriate level of challenge was central for experiencing motivation or competition with oneself, particularly within the WMU group, but this association was also evident among AC participants. Taken together, these findings indicate that the AC intervention may already have provided a sufficient challenge to elicit cognitive improvements, implying that the specific training paradigm may be less critical than ensuring an adequately demanding task. Clinically, these results suggest that cognitive training should be tailored to achieve an optimal level of difficulty that both challenges and motivates the individual.

The findings from study III further indicate that participants are actively engaging with and reflecting on cognitive training. Although additional research is needed to clarify the relationship between such training experiences and changes in cognitive test performance, participants described a process through which knowledge and skills learnt during training were transferred to everyday life. This highlights the potential value of supporting such reflection and facilitating discussions that help individuals recognize and apply these strategies in daily life. Some concrete suggestions of topics to discuss during cognitive training that may encourage motivation during training as well as transfer to everyday life are depicted in Figure 4.

Figure 4

Components to Process-based Cognitive Training Together with Concrete Suggestions of Discussion Topics to Enhance Motivation and Transfer to Everyday Life



Lastly, although neither training group exhibited clinically elevated levels of depression or anxiety, findings concerning psychological health may be of clinical interest. For instance, study II indicated that participants in the AC group reported reduced depressive symptoms at follow-up. Study III further revealed that participants experienced training-related increases in self-confidence, a greater willingness to take on everyday challenges, and a sense of achievement, which are constructs or experiences commonly associated with psychological health. Overall, these findings suggest that cognitive training may influence psychological health and shows the importance of addressing psychological responses to training with participants before, during, and after the intervention to ensure adequate support.

Strengths and Limitations

There are several strengths and limitations to this thesis. I will discuss these different considerations study-wise below.

Regarding study I, although its multimodal perspective on changes following WMU training is a strength, the overall design can still be considered suboptimal. A more rigorous approach would include repeated measurements before, during, and after the intervention (Kazdin, 2021; Tate & Perdices, 2020). Such a design would provide a more reliable and stable baseline, enable visual inspection of individual trajectories of change, and offer deeper insight into when and how training effects emerge. Together, these design refinements would substantially improve the interpretability, reliability, and scientific rigor of findings derived from study I.

Moreover, the participant in this single-subject study has early-onset Parkinson's disease (EOPD), defined as the onset of symptoms between age 21 - 50 (Mehanna et al., 2022). Evidence suggests that EOPD follows a different clinical course than late-onset Parkinson's disease (LOPD), typically showing slower disease progression and potentially requiring a more individualized management approach (Bovenzi et al., 2023; Ferguson et al., 2015). With regard to cognitive symptoms, Seubert-Ravelo et al. (2016) reported that individuals with EOPD exhibit cognitive deficits or mild cognitive impairment (MCI) at rates comparable to those with LOPD. However, people with EOPD tend to perform better on cognitive screening measures than those with LOPD of similar disease duration and also show slower cognitive decline over time (Santos-Garcia et al., 2023; Tang et al., 2016). These distinctions between EOPD and LOPD may therefore affect the generalizability of the present findings.

Nevertheless, the strength of study I lies in its solid theoretical foundation and the multi-domain scope of its outcome measures. The study was motivated by evidence that WMU training is associated with increased dopamine availability and enhanced striatal activity in healthy individuals. By assessing cognition, psychological health, goal-directed movement, and cerebral activity in one individual with PD, we were able to characterize patterns of change across multiple domains, which has been encouraged in this research field.

A key strength of study II is the inclusion of an active control group that mirrors the intervention in every respect yet does not involve WMU. Many previous intervention studies have relied on passive controls or have used control interventions that differ substantially from the training program, which can introduce expectation bias (Dougherty et al., 2016; Redick, 2019). To reduce this bias and maintain blinding, both arms were presented as equivalent interventions. Participants and the assessor also reported on the intervention they believed they were allocated to after training, allowing for the evaluation of whether unblinding influences the outcomes. These analyses did show that blinding was partial, especially in relation to blinding of the assessor. Moreover, unblinding of the assessor showed an effect on the immediate outcomes of the working memory composite and the total cognition composite within the WMU group, whereby unblinding led to smaller improvements of these outcome measures. This may indicate that unblinding did not lead to the overestimation of effects yet instead minimized them immediately after training.

Another methodological strength of study II is the use of composites to obtain more reliable estimates of cognitive performance across domains. Combining multiple tests stabilizes variance, reduces task impurity, i.e. that most cognitive tasks draw on multiple underlying processes, and improves test–retest reliability (Noack et al., 2014; Schmiedek et al., 2014; Smid et al., 2020; Snyder et al., 2015). Ideally, each cognitive construct should be measured with at least three individual tests and analyzed using a latent-variable approach. A second-best approach is the use of composites for each cognitive domain. Nevertheless, some domains (e.g., episodic memory and problem solving) were still represented by only a single task. It should also be noted that composites not only have advantages, as they can also mask or dilute effects specific to individual tasks (Schneider & Goldberg, 2019). Therefore, we visually inspected all individual outcomes over time and examined which specific test was driving change seen in the composite.

In relation to internal and ecological validity, study II includes both cognitive test performance and self-reported everyday memory failures, allowing for a broader view on cognition and increasing its ecological validity. Cognitive test performance and self-reported cognitive difficulties can be seen as complementary measures of cognition, reflecting different cognitive phenomena (Snyder et al., 2021; Toplak et al., 2013), thus combining these measures is an added strength to the study. Moreover, a recent literature review reported that several of the cognitive tests used in this thesis have good to excellent reliability and validity, as well as being sensitive to change (Biundo et al., 2025).

On another note, several complementary statistical methodologies were applied to strengthen the robustness and interpretability of the findings in study II. For instance, Bayesian analyses were used alongside traditional frequentist methods to enhance the robustness of the conclusions and per-protocol analyses were conducted to examine whether results were consistent when restricting the sample to participants who fully adhered to the intervention protocol. Employing multiple approaches in data analysis reflects the principles of self-correcting science (Chambers, 2017; Romero & Sprenger, 2020), in which conclusions are tested from different methodological angles to reduce the likelihood that findings are driven by statistical artifacts or data analysis decisions.

Concerning study III, its strength is foremost its use of a scientific methodology, i.e. qualitative analysis, that is scarcely employed in cognitive training research. However, one factor that may have influenced the findings of study III is the research context of the study. This might have shaped participants' expectations, encouraging them to focus on the more objective outcome measures of cognitive performance and psychological health rather than their personal experience of the training. Also, as the interviews were held 0 – 13 months after completion of cognitive training, this may affect the participants' ability to remember their experience of cognitive training, though few participants explicitly reported this issue.

Directions for Future Research

Several potential avenues for future research emerge from the findings of this thesis. First, as the conceptualization of the iPARK trial comes from the observation that WMU training led to increases in dopaminergic availability in healthy populations, future studies are encouraged to assess if such neurobiological changes occur after WMU training in people with PD. The findings from study I are in support of the hypothesis that WMU training engages the dopaminergic system (through showing increased striatal activity) and displayed change in several domains reliant on dopaminergic availability. Larger, well-designed trials assessing the neurobiological underpinnings of WMU training are thereby a necessary next step in increasing our understanding of this topic.

Furthermore, future studies are encouraged to focus on the association between the experience of cognitive training and change in cognitive test performance. Through using a mixed-method design, a more thorough integration of quantitative and qualitative results can be achieved. One option could be through Qualitative Comparative (QCA), which is a set-theoretical approach that identifies the necessary and sufficient conditions for an outcome (Ragin & Rihoux, 2004). For example, QCA could examine which experiences from study III (i.e. conditions) were necessary or sufficient for improvements to occur in the cognitive measures.

Moreover, future interventions consisting of both process-based cognitive training and psychoeducational aspects related to the experiences from study III are of interest. Along these lines, Myklebost et al. (2024) has shown that a process-based training program with psycho-educational elements led to improvements in both depressive symptoms and self-reported cognitive difficulties in people with depression. Moreover, Aidman (2020) also provides a different perspective on cognitive training with the Cognitive Fitness Framework theory. Aidman (2020) suggests that the field needs to combine the different ingredients that together focus on training cognitive abilities, amongst others process-based cognitive training, psychoeducation, and strategy-based methods. Furthermore, there are other examples of studies aiming to fuse different cognitive training perspectives (Capodieci et al., 2019; Jaeggi et al., 2023; Verhülsdonk et al., 2023). It is of interest to examine such interventions in people with PD whereby the training focuses on increasing metacognitive knowledge and skills, as well as underlying cognitive functions through process-based cognitive training.

Lastly, in the heterogeneous population of people with PD, individual differences in the effect of process-based cognitive training must be further examined. For example, Borella et al. (2017) reported that age, education, and baseline WM performance affects training gain and transfer after cognitive training in a population of healthy older people. Their findings displayed both magnification (i.e. those with higher baseline performance improved more) and a compensation effect (i.e. those with lower baseline performance improved more) (Lovden et al., 2012). However, one meta-analysis on the topic concluded that the compensation effect has received most support, as opposed to the magnification effect (Traut et al., 2021). The examination of individual differences in the iPARK trial may provide a better understanding of who improves most on process-based training.

Conclusion

In sum, the papers included in this thesis provide evidence that WMU training for people with PD is feasible, and that it leads to measurable cognitive benefits. Specifically, the findings demonstrate immediate improvements in cognitive test performance on tasks closely resembling the training tasks, alongside delayed improvements that extend to broader, untrained cognitive domains. Beyond these performance-based outcomes, the results also offer valuable insight into how people with PD experience cognitive training over time. Participants described emotional, motivational, and metacognitive changes that emerged and evolved throughout the training period, suggesting that cognitive training influences not only cognitive processes but also participants' attitudes toward their own cognitive functioning. Taken together, the delayed, broader cognitive improvements measured after WMU training may therefore be dependent on both engagement in challenging WMU training tasks enabling increased cognitive ability as well as metacognitive changes acquired during cognitive training that support cognitive efficiency.

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The Effects of Working Memory Updating Training in People with Parkinson's Disease

Cognitive deficits are common in people with Parkinson's disease (PD), reduce quality of life, and are poorly addressed by medication. This thesis investigated whether working memory updating (WMU) training can represent a promising cognitive intervention for people with PD. Across three studies, including a feasibility study, a randomized controlled trial, and a qualitative study, the thesis examined the feasibility, effects, and experience of WMU training. The results showed that WMU training is feasible and leads to measurable cognitive improvements. Immediate gains were observed on tasks that share cognitive processes with the training, and delayed improvements in broader cognitive domains. Participants also described emotional, motivational, and metacognitive changes during training that supported transfer to everyday life. Together, these findings may suggest that WMU training enhances both cognitive ability and cognitive efficiency in people with PD.

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