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MOTOR AND COGNITIVE ABILITIES IN PARKINSON'S DISEASE WITH A BRAIN ACTIVITY PERSPECTIVE: PERFORMANCE AT BASELINE AND THE EFFECTS OF A BALANCE TRAINING PROGRAM

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Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-472-6

MOTOR AND COGNITIVE ABILITIES IN PARKINSON'S DISEASE WITH A BRAIN ACTIVITY PERSPECTIVE: PERFORMANCE AT BASELINE AND THE EFFECTS OF A BALANCE TRAINING PROGRAM

THESIS FOR DOCTORAL DEGREE (PhD)

By

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The thesis will be defended in public at, H2, Alfred Nobels allé 23, Huddinge, 11th of February, 13.00

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POPULAR SCIENCE SUMMARY OF THE THESIS

Around one in a hundred persons over 60 years of age has Parkinson's disease. Parkinson's disease is a neurodegenerative disease, meaning that brain cells gradually stop working. People with Parkinson's disease experience a wide range of symptoms affecting most aspects of daily life. The symptoms include movement difficulties such as slowness, stiffness, problems with walking and keeping one's balance, as well as problems with mental processes such as organising and focusing.

Medications reduce many symptoms of Parkinson's disease, but problems with balance, walking and mental processes often persist. These remaining symptoms result in problems with many activities in daily life and an increased risk of injurious falls. Previous research has found that physical exercise can complement medication for people with Parkinson's disease and improve symptoms such as balance and walking problems. Unfortunately, we still do not know which type of physical exercise is most effective in improving symptoms of Parkinson's disease.

In one study of the present thesis, we investigated if it is more difficult for people with Parkinson's disease to learn a new motor task than for healthy individuals. We also investigated whether there were differences in brain activity between the two groups while learning the motor task. The results showed that it was somewhat more difficult for the participants with Parkinson's disease to learn the motor task than for the healthy participants. The results could indicate that people with Parkinson's disease need more time to practice and repeat when learning and doing motor tasks/physical activities. We did not find any group differences in brain activity.

In another study, we investigated whether a balance training program developed by our research group could improve balance, walking and mental processes in people with Parkinson's disease. We have previously seen positive effects for persons who train this balance program in comparison to persons who do not participate in a training program. We now compared the balance training program to a speech-and communication training program so that half of the participants participated in the balance training program and the other half in the speech- and communication training program. By comparing the balance training program to another training program, we could see whether there were so-called *specific* positive effects of our balance training program i.e., positive effects that were due to the exercises in the program, and not positive effects due to social interaction, attention, expectations and the like. We compared changes in balance, walking speed, mental processes and also brain activity between the two groups. We could unfortunately not find any positive specific effects of our balance training program for people with Parkinson's disease. We encourage more large, high-quality studies of physical exercise for people with Parkinson's disease so that we can find effective ways to improve the symptoms of this serious disease.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Ungefär en hundra av alla över 60 år har Parkinsons sjukdom. Parkinsons sjukdom är neurodegenerativ sjukdom vilket betyder att hjärnceller gradvis slutar att fungera. Personer med Parkinsons sjukdom har många olika typer av symptom som påverkar stora delar av det dagliga livet. Symptomen består av rörelsebegränsningar som långsamhet, stelhet, balans-och gångproblem och även problem med mentala processer som förmågan att organisera och fokusera.

Medicinering minskar många Parkinsonrelaterade symptom men problem med balans, gång och mentala processer kvarstår ofta. De här kvarvarande symptomen leder till problem med många vardagssysslor och även en ökad risk för att ramla på ett skadligt sätt. Tidigare forskning har sett att fysisk träning kan fungera som komplement till medicin för personer med Parkinsons sjukdom och förbättra till exempel balans- och gångförmåga. Tyvärr så vet vi dock fortfarande inte vilken typ av fysisk träning som är mest effektiv för att förbättra Parkinsonrelaterade symptom.

I en av studierna som ingår i denna avhandling, så undersökte vi om det är svårare för personer med Parkinsons sjukdom att lära sig en ny motorisk uppgift än för friska personer. Vi undersökte också om hjärnaktiviteten skiljde sig åt mellan grupperna under inlärning av den motoriska uppgiften. Resultaten tyder på att det var något svårare för personerna med Parkinsons sjukdom än för de friska personerna, att lära sig den motoriska uppgiften. Resultaten kan tyda på att personer med Parkinsons sjukdom behöver mer tid att öva och repetera när de lär sig och utför motoriska uppgifter/fysiska aktiviter. Vi hittade inga gruppskillnader i hjärnaktivitet.

I en annan studie, så undersökte vi om ett balansträningsprogram utvecklat av vår forskargrupp, kunde förbättra balans, gång och mentala processer för personer med Parkinsons sjukdom. Vi har tidigare sett positiva effekter för personer som tränar detta balansprogram i jämförelse med personer som inte deltar i något träningsprogram. Vi jämförde nu balansträningsprogrammet med ett röst- och kommunikationsträningsprogram på så sätt att hälften av deltagarna deltog i balansträningsprogrammet och hälften i röst- och kommunikationsträningsprogrammet. Genom att jämföra balansträningsprogrammet med ett annat träningsprogram, så kunde vi se om det fanns några så kallade *specifika* positiva effekter av vårt balansträningsprogram. Med andra ord om de positiva effekterna tillkom på grund av övningarna i programmet och inte på grund av social interaktion, uppmärksamhet, förväntningar eller liknande. Vi jämförde förändringar i balans, gånghastighet, mentala processer och även hjärnaktivitet mellan de två grupperna. Vi kunde tyvärr inte finna något stöd för positiva effekter av vårt balansträningsprogram för personer med Parkinsons sjukdom. Vi anser att fler stora, högkvalitativa studier av fysisk träning för personer med Parkinsons sjukdom bör göras, så att vi kan hitta effektiva sätt att minska symptomen av denna allvarliga sjukdom.

ABSTRACT

Background: Around one per cent of the population over 60 years of age have Parkinson's disease (PD). PD is a progressive and complicated disease presenting a wide range of symptoms. More knowledge of the common impairments in balance, gait, cognition, and motor learning is needed. There is also a need for more studies of physical exercise as a complement to pharmacological treatment for people with PD. Our research group has previously observed positive effects of a highly challenging balance training program (HiBalance) for people with PD in comparison to a passive control group. It is of considerable interest to further investigate the effects of the HiBalance program using an enhanced design quality such as an active control group, blinded assessors as well as by the inclusion of measures of brain activity and neuroprotective factors (BDNF).

Aims: The first aim of this thesis was to develop feasible methods of investigating motor and cognitive abilities in people with PD as well as the effects of the HiBalance program. The second aim was to investigate motor and cognitive abilities as well as the effects of the HiBalance program for people with PD. This also included investigating the neural correlates of motor and cognitive baseline performances as well as the effects of the HiBalance program.

Methods: *In Paper I*, feasibility aspects relating to the recruitment process, measurement methods, and the participants' experience of the assessments and the two interventions to be used in Paper IV were investigated. *In Paper II*, feasibility aspects of two computer-based tasks created to measure implicit motor sequence learning and dual-task ability were investigated. These tasks were to be used in Paper III and IV for task-induced functional magnetic resonance imaging data. Feasibility aspects investigated included task fatigue, difficulty level and possible ceiling effects. *In Paper III*, people with PD and healthy individuals performed the implicit motor sequence learning task during the acquisition of functional magnetic resonance imaging data. *In Paper IV*, we investigated a wide range of outcomes of the HiBalance program for people with mild to moderate PD. Our primary outcome was balance and secondary outcomes included gait speed, executive functions, and measures of brain activity during implicit motor sequence learning as well as measures of the brain-derived neurotrophic factor. We used a double-blinded randomised controlled design with an active control group.

Results: *In Paper I*, we found the feasibility of the randomised controlled design for investigating the HiBalance program to be overall acceptable but with some important modifications needed. *In Paper II*, we found the feasibility of the two computer-based tasks to be overall acceptable. *In Paper III,* we found support for the hypothesis that implicit motor sequence learning is impaired in people with PD. Exploratory analyses suggested that this impairment may be due to a lower learning rate. We found no statistically significant group changes in the task-induced brain activity. The results of *Paper IV* did not support the

hypothesis of beneficial effects of the HiBalance program in comparison to our control group, for people with mild to moderate PD.

Discussion: The two feasibility studies guided us in design aspects that needed improvement before use in Paper III and Paper IV. We hope that our feasibility studies can also help other researchers in their study designs and thereby decrease unnecessary efforts for study participants and increase the value of research investments. As for paper III, impaired motor sequence learning in people with PD is an interesting finding as motor learning ability is of crucial importance for motor performance. If implicit motor sequence learning has a lower learning rate in people with PD than healthy individuals, this could mean that people with PD need more time to practice and repeat when learning and doing motor tasks and physical exercise. As for paper IV, the lack of support for the HiBalance program in its investigated form is discouraging. This is however an important finding that we hope will spark future rigorous projects aiming to find interventions of physical exercise with robust, replicable positive effects for people with PD.

LIST OF SCIENTIFIC PAPERS

I. Johansson, H., Freidle, M., Ekman, U., Schalling, E., Leavy, B., Svenningsson, P., Hagstromer, M., & Franzen, E. Feasibility Aspects of Exploring Exercise-Induced Neuroplasticity in Parkinson's Disease: A Pilot Randomized Controlled Trial, *Parkinson's Disease*, *2020*, 2410863.

II. Freidle, M., Johansson, H., Lebedev, A. V., Ekman, U., Lövdén, M., & Franzen, E. Measuring implicit sequence learning and dual task ability in mild to moderate Parkinson's disease: A feasibility study. *PloS One*, 2021: *16*(5), e0251849.

III. Freidle, M., Thompson, W. H., Albrecht, F., & Franzén, E. Implicit motor sequence learning in people with mild to moderate Parkinson's disease: behaviour and related brain function. *Manuscript.*

IV. Freidle, M.[§], Johansson, H.[§], Ekman, U., Lebedev, A. V., Schalling, E., Thompson, W. H., Svenningsson, P., Lövdén, M, Abney, A., Albrecht, F., Steurer, H., Leavy B., Holmin, S., Hagströmer, M., Franzén, E. Behavioural and neuroplastic effects of a double-blind randomised controlled balance exercise trial in people with Parkinson's disease. *npj Parkinson's disease. In press.*

[§] Shared first authorship

CONTENTS

LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
BDNF	Brain-derived neurotrophic factor
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
EXPANd	EXercise in PArkinson's disease and Neuroplasticity
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
Mini-BESTest	Mini-Balance Evaluation Systems Test
MRI	Magnetic resonance imaging
OSF	Open science framework
PD	Parkinson's disease
PET	Positron emission tomography
RCT	Randomised controlled trial
SRTT	Serial reaction time task

1 INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder, mainly characterised by a lowered production of dopamine. The disease manifests itself through a wide range of symptoms where motor and cognitive abilities are two main domains. Prominent motor symptoms include tremor, muscle stiffness (rigidity), lack of or smallness/slowness in movement (bradykinesia), balance and gait problems[1] as well as impairments in motor learning[2]. As for cognition, executive functions such as planning and goal-directed behaviour are typically impaired, but impairments in other cognitive domains are also common[3]. Approximately 80% of people with PD will develop dementia within 20 years of diagnosis[4]. Both motor and cognitive symptoms increase with the progression of the disease. The standard medical treatment for people with PD is levodopa which increases brain dopamine levels[1]. Levodopa effectively ameliorates several motor symptoms but have less or possibly even a worsening effect on balance control, certain gait parameters, some cognitive functions and plausibly motor learning[5–7]. Levodopa becomes less effective as the disease progresses[1]. As a complement to medication, physical exercise has frequently been reported to ameliorate symptoms of PD[8–11] but robust conclusions on which are the most beneficial interventions, are yet to be made. Our research group has previously developed a highly challenging balance training program (HiBalance) with promising results in academic and hospital settings[12,13].

The four papers presented in this thesis build on the EXPANd (EXercise in PArkinson's disease and Neuroplasticity) project and investigated motor and cognitive abilities in people with PD with a brain activity perspective, in contrast to healthy individuals and the effects of the HiBalance program in comparison to an active control group.

2 LITERATURE REVIEW

2.1 EPIDEMIOLOGY

PD is the fastest growing neurological disorder and above 6 million people worldwide live with PD[14]. The most important risk factor for PD is age, with incidence and prevalence increasing steadily from middle age and peaking around 80 years of age[15,16]. The prevalence of PD has been estimated to be around one per cent in people over 60 years of age[17]. Gender is another risk factor with estimated ratios between men and women of 1.16/1 and 1.5/1[1,18].

2.2 DIAGNOSING PARKINSON'S DISEASE

It is difficult to correctly diagnose a person with PD, especially at the early stages in the disease progression. For this reason, several guidelines and criteria have been introduced[19]. A common way to diagnose PD is to use the UK Parkinson´s Disease Society Brain Bank clinical diagnostic criteria[20]. The process is done in three steps. First, if the patient presents with bradykinesia and one or several of the following symptoms: rest tremor, rigidity and postural instability, the patient is given the diagnosis of Parkinsonian syndrome. Second, several exclusion criteria for a diagnosis of PD are controlled for e.g., other neurological features or repeated head injury. Third, for a diagnosis of PD, the patient needs to present at least three supportive criteria e.g., excellent response to levodopa, a progressive course or unilateral onset. The Movement Disorder Society (MDS) has proposed revised criteria for a PD diagnosis where postural instability is not included in the first evaluation step. They suggested postural instability be removed as impaired balance at an early stage may indicate a different diagnosis[21]. Single-photon emission computed tomography (SPECT) or positron emission tomography (PET), can sometimes be used as a complementary tool for diagnosing PD by assessing reduction of the dopamine-producing neurons in the substantia nigra pars compacta[1].

2.3 OVERVIEW AND PROGRESSION OF SYMPTOMS

PD is a complex disorder in that it is both progressive and presents with a wide variety of symptoms. Many non-motor symptoms are present years before the onset of the classical motor symptoms and diagnosis. These include sleep disorders (disturbance in the rapid-eye-movement sleep stage), constipation, depressive symptoms, excessive tiredness, olfactory dysfunction. With time, motor symptoms develop and include bradykinesia, muscular rigidity, rest tremor, balance and gait impairments and impairments in motor learning[1,2]. Impairments in balance and gait, including falls, can be present at all stages of PD, including in mild to moderate PD[22,23]. Apathy and decreased motivation are highly prevalent with, but also without a concurrent diagnosis of depression[24,25]. Cognitive impairments are often present early on where 15-20% show mild cognitive impairment (MCI) at time of diagnosis[26].

Ten years after diagnosis, approximately 50% of people with PD present with dementia and 20 years after diagnosis, the prevalence of dementia has risen to 80%[4]. Speech impairments are also with prevalence estimates as high as 89%. Speech impairments result from both motor and cognitive impairments and can be present already at the early stages[27].

With time, the long-term symptomatic treatment can itself give rise to complications. These include fluctuations in the degree of the motor as well non-motor symptoms such that there is a notable difference in good and reduced symptom control. Other possible complications of long-term medication are involuntary movements (dyskinesia) and psychotic symptoms such as hallucinations[1].

2.4 MEDICATION AND DEEP BRAIN STIMULATION

Dopaminergic treatment is the default medication in PD and is successful in ameliorating many motor symptoms, especially the first period after diagnosis. Dopaminergic treatment consists of medications that either enhance dopamine levels or stimulate dopamine receptors. Levodopa is the most common medication for enhancing dopamine levels (other medications are monoamine oxidase type B inhibitors, Catechol-O-methyltransferase and amantadine) and so-called dopamine agonists bind to and stimulate dopamine receptors[1].

Bradykinesia and rigidity respond well to dopaminergic treatment but unfortunately, impairments in balance, gait and some types of cognitive problems often persist[1,5]. Dopaminergic treatment also comes with other limitations and side effects. These include that the effect tends to diminish with time, fluctuations in function and side-effects such as dyskinesia and hallucinations as a consequence of long-term use[1]. As for cognitive functions, there are indications that some types of cognition improve with dopaminergic treatment, some are unaffected, and some are possibly even worsened by dopaminergic treatment[7,28]. That dopaminergic treatment can worsen some cognitive functions is often explained by the so-called dopamine overdose hypothesis. This theory postulates that since not all dopamine-dependent brain areas are equally damaged in PD, especially in the earlier stages, some areas might suffer from an impairing overdose of dopamine during dopaminergic treatment[7].

Dopaminergic medication can be complemented with medications targeting serotonin, norepinephrine and acetylcholine levels. These medications are mostly used to ameliorate non-motor symptoms[29].

With time, dopaminergic treatment might result in motor symptom fluctuations and dyskinesia and an alternative treatment is deep brain stimulation of the subthalamic nuclei, globus pallidus (both nuclei of the basal ganglia) or the thalamus[1]. Individuals with deep brain stimulators were however excluded from the EXPANd project since it would have restricted the magnetic resonance imaging (MRI) assessments for safety reasons.

2.5 NEURONAL DYSFUNCTION AND DEGENERATION IN PD

The neurodegeneration and death of the dopamine-producing neurons of the substantia pars compacta is a core characteristic of PD and give rise to many of the typical motor deficits in PD. PD is however also characterised by widespread neuronal aggregation of the protein α-synuclein[30]. Here follows an overview of the impact of both these processes beginning with the impact of α-synuclein aggregation.

2.5.1 The role of α-synuclein

α-synuclein is present in the synaptic terminals of the healthy brain where it controls the release of neurotransmitters. In some circumstances, α-synuclein can form insoluble filamentous aggregates and disturb neuronal function. These α-synuclein aggregates form the basis of Lewy bodies and Lewy neurites which are often found in the brain of people with PD. The aggregates contribute to both synaptic and axonal degeneration and ultimately neuronal death[30].

The aggregation of α-synuclein is gradual and most probably begin before the onset of the PD typical motor symptoms and when a clinical diagnosis can be made. The so-called Braak hypothesis suggests that the aggregation of α-synuclein does not begin in the substantia nigra pars compacta, causing impaired dopamine production, but rather in the peripheral nervous system from where it spread to the brain stem and olfactory areas of the cortex before reaching the substantia nigra where it causes damage and death of dopamine-producing neurons. At later stages, the α-synuclein aggregation may spread widely to several parts of the cortex, causing a wide range of symptoms including dementia[30,31]. As the aggregations of α-synuclein are not confined to the dopamine-producing cells in the substantia nigra but also other cells, other neurotransmitters and their projection systems such as the noradrenalin, serotonin and acetylcholine, are also affected[32]. The Braak hypothesis has been intensely discussed. It has gained several types of empirical support, but a major limitation of the Braak hypothesis seems to be that it does not correctly describe the disease progression for all individuals with PD, but only individuals with an early onset and a long duration[33,34]. To conclude, that α-synuclein aggregations have some impact on PD, is generally agreed on, but the specifics are yet to be understood[1,30].

2.5.2 Dopamine depletion and affected dopamine-dependent circuits

In PD, the dopamine-producing neurons in the substantia nigra pars compacta degenerate and die, resulting in lowered brain dopamine levels The substantia nigra pars compacta is part of the basal ganglia, a collection of subcortical nuclei. Dopaminergic fibres from the substantia nigra pars compacta project into the putamen and the caudate, other nuclei of the basal ganglia. The putamen and the caudate together with the nucleus accumbens are often called the striatum. Several distinct but parallel circuits involving the basal ganglia are recognised[35].

All circuits receive input from the multiple parts of the cortex, send signals through the basal ganglia and relay in the thalamus before sending signals back to the cortex including the

frontal lobe. The close connections of the basal ganglia with the frontal cortex, are often described as the fronto-striatal circuits. These circuits are important for motor, cognitive, motivation and learning and reward functions. The death of dopaminergic neurons projecting to the striatum in people with PD, result in impaired functionality of the fronto-striatal circuits with a wide range of symptoms[35].

2.6 AN OVERLAP OF MOTOR, COGNITIVE AND MOTIVATIONAL FUNCTIONS

It is important to clarify that for pedagogical and other reasons, it is sometimes convenient to talk about motor functions and non-motor functions (e.g., cognitive functions and motivation), separately. There are however constant interactions between these functions where for example different types of motor learning demand different levels of cognitive efforts or the fact that daily life often demands that we perform motor and cognitive tasks in parallel e.g., walking and talking. Motivation, commonly decreased in people with PD, also have important overlaps with motor and cognitive functions[6,36] and the same is true for depression[37,38]. As described in the previous section, the dopamine depletion characteristic of PD affects several brain circuits spanning motor and cognitive functions and motivation[35]. Additionally, other neurotransmitters than dopamine are also affected in people with PD and for some functions, it is difficult to be certain on whether the impairment is caused primarily due to dopamine loss, due to connections with areas/circuits damaged due to dopamine loss or because of changes part of PD pathology but not primarily dopamine[1].

I will now continue by explaining the motor and cognitive difficulties characteristic to PD that this thesis focuses on, separately, but also in relation to each other and related functions such as motivation.

2.7 MOTOR LEARNING

There is little scientific agreement on the exact definition of motor learning but a common description would involve the acquisition and refinement of new movements or sequence of movements through repetition[39]. A well-learned motor task becomes what is often called automatised e.g., performed without a high cognitive load. To better understand motor learning in PD is of considerable interest as people with PD show deficits in learning and maintaining motor skills as well as using automatised motor tasks in daily life. Deepened knowledge on these impairments may also guide rehabilitation[6,40].

The are many terms in the literature used to describe motor learning and the storage of motor memories and is not always clear how the terms relate and overlap[6]. A traditional distinction is between explicit and implicit learning and memory. Explicit learning is defined as intentional, effortful learning demanding cognitive resources while implicit learning refers to learning without intention or awareness of what has been learned[41,42].

Motor learning is however a complex multistep process that often includes both explicit and implicit processes. The classical view of motor learning encompasses three phases: a cognitive, an associative and the autonomous phase. The first cognitive phase is mostly an explicit process where the learner tries to understand what to do through observation and verbal instructions. This is an effortful, slow and error-prone process. In the associative phase, the learning is more gradual with minor adjustments not always perceivable to the learner i.e., the process the learning has become mostly implicit. In the third phase, the task has reached automatisation and no longer demand explicit, cognitively demanding processes and is robust against interference from parallel tasks. In some circumstances, a task is presented to the learner without detailed verbal instructions on what to do or learn. The learner might still learn the task but with less explicit processes and more implicit[6].

Empirical evidence suggests that motor learning degrades in people with PD such that it takes a longer time or more repetitions, has a decreased maximum amplitude and possible less generalisability to other tasks, compared to healthy individuals[2,40]. Importantly, there is also evidence that retention i.e., long-term storage of newly learned motor tasks is impaired in people with PD[6], as well as that people with PD have difficulties with automatic adjustments and reactions to changing environments[2]. It has been suggested that implicit learning is more impaired than explicit learning in people with PD even though there are still disagreements on the matter and several studies have found impairments in both types of learning[2].

The broad impairments in motor learning are thought to contribute to the deficits in balance and gait that people with PD experience. Another plausible indication of impaired motor learning is that interventions of physical exercise for people with PD probably benefit from extensive repetition, a range of variations of exercises, the inclusion of tasks similar to daily life situations, for an increased chance of learning and generalisable effects[2,40].

2.8 BALANCE AND GAIT IN PD

As mentioned, balance and gait impairments often remain with dopaminergic medication. These deficits manifest in several ways where slowed gait and falls might be the most salient outcomes. Falls have been reported to occur three times as often in people with PD than in healthy individuals of similar age[43] and around 46 % of individuals with PD experience at least one fall within three months[44]. Additionally, it has been estimated that 75% of hospitalisation occurrences in PD are due to falls or fractures[45].

In healthy individuals, balance control and walking are to a large extent automatic, meaning that we do not have to allocate much attention and other cognitive resources to the details of maintaining balance or walking. For people with PD, this automaticity deteriorates over time resulting in more cognitive resources being directed to maintaining balance and walking. Loss of automatisation results in processes taking more time, plausibly less cognitive resources left for other tasks and not the least, that maintaining balance and walking are more sensitive to stressors[46].

Balance is a complex ability and Horak and colleagues[47] have suggested a framework to better understand the different domains of balance. The model includes six aspects of balance and possible impairments:

I: Biomechanical constraints. Constraints such as a stooped/flexed posture or weakness in ankles or hips can impact balance.

II: Stability limits. Constraints in how far one can move the centre of mass over our base of support can impact balance.

III: Anticipatory postural adjustments. Refers to small adjustment in posture before initiating movement and impairments may cause instability before initiating for example gait.

IV: Postural responses. Refers to adjustments we make during movement in response to trips, slips or pushes.

V: Sensory orientation. Refers to the capability to integrate sensory information. Impairments may lead to instability and disorientation.

VI: Gait stability. As the name suggests, refers to stability during gait, including when gait is challenged by speed changes or obstacles.

The model of balance and balance impairments suggested by Horak and colleagues is the basis of the HiBalance program investigated in this thesis (Paper IV) as well as the measure used to assess balance, the Mini-Balance Evaluation Systems Test (Mini-BESTest)[48].

As for gait, gait speed, step length and arm swing are the gait components most impaired at the earlier stages of PD. Later, in mild to moderate PD, these impairments progress, become bilateral and are followed by difficulties to lift the feet of the ground (resulting in shuffling steps), a stooped posture, impairments in gait initiation, turning sudden hasten of footsteps (festination) or abrupt stops, so-called freezing of gait[49–51].

2.9 DUAL-TASK ABILITY IN PD

Dual-tasking is an umbrella term that refers to the ability to perform two tasks in parallel. It has been defined as '*the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals. the concurrent performance of two tasks with distinct and separate goals*'[52]. A dual-task that is quite easy for healthy adults is walking and talking at the same time. We can all be affected by the extra effort needed to perform a task in parallel with another task in comparison to in isolation. It is plausible that the overlap of neural networks between the two tasks performed in parallel, affect the degree of dual-task difficulty[53].

Dual-tasking tends to become more difficult with age[53,54] and there are indications that dual-task ability is even more impaired in people with PD, even though results are inconclusive[55–

[57]. A plausible explanation to why people with PD should present with dual-task difficulties is the loss of automaticity in balance, gait and other motor skills together with cognitive impairments such as attention and executive functions[58]. To perform tasks with lower automaticity, demand more attentional and other cognitive resources and presumable leaves fewer resources left for additional tasks such as talking or other cognitively demanding tasks[59].

2.10 NEURAL CORRELATES OF MOTOR LEARNING AND MOTOR FUNCTIONS

As described, the dopamine depletion in PD leads to dysfunction of the basal ganglia, including the striatum, and affects the fronto-striatal circuits important for both motor, cognitive and motivational functions. Among other brain areas, the cerebellum and the Hippocampus are also involved in motor functions and cognition.

There are several ways to acquire data aimed at measuring brain activity e.g., using electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), PET, functional near-infrared spectroscopy (fNIRS), with different characteristics. fMRI is an indirect measure of brain activity with a higher spatial resolution but a lower temporal resolution than for example EEG[60]. Activity in a brain area requires oxygen and thereby increased blood flow with oxygenated blood. fMRI uses the so-called blood oxygenation level-dependent (BOLD) contrast technique. The BOLD signal consists of local increases in the ratio between oxygenated arterial blood and deoxygenated venous blood and is thereby an indirect measure of neural activity. Importantly, there is a delay in the BOLD signal as it takes several seconds before an increased activity is followed by increased arterial blood flow. This is called the hemodynamic response function and needs to be accounted for in the analyses of the BOLD signal[61]. In addition to imaging techniques, measures of the so-called brain-derived neurotrophic factor (BDNF) can be used as an indicator of neuroprotection and neuroregeneration[62,63].

I will now give a brief overview of plausible neural correlates of motor learning and motor functions and how these might be altered in people with PD.

As for motor learning, Doyon & Benali[64] proposed a model for explicit as well implicit motor learning with a focus on a cortico-striatal system and a cortico-cerebellar system. During the first phase of learning, both the cortico-striatal system and a cortico-cerebellar system are recruited with important interconnections between the two systems. When the motor learning proceeds and becomes more implicit and approaches automatisation, the cortico-striatal system becomes more important than the cortico-cerebellar system. Because the cortico-striatal system is negatively affected in people with PD, Doyon[65] suggested that people with PD use compensatory or altered brain systems or regions during motor learning. This would include the cerebellum and the cortico-cerebellar system but possible also other brain areas. Focusing specifically on implicit motor learning, the idea of compensatory mechanisms in

people with PD has gained support from several empirical studies but findings are still inconclusive as to which areas that show an altered activity and whether the brain regions show a decreased or increased activity in individuals with PD compared to healthy participants. Summarising theoretical models, the proposed altered activity presented in Doyon[65] together with empirical studies of implicit motor learning, it is plausible that the striatum, the cerebellum, the hippocampus, and the dorsolateral prefrontal cortex (DLPFC), as well as the cortico-striatal and the cortico-cerebellar systems, have altered activity in people with PD compared to healthy individuals during implicit motor learning[64–68].

In healthy individuals, walking and maintaining balance are well-learned skills and to a large extent automatised. In line with the model by Doyon & Benali[64], empirical studies focusing on automatised motor functions suggest that automatisation leads to a more effective pattern of brain activity than non-automatised performances. Findings suggest that brain activity is decreased within several brain regions e.g., the DLPFC, the parietal cortex, the cerebellum, and some cortical motor areas during automatisation. As for connectivity between regions, a common empirical finding is enhanced connectivity between brain areas primarily involved in motor function such as the striatum, several cortical motor areas and the cerebellum and a decreased connectivity between the DLPFC, the anterior cingulate cortex (ACC) and motor areas. The lesser involvement of the DLPFC and the ACC can be interpreted as support for lower recruitment of attentional networks[58].

There are fewer imaging studies of motor automaticity in people with PD than in healthy individuals. The pattern of results points towards weakened connectivity between the motor areas important for automatic motor behaviour and increased activity within several regions e.g., the cerebellum, the DLPFC, the premotor cortex, the parietal cortex compared to healthy individuals. A decreased activity of the supplementary motor cortex has also been reported. The different pattern of activity is possibly an effect partly due to dopamine depletion and the dysfunction of the basal ganglia in people with PD[58,69–72]. Altogether, both models and empirical studies of the motor learning process and automatised tasks in people with PD, suggest alterations in brain activity that can broadly be summarised as a less focused activity for people with PD compared to healthy individuals[58,65].

2.11 COGNITION IN PD

It is not unusual that cognitive symptoms are present already early in the disease. A British study of people newly diagnosed with PD reported that 36% of the participants showed some form of cognitive impairment while a Swedish study reported that 15-20% of people with PD were diagnosed with MCI at the time of diagnosis[26,73].

With the progression of the disease, cognitive impairments become more prevalent and impairing[3]. People with PD can experience a wide range of cognitive impairments, but the perhaps most typical impairment is in so-called executive functions. Impairments in executive functions and related attentional functions can in turn affect motor learning and

automatised tasks, as described in previous paragraphs[46,58]. There are several definitions of what constitutes executive functions but commonly the term refers to a range of cognitive abilities including goal-directed behaviour such as planning, initiating as well inhibiting behaviour, decision making, directing, and shifting attention and manipulating and updating information. This means that executive functions are crucial to most daily activities[74]. Impaired executive functions in people with PD are quite consistently found over different tests. A meta-analysis reported impaired executive functions for people with PD in comparison to healthy adults with effect sizes in the form of Hedge's *g* ranging from 0.43 to 0.94[75]. With time, up to 80% of people with PD develop dementia where the most commonly impaired cognitive functions include executive functions, attention, language, visuospatial function and memory[4].

2.12 PHYSICAL EXERCISE IN PD

There is a rapidly growing research field investigating physical exercise as a complement to medication in people with PD, with positive effects reported for both motor and non-motor symptoms[8–11,76]. The type of physical exercise studied in people with PD has varied broadly including treadmill and other aerobic exercise, strength training, dance, and as investigated by our research group, highly challenging exercise with a focus on balance and gait[12,13,77–80].

Several meta-analyses and systematic reviews have reported positive effects of various physical exercise programs for motor-related outcomes such as balance, gait, and strength. These reviews and meta-analyses have included studies with a considerable range of different types of physical exercise as well as intensity level and length[8–11]. It is plausible that some types of interventions are more effective than others, but there is yet no firm conclusion on which type of physical exercise that has the largest effects.

Positive effects of physical exercise on cognition for people with PD have also been reported. More specifically, positive effects have been reported for global cognitive function, attention, processing speed and mental flexibility for individuals with mild to moderate PD[76].

Because PD is a neurodegenerative disease, the neural underpinnings of behavioural effects (e.g., motor and cognitive effects) of physical exercise are of interest for a more complete understanding of the disease as well as the mechanisms of symptom alleviation by physical exercise. Investigating neural changes as an effect of physical exercise has gained intensive interest with studies performed on varying populations of both animals and humans, including individuals with neurodegenerative disorders such as PD. The interest has been divided on both motor and cognitive outcomes and their potential neural correlates and the methods have varied widely. A review and meta-synthesis by our research group[81] summarised studies investigating any type of neural changes due to physical exercise in people with PD. Thirteen studies were included for a qualitative analysis and out of these three were included in a quantitative analysis. The 13 studies differed in methods and outcomes and investigated changes in brain structure, brain activity and also different

measures of BDNF used as indices of neuroprotection and neural changes[82]. The review found that overall samples sizes were small (n = 1-34) and that other quality problems were frequent. Some studies did report neural changes in relation to physical exercise, but overall, the current level of evidence was deemed to be low. Clearly, the field calls for studies of higher quality, including larger samples.

2.12.1 THE HIBALANCE PROGRAM

Our research group has developed a highly challenging balance exercise program targeted at people with PD: the HiBalance program[12]. The HiBalance program was developed based on the principles that exercise should be specific to the impaired functions, exercise should be performed in both a progressive and varied way and exercise should be performed near or at the limit of one's capacity[12,83,84]. With the progression of the program, dual-tasks i.e., two tasks performed in parallel, were used to increase the difficulty of the tasks. Our earlier studies of The HiBalance program include a well-powered randomised controlled trial (RCT) and implementation study which both showed promising effects on balance and gait ability[12,13]. The RCT showed improved gait and balance for the training group compared to a passive control group as well improved cognitive task performance in dual-task walking with between-group effect sizes (Cohen's *d*) of 0.48 - 0.82[12,85].

2.13 RATIONALE

PD is a complicated and debilitating disease for which we still need to deepen our understanding both for the motor and cognitive deficits that develop with the disease and the promising possibility of physical exercise used as a complement to pharmacological treatment.

Despite a large research interest and many performed studies, there is a lack of consensus on the specifics of important deficits in PD e.g., motor learning, dual-task ability and their neural correlates which are of special interest since PD is a neurodegenerative disease. Neither do we know which interventions of physical exercise that result in the largest benefits for people with PD.

As our research group has earlier observed promising effects of the HiBalance program, it is of large interest to further investigate the effects of the HiBalance program using an enhanced design quality as well as by the inclusion of measures of brain activity and neuroprotective factors (BDNF).

I hope that the studies of the present thesis can contribute to answering these intriguing questions.

3 RESEARCH AIMS

The general aim of this thesis was twofold: to develop feasible methods to investigate motor and cognitive abilities in people with PD as well as the effects of the HiBalance program, and to investigate motor and cognitive abilities as well as the effects of a highly challenging balance training program. The specific aims of the studies were:

Paper I: To systematically evaluate the process and scientific feasibility of a trial design to investigate exercise-induced neuroplasticity of the HiBalance program.

Paper II: To explore the feasibility aspects of two computer-based tasks aimed to measure implicit sequence learning and dual-task ability in people with mild to moderate PD and healthy individuals.

Paper III: To investigate whether implicit sequence learning is impaired in people with mild to moderate PD in comparison to healthy individuals and whether there are associated group differences in brain activity as measured with fMRI. Additionally, we will explore whether the behavioural outcome, as well as the neural correlates, change over the learning process for the two groups.

Paper IV: There were two broad aims of Paper IV. First, to evaluate the effect of the HiBalance program on our behavioural outcomes including balance, gait, and executive function. Second, to investigate the relationship between changes in balance, gait, and executive function with changes in task-evoked brain activity as measured with fMRI and changes in BDNF.

4 MATERIALS AND METHODS

4.1 OPEN SCIENCE PRACTICES

In recent years, there has been a growing awareness that many scientific fields need to improve methods as well as transparency about methods to enhance the quality of the research made and the ability for others to fairly judge the quality of one's work[86,87].

There is a wide range of possibilities for improvement where one of the most commonly suggested methods is to write a detailed preregistration or analysis plan including the hypotheses aimed to be tested and details of the analyses to be made in the study[87–89]. Such a plan is preferably written and published before data collection but at least before commencing the data analyses. One important reason for encouraging preregistrations or analysis plans is that researchers often have a very high degree of freedom in choosing both the reported outcomes of a study and the details of the analyses[90,91]. There is empirical evidence that the same data can yield different results and conclusions depending on the exact path chosen by the researcher[92]. In addition, if several outcomes or modifications of the analyses are used, the risk of false positives e.g., significant findings that do not represent a true effect, increase[90]. A detailed analysis plan also helps the researchers in a project to formalise the hypotheses and analyses to be made and can align the expectations of the authors, raise important theoretical discussions, and point out areas where more information or skills are needed, at an early stage. And perhaps most important, a detailed preregistration or analysis plan helps the readers to evaluate the quality of a study and enables a higher level of trust in the results[87]. For the two papers where we performed hypothesis testing e.g., Paper III and Paper IV, we therefore published detailed analysis plans before commencing any analyses but after data collection (a less detailed preregistration for Paper IV was however made before data collection).

To further enhance the transparency of our studies, we published all scripts (or related files) of the statistical analyses performed, but for Paper I where scripting was not used. Due to the Swedish and EU personal data legislation (GDPR), to openly publish research data comes with many difficulties. However, for Paper II, we had the possibility to anonymise the data (deleting all documents where personal data could be linked to other personal information and enabling identification), and we could therefore publish the data in an anonymised way. We have also published all software files needed to run our computer-based tasks of implicit motor sequence learning and dual-task ability, used in our studies.

4.1.1 Online study documentations

Below are links leading to the EXPANd project's pages on the Open Science Framework's (OSF) web platform and the preregistration at clinicaltrials.gov.

The documentation includes a study protocol and analyses plans, scripts and other files for statistical analyses and the software files needed to run the two computer-based tasks of implicit motor sequence learning and dual-task ability.

Paper II: osf.io/x9baq/

Paper III: osf.io/abprn/

Paper IV: osf.io/s952g/ and clinicaltrials.gov: registration number NCT03213873

4.2 ETHICAL CONSIDERATIONS

All studies within the thesis were conducted according to the ethical principles of the Declaration of Helsinki[93]. Written informed consent was obtained prior to data collection. The EXPANd project was approved by the regional ethical board in Stockholm County with the following registration numbers:

Paper I: 2016/1264-31/4 and 2017/1258-32

Paper II: 2016/1264-31/4 and 2017/1258-32 and 2018/1445-32

Paper III and IV: 2016/1264-31/4 and 2017/1258-32, 2017/2445-32, 2018/1445-32

The ethics of conducting a study with many energy and time-consuming assessments and/or a randomised design, always need some thought as to the pros and cons for the participants. In our case, we only randomised to active interventions both of relevance to common problems in individuals with PD i.e., no passive control intervention. We also guided participants who could not be included in the study and participants who after completion of the study were interested to continue with either of the interventions investigated or similar activities.

Both the interventions and the assessments came with a small risk of accidents such as falling or MRI related incidents. Precautions to counteract these risks were made, including several trainers and assessors to prevent falls as well as multiple thorough checks for any contra-indications of undergoing MRI assessment.

Another ethical aspect concerns statistical power and other methodological issues. I deem it unethical to perform low powered, low-quality studies in general and especially if study populations are fragile due to disease or age. The time, effort and money put into a study must roughly mirror the value of what comes out, meaning that measures must be taken to produce reliable results that gain the research process and not the least the population the participants were sampled from. As for the EXPANd project, a power calculation for the

RCT was done as best as possible based on previous studies of the HiBalance program. No power calculation was done for the feasibility studies as they were not used for hypothesis testing, or for Paper III as cross-sectional investigations were not the focus of the EXPANd project.

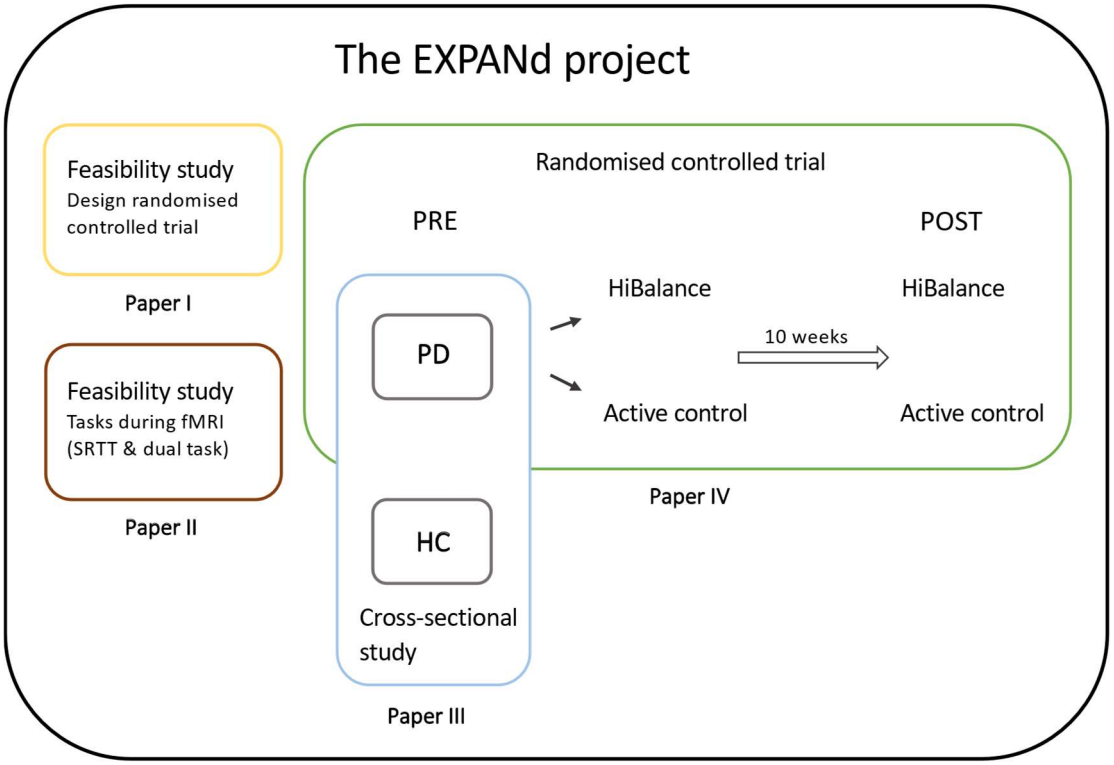

Figure 1. Overview of the four studies in the thesis. Paper I: evaluating the planned RCT design of Paper IV, Paper II: evaluating the tasks for the fMRI data collection of Paper III and Paper IV, Paper III: investigating implicit motor sequence learning in people with PD compared to healthy individuals, Paper IV: investigating the effects of the HiBalance program with a double-blinded RCT. fMRI = functional magnetic resonance imaging, SRTT = serial reaction time task, PD = Parkinson's disease, HC = healthy controls, PRE = assessments before intervention, POST = assessments after intervention.

4.3 THE EXPAND PROJECT

The primary aim of the EXPANd project was to increase the knowledge of the effects of the HiBalance program. Another aim of the EXPANd project was to increase the knowledge of impairments present in people with PD in comparison to the healthy population. For both aims we were interested in behavioural measures such as balance, gait, and motor learning, but also the neural correlates of the impairments that people with PD experience and of the effects of the HiBalance program. Before commencing the data collection that Paper III and Paper IV are based on, we conducted the studies presented in Paper I and Paper II to enhance the probability that the study designs were feasible (Figure 1).

4.4 PARTICIPANT SAMPLES

In the EXPANd project, we included individuals with mild to moderate PD defined as stage 2 or 3 on the Hoehn and Yahr scale[94] in the ON state of PD medication. The range was chosen so that the participants would show some balance deficits (less pronounced in Hoehn and Yahr Stage 1) while still able to walk indoors without the need for assistance (present in Hoehn and Yahr Stage 4). This is the range of the symptom severity where we believe a balance training program such as the HiBalance program, would be feasible and have the largest effects. For all four studies, we also used the lower age limit of 60 years. As cognitive deficits are often present already at an early stage of PD, we included individuals with a MOCA score of at least 21 which is lower than suggested values cut off-scores of 23 or 24 for older individuals [95,96]. For the healthy individuals, we included those with a MOCA score of at least 23.

4.5 THE HIBALANCE PROGRAM

The HiBalance program consists of highly challenging balance and gait focused exercises. The program was created to target four areas in balance that are often impaired in people with PD. These areas are part of the model of balance suggested by Horak and colleagues[47]: sensory orientation, anticipatory postural adjustments, stability in gait and stability limits.

The HiBalance program was led by physiotherapists and spanned 10 weeks, with two group training sessions per week complemented with home-based exercises to be performed once a week. Tasks were presented in a progressive way where the addition of parallel tasks was used to increase difficulty. The group exercises were also individually adapted so that each participant would be sufficiently challenged. The home-based exercises consisted of functional aerobic and strength exercises to be performed progressively.

4.6 THE ACTIVE CONTROL GROUP INTERVENTION

The HiCommunication program was used as our active control group in Paper I and IV. The main point of using an active control group was to control for so-called non-specific factors that could confound the specific effects of the HiBalance program. These non-specific factors include participant motivation and expectations, social interaction, to go somewhere physically for the group training etc[97–99].

The HiCommunication program was led by speech therapists and focused on speech- and communication ability, a common area of impairment for people with PD[27]. The program targeted four main areas of relevance for speech and communication: voice sound level, articulatory precision, word retrieval, and memory. The HiCommunication program was performed in the same format as the HiBalance program, with group training sessions including individual adaption, varied exercises presented progressively with the help of

background noise, memory tasks and dual-tasks. The program also included a home-based program[100]. See Table 1 for an overview of both interventions.

Table 1. Description of the core components and the progression of the HiBalance program and the active control group program

	HiBalance program	**HiCommunication program** *Control group*
Core components	Sensory integration Anticipatory postural adjustments Motor agility Stability limits	Voice sound level Articulatory precision Word retrieval Memory
Progression		
Block A *Weeks 1-2*	Exercises were performed with a focus on movement quality, familiarization of the exercises and task-specific motor learning. Single task performance of exercises pertaining to each of the core components.	Exercises were performed with a focus on phonation, articulation and breathing. Increased vocal loudness was established while maintaining good voice quality
Block B *Weeks 3-6*	Increased level of difficulty and complexity of the exercises was established through variation of the exercises within the core components and by introducing cognitive and motor dual tasks.	Increased level of difficulty and cognitive load during the exercises was established by introduction of memory games and associational tasks.
Block C *Weeks 7-10*	Complexity further increased through task variation, by combining exercises from all four core components, and by integrating simultaneous cognitive and motor dual tasks.	Complexity further increased by enhanced difficulty of memory games, by incorporating more interaction between participants and by adding background noise.

4.7 MESURE OF BALANCE PERFORMANCE

The primary outcome of the RCT in Paper IV was balance performance as measured with the Mini-BESTest. The Mini-BESTest is a 14-item clinical test of dynamic balance where four sub-components of balance control are assessed: anticipatory postural adjustments, reactive postural control, sensory integration, and dynamic gait. The Mini-BESTest has been reported to have good inter-rater and test-retest reliability in a sample of people with mild to moderate PD[48].

4.8 COMPUTER-BASED TASKS OF IMPLICIT SEQUENCE LEARNING AND DUAL-TASK ABILITY

When using fMRI to acquire task-induced brain activity, the task performed need to be possible to perform lying down and with minimised movements. Within the EXPANd project, we wanted to investigate the brain activity associated with motor ability and the possible effects of the HiBalance program for people with mild to moderate PD. Earlier studies of neural correlates of motor ability in people with PD have used imaginative walking paradigms, pedal rate paradigms or a computerised task called the serial reaction time task (SRTT)[101–103]. The SRTT has the benefit of requiring actual motor action but only minimal finger movements, unlikely to induce head movements to a large extent. The SRTT is a classical task to measure implicit motor sequence learning. As explained in paragraph 2.7 on motor learning, empirical studies point towards impairment in implicit motor sequence learning in people with PD[104] and this deficit can plausibly contribute to the balance and gait problems experienced by the patient group[2].

In the SRTT, participants choose and press a button as fast and accurate as possible, depending on the stimuli presented on a screen. Unknowingly to the participants, certain trials follow a repeating sequence (sequence trials) while the remaining trials are presented in a random order (random trials). If the reaction time (RT) of the sequence trials is lower than the RT of the random trials (and the participant report unawareness of the sequence) it is interpreted as implicit learning i.e., unaware learning of the sequence. See Figure 1, left panel, for our set-up of the SRTT.

Within the EXPANd project, we also wanted to investigate the neural correlates of dual-task ability in people with PD. For this, we used a task similar to the SRTT but without the sequence trials. The task added to the button pressing was to count the occurrence of a flashing plus-sign shown above the line of circles. See Figure 1, right panel, for an overview of the set-up.

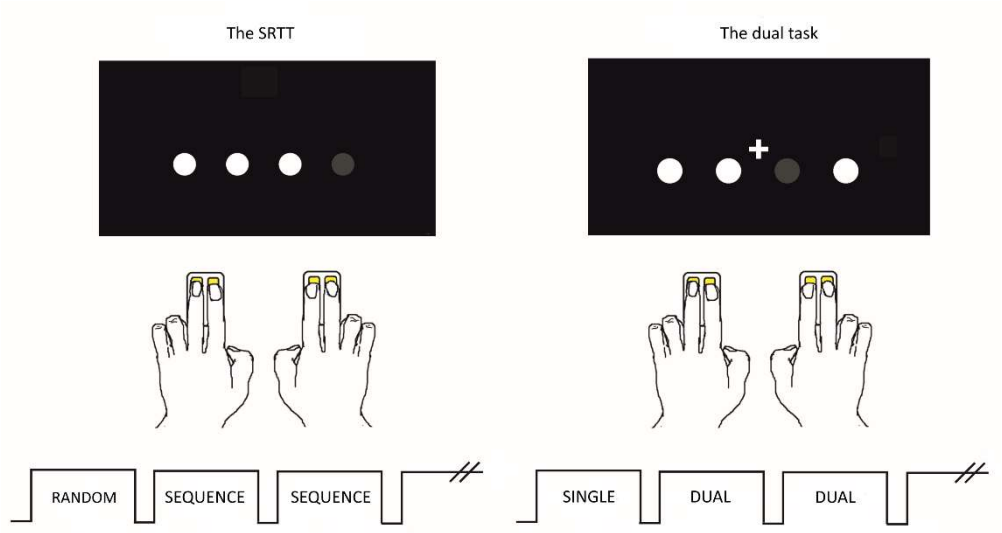

Figure 2. Set up of the SRTT and the dual-task used. The feasibility of both the SRTT as well as the dual-task was evaluated in Paper I and II. The SRTT was also used in Paper III and IV. Left: the SRTT. Interleaved random and sequence trials. The difference in RT between the random and the implicit blocks were used as a measure of implicit sequence learning. Right: the dual-task. Interleaved single and dual-task blocks. We investigated the differences in RT and per cent correct responses between the single blocks and the dual blocks as well the performance of correctly counting the plus signs, as measures of dual-task ability. Reproduced from Freidle et al.[105].

4.9 MEASURES OF BRAIN ACTIVITY

One way to analyse task-induced fMRI data is to focus on within-region activity e.g., investigating the BOLD signal within the striatum through contrasting a task with a control condition. Another type of analysis is to investigate the level of parallel activity between two or several brain regions e.g., contrasting the correlation of the BOLD signal between the striatum and the primary motor cortex during a task with the same correlation during a control condition. The latter is called functional activity. In Paper III, analyses of functional connectivity were made on task-induced fMRI data and to include the task conditions in the analyses, a method called psychophysiological interaction[61] was used.

Before any of the above analyses can be made, the fMRI data needs to be preprocessed in several steps. Preprocessing is necessary to remove artefacts and maximise the sensitivity of later statistical analyses. The preprocessing includes realigning the individuals' data to a template so that activity within an area of one individual can be compared to activity within the corresponding area of another individual. The preprocessing also includes several other steps[106,107]. The details of these steps can vary depending on software programs and the many choices that the researcher must make. To increase the reproducibility of this process, several well-documented pipelines have been created in recent years. We have used the well-known pipeline fMRIPrep[108] for the preprocessing of the fMRI data. A boilerplate of the exact details of the preprocessing by fMRIPrep for the papers of this thesis can be found on the EXPANd project's OSF page.

4.10 SPECIFIC METHODS OF THE PAPERS

4.10.1 Paper I: Feasibility Aspects of Exploring Exercise-Induced Neuroplasticity in Parkinson's Disease: A Pilot Randomized Controlled Trial

To investigate the feasibility of the planned RCT design, we conducted a small study using the methods and design planned for the RCT. Thirteen participants were included, all had idiopathic PD and were ≥ 60 years old. All outcomes planned for the coming large RCT were assessed before and after the interventions. This included assessments of balance- and gait, cognitive functions, speech -and vocal abilities and measures of BDNF levels and structural and functional brain measures by the use of MRI. fMRI data were acquired during the SRTT, the computer-based dual-task as well as during rest. We evaluated a wide range of feasibility aspects including the recruitment process, the measurement methods, and the participants' experience of assessments and the two interventions.

4.10.2 Paper II: Measuring implicit sequence learning and dual-task ability in mild to moderate Parkinson s disease: A feasibility study

To investigate the feasibility and improve the study design of the two computer-based tasks to be performed in the scanner during the RCT, we did a small pilot study of the tasks performed out of the scanner. We included 12 participants with mild to moderate PD and 12 healthy participants, all ≥ 60 years old. The task we used to measure implicit sequence learning was the SRTT. A similar task to the SRTT but with only random trials and an additional counting task was used as a measure of dual-task ability. We assessed a wide range of feasibility aspects including task fatigue, difficulty level and choice of outcomes.

4.10.3 Paper III: Implicit sequence learning in people with mild to moderate Parkinson’s disease: behaviour and related brain function

We included 91 participants from the EXPANd trial, 57 participants with PD and 34 healthy participants. We compared the pre-intervention measures for the participants with PD with the healthy participant’s assessment. We used the version of the SRTT that we had previously evaluated and modified in Paper I and II. We also analysed the fMRI data acquired during the performance of the SRTT with a focus on activity within and between areas known to be important and/or impaired in implicit sequence learning for people with PD. We made a detailed hypothesis and analysis plan before commencing any analyses.

4.10.4 Paper IV: Behavioural and neuroplastic effects of a double-blind randomised controlled balance exercise trial in people with Parkinson's disease

We randomised 95 people with PD to either the HiBalance program or the active control group. As in Paper I, both interventions consisted of two group training sessions per week and a weekly home exercise program for a total period of 10 weeks. We investigated a wide range of measurements including balance, gait and other motor functions, executive functions, voice-and speech assessment and levels of BDNF and fMRI data acquired during performance of the SRTT. All assessors were blinded to the participant's group allocation. We made a detailed hypothesis and analysis plan before commencing any analyses.

5 RESULTS

5.1 PAPER I

5.1.1 Results

Thirty-one per cent of the individuals screened for participation were included in the study. There were possible ceiling effects of the dual-task performed during walking. We observed problems with sleepiness and diplopia during the tasks performed in the scanner. The participants took part in the group interventions to a high extent and deemed them to be acceptable.

5.1.2 Main conclusion

The study provides overall support for the feasibility of the assessments and the two interventions planned for the design of the future RCT. Some important modifications are to be made, including further piloting of the two tasks performed in the scanner.

5.2 PAPER II

5.2.1 Results

All participants understood the instructions of the task and the difficulty level was deemed acceptable. The participants, especially those with PD, showed signs of task fatigue. The task fatigue needs to be considered in the choice of analysis method and in the conclusions that can be made. There were ceiling effects in the accuracy outcome for the healthy participants.

5.2.2 Main conclusion

We found the design of both tasks to be feasible to use for both people with PD and healthy individuals, all ≥ 60 years of age. Awareness of task fatigue is needed and reaction time and not accuracy should be the outcome when comparisons are made between people with PD and healthy older individuals.

5.3 PAPER III

5.3.1 Results

The group of people with PD showed a small, statistically significantly lower level of implicit learning than the group of healthy individuals as measured by RT during the SRTT. The descriptive pattern seen in the data when dividing the SRTT into three parts, suggests that the group with PD need more time to learn the sequence than the healthy group and that the level of learning is similar at the end of the SRTT (Figure 2). We did not find any significant group differences in the fMRI data.

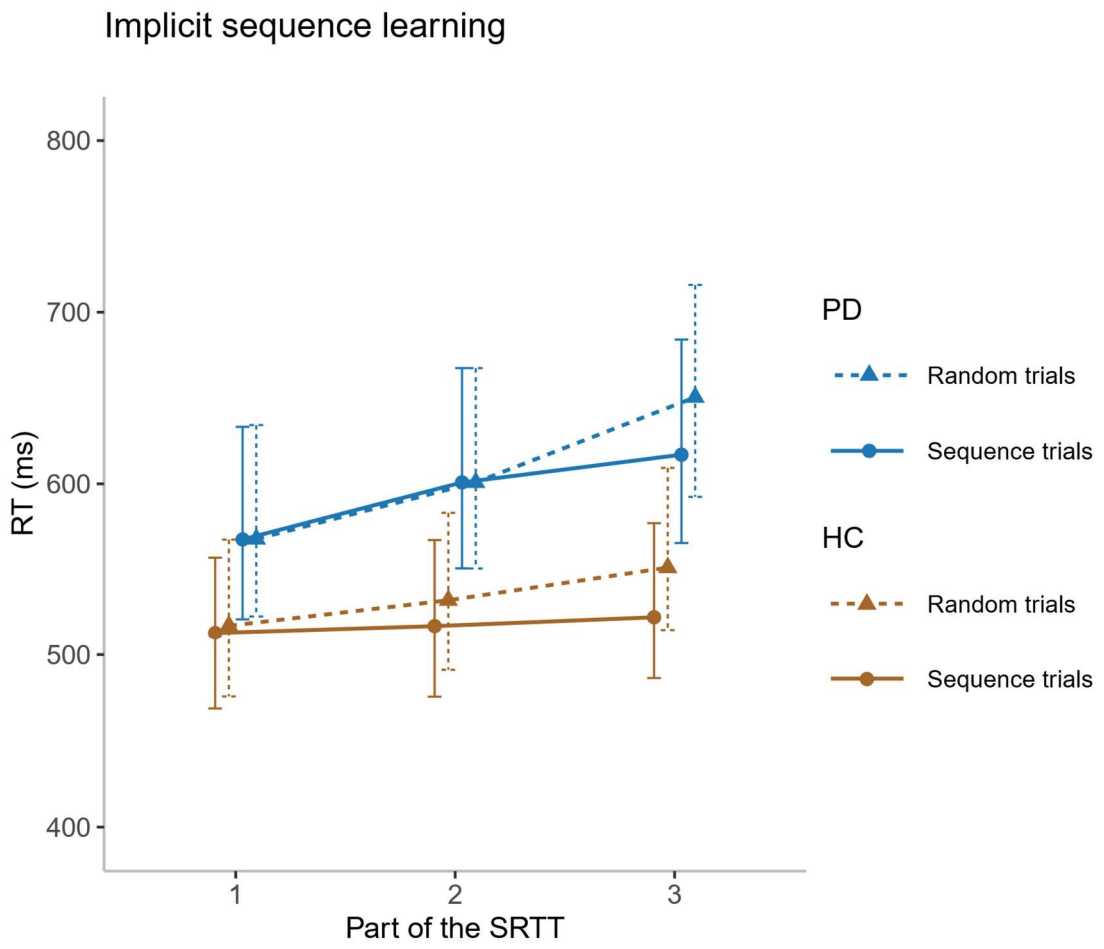

Figure 3. Reaction time as a measure of implicit motor sequence learning for both groups showed for each part of the SRTT. The point values represent the observed median RTs of the trials in the two blocks included for each point, the error bars represent the semi-interquartile ranges. Part 1: random trials from blocks 1 and 4 and sequence trials from blocks 2 and 3, part 2: random trials from blocks 4 and 7 and sequence trials from blocks 5 and 6, part 3: random trials from blocks 7 and 10 and sequence trials from blocks 8 and 9.

5.3.2 Main conclusion

The data lend some support to our hypothesis that people with PD have a lower level of implicit sequence learning than healthy individuals of a similar age.

5.4 PAPER IV

5.4.1 Results

We found no statistically significant group by time interaction effect for our primary outcome Mini-BESTest (b = 0.4 [95% CI = -1, 1.9], p = 0.57, Cohen's d = 0.14). There were also no statistically significant group by time interaction effects favouring the HiBalance program for any secondary outcomes (behavioural and BDNF outcomes). There were no statistically significant group by time interaction effects for any of our regions of interest. Lastly, there were no statistically significant differences between the HiBalance group and the active control group for the behavioural difference scores correlated with the fMRI data difference scores, nor for the behavioural difference scores correlated with the difference scores of the BDNF values.

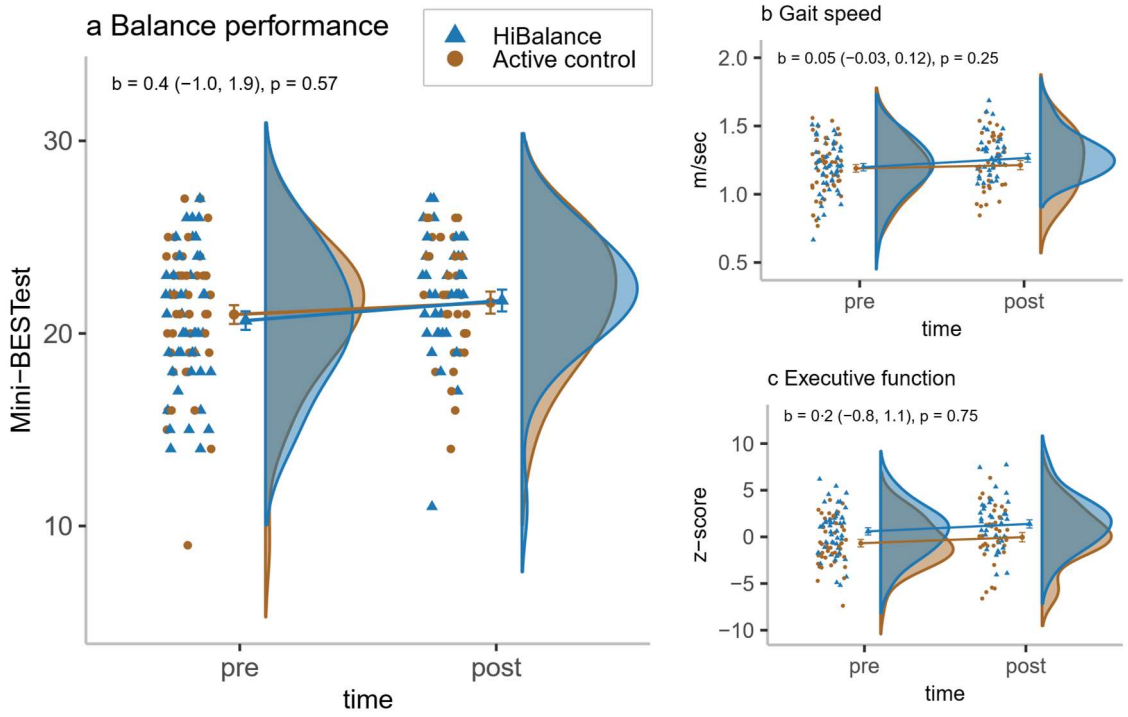

Figure 4. Group dependent change for the outcomes Mini-BESTest, gait speed, and executive function. The mean values, their 95% CIs (error bars) as well as the b values, e.g., the unstandardised estimates of the time by group interaction, and their 95% CIs, are predicted values based on the intention to treat analyses. The participants' point estimates, and their distributions are observed values. a) Mini-BESTest (range 0-28), b) Gait speed (cm/s), c) Executive function (composite score of four tests from the Delis-Kaplan Executive Function System and the Wechsler Adult Intelligence Scale, z-scores). Reproduced with permission from Springer Nature.

5.4.2 Main conclusion

The study cannot provide support for that are beneficial effects of the HiBalance program in its investigated form, in people with mild to moderate PD.

6 DISCUSSION

6.1 SUMMARY OF FINDINGS

This thesis had two types of aims: to develop the feasibility of the study designs and to investigate motor and cognitive deficits and the effects of the HiBalance program in people with mild to moderate PD. Our feasibility studies i.e., Paper I and II, served their purpose by guiding us in what aspects of the study designs worked well, and which areas needed improvement before collecting data that are the basis of Paper III and Paper IV. Paper III can be summarised such that we found a small impairment in implicit sequence learning for the participants with PD compared to a healthy control group, but with no associated differences in brain activity. Paper IV could not lend support for the hypothesis that the HiBalance program results in beneficial effects for people with mild to moderate PD.

6.2 THE FEASIBILITY OF THE RCT DESIGN AND THE FMRI TASKS

In Paper I and II, we concluded that the RCT design and the fMRI tasks were both overall feasible. Importantly, we did however observe several aspects that needed improvement before conducting the data collection that forms the basis for Paper III and Paper IV. This highlights the value of conducting feasibility studies for enhancing the quality of one's planned studies[109]. We also hope that publishing the results of our feasibility studies can help other researchers in their study designs and thereby decrease unnecessary efforts for study participants as well as valuable research investments.

The feasibility of a study design is however put to its ultimate test when the designed studies are used for the final purpose e.g., investigation of the research question they were created for[109]. In Paper II, no participant had <70% accuracy while in Paper III, 19% of the participants had <70% accuracy and were excluded as a low accuracy makes it difficult to interpret whether motor sequence learning has taken place. The high exclusion rate of Study III was unfortunate as it resulted in a smaller sample and lowered statistical power. The most salient difference between Paper II and Paper III was that the SRTT was performed inside the MRI scanner in Paper III but not in Paper II. Performing a task inside a scanner is different from performing it on a desk in that it is much noisier, can be uncomfortable and anxiety evoking and that the participant is lying down and have a very limited or no view of the response pads used for the button presses. The lesson to learn from the discrepancy of correct responses of Paper II and III is that the use of a mock scanner for feasibility studies of tasks to be performed in a scanner, probably result in a better evaluation of the feasibility of the task to be performed inside a scanner.

Concerning feasibility in the RCT study (Paper IV), we see two major limitations. The first one concerns the quite low participant adherence to the home-exercise program, especially in that many participants did not progress the difficulty of the home-exercise program. This was noticed in Paper I and modifications thought to be sufficient were made. The modifications

included that the trainers of the HiBalance program to a larger extent emphasised the importance of progression in the home-based exercise program and this was also made clearer in the instruction booklet for the home-exercise program. Unfortunately, these modifications did not satisfactory circumvent the problem as a third of the HiBalance program participants in Paper IV, reported that they had not progressed the home-based exercises. Related, the participants of the first RCT of the HiBalance program were given physical exercise on prescription after the intervention period to continue exercising or be physically active on their own, but compliance was low[110]. Additionally, the implementation study of the HiBalance programs showed no increased level of physical activity in daily life for the HiBalance group[13]. Earlier reports of barriers to physical exercise in people with PD highlights the lack of someone to motivate them as a significant other, a personal trainer or a training partner[111,112], social factors inherent to group-based training. Depression has also been found to negatively affect the level of physical exercise[111]. Altogether, low levels of self-initiated home-based physical exercise is likely a problem that future-wise need more attention in interventions for people with PD. The use of e-health tools such as computer-based platforms or mobile programs presenting exercises and possibilities for interaction with trainers should be investigated for this purpose.

The second limitation of Paper IV that could be seen as a feasibility aspect concerns the somewhat different characteristics of the samples in our first RCT of the HiBalance program[12] and the RCT presented in Paper IV. Descriptively, the sample of the present RCT showed somewhat less general motor symptoms and balance impairment than the first RCT of the HiBalance program. We find it plausible that the unintentional somewhat healthier sample in Paper IV compared to the first RCT of the HiBalance program, was the effect of the increased exclusion criteria due to the MRI assessment as well as the extra strain on the participants due to the expanded test battery spanning three days instead of one as in the first RCT.

6.3 IS IMPLICIT MOTOR SEQUENCE LEARNING IMPAIRED IN PEOPLE WITH PD?

The SRTT has been used in several previous studies to make inferences on implicit motor sequence learning ability in PD. Many studies have however been under-powered and both sample and design characteristics have varied to such an extent that firm conclusions on implicit motor learning as measured with the SRTT, are difficult to make[104].

As for our study of implicit motor learning, i.e., Paper III, we used a somewhat different approach to analyse the results of the SRTT than most previous studies e.g., Vandenbossche et al.[113] and Werheid et al.[68]. Instead of comparing the reaction time between sequence and random trials at the end of the task, we included all trials of the SRTT in a multilevel model and performed an interaction analysis of group and trial type. The idea was that using all trials is a more efficient use of data and should increase the statistical power of the analysis.

This analysis showed a small but significant difference in the direction that the group with PD showed a lower degree of implicit motor learning as measured by the task. However, when we in a more exploratory way compared the level of implicit motor learning for the three parts of the SRTT, we found indications that the level of the implicit motor learning was equal for the two groups at the end of the SRTT but lower in the second i.e., middle part for the group with PD than the healthy group. In line with existing theories on motor learning deficits in people with PD[2], a plausible interpretation is that people with mild to moderate PD can achieve a similar level of implicit motor sequence learning as healthy individuals of a similar age, but that it takes more repetitions of the sequence. It would be interesting to follow up on this hypothesis with a study well-powered and more optimally designed for the question. Deepened empirical support that people with mild to moderate PD indeed have the possibility for equal implicit motor learning as healthy individuals of similar age but need more time/training, would be valuable information. It would strengthen the theoretical support for physical exercise programs that focus on extensive repetitions of basic tasks, much like the HiBalance program in the initial phases. It could also amplify the individual's motivation for extensive practice of tasks important in daily life and physical exercise.

In this context, it is however inevitable to discuss the SRTT as a measure of implicit sequence learning and how results from the SRTT can be generalised. The problem of generalisability of experimental designs has recently been highlighted with calls for more naturalistic designs with increased ecological validity[114]. The SRTT is perhaps the most common task used to measure implicit motor sequence learning in experimental settings but unfortunately, we do not know to what extent it is a valid measure of implicit motor learning in daily life. To my knowledge, there is no empirical study that has investigated whether performance on the SRTT is associated or transferable to motor performance in daily life i.e., whether it is a measure with ecological validity. This would be an empirical effort of profound interest and benefit the research field.

6.4 DO PEOPLE WITH PD HAVE AN ALTERED BRAIN ACTIVITY DURING IMPLICIT SEQUENCE LEARNING?

There are several reasons why it is theoretically plausible that individuals with PD would have a modified brain activity during the performance of the SRTT and other measures of implicit motor sequence learning. First, the striatum that is affected by dopamine loss in people with PD, is implied to have an important function in implicit motor sequence learning[1,64]. Second, several empirical studies and meta-analyses point to a deficit of implicit motor sequence learning in people with PD as measured with experimental designs such as the SRTT[104]. Related, existing theories propose that people with PD have difficulties with motor learning[2]. It is likely that impairments showed in either experimental designs of implicit motor sequence learning or related motor learning functions in daily life, would be associated with altered brain activity.

Empirical studies of neural correlates of SRTT in people with PD have reported results that are sometimes overlapping and sometimes non-overlapping as to altered activity and affected brain regions in comparison to healthy individuals. The discrepancy is expected given the differences in set-up and sample characteristics and not the least the low signal-to-noise ratio that is inherent to task fMRI and the commonly used small sample sizes[67,115–117].

We chose to focus our analyses on a few brain regions theoretically and empirically suggested to be involved in implicit sequence learning as well as possibly affected in people with PD. As described, we could not find any differences that significantly differed between the group of people with PD and the healthy group. Because we plausibly had a sub-optimal statistical power, the results can only be interpreted in a very humble way. We did not find support for group differences in brain activity, but we still cannot rule out that group differences exist as we might just not have had the statistical power to capture them. The same insecurity applies to significant results in studies with suboptimal statistical power i.e., had we found a significant result, it would still have to be interpreted very cautiously. Low or presumably low power is very common in fMRI studies, and this severely limits the conclusions that can be made from both significant and non-significant results[116,118].

If the above and related limitations are acknowledged, results can still be discussed with a humble and hypothesis-generating approach. Within this type of discussion, it is worth mentioning the perhaps most interesting finding of the brain activity analyses in Paper III. In the functional activity analyses of the three parts of the SRTT, a pattern of increased connectivity between the motor cortex and the cerebellum over the progression of the SRTT was suggested for the PD group but not the healthy group. If this represents a true difference between the groups, it is in line with the suggested compensatory role for the cerebellum in people with PD e.g., that striatal malfunctioning is followed by increased cerebellar activity or connectivity with the frontal lobe[65].

6.5 IS THE HIBALANCE PROGRAM EFFECTIVE FOR PEOPLE WITH MILD TO MODERATE PD?

As described, we could not find any support for the HiBalance program in our double-blinded RCT i.e., Paper IV. These discouraging results imply several points worth discussing. The most salient discussion point is the possibility that the HiBalance program simply does not work for people with mild to moderate PD. At a first glance, this possible conclusion contrasts our earlier studies of the HiBalance program[12,13] and partly the generally accepted conclusion that physical exercise ameliorates symptoms in people with PD. However, there are several important notes to be made on the matter. First, we know that non-specific treatment effects (sometimes called placebo/nocebo effects, contextual effects) can have large effects on a range of symptoms[97–99]. Non-specific treatment effects are the effects that likely could be the result of several, differently targeted interventions e.g., in this case, effects not exclusive to the HiBalance program. Non-specific effects can be the cause of the participant's

motivation and expectations, social interaction and the like[99]. We also know that unblinded assessors i.e., assessors aware of the intervention allocation of a participant, can induce bias in the direction of more positive outcome assessments for the intervention that the assessor has some preference/allegiance for[119]. Please note that the assessors should not be blamed for this type of bias, but rather that this is an inherent problem in unblinded designs. It is likely that both these factors, to an unknown extent, contributed to biased, overly positively estimated effects of the HiBalance program in both the first RCT[12] and the implementation study of the HiBalance program[13] as neither blinded assessors nor an active control group were used. To conclude, the discrepancy in the results between our first RCT[12], the implementation study[13] and the present RCT of the HiBalance program (Paper IV), could at least partly be explained by successful blinding of the assessors as well as a reduction of non-specific effects in Paper IV.

We also consider the possibility that the discrepancy between the previous investigations of the HiBalance program and Paper IV could partly be explained by sample differences. The sample in Paper IV had milder general motor symptoms and less balance impairment than in the first RCT of the HiBalance program measured with mean scores (MiniBESTest: m = 18.6 and m = 20.85, UPDRS-III: m = 36.5 and m = 31.5, the first RCT [12] and Paper IV respectively). A previous responsiveness study of the HiBalance program reported that participants more affected by their PD benefitted to a larger extent from the HiBalance program than participants less affected[120]. Related, there are some indications in Paper IV that individuals with a lower gait speed benefitted to a larger extent from the HiBalance program than those with a higher gait speed at baseline.

Another discussion point of significant importance is that Paper IV and the first RCT of the HiBalance program also differ in that Paper IV used two instead of three group training occasions per week. For ease of implementation in clinical care, the third weekly group training was substituted with a home-exercise program. Because balance exercises come with a risk for falls and injuries, the unsupervised home exercises were instead focused on functional aerobic and strength exercises. The loss of a third balance focused training per week in combination with previously discussed low adherence to the home-exercise program could have resulted in the home-based exercises being an inadequate substitute for a third weekly group session. A dose-response effect of physical exercise has been reported for several types of physical exercise and outcomes and also for the HiBalance program[120–123], and so the possibility of a dose-response effect as a partial explanation of our non-significant findings could be further investigated.

I would also like to discuss the results of Paper IV in relation to other research groups' investigations of physical exercise interventions for people with PD. Meta-analyses point to that physical exercise ameliorates PD related symptoms including balance and gait. The field is however relatively new, and many quality characteristics are often absent or not reported on including statistical power calculations, randomisation procedures, intention-to-treat analyses, blinded assessors, blinded participants and active control groups. There is also a

very wide range of interventions investigated and few (direct) replications, especially by independent research groups[8–11]. Altogether, this means that the conclusions that can be made from the present literature are not as robust as one could wish for. There are however at least two other RCTs of physical exercise for people with PD that used blinded assessors and active control groups, which also found mostly non-significant results[124,125].

As in section 6.3. on brain activity during implicit motor sequence learning, a note on interpreting non-significant results is in place. We estimated the sample size of the RCT in Paper IV to enable us to find what we deemed to be clinically interesting (a two-point group difference) for our primary measure, the Mini-BESTest, with 80% power. Based on our previous studies, we also thought this would give a decent power for several of our secondary outcomes but no formal power calculation for these was made. In the light of this, the most correct interpretation of the non-significant results in Paper IV is that it is unlikely that there are any specific beneficial effects of the HiBalance program of the effect size that we powered the RCT for (or larger), with the specific design of the HiBalance program used. This leaves the possibility of beneficial specific effects of the HiBalance program smaller than what we powered the study for. However, a smaller effect size is of less clinical relevance.

As for our measures of brain activity and BDNF, the non-significant results are not surprising in the light of the non-significant behavioural results. A possibility that there were effects that we could not find due to a limited statistical power should however be acknowledged.

7 POINTS OF PERSPECTIVE

7.1 QUALITY AND OPEN SCIENCE-RELATED ASPECTS

By publishing feasibility studies for both the RCT design and the computer-based tasks of implicit motor learning and dual-task ability as well as transparently discussing remaining feasibility limitations in Paper III and Paper IV, we hope that other researchers can benefit from our findings when designing and conducting their experiments. Additionally, we believe that our detailed analysis plans, our shared scripts, and detailed methods descriptions, as well as our publications of non-significant findings, can help in the evaluation of our results and guide future studies. With more feasibility studies published as well as increased transparency all through research processes, time and efforts for both researchers and study participants can be saved. And in the wider perspective, these practices will accelerate the progression rate of important discoveries[88,116].

We rightfully pride ourselves on publishing feasibility studies and non-significant findings, using high levels of transparency and not least the improved design quality of the RCT presented in Paper IV compared with the first RCT of the HiBalance program[12], including an active control group and blinded assessors. However, there are several aspects of the studies included in this thesis that yet deserve to be discussed.

One aspect where our quality could have been further improved concerns the analysis plans. Analysis plans should always be encouraged no matter if produced before or after data collection (but of course before analysis) and the level of detail. However, detailed analysis plans written before data collection are of course better than non-detailed analysis plans written after data collection. We wrote our detailed analysis plans after the data collection but with a fairly high detail level (and also a less detailed preregistration of Paper IV before data collection, clinicaltrials.gov NCT03213873, and a study protocol[126]). In hindsight, I could however have been even more detailed on the analyses of the fMRI data for both analysis plans (Paper III and Paper IV), especially concerning the methods for corrections for multiple testing. Concerning the study protocol, to not disclose that we investigated implicit learning for any future participant, we deliberately choose to not describe the SRTT as a test of implicit motor sequence learning.

Another aspect of interest concerns two of the main discrepancies between the first RCT of the HiBalance program and the here presented RCT (Paper IV): the observed sample differences in motor and balance characteristics and the differing number of group training sessions per week. As both RCTs investigated the effects of the HiBalance program but with important differences, Paper IV can be seen as a so-called conceptual replication of the first RCT of the HiBalance program[127]. As previously explained, the sample difference was unintentional while the lower number of group training sessions was an effort to ease the clinical implication of the intervention. To ease clinical implication is a very valuable

intention but such changes in design between studies can also be discussed in relation to the benefits of conducting direct replications rather than conceptual replications. As the name suggests, a direct replication keeps the study design and sample characteristics as close to the original study as possible. Direct replications are a necessity to draw firm conclusions on the effects of an intervention and any other research results[127] but are unusual within many research fields, including the field of physical exercise interventions[128,129]. That Paper IV was a conceptual rather than a direct replication of the first RCT of the HiBalance program, with several important differences, largely contributes to that we now are relatively uncertain on the reason for the discrepancy in results between the first RCT and Paper IV. With Paper IV we cannot corroborate the support for the HiBalance program for people with mild to moderate PD, but as it was not a direct replication, we can neither rule out that the HiBalance program is effective if the frequency/dose of group training sessions is at least three per week and/or effective for a sample with somewhat higher symptom levels, as in the original RCT of the HiBalance program[12].

To increase the number of direct replications, as well as the use of quality-enhancing study characteristics such as high statistical power and detailed analyses plans, I believe that major reforms of the academic incentives and structures are needed. Hopefully, the recent intensification of discussions of study flaws and the many suggested possible ways to improve the scientific process[88,90,116,129,130] will make funders and academic institutions realise that now is the time for a change.

7.2 FUTURE STUDIES OF PHYSICAL EXERCISE FOR PEOPLE WITH PD

In my opinion, it is now time for researchers within the field of physical exercise for people with PD, to come together and thoroughly consider all evidence at hand for the very wide range of interventions that have been investigated. Using extensive collaboration and common resources we can then strive to 1) prioritise direct replications of the interventions with the most promising results using all characteristics of high-quality studies, and 2) contrast the most promising interventions with each other directly i.e., within the same study for increased comparability. By using such a collaborative approach, we would benefit from each other's competencies, and it could also ease the burden of the expensive and logistically demanding data collection needed to achieve a decent statistical power and other aspects of high-quality studies. However, collaborations and multi-centre studies come with their own logistical complications such as streamlining and quality-ensure the assessments and interventions, and of course also with financial complications where for example replications are not prioritised to a sufficient extent. To help individual research groups overcome or decrease these difficulties, national, EU-based or international organisations could have an overarching role in both organising, directing and prioritising funding of such projects.

Until one or several specific interventions of physical exercise have gained robust support for people with PD, one crucial question remains, namely what the clinical health care system

should offer people with PD in terms of physical exercise today. One could argue that because several meta-analyses of physical exercise for people with PD have reported positive effects (for several types of interventions)[9–11] and because we know that physical exercise comes with many positive health aspects and few severe side effects for people in general[131,132], some or several types of physical exercise should be offered people with PD but without focusing on a particular intervention. The National Board of Health and Welfare in Sweden recommend gait or gait and balance focused training for people with PD but no specific intervention program[133].

7.3 WHEN AND HOW SHOULD WE USE MEASURES OF BRAIN ACTIVITY?

In recent decades, the studies using functional fMRI to investigate brain activity have increased at a high rate[134]. It is indeed very exciting to try to improve our understanding of brain function and associated behaviour, that is an important reason for why I once applied to get onboard the doctoral project here presented. However, over the years of my doctoral education, I have come to realise that there is a substantial overuse of studies trying to measure and interpret brain activity and other brain-related outcomes. Let me try to justify my opinion from a few different perspectives, focusing on task fMRI.

First, fMRI is a noisy and indirect measure of brain activity[115]. The raw data from the scanner needs to pass a high number of processing steps before it can be analysed on a group level i.e., the level of most interest to most studies[106]. A large number of processing steps comes with a large number of decisions on a large number of parameters i.e., the researcher's degree of freedom is very high, and decisions made at an earlier stage can affect all succeeding processing steps[116]. The introduction of well-documented and streamlined preprocessing pipelines such as fMRIPrep[108] as well as the practice of preregistrations or detailed analysis plans, are welcome and decrease the problem but even after this, a high level of researcher's degree of freedom persists, giving way for results strongly affected not only by true effects but also the researcher's choices.

Second, it is resource-demanding to use fMRI both in terms of time and comfortableness for the participant, cost for using the scanner and the time spent by the researchers for data collection as well as the analyses. The costs are a probable reason for why an abundance of fMRI studies use small samples and thereby significantly lack statistical power resulting in a lower replicability[135,136]. Underpowered studies should very cautiously be used for hypothesis testing and evaluated primarily as exploratory. There is nothing wrong per se with hypothesis-generating exploratory analyses, they should perhaps be used even more often[137]. However, severe problems arise when exploratory results are presented and interpreted as confirmatory (a common problem) and when exploratory results are seldomly put to test by well-powered confirmatory studies[89]. In addition, not only costs contribute to the common low-powered fMRI studies or studies with unknown power, but also the absence of relatively

easy and streamlined ways to calculate the statistical power for fMRI analyses. Alternatives are however emerging[138,139].

Third, fMRI demands that the participant is lying down and that movements are minimised. This substantially limits the tasks that can be performed during the acquisition of fMRI data. Our use of the SRTT as a measure of motor ability in Paper IV is an enlightening example of this. As two of our main outcomes were balance and gait ability, a measure of brain activity during a balance or gait task would naturally be more ecologically valid but not feasible during fMRI. For this, options such as fNIRS or possibly EEG could work better.

The fourth aspect I wish to discuss is related to all the above aspects. Resources in science are limited and tough prioritising is needed. I think there is a need for a more in-depth discussion on the cost of conducting fMRI studies in relation to the value of the output. The value of the output is related to the quality of the study, outlined above as something that is often, but not always, suboptimal in fMRI studies. The value of the output is also related to how the results can be used and when in the scientific process knowledge of neuronal correlates are most valuable. As the results of Paper IV together with other studies in the field of physical exercise for people with PD have shown, we still have a long way before we know which interventions of physical exercise that have the largest effects for people with PD. Until we have robustly outlined what interventions are most promising using clinical measures, I suggest that future research efforts within the field are used primarily for investigating behavioural effects of interventions. When we gain robust support for an intervention, it is of course interesting to again try to associate improvements in symptoms with changes in brain function if studies are well-powered, use ecologically valid and feasible tasks as well as detailed analysis plans.

8 CONCLUSIONS

This thesis investigated both feasibility aspects and results of empirical studies of motor and cognitive abilities in people with PD with a brain activity perspective, in contrast to healthy individuals and the effects of the HiBalance program in comparison to an active control group.

We found some support for the hypothesis that people with mild to moderate PD have impaired implicit motor sequence learning compared to healthy individuals. Exploratory analyses showed a possibly lower learning rate for the participants with PD. We could not find support for the HiBalance program for any of our outcomes in the investigated form for people with mild to moderate PD. This is an important finding that will hopefully spark interest in future rigorous projects aiming to find interventions based on physical exercise with robust, replicable positive effects. When this goal has been achieved, it would again be interesting to investigate the neural correlates of physical exercise in PD with well-powered studies using reliable and ecologically valid tasks and detailed analyses plans.

9 ACKNOWLEDGEMENTS

First of all, my deepest thank you to *all participants* who participated in the EXPANd project. Thank you for enduring all our demanding assessments! Only together can we pave the way for more effective treatment of this disease.

I also want to thank *all the assessors and all the trainers* of both the HiBalance program and the HiCommunication program and their related outcomes. *Petra Koski*, I am so grateful for all your logistic work of recruitments, assessments, demanding phone calls and data handling. *Elvira Grahn* and *Mattias Söderberg,* thanks for making the MRI assessments doable and for interesting discussions. I also want to thank all staff at the MR centre, Huddinge, including *Maria, Kerstin, Soroush* and *Sven* for all invaluable help. *Heather Martin*, without your assistance, we would never have been able to acquire MRI data for so many participants.

Erika Franzén: My main supervisor. Thank you for introducing me to the exciting world of physical exercise and the debilitating effects of living with Parkinson's disease. I highly appreciate that you have been so accessible and quick to always give a helping hand, also with practical issues. You constantly juggle an admirable number of balls, and my (highly qualitative) judgement is that your executive functions are quite something.

William H. Thompson: My co-supervisor. I am so grateful for your help, your availability, and your will to discuss the complicated paths of doing valuable research including fMRI data. If not for you, I am not sure I would have been able to finish this doctoral project. ‘

Alexander V. Lebedev: My co-supervisor. Thank you for introducing me to the world of MRI, Psychopy experiments and helping with designing the computer-based tasks used in the thesis.

Maria Hagströmer: My co-supervisor. You are so good at giving constructive input. "How would Maria have put this?" will be my mantra for more discussions.

Karin Jensen: My mentor. A massive thank you for being so supportive when I needed it the most, emotionally, and not the least in practice.

Initiators and attendees of the ReproducibiliTea journal club: thanks for invaluable discussions on the wide range of possibilities to make research and academia better, much better.

Hanna Johansson: thanks for an excellent collaboration all through the EXPANd project.

Franziska Albrecht: thanks for repeatedly saving me in the midst of software troubles and for always being up for discussions free of the implicit rules of Swedish culture.

Other colleagues (in the research group, in the EXPANd project, in the Oscher corridor and at ARC): Thanks for excellent collaborations, interesting discussions and fun.

Erland and Sigrid: I am so very lucky to have you both in my life!

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