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BALANCE AND GAIT IN PARKINSON'S DISEASE: FROM PERCEPTIONS TO PERFORMANCE

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BALANCE AND GAIT IN PARKINSON'S DISEASE: FROM PERCEPTIONS TO PERFORMANCE

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hörsal 2, Alfred Nobels allé 23, fredagen den 23 oktober kl 09:00.

Such understated power here, in these tottering dancers who exert stupendous effort on tasks most view as insignificant. Such quiet beauty here, in these, my soft-voiced, stiff-limbed people; such resolve masked by each placid face. There is immensity required in growing small, so bent on such unbending grace.

From the poem No Signs of Struggle

By Robin Morgan

ABSTRACT

The overall aim of this thesis was to explore perceptions and performance of balance and gait in people with Parkinson's disease (PwPD), and to evaluate both the current evidence for exercise-induced neuroplasticity and the feasibility of investigating exercise-induced neuroplastic changes among PwPD.

This thesis includes four papers of different designs; a qualitative interview study (paper I), a systematic review and meta-analysis (paper II), a pilot RCT (paper III) and a cross-sectional study (paper IV). Participants in papers I, III & IV were recruited through advertisement in newspapers and through the Parkinson association in Stockholm (sample sizes n=18, n=13 and n=93, respectively), whereas paper II selected studies from database searches (included studies n=13, total participant sample n=213).

Five themes emerged from the qualitative content analysis of the interviews, the underlying patterns of which formed the overarching theme "Focus and determination to regain control over shifting balance". In paper II, the narrative synthesis revealed that a majority of the studies indicated that exercise can possibly induce positive neuroplastic changes in PwPD, but the evidence according to the GRADE analysis was very low. In paper III we found that a proposed design to explore associations between changes in behavioral outcomes and neuroplasticity after ten weeks of the HiBalance training was feasible and acceptable given a few modifications ahead of the RCT. Finally paper IV showed that people with mild to moderate PD exhibited impaired performance across most domains of gait when simultaneously having to concentrate on a cognitive task (dual tasking). Impaired cognitive function was associated with higher costs on gait, as well as a tendency to use a posture-second prioritization in which the cognitive task was prioritized over walking.

Balance was perceived as both bodily equilibrium and a mind-body interplay. The meaning of balance was described through concepts of control and the ability to control one's body in everyday life. Regarding exercise-induced neuroplasticity in PD, published studies showed promising results, but more high-quality RCTs, using scientifically sound methodology are needed in order to drive this research field forward. Our proposed RCT design to evaluate neuroplastic changes after the HiBalance training was feasible, but needed strengthening regarding blinding procedures, the MRI paradigm and the dual task gait assessment. Walking while simultaneously concentrating on a cognitive task impaired performance on both tasks, especially among those with cognitive impairment. These findings provide preliminary evidence to suggest that dual task training and assessment should be planned and instructed differently according to cognitive status in PwPD.

SAMMANFATTNING

Det övergripande syftet med denna avhandling var att utforska uppfattningar och utförande av balans och gång hos personer med Parkinsons sjukdom (PmPS), samt att utvärdera både den tillgängliga evidensen för träningsinducerad neuroplasticitet, och genomförbarheten av att utvärdera träningsinducerade neuroplastiska förändringar hos PmPS.

Denna avhandling inkluderar fyra studier av olika designer; en kvalitativ intervjustudie (studie I), en systematisk litteraturöversikt och meta-analys (studie II), en pilot RCT (studie III) och en tvärsnittsstudie (studie IV). Deltagarna i studie I, III & IV rekryterades via annonsering i tidningar samt via Parkinsonförbundet i Stockholm (n=18, n=13 och n=93 i respektive studie), medan studie II inkluderade studier via databassökningar (inkluderade studier n=13, totalt antal deltagare n=213)

Den kvalitativa innehållsanalysen resulterade i fem huvudteman vilkas underliggande mönster bildade det övergripandet temat ”Fokus och beslutsamhet för att återvinna kontroll över en föränderlig balans”. I studie II visade den narrativa analysen att en majoritet av studierna pekade mot att en period av träning kunde inducera positiva neuroplastiska förändringar hos PmPS, men den sammanvägda evidensen enligt GRADE var väldigt låg. I studie III fann vi att den föreslagna RCT designen för att utvärdera associationer mellan förändringar i beteendemått och neuroplasticitet efter tio veckors högutmanande balansträning var genomförbar givet några modifikationer inför den större studien. Slutligen visade studie IV att personer med mild till måttlig PS försämrades i de flesta gångdomäner när de samtidigt fick koncentrera sig på en kognitiv uppgift. Kognitiv nedsättning var associerat med större grad av försämring vid gång, och personer med kognitiv nedsättning hade även en tendens till att prioritera utförande av den kognitiva uppgiften istället för gången.

Balans uppfattades både som kroppens jämvikt och som ett samspel mellan kropp och sinne. Betydelsen av balans beskrevs i kontexten av kontroll och förmågan att kontrollera kroppen i dagliga livet. Gällande träningsinducerad neuroplasticitet vid PS så visade de publicerade studierna positiva resultat, men fler högkvalitativa RCT studier där man använt vetenskapligt sund metodologi behövs. Vår föreslagna RCT design för att utvärdera neuroplastiska förändringar efter HiBalance träningen var genomförbar, men behöver stärkas med avseende på blindning, upplägg av MRI undersökning samt gång-undersökning med samtidig kognitiv uppgift. Vid gång med samtidig kognitiv uppgift försämrades utförandet på båda uppgifterna, speciellt hos personer med kognitiv nedsättning. Dessa resultat påvisar preliminär evidens för att undersökning och träning av att gå och samtidigt utföra en kognitiv uppgift skall planeras och instrueras olika beroende på kognitiv förmåga.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Johansson H, Franzen E, Skavberg Roaldsen K, Hagströmer M, Leavy B. Controlling the Uncontrollable: Perceptions of Balance in People with Parkinson Disease. Physical Therapy. 2019;99(11):1501-10.

II. Johansson H, Hagströmer M, Grooten WJA, Franzen E. Exercise-Induced Neuroplasticity in Parkinson's Disease: A Metasynthesis of the Literature. Neural Plasticity. 2020;2020.

III. Johansson H, Freidle M, Ekman U, Schalling E, Leavy B, Svenningsson P, Hagströmer M, Franzén, E. Feasibility Aspects of Exploring Exercise-Induced Neuroplasticity in Parkinson's Disease: A Pilot Randomized Controlled Trial. Parkinsons Disease. 2020;2020.

IV. Johansson H, Ekman U, Rennie L, Peterson DS, Leavy B, Franzén E. Performance, prioritization and the role of cognitive status during motor-cognitive dual-tasking in Parkinson's disease. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

APA	Anticipatory Postural Adjustment
BETA-PD	Balance, Elderly, Training and Activity in Parkinson's Disease
BDNF	Brain-Derived Neurotrophic Factor
DT	Dual task
EXPANd	EXercise in PArkinson's disease and Neuroplasticity
fMRI	Functional Magnetic Resonance Imaging
H&Y scale	Hoehn and Yahr scale[1]
ICF	International Classification of Functioning, Disability and Health[2]
MCI	Mild Cognitive Impairment
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale[3]
Mini-BESTest	Mini-Balance Evaluation Systems Test[4]
MoCA	Montreal Cognitive Assessment[5]
MRI	Magnetic Resonance Imaging
PD	Parkinson's disease
PFC	Prefrontal Cortex
PwPD	People with Parkinson's disease
RCT	Randomized Controlled Trial
RT	Reaction Time
SDRT	Standard Deviation of Reaction Time

DEFINITION OF CONCEPTS

Dual tasking	"The concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals."[6]
Exercise	"A physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective."[7]
Idiopathic PD	Parkinson's disease with an unknown cause.
Neural Plasticity	"Any change in neuron structure or function that is observed either directly from measures of individual neurons or inferred from measures taken across populations of neurons."[8]
Meta-analysis	"The use of statistical techniques in a systematic review to integrate the results of included studies."[9]
Meta-synthesis	"Qualitative approach for drawing inferences from similar or related studies, identifying key features and presenting findings representative of all data."[10]
Pilot study	"A study in which a future study or part of a future study, is conducted on a smaller scale to ask the question whether something can be done, should we proceed with it, and if so, how."[11]

1 INTRODUCTION

Choosing a title that captured the essence of over four years of work was challenging. As some of the words in this title hold more than one interpretative possibility, this first section is devoted to introducing their meaning in the context of this work.

Balance is a word that can have many meanings as well as synonyms. Throughout the greater part of this thesis I have chosen to use the word balance as opposed to postural control or balance control, mainly as a way to be consistent but also because this is a word that most people can relate to. There are however slight theoretical differences between these constructs. I have therefore used one of the other synonyms in some paragraphs, especially when I considered findings from other researchers to be more correctly interpreted when the original word was used.

The concept of perception as used in this thesis relates to the naturalistic theory of perception, i.e. to the nature of perceiving.[12] This is not to be confused with sense-perception which merely concerns how we observe and recognize objects using our bodily organs. How we perceive things in the naturalistic sense varies from person to person and depends on for example, memories, expectations and emotions. Because we as humans perceive things differently, we also create different ways of knowing and understanding.

This thesis is based on a foundation of pragmatism and the belief that both subjective and objective knowledge should be valued. It therefore utilizes methodological pluralism as a means of exploring balance and gait in PD from both these perspectives. Balance and gait impairments, as will be outlined in the following sections, with their basic yet complex manifestations affect the lives of people with Parkinson's disease (PwPD) at several levels from the very onset of the disease. By focusing on both the perceptions and performance of balance and gait, we can not only develop a better understanding of these symptoms but also of the person experiencing them.

2 BACKGROUND

2.1 PARKINSON'S DISEASE

The first medical description of Parkinson's disease (PD) dates back more than two centuries, to a case series in which James Parkinson described six people with "involuntary tremulous motion" and with a propensity to bend the trunk forward.[13] Since then, research efforts have elucidated a much fuller description of the symptomatology and anatomical origin of PD, as well as developed various treatment designs.[14] There is still however much work to be done, and many questions to be answered. What we do know is that PD is a neurodegenerative disease, the pathophysiology of which involves the loss of dopaminergic neurons in the basal ganglia-related nuclei substantia nigra pars compacta (SNpc). The basal ganglia and related nuclei can be categorized into input, output and intrinsic nuclei. The input nuclei, which consists of the putamen, caudate nucleus and accumbens nucleus, are those structures that receive information from other parts of the brain. The output nuclei – globus pallidus and substantia nigra pars reticulata, are instead responsible for communicating basal ganglia information to the thalamus. Finally, placed between the input and output nuclei are the intrinsic nuclei SNpc, the external segment of the globus pallidus and the subthalamic nucleus. The intrinsic nuclei relay information between the input and the output structures. For the basal ganglia system to function properly, it requires dopamine to be released to the input nuclei.[15] Through complex communication with the cerebral cortex and the cerebellum, the basal ganglia is a main regulator of not only planning movements, but also of the cognitive processes involved in movement strategies and emotions and motivation that help drive movement behavior.[16] The alterations in the basal ganglia-cortical-cerebellar pathways caused by dopamine depletion in PD result in both motor and non-motor symptoms, as will be described in later paragraphs. A pathological hallmark of PD is the presence of protein aggregates called Lewy bodies. Based on the spreading of Lewy bodies, Braak and colleagues suggests that PD progresses in six stages, starting in the dorsal motor nucleus of the vagus nerve and moving in an upward course through the brain, finally extending to the cerebral cortex.[17] Although corresponding to disease initiation and progression in a majority of PD cases, the Braak staging system does not seem to be valid for all PD subgroups and therefore needs further elucidation.[18]

2.1.1 Diagnosing a person with PD

Diagnosing an individual with PD is commonly done using the UK Parkinson´s Disease Society Brain Bank clinical diagnostic criteria, a three-step diagnostic tool. In the first step a diagnosis of Parkinsonian syndrome is made if an individual present with

bradykinesia and at least one of the following: rigidity, rest tremor or postural instability. In step two, a number of exclusion criteria are controlled for, and in step three a number of supportive criteria are controlled for. At least three supportive criteria, for example unilateral onset or progressive disorder, are required for a diagnosis of PD.[19] In 2015, the Movement Disorder Society (MDS) proposed revised criteria for PD diagnosis, intended to be used both in research and as a clinical guide.[20] Unlike the UK Brain Bank Criteria, the MDS version does not include postural instability in the first step when diagnosing parkinsonism. A diagnosis of PD is then established if there is 1) absence of absolute exclusion criteria, 2) at least two supportive criteria, and 3) no red flags (for example early bulbar dysfunction or inspiratory respiratory dysfunction). The reason, stated by the MDS, for removing postural instability as a criterion for parkinsonism caused by PD is that early presence of impaired balance may suggest an alternative diagnosis.[20]

2.1.2 Epidemiology and etiology

Over 6.1 million people worldwide live with PD,[21] and of these approximately 22 000 reside in Sweden.[22] Parkinson's disease is now the fastest growing neurological disorder.[23] The prevalence differs in relation to sex, age and geographic location among other factors. There is a male preponderance in all age groups, [24] and it has been suggested that estrogens may have a protective effect in women, but also that men might be at higher risk of PD because of recessive susceptibility genes on the X chromosome and a higher frequency of occupational toxin exposure as well as minor head trauma.[25] Prevalence rises with age, from 41 per 100 000 in individuals 40 to 49 years, to 1903 per 100 000 in individuals over the age of 80.[24] A majority of included participants in this thesis were ≥60 years of age as this was an inclusion criteria for papers III and IV. This is also representative of the distribution of PwPD in Sweden as over 90% are ≥60 years (45.6% women).[22]

2.1.3 Pharmacological and surgical treatment

As of today, all available therapy options are symptomatic, meaning that they are not curative, neuroprotective or disease-modifying in nature. Pharmacological treatment differs depending on the target symptom. Medication for the relief of motor symptoms are primarily based on dopamine, whereas drugs targeting non-motor symptoms are mostly based on other neurotransmitters such as serotonin, acetylcholine and norepinephrine.[26] Dopaminergic therapies are drugs that either stimulate dopamine receptors or enhances intracerebral dopamine concentrations, and include for example levodopa, dopamine agonists and monoamine oxidase type B inhibitors.[27] Unfortunately, long term dopaminergic therapies may come with side effects. These include dyskinesias (involuntary dystonic or choreiform movement), and motor and non-motor fluctuations.[26] Fluctuations are alterations between periods of good

symptom control (referred to as ON) and periods of reduced symptom control (referred to as OFF).[27]

Both dopaminergic and cholinergic systems are implicated in cognitive impairment in PD, and pharmacological treatment results are variable. Dopaminergic treatment effects on cognition vary with task demand, whether the person has cognitive impairment, genetic factors and other aspects. Cholinesterase inhibitors have a documented positive effect on cognition and behavior in PD dementia (PDD), but evidence is less documented in PD mild cognitive impairment (PD MCI).[28]

Surgical treatment for motor symptoms can be considered in moderate to severe PD and usually entail deep brain stimulation of globus pallidus interna or the subthalamic nucleus.[27] People who have undergone deep brain stimulation are under-represented in this thesis as this surgical treatment was an exclusion criteria for papers III-IV, and for several of the included studies in paper II.

2.1.4 Motor symptoms

The cardinal motor symptoms of PD include bradykinesia, muscular rigidity, rest tremor and postural instability.[27] The focus of this thesis will be on postural instability, here referred to as balance impairments, but the first three motor symptoms will be briefly outlined as they will be evaluated and/or discussed throughout all included papers. Bradykinesia entails a slowness when initiating movements, and a reduction in speed and amplitude when performing repetitive actions. Hypomimia, the loss of facial expressions, is one example of bradykinesia. Rest tremor usually presents in the upper extremities, but with disease progression may also occur in the lower extremities, face and neck. Rigidity is an increased muscle tone causing stiffness of both the limbs and trunk.[29] The most commonly used scale to assess disease severity, the Hoehn and Yahr scale (H&Y scale), is based on clinical motor symptoms and functional disability. In its original version, the scale is from 1-5, with 1 meaning *"unilateral involvement only usually with minimal or no functional disability"* and 5 meaning *"confinement to bed or wheelchair unless aided".*[1] Scoring on the H&Y scale is usually preceded by an examination of motor function according to the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III.[3] The MDS-UDPRS scale, which in its entirety consists of four parts is a more comprehensive measure of disease severity. Throughout this thesis the H&Y scale and the MDS-UPDRS has been used to describe disease severity. The H&Y scale has also been used as an inclusion criterion in papers I, III and IV.

2.1.5 Non-motor symptoms

Non-motor features of PD are under-recognized and under-treated even though they are common and often precede motor symptoms.[27] Non-motor symptoms include neuropsychiatric symptoms such as depression, anxiety, apathy and cognitive impairments, but also sleep impairments, autonomic symptoms, gastrointestinal symptoms and sensory symptoms.[27] Impaired ability to communicate is another set of non-motor symptoms prevalent even in the earlier stages of PD. A survey study in Sweden revealed that within the first five years of PD diagnosis, 44% experienced worsening of speech.[30] The three most frequently reported symptoms related to speech and communication were weak voice, problems with word-finding and imprecise articulation.[30] In paper III, the control group intervention (HiCommunication) specifically targets speech and communication impairments.

2.1.5.1 Cognitive impairment

Impaired cognitive function in PwPD ranges on a spectrum from subjective symptoms (with unimpaired performance on cognitive tests), to PD MCI; a transitional zone in which cognitive impairment is present, but where functional activities of daily living are mainly preserved, and PD dementia (PDD).[31] It has been noted that even at time of diagnosis, approximately 15-20% have developed PD MCI.[32] Longitudinal studies of incident cohorts have shown that two-thirds of PwPD in the early stages will develop cognitive impairments within 3.5 years from disease onset.[33, 34] Approximately 50% of PwPD will develop dementia within 10 years, and 80% within 20 years of diagnosis.[35]

It is well established that executive function is especially affected among PwPD compared to healthy controls.[36, 37] Executive function is an umbrella term for several different actions primarily executed from the prefrontal cortex (PFC) in relation to goal directed behavior. Miyake et al advocates that executive function incorporates inhibition, working memory-updating, and cognitive flexibility, and concludes that these functions contribute differentially to complex executive function tasks.[38] Executive function is what we rely on in moments when we need to concentrate and pay attention and involves the mental processes we use in moments when we cannot or should not rely on automatic or instinctual behavior.[39] In PwPD, impaired executive function results in various problems with, for example, set shifting, planning, inhibition, decision making and dual-task performance.[36] Moreover, impaired executive function may be related to other non-motor symptoms such as depression and apathy, but also to motor symptoms such as balance and gait impairments.[36]

2.2 A FOCUS ON BALANCE AND GAIT

Balance and gait impairments are independent measures of mobility and are often evaluated separately, but due to their overlapping nature they will be discussed here in

tandem. Deterioration of balance and gait ability occurs in line with PD progression, but may be present at all stages of the disease, even at time of diagnosis.[40]

2.2.1 Neurophysiology

Balance and gait are controlled through voluntary movements and automatic processes. Our goal-directed movements start by a command from the cerebral cortex which is then transferred to the brainstem and the spinal cord. The automatic processes include regulation of muscle tone and balance adjustment. The cerebellum acts as a regulator between volition/cognition and automatic processes, whereas the basal ganglia has been suggested to modulate each process through its projection of gamma-aminobutyric acid (GABA) to the cerebral cortex and the brainstem.[41]

Although PD is primarily associated with impaired basal ganglia function, one cannot overlook the impact that alterations to other brain structures and functions has on balance and gait.[42] According to a framework of supraspinal locomotor control in PD, slowness of gait is related to an altered basal-thalamo-cortical loop and an impaired function of the cholinergic system. Gait variability and asymmetry increase as the volitional control of gait increases as a response to decreased automatic control. Lastly, balance impairments are related to impaired function in brainstem activity.[42]

2.2.2 Constructs of balance and gait

Horak and colleagues have previously suggested a framework for understanding the complex nature of balance. They defined six domains that affects balance: biomechanical constraints, stability limits, anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait. According to this model, weakness of ankles or hips, as well as stooped/flexed posture (i.e. constraints to the biomechanical system) can lead to compensatory steps or the use of ankle strategy when recovering balance. Stability limits refers to how far we can move our center of mass over our base of support and constraints to these limits may lead to body tilt or inflexible postural alignment. Anticipatory postural adjustments (APAs) are as the term implies the small adjustments, we make to stabilize ourselves before initiating movements. Constraints in APAs lead to increased instability in for example gait initiation or when rising from a chair. Our postural responses concern the speed, amplitude and strength with which we respond to slips, trips and pushes. Sensory orientation relies on our vestibular system and the capacity to integrate sensory information, and constraints in this domain may lead to disorientation and instability. Finally, stability in gait concerns both the dynamic coordination between the spinal cord and the brain stem, as well as executive and attentional control.[43] See Fig 1 for an overview of the main concepts of the described model. This framework forms the basis of a main outcome measure in this thesis – the

Mini Balance Evaluation Systems Test (the Mini-BESTest), [4] as well as the intervention in paper III.[44]

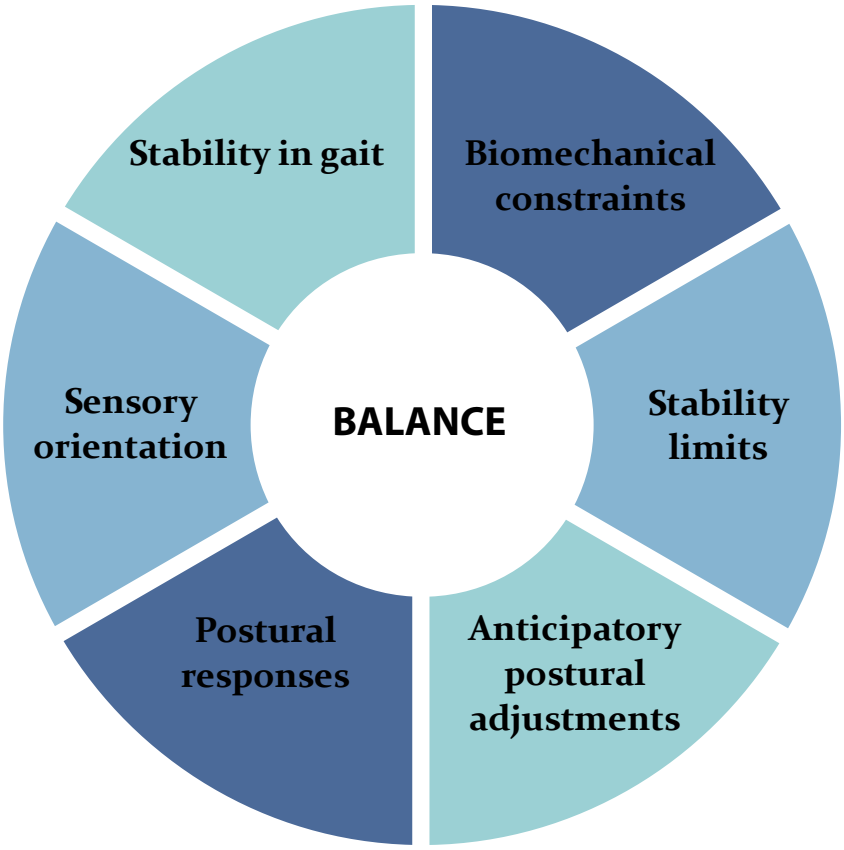

Figure 1. Model of systems underlying postural control. Modified from Horak et al, [43] with print permission from Oxford University Press.

Gait disturbances in PD are either continuous or episodic,[45] and various techniques such as electronic walkways and body-worn sensors can be used to quantitatively capture these outcomes throughout the gait cycle. Examples of episodic disturbances of gait are *festination*, which involve rapid and small steps in combination with an involuntary forward leaning of the trunk and *freezing of gait* where the person temporarily experiences an inability to move the feet forward. Even though episodic disturbances of gait are very debilitating, this thesis is mainly concerned with continuous gait. Lord et al used principal component analysis on 16 gait parameters in order to build a model for understanding continuous gait in PwPD. Five independent domains of gait were identified: pace, rhythm, variability, asymmetry and postural control,[46, 47] see Figure 2 for an overview of this model. Within these domains are gait parameters that are either spatiotemporal characteristics of gait, expressed as means over several steps, or dynamic features which are measures of variability in the spatiotemporal characteristics. As seen in Figure 2, some domains contain measures of both spatiotemporal and dynamic characteristics, whereas the variability domain solely contains dynamic measures.

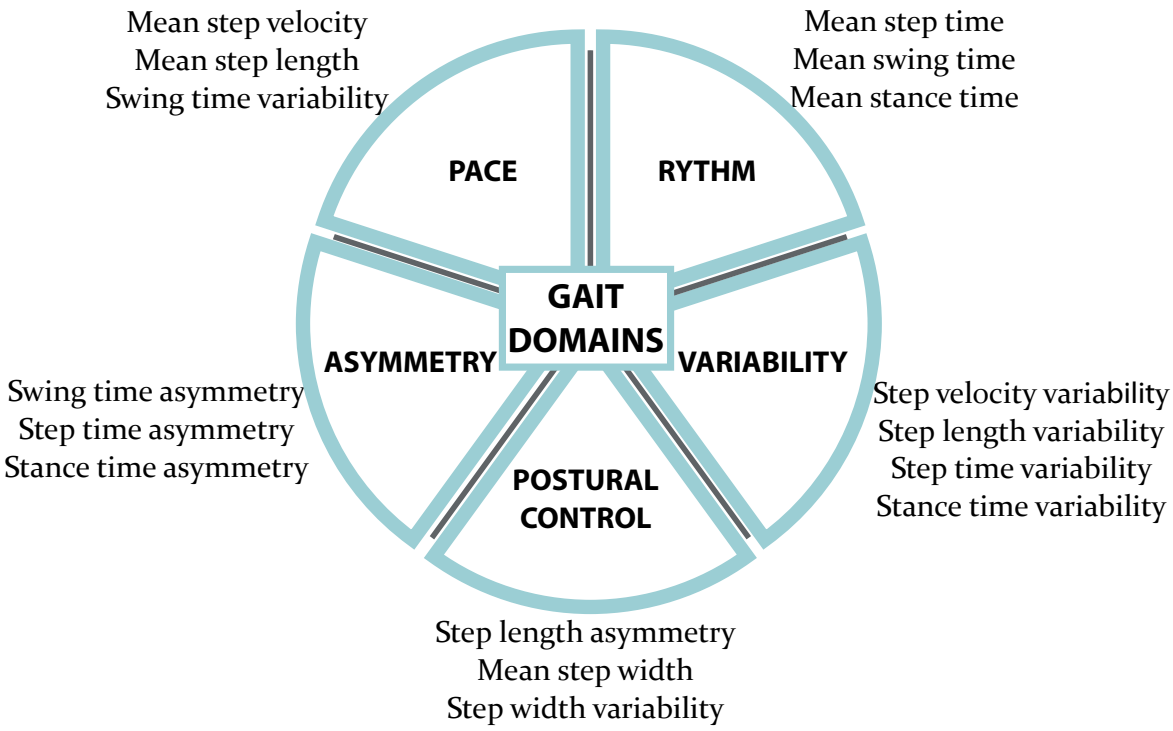

Figure 2. Model of continuous gait domains. Modified from Lord et al, [47] with print permission from John Wiley and Sons.

2.2.3 Gait characteristics in PD

Even in the early stages of PD subtle alterations of gait are noticeable - gait speed slows down, step length shortens and arm swing amplitude decreases. Later, in the mild to moderate stages these changes progress, and usually also manifest bilaterally. This is the stage where the typical parkinsonian gait emerges, with shuffling steps and stooped posture. Problems with turning and gait initiation might appear now, as well as festination and freezing of gait. In the advanced stages of the disease, gait changes are more severe, and further complicated by motor fluctuations and dyskinesia.[48]

Compared to healthy controls, PwPD present with alterations in all gait domains, but typically most pronounced in the pace, variability and asymmetry domains.[49] The combination of reduced gait speed and increased variability is considered to especially predispose to an increased risk of negative outcomes, such as falls.[42] A longitudinal study, following PwPD from diagnosis, revealed that at the last follow-up (54 months following diagnosis), 79.7% had fallen. Of these, 10.7% had fallen once, whereas as 89.3% were recurrent fallers.[50]

2.2.4 Dual task and related terminology defined

Dual tasking has been defined as *"the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals"*.[6] By this definition, a dual task (DT) can consist of either two motor tasks, two cognitive tasks or

the combination of one motor task and one cognitive task. In this thesis, I will primarily focus on the latter. The term interference is commonly used to describe that performance of a certain task is interrupted by a second task which is performed simultaneously. In this thesis, I use the terms DT effect to describe the overall effect, DT cost to indicate a decline in performance and DT benefit to indicate improvement in performance.

Different possible scenarios for how performance during motor-cognitive DT compares to single task execution have been described by Plummer et al.[51] They have further illustrated this pattern of motor-cognitive interference in a conceptual model,[52] see Figure 3 for a modified version. In this model, the DT effect as expressed in percent (%) for each of the tasks (i.e. the ratio from single to DT performance) are plotted. Depending on where in the graph the dot is located, one can interpret whether it was a DT cost or DT benefit on respective task, and also to what extent one task may have been prioritized over the other. With this in mind, it is important that we evaluate the DT effect on both tasks, and not focus on gait alone. Prioritization may have important clinical implications as it has previously been suggested that PwPD use a hazardous posture-second strategy.[53] In Figure 3, a dot in the upper left quadrant implies a posture-first strategy, and a dot in the lower right quadrant a posture-second strategy.

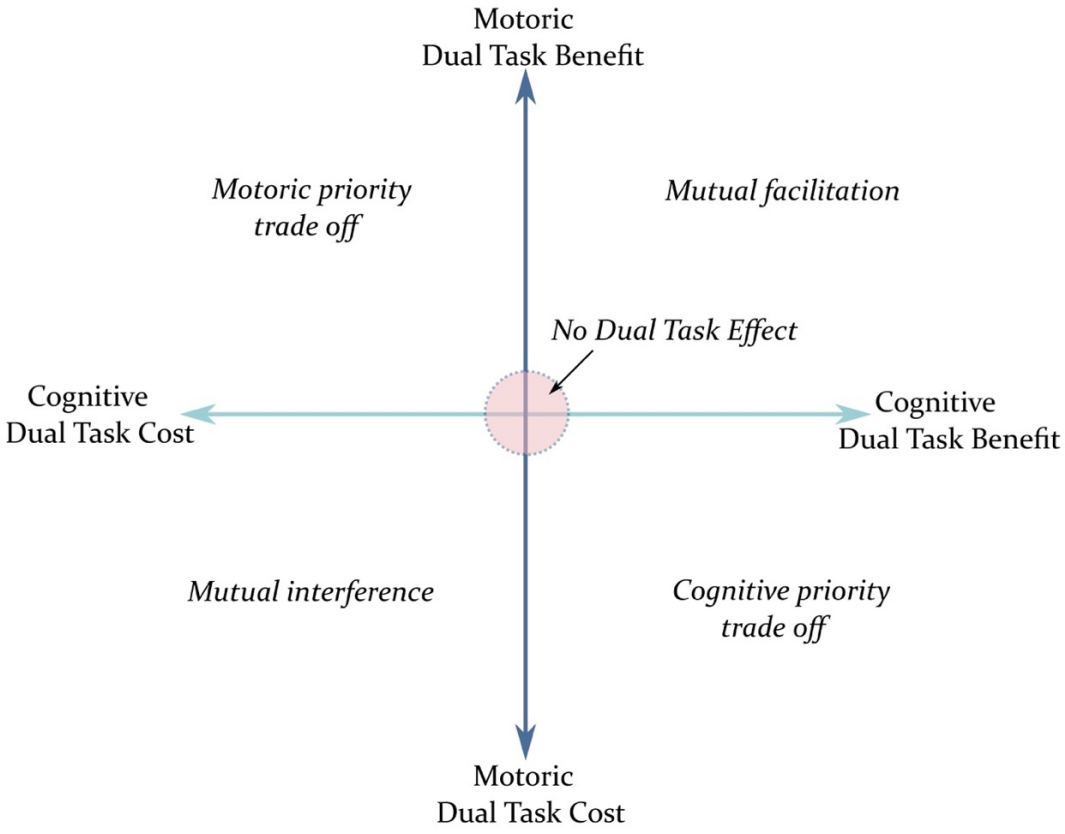

Figure 3. Potential patterns of interference or facilitation when performing a motor-cognitive dual task, modified from Plummer et al.[52]

2.2.5 Possible theories on the dual task paradigm

A key feature of PD is the gradual loss of automaticity. Automaticity in this context relates to the performance of movements without having to direct attention towards the details of those movements.[54] Imaging studies have revealed that in the healthy brain, as a movement becomes automatic, brain activity decreases in several areas (for example in the dorsolateral PFC and the anterior cingulate cortex which are both important for attention), but the connectivity between different motor areas and the putamen instead increases.[55] In PD, due to dopamine depletion in the putamen, no such increase in connectivity strength to motor areas takes place, which leads to difficulties in acquiring automaticity.[55]

What this loss of automaticity leads to in terms of balance and gait is that PwPD shift from an automatic processing to an executive control strategy during movement. Using this compensatory strategy for ambulation is concerning for multiple reasons. One disadvantage is that compared to automatic processing, it takes a longer time for the cerebrum to process peripheral inputs. It is also possible that using executive control for ambulation may tax the available executive resources. Lastly, an executive control strategy is more susceptible and sensitive to stressors in the environment, for example a busy street-crossing, which can potentially lead to a deterioration in locomotor control.[56]

Compared to healthy controls, people with neurological disease typically experience more difficulties when performing two or more tasks simultaneously.[57, 58] Although not yet fully understood, it is believed that the loss of automaticity, together with impaired executive function and decreased attentional resources may partly explain the impaired ability to DT .[55] Two of the most widely accepted theories of DTs and how they affect performance are *the capacity-sharing theory* and *the bottleneck theory*. Whereas the first relates to how DT effects are caused by a limited amount of processing capacity, the latter postulates that interference occurs when two tasks use the same neural processor leading to a serial processing and a delay and/or impairment in performance. Both theories, however, are also described as potentially, yet partially, voluntary, meaning that individuals to some extent can choose which task to prioritize.[59]

2.2.6 Dual tasking in PD

Gait impairments during DT walking are well documented in PwPD. Most reported are DT costs within the pace domains, with decreased gait speed, [60-69] step length, [60, 64, 65, 68, 69] and increased swing time variability [60, 65, 69]. It is perhaps not surprising that most DT costs are reported from the pace domain, as most studies reporting on gait tend to use speed as the priority outcome. There are however reports on DT costs also within the rhythm domain, [64, 65, 67-69] and variability domain [61, 65, 66, 69]. Given the heterogeneity

in type of DT used and gait parameters reported, combining data from studies is problematic. To date, only one meta-analysis exists where data from existing literature on DT costs on gait speed have been aggregated.[70] Using a random effects model, data on single and DT gait speed from 28 studies were meta-analyzed. Results showed a medium to large effect size for reduced gait speed when adding a DT.

2.2.7 Perceptions of balance and gait in PD

For all we currently know about the quantitative measures and manifestations of balance and gait in PD, far less is known about the experience of these impairments. We cannot measure the depth of human experience in numbers. Rating an emotion or ranking a situation is far from understanding the extent of a personal experience. In interviews, PwPD have described how progressively impaired balance lead to emotional distress.[71] It may manifest in a fear of falling which creates a sense of insecurity in everyday life situations and may lead to activity avoidance.[72] There is a large divergence in how different individuals with PD perceive balance and falls, with some describing falls as unavoidable and non-dramatic, while others catastrophize falling.[71] Walking has been described as attention-demanding, especially in narrow spaces or when negotiating obstacles. Narrow spaces can induce feelings of discomfort, of being constrained or even suffocated.[73] Concentrating on walking is required even at an early stage of the disease in order to maintain basic rhythm and cope with distractions, something that is experienced as both tiring and frightening at times.[74]

2.2.8 Exercise and training interventions for balance and gait

Compared to other PD motor symptoms, balance and gait impairments are less responsive to levodopa treatment.[75] Gait speed and step length, both variables within the pace domain, do improve to some extent with levodopa, while other gait parameters and balance are unaffected or even worsened.[76] This unresponsiveness may be explained by gait and balance being more influenced by an impaired function of the cholinergic system, as opposed to the dopaminergic system.[49, 77] Although levodopa medication does not successfully improve or manage these symptoms, balance and gait seem to respond well to other management options such as physical therapy and exercise, therapies which are therefore recommended as an adjunct to levodopa by the Movement Disorder Society.[78]

Although exercise is widely accepted as a non-pharmacological treatment, there is still a paucity in the synthesized evidence of its effect in PD. This is not due to a lack of published articles on the topic, but rather due to the problematic issue of aggregating data with heterogenous interventions and heterogenous outcomes. One of the most frequently cited Cochrane review on this topic, found evidence for the benefits of physical therapy in the short term (less than three months) for outcomes concerning

balance and gait speed and functional mobility. The meta-analyses are however based on few studies and should be interpreted with caution.[79] An update review by the same group also concludes that there is not enough evidence to favor one physical therapy intervention over another, in the short term.[80] It seems however, that when comparing the long term effects of training, that balance training followed by gait training are the modalities with the longest carry-over effects, with results maintained for 6-12 months.[81]

2.2.9 HiBalance

As part of the project Balance Elderly Training and Activity in Parkinson's Disease (BETA-PD) our research group has developed the HiBalance program.[44] This is an intervention consisting of highly challenging balance exercises that target four areas of balance commonly impaired in PD (sensory orientation, APAs, stability in gait and stability limits).[44, 82] The ten-week, supervised, group-training is founded on basic training principles such as specificity, progressive overload and variability.[83, 84] As part of the progression, both cognitive and motor DTs are incorporated with the balance exercises. The HiBalance program has been evaluated both in a controlled research environment,[82] and as implemented in clinical practice.[85] To what extent the improvements shown on balance and gait function after the HiBalance training correlates with changes in the brain has however not yet been determined.

2.3 NEUROPLASTICITY AND EFFECTS OF EXERCISE

2.3.1 Defining and investigating neuroplasticity

Neuroplasticity relates to the potential of the central nervous system to modify itself in response to internal and external pressures. In short, it is the way in which neurons alter their structure and function.[86] Although most often discussed as something positive, abnormalities in behavioral and neural signals can also give rise to maladaptive plasticity such as epilepsy, neuropathic pain, tinnitus and dystonia.[8] Neuroplastic changes can be measured at several levels; molecular, cellular, structural, functional and behavioral.[87] Behavior in this respect relates to for example motor, cognitive or sensory changes, and these are indirect measures of neuroplasticity.[8] There are several different techniques for evaluating neuroplasticity at these various levels, and the choice of methodology needs to be determined by the research question. As part of this thesis I have explored feasibility aspects of investigating neuroplastic changes at the molecular, structural, functional and behavioral levels. There are many different techniques available, but in this background, I will only introduce the methods used in paper III.

On a molecular level Brain-Derived Neurotrophic Factor (BDNF), a nerve growth factor that promotes synaptic plasticity as well as neuronal survival and regeneration, can be detected in blood or cerebrospinal fluid. Levels of BDNF are reduced in PD compared

to healthy controls[88] , and it appears that the reduction is more intense in the early stages of the disease.[89] At the structural and functional levels, different brain imaging techniques can help researchers understand the complex networks of interconnected neurons of the human brain. Techniques based on magnetic resonance imaging (MRI) allows researchers to investigate cortical thickness, regional cerebral blood-flow, task-evoked brain responses and functional connectivity among other factors.[90] The exploration of brain structural and functional changes and how they relate to behavioral changes after an intervention is becoming an increasingly popular way of evaluating the potential effect an intervention has on neuroplasticity.[91]

2.3.2 Exercise-induced neuroplasticity in PD

Over the last decades there has been an increasing interest in whether physical exercise has neuroprotective mechanisms in PD.[92, 93] *Animal studies indicate that physical exercise may have the ability to induce neuroplasticity in PD,* [94-97] but few studies have thus far been conducted on humans. Human clinical studies are not only scarce, but unfortunately also difficult to draw conclusions from, or to compare due to several reasons. *The handful of reviews which have set out to compile the evidence do however point in a positive direction, towards exercise having a possible neuroprotective effect in PD.*[92, 93, 98-100] Small sample sizes, heterogeneous interventions, heterogeneous evaluative methods of neuroplasticity, as well as underreporting or missing information on correlations between behavioral improvement and changes in neuroplastic outcomes, to name a few examples of the challenges faced when attempting to synthesize the current evidence.

2.4 THEORETICAL CONSIDERATIONS

This thesis intended to use a holistic approach to research, in which an individual is seen as a whole and not only as a sum of its parts. The International Classification of Functioning, Disability and Health (ICF), endorsed by the World Health Organization in 2001, is a holistic framework where one looks at disability not merely through the lens of medicine or biology, but also at the impact that it has on a person's functioning and life experience.[2] Within the ICF framework the health condition is classified according to *Body Structure and Function (*physiology and anatomy), *Activity* (how a task or an action is executed) and *Participation* (involvement in life situations) while also considering *Contextual factors* (environmental and personal).[2] This thesis uses the ICF to classify and map out the multitude of outcome measures, while also complementing with other theories and conceptual models for interpretation of findings as appropriate.

2.5 RATIONALE

Exercise and physical therapy can improve balance and gait function in PwPD,[79, 81] yet the majority of this population does not uphold optimal levels of physical activity.[101-103] Sustained engagement in exercise is important as it is perceived by PwPD to improve both physical and psychological symptoms, and thereby enhances the overall sense of well-being and quality of life.[104] Barriers to exercise are spread throughout the ICF domains,[105, 106] and as therapists we need to understand how we can help our clients overcome them. However, in order to better interpret the barriers, we need to gain an understanding of how PwPD perceive their symptoms and how they make sense of them.

Over the last decades the increased interest in exercise-induced neuroplasticity has resulted in a number of experimental studies in both animals and humans with PD. Synthetizing findings and establishing current evidence within this field of research may help develop a neurorehabilitation which focuses on therapies that maximizes neuroplasticity. To date however, only one review published on this topic has been conducted in a systematic manner, but this focused on one neuroplastic outcome only.[93] There is a need to do an updated systematic review of the field in order to synthesize current evidence across all possible outcomes of neuroplastic changes induced by a period of exercise. In order to move this body of research forward we also need to establish what components of our evaluative methods and our interventions that are feasible to perform and acceptable to the people we serve. In line with this, we now also seek to explore the feasibility of evaluating any associations between behavioral improvements after the HiBalance training with neuroplastic changes.

Impaired DT abilities are well-recognized in PwPD, and much research has been done to explore how gait is affected and to what extent tasks are prioritized differently compared to healthy controls.[70, 107] Few studies have however explored DT impairments across all domains of gait, and perhaps even less reported is the cost on the secondary task. Without a complete description of all gait parameters and on the secondary task, we cannot fully understand the extent of the DT impairment or of the strategy used. It has been suggested that PwPD use a posture-second strategy whereby they prioritize the cognitive task at the expense of safe walking,[53] but to what extent this is equally true in individuals with and without PD MCI has been questioned.[108] Given the heterogeneity in cognitive profiles among PwPD, it is of further interest to explore to what extent DT impairment and the strategies used differ in relation to cognitive status.

3 AIM

The overall aim of this thesis was to explore perceptions and performance of balance and gait in PwPD, and to evaluate both the current evidence for exercise-induced neuroplasticity and the feasibility of investigating exercise-induced neuroplastic changes among PwPD.

3.1 SPECIFIC AIMS

Paper I

To explore the meaning of balance for PwPD and the beliefs they hold regarding their ability to influence their balance in everyday life.

Paper II

To establish the current evidence on postintervention effects of a period of physical exercise on neuroplasticity in PwPD.

Paper III

To systematically evaluate the process and scientific feasibility of a trial design to investigate exercise-induced neuroplasticity of the HiBalance program in people with mild to moderate PD.

Paper IV

To explore DT effects during simultaneous performance of a motor task (gait) and a cognitive task (auditory Stroop task) in people with mild to moderate PD.

4 METHODS

4.1 DESIGN

Paper I used a **qualitative design**. Paper II was a **systematic review and meta-analysis**. Paper III was a **pilot randomized controlled trial**. Paper IV used a **cross-sectional design**. For the purpose of increasing reading comprehension, the studies will be explained separately or combined, as appropriate, in the methods section. The following paragraphs outline details of the different methods used in the papers, and an overview can also be found in Table 1.

4.2 PARTICIPANT AND STUDY SELECTION

4.2.1 Recruitment and eligibility criteria

Papers I, III-IV

Participants were recruited through advertisements at the Swedish Parkinson Association and in local newspapers. Sampling methods differed between paper I and studies III-IV, which naturally led to eligibility criteria differing somewhat. Two overall criteria for inclusion in papers I and III-IV were that participants I) had a diagnosis of idiopathic PD, and II) scored ≥21 on the Montreal Cognitive Assessment (MoCA).[5] This test of global cognitive abilities is brief and has a maximum score of 30, and is widely used as a screening tool for possible cognitive impairment in PD.[109] Participants were excluded if they scored <21 as this is the recommended cutoff for possible dementia. In paper I, people of all ages, and in Hoehn and Yahr stages I-V, were considered for inclusion, whereas in paper III and IV, participants had to be ≥60 years of age and in Hoehn and Yahr stages II-III. In paper I, recruitment was based on a maximum variation sampling, as our intention was to include participants with different experiences of balance.[110] We therefore strived to include participants who differed with regard to time since diagnosis, age, sex, physical activity level, and self-perceived balance, etc. In studies III and IV, on the other hand, a purposive sampling method with narrower inclusion and exclusion criteria was used. The reasons for this were multifold, but the primary one was that these studies build and extend on previous explorations of the HiBalance program with similar eligibility criteria.[82] We also had to add exclusion criteria for safety reasons in the MRI environment. Due to this environment, some specific exclusion criteria were added for paper III, and by extension also for paper IV, as this was based on baseline data for a larger RCT, where MRIs are performed. Participants were excluded here if they had MRI incompatible implants or claustrophobia.

Table 1. Overview of design and methods for papers I-IV.

	Paper I (n=18)	**Paper II** (13 studies, n=213)	**Paper III** (n=13)	**Paper IV** (n=93)
Design	Qualitative	Systematic review and meta-analysis	Pilot randomized controlled trial	Cross-sectional
Data collection and Study selection	In-depth interviews Clinical assessment Questionnaires	Exhaustive database searches in: Medline, Embase, Cinahl, and Pedro	Feasibility data Clinical assessment Questionnaires	Clinical assessment Questionnaires
Setting	Participants' home University	Hospital (inpatient and outpatient) University	University Hospital	University
Data analysis*	Qualitative content analysis Descriptive statistics	Narrative synthesis Meta-analysis of subsample GRADE analysis	Descriptive statistics	Descriptive statistics Linear regression
Study population				
Age, mean (SD)	*69.8 (8.6)*	*64.6 (7.6)*[a]	*69.2 (5.1)*	*71.0 (6.1)*
Sex, women n (%)	*9 (50.0)*	*75 (38.1)*[a]	*4 (30.8)*	*34 (36.6)*
Hoehn & Yahr, range	*1-4*	*1-3*[a]	*2-3*	*2-3*
MoCA, mean (SD)	*25.4 (2.9)*	*NA*	*26.5 (2.1)*	*25.8 (2.4)*
Years with PD, mean (SD)	*8.8 (5.7)*	*NA*	*8.0 (3.2)*	*5.2 (4.5)*

*See Table 3 for detailed information on descriptive and inferential statistics used in the thesis.

[a]Calculated without ref Fisher et al. 2008,[111] because of missing information.

Paper II

In order for studies to be eligible for inclusion in the systematic review, they were to be intervention studies conducted on humans with idiopathic PD. The intervention of interest for our aim included any type of physical exercise performed repeatedly (i.e., performed on more than one occasion). We also included studies where the intervention was a combination of physical and mental training, as long as the majority of the intervention was the physical exercise part. Studies were not excluded based on any of the following criteria: disease stage, age, sex, medication, publication date or language. Studies were, however, excluded if they only examined acute effects (<24 hours) of exercise, or if in a combined intervention the mental training made up the majority of the intervention.

4.3 ETHICS

All studies within the thesis were conducted according to the ethical principles of the Declaration of Helsinki. [112] Papers I, III and IV were approved by the regional ethical board in Stockholm County with the following registration numbers:

Paper I: 2016/201-31/2 with amendment 2016/1973-32

Papers III and IV: 2016/1264-31/4 with amendments 2017/1258-32 and 2017/2445-32

4.4 DATA COLLECTION

Data collection for this thesis commenced in November 2016 and concluded in September 2019. The setting depended on where data was collected or intervention was performed, and varied among participants' homes (paper I), university settings and/or clinical settings (papers II-IV). For clinical testing of balance, gait and motor function in papers I and III-IV, participants were assessed in their ON stage of levodopa medication. See Table 2 for the full list of self-rated as well as clinically assessed outcomes in papers I, III and IV.

Table 2. Overview of self-rated and clinically assessed outcomes reported in papers I, III and IV

Outcome	Instrument	Paper		
		I	III	IV
Contextual factors				
Age	Interview	•	•	•
Sex	Interview	•	•	•
Education	Interview			•
Years since diagnosis	Interview	•	•	•
Disease severity	Hoehn & Yahr scale	•	•	•
Medication	Levodopa Daily Equivalent Dose		•	•
History of falls	Interview	•	•	•
Walking aids	Interview	•		
Body function & structure				
Body mass	Body Mass Index		•	•
Brain structure	Magnetic Resonance Imaging (MRI)		•	
Brain function	Resting state functional MRI (fMRI)		•	
	Task evoked fMRI		•	
Nerve growth factor	Brain-Derived Neutrophic Factor in blood plasma		•	
Motor function	MDS-UPDRS III	•	•	•
	MDS-UPDRS IV			•
Speech	Voice intensity		•	
	Dysarthria		•	
	Word intelligibility		•	
	Sentence intelligibility		•	
Global cognition	Montreal Cognitive Assessment	•	•	•
Executive function	Trail Making Test, trial IV		•	•
	Color Word Interference Test		•	•
	Verbal fluency		•	•
Attention/working memory	Trail Making Test, trials I-III		•	•
	Digit span		•	•
Episodic memory	Brief Visuospatial Memory Test – Revised (BVMT-R)		•	•
	Rey Auditory Verbal Learning Test (RAVLT)			
Visuospatial functions	Copy condition from BVMT-R		•	•
Depression and anxiety	Hospital Anxiety and Depression Scale		•	•
Experiences of daily living	MDS-UPDRS I		•	•
	MDS-UPDRS II		•	•
Activity & participation				
Balance	Mini Balance Evaluation Systems test	•	•	•
	Activities-specific Balance Confidence Scale	•	•	•
Gait/walking	Electronic walkway*		•	•
	Walk 12	•	•	•
Mobility	Timed Up and Go	•	•	•
Physical activity	Physical Activity Scale for the Elderly	•		
	Frändin & Grimby		•	
	Accelerometer Actigraph		•	
Well-being				
	EuroQol 5 Dimensions, Index		•	
	EuroQol 5 Dimensions Visual Analogue Scale		•	•
	Parkinson's disease Questionnaire -39		•	•

4.4.1 Paper I

For paper I, semi-structured, in-depth interviews were performed by the author of this thesis. An interview guide with predefined themes and open-ended questions were developed and used. The interviews had an average length of 51 minutes (range 22-75

minutes) and were recorded using a digital Dictaphone (Olympus VN-741PC). All interviews were transcribed verbatim. For descriptive purposes, a second visit with the participants was conducted in order to perform clinical testing and to collect self-reported questionnaires. The clinical testing was purposefully always scheduled after the interviews as we did not want the participants' thoughts or views to be influenced by how they had performed on balance tests, or by the type of questions posed in the questionnaires.

4.4.2 Paper II

A study protocol was established and registered in Prospero (ID CRD42017057834). After agreeing on a suitable search strategy among the authors, librarians assisted with performing exhaustive searches in February 2017 in the following databases: Medline (Ovid), Embase, Cinahl (EbscoHost) and PEDro. An update search was performed in November 2017. During the study selection phase, all studies identified through database searches were screened for eligibility by two review authors blinded to each other´s decisions using the web-based tool Rayyan. [113] Any disagreements after the initial screening were resolved through a third review author. The two initial reviewers then screened the potential articles in full text, once again blinded to each other's decisions. After this screening process, a final decision was then taken as to which studies to include. (See paper II, Figure 1, for a PRISMA flow diagram of the screening process.) Data was then extracted based on predefined outcomes. Of special relevance was information on the neuroplastic outcome, but we also retrieved data pertaining to sociodemographic information, disease severity, eligibility criteria, setting and intervention (type, intensity, frequency and length), etc.

4.4.3 Paper III

Feasibility studies commenced before a future RCT are designed to evaluate whether or not the planned RCT can be done, and if so how. A pilot trial falls under the umbrella term of feasibility studies and is usually a smaller-scaled version of the future RCT.[114] In conducting a pilot trial ahead of the future RCT, researchers are given the opportunity to evaluate various features of the design and an opportunity to make changes when needed. In pilot studies, the aspects of feasibility monitored can be grouped into *process*, *resources*, *management* and *scientific*.[115]

In paper III, the main focus was on evaluating feasibility aspects of the trial design in order to support the development of a future, appropriately powered RCT. We primarily evaluated and reported process feasibility, such as recruitment rates and retention rates, and scientific feasibility, such as safety of interventions and trends in treatment response.[115] The trial design was monitored from the study launch, i.e. from

advertisement and initial telephone screening, to study completion, i.e. until last post assessments (see Figure 4 for details).

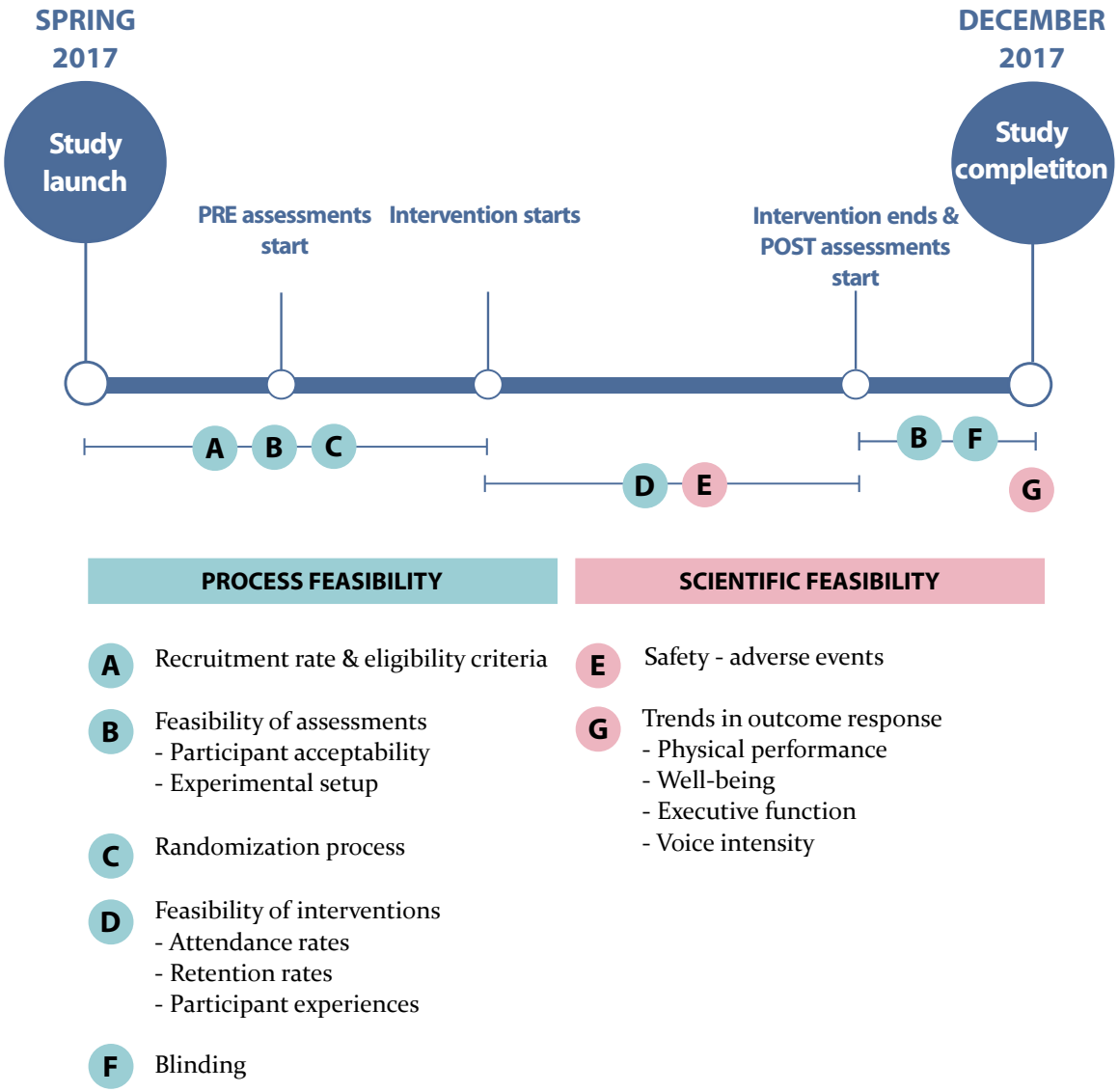

Figure 4. Timeline of the pilot trial, paper III, from study launch to study completion with overview of process and scientific feasibility outcomes

Pre- and post-assessment sessions consisted of three sessions each. The first pre-assessment session was done in order to confirm eligibility, and to evaluate physical function (balance, gait, motor function, etc.). The following two sessions consisted of I) structural and functional brain imaging, and II) evaluation of cognitive function as well as voice intensity and speech intelligibility. All three sessions lasted 90-120 minutes each.

4.4.4 Paper IV

Paper IV is based on baseline data from the EXPANd trial (see Franzén et al. for study protocol).[116] Data used for paper IV was collected on two separate occasions in order to

avoid fatigue. During the first session, eligibility was confirmed, and demographic information collected. Participants were then assessed based on balance and DT gait performance, as well as motor function. During the second session, participants were assessed with a neuropsychological test battery. Both sessions lasted 90-120 minutes each.

4.4.5 Self-reported and clinically assessed outcomes

In all studies, socio-demographic information was collected (papers I, III and IV) or extracted (paper II). The diagnosis of idiopathic PD was handled differently in the different studies. In paper I, a pragmatic approach was chosen in which information regarding diagnosis was provided by the participants themselves. In paper II, this was based on inclusion criteria in each study. In papers III and IV, participants were to provide a certificate from their neurologist or excerpts from their hospital record confirming the diagnosis. A plenitude of methods was used to assess participants' function throughout papers I, III and IV. The following paragraphs describe those assessments of greatest importance for the comprehension of this thesis.

4.4.5.1 Balance

In papers I, III and IV, balance was assessed using the Mini-BESTest. This is a clinical test covering four components of balance: anticipatory postural adjustments, reactive postural control, sensory integration and dynamic gait. It ranges from 0 to 28 points with higher scores indicating better balance performance.[4] Psychometric evaluation has shown that this tool has good inter-rater and test-retest reliability in PD. Evaluations of agreement, however, have shown large measurement errors, especially in the reactive postural control subcomponents.[117]

Balance confidence was measured with the help of the Activities-specific Balance Confidence scale (ABC), a self-report questionnaire where participants subjectively rated their confidence in performing various ambulatory activities without falling. More specifically, participants rate to what extent they feel confident in performing 16 activities on a scale from 0 to 100.[118] The ABC scale has been used extensively in PD and has very good internal consistency and test-retest reliability in this population.[119]

4.4.5.2 Single and dual task gait

Temporal and spatial gait parameters during single and dual task walking was captured using the electronic walkway system GaitRite© (CIR Systems, Inc., Haverton, PA, USA). A distance of three meters at both ends of the walkway was used for acceleration and deceleration distances, thereby ensuring steady state walking.[120] Participants walked at self-selected usual speed during single and DT conditions. For paper III, only gait speed was reported, whereas in paper IV 16 gait variables were calculated and reported. These

16 gait variables are the same as those described in the background, paragraph *2.2.2 Constructs of balance and gait*. Asymmetry variables were calculated as the absolute difference between left and right leg, whereas variability variables were calculated in Excel (Excel®, Microsoft, USA) as described by Galna et al. [121]

$$SD_{Left\ \&\ Right} = \sqrt{\frac{(Variance_{Left\ Steps} + Variance_{Right\ Steps})}{2}}$$

For the secondary aims of paper IV, two gait variables were chosen: gait speed and step time variability. Speed, which is a global measure of gait,[122] is perhaps the most intuitively interpretable gait parameter, whereas step time variability on the other is interesting, as it has previously been used as a surrogate marker for both fall risk[123] and gait automaticity.[124] Step time variability has also been suggested to be independent of gait speed, and perhaps more reliant on balance-control mechanisms.[125]

In paper III, two different cognitive DTs were compared: the auditory Stroop task[126] and an n-back task (two-back).[127] Based on the results of the feasibility investigation in paper III, we decided to continue using the auditory Stroop task for the large scale RCT (and thereby also for paper IV of this thesis). During the DT condition, participants were introduced to the auditory Stroop, which is a task addressing set shifting and inhibition. It is both valid[128] and reliable[129] for DT gait assessment in PD. During this task, participants used wireless headphones through which they were presented with the Swedish words for "high" or "low" in congruent or incongruent high and low tones. Participants were instructed to respond verbally to the corresponding tone as quickly as possible. The auditory Stroop task was performed both as a single (in a seated position) and DT (during walking), and a randomization process decided which condition came first. In the DT, walking participants were instructed to pay equal attention to walking and the auditory Stroop task. Reaction times (RT, beginning of stimulus to beginning of response) on the auditory Stroop task was analysed using MATLAB (R2017b).[130] See Figure 5 for example of audiofile as analysed in Matlab. The script provided mean reaction times as well as standard deviation of reaction times (SDRT); the latter was used as a measure of intraindividual variability.

Perceived walking difficulties were assessed using the Walk-12 scale, a questionnaire of self-reported walking ability.[131] This scale is valid and reliable in PD populations.[132]

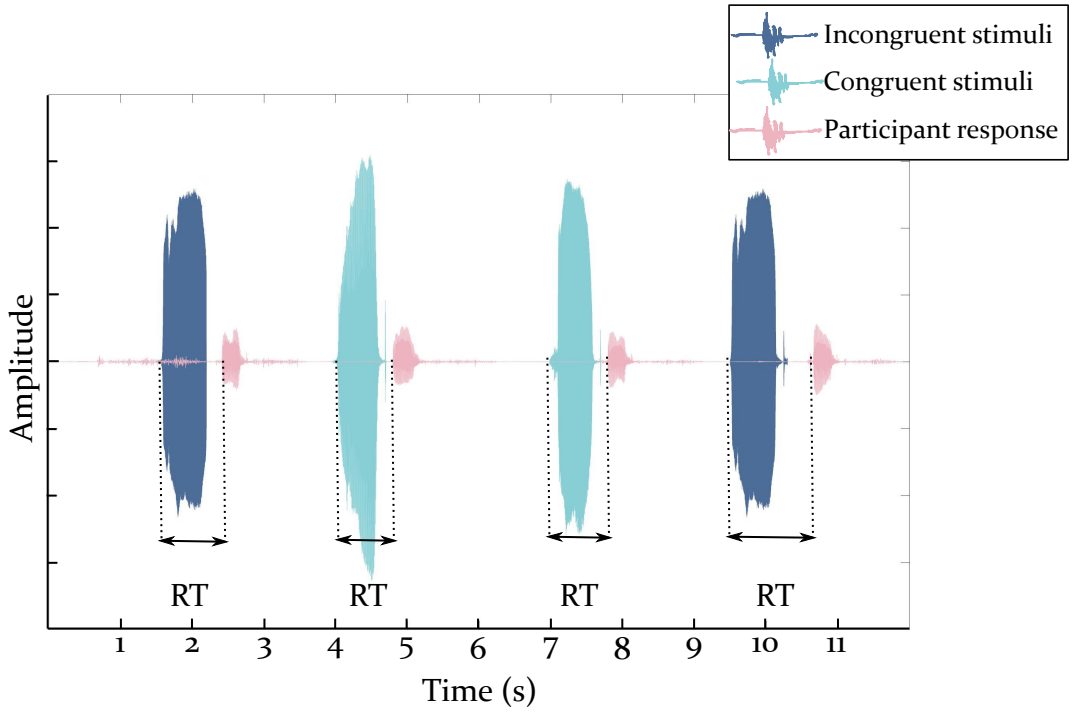

Figure 5. Example of audiofile, with reaction times (RT).

4.4.5.3 Motor function and disease severity

In paper I, motor function was assessed using the Unified Parkinson Disease Rating Scale (UPDRS), whereas the revised version MDS-UPDRS was used in papers III-IV.[133] In full, both scales contain four parts pertaining to motor and non-motor experiences of daily living, a motor examination and a section pertaining to motor complications. Although restructured in order to improve clarification, the later version correlates highly with the original scale (total score r=0.96), thereby showing a strong concurrent validity.[3] This thesis mainly focuses and reports on part III, the motor examination, which is also strongly correlated between the UPDRS and the MDS-UPDRS (r=0.96). All parts of MDS-UPDRS have proven to have high internal consistency, with part III (motor part) having the highest (Crohnbach´s alpha=0.93).[3]

As part of the UPDRS and MDS-UPDRS scales, participants are also scored on the H&Y scale, a five-point disease rating scale ranging from 1, meaning minimal or no disability, to 5, where the person is confined to bed/wheelchair unless aided.[1] The H&Y scale was used during eligibility screening for studies I, III and IV, and will be used as a measure of disease severity in this thesis.

4.4.5.4 Markers of neuroplasticity

Papers II and III evaluate different aspects of exercise-induced neuroplasticity. Where paper II investigates the current evidence based on published trials, the focus in paper

III is instead on the feasibility aspects of using neuroplastic outcomes to evaluate the HiBalance program.

As the aim of paper II was to compile all available published evidence to date, we were interested in any outcome measure of neuroplasticity. We have divided them into three subdomains: *neurochemical, brain function* and *brain structure*. For a full list of methods used within each subdomain, see paper II, Table 1.

In paper III, participants underwent structural MRIs, resting state fMRIs and two task-based fMRI scannings before and after the intervention period. For this assessment, a Philips Ingenia CX 3 Tesla MRI scanner was used. In an attempt to investigate the same abilities as during gait analysis we designed the task fMRI sequences to be one single task (motor task, using index and middle fingers on both hands to push buttons) and one DT (similar motor task as in single, but with added cognitive task where participants counted plus signs).

Levels of brain-derived neurotrophic factor (BDNF) in plasma was measured at two time points in paper III. Blood samples were collected at each training site before the first and last training session by a registered nurse.

4.4.5.5 Cognitive function

As part of the eligibility screening for studies I, III and IV, global cognitive function was assessed using MoCA.[5] In studies III and IV, participants were further examined with a neuropsychological test battery. This battery took in a total of 60-70 minutes and targeted four cognitive domains: executive function, attention/working memory, episodic memory and visuospatial functions. For paper IV the neuropsychological test battery was used in order to classify participants as PD non-MCI or PD MCI, according to the Movement Disorder Society task force level II category.[134] See paper IV for a detailed description of the classification process.

4.4.5.6 Well-being

Quality of life and health status was measured using either PD-specific or -generic questionnaires. Parkinson Disease Questionnaire -39 (PDQ -39) is an instrument that covers the impact that PD has on various aspects of both functioning and well-being.[135] The scale has good content and construct validity, as well as good internal consistency for the scale total (Crohnbachs alpha 0.84-0.94).[136] In the papers included in this thesis, only the summary index, a score derived by dividing the sum of the subscores by eight (the total number of subdomains), of the PDQ -39 is reported.

Further, participants completed the Euroqol 5 dimensions (EQ5D),[137] a widely used generic instrument where the respondent rates his or her problems with mobility, self-

care, and usual activities, as well as pain and anxiety/depression, on a three-level scale. The respondent further rates his/her health on a scale from 0, meaning the worst health imaginable, to 100, meaning the best health imaginable. In the papers included in this thesis, only the last part (health rating) is reported.

4.4.6 Feasibility outcomes

4.4.6.1 Process feasibility

As already mentioned, the focus of paper III was not on the efficacy of the intervention, but on the feasible aspects of our proposed RCT design. With regards to feasibility of pre- and post-assessment sessions we focused on the experimental setup of those methods not previously conducted in the BETA-PD project. Several aspects of the DT gait assessment for paper III demanded attention. As described in paragraph *4.4.5.2 Single and dual task gait,* we compared two different types of cognitive DTs (auditory Stroop and n-back) during walking with the intention of choosing one of them for the future RCT. Whereas some feasibility aspects of DT gait lent themselves to descriptive explorations, such as accuracy (% correct answers), others, such as participants' ability to understand instructions, were evaluated in a more pragmatic manner through discussions within the research team. The brain imaging session was evaluated both by means of pure image quality, but also to patient-related measures/symptoms such as pain/discomfort, drowsiness, diplopia, etc. Lastly, we monitored participants' compliance with blood sampling and noted whether any participants refused this type of examination.

Attendance at each training session was reported by the trainers. Compliance with the home exercises was monitored using a simple diary where participants reported whether or not they had performed the exercises each week. Participant acceptance of the HiBalance training and the HiCommunication training was further explored using anonymous questionnaires after the last training session. Here, participants answered questions relating to whether they felt that the intervention had improved (or worsened) symptoms related to balance, voice/speech or other symptoms, and whether they had experienced any side effects such as pain or fatigue from the training sessions. They also rated to what extent they would recommend this type of training to other people with PD.

Assessors of physical performance were to be blinded as to which intervention participants were allocated. The blinding process was evaluated with a questionnaire inspired by Minns Lowe et al.,[138] in which the assessors after the last post-assessment session stated whether or not they knew which group the participant had taken part in, and whether this was a guess or if the participant had in fact revealed it.

4.4.6.2 Scientific feasibility

Adverse events during the group training sessions were noted by the trainers, whereas adverse events during home exercises were noted by participants.

Trends in treatment response were explored descriptively, with a specific focus on physical performance, well-being, executive function and voice intensity.

4.4.7 Interventions

4.4.7.1 Paper II

Various types of physical exercise interventions were conducted in the trials in paper II, including exercise bike, treadmill training, balance training, motor rehabilitation, multidisciplinary rehab, improvisational dance and gait training.

4.4.7.2 Paper III

The intervention in paper III was the HiBalance training. The efficacy and effectiveness of this program was evaluated by our research group previously.[82, 85] The HiBalance program consists of highly challenging balance exercises targeting four areas of balance: sensory integration, anticipatory postural adjustments, motor agility and stability limits. Exercises were performed in a group setting twice a week for ten weeks in an increasingly challenging manner. Exercises were primarily progressed by adding cognitive and/or motor DTs. Participants were also instructed to perform a home exercise program (HEP) that focused on functional aerobic and strength exercises once a week.

The active control group intervention was developed and tested for the first time in paper III. Participants in the control group received speech and communication training, and the program was subsequently called HiCommunication. Exercises here instead focus on four areas important for communication in PwPD: voice intensity, articulatory precision, word retrieval and memory. Participants were also instructed to perform a HEP that focused on voice and speech function once a week.

See paper III, Table 1 for a detailed description of intervention and control group interventions.

4.5 ANALYSIS

Descriptive data in this thesis was analysed using IBM SPSS Statistics for Macintosh, Version 25.0 and 26.0 (Armonk, NY: IBM Corp.) The overall approach presents mean and standard deviations for normally distributed data, but median and interquartile range (or range) for non-normally distributed data and small samples as appropriate throughout all studies. Normality was assessed with kurtosis and skewness values, Shapiro-Wilks values and by visual inspection of QQ-plots and histograms. Specific statistical tests are summarized in Table 3.

Table 3. Descriptive and inferential statistical methods used in the thesis.

Statistics	Paper I	Paper II	Paper III	Paper IV
Descriptive				
Counts	•	•	•	•
Percentages		•	•	•
Range	•			
Mean (and SD)	•	•		•
Median (and IQR, range)			•	•
Inferential				
Confidence intervals		•		•
Hedges' *g*		•		
Wilcoxon signed rank test				•
Single sample t-test				•
Pearson's correlation coefficient				•
Univariate linear regression				•
Multiple linear regression				•

Abbreviations: IQR, interquartile range; SD, standard deviation

4.5.1 Paper I

Interview transcripts were analysed using content analysis, a systematic method of capturing central themes from text.[139] All transcripts were read repeatedly, after which meaning units were identified. The meaning units were then coded in several cycles, where they were first assigned descriptive information codes during the first cycle and pattern codes during the second cycle.[140] Conformability of the analysis process was ensured through a series of team debriefing meetings where all authors discussed coding and categorization. All authors were also involved in developing and refining subthemes, main themes and the overarching theme.

4.5.2 Paper II

Upon inclusion in the review, all studies were assessed based on research quality. The critical appraisal method chosen was the 27-item Downs and Black checklist, which was modified for the purpose of this review. The Downs and Black checklist ultimately provides an overall index by including the following domains: reporting, external quality, internal validity bias and internal validity confounding.[141] An overall quality index grade was then applied according to the suggestion by O´Connor et al: excellent, good, fair or poor.[142]

Two types of syntheses were conducted in paper II, a narrative (qualitative) where all included studies within each outcome subdomain were included, as well as a meta-synthesis (quantitative) within the neurochemical subdomain. The narrative synthesis reported the direction of change (positive, negative or absence) within each neuroplastic outcome subdomain. For the meta-synthesis, only the neurochemical subdomain was included, as this was the only subdomain that provided aggregable and comparable outcome data. The Meta-essentials workbook 4 was used, in which effect sizes were generated using a random effects model.[143]

An overall level of evidence as to whether exercise can induce neuroplasticity in PwPD was assessed using the GRADE method.[144] After having set an initial level of evidence based on a judgement of paper phase, the following factors were considered for further downgrading: study limitations, inconsistency, indirectness, imprecision and publication bias. Lastly, an overall four level of evidence was set: ++++ (high), +++ (moderate), ++ (low), or + (very low).

4.5.3 Paper III

Due to the small sample size (n=7 in the HiBalance group and n=6 in the HiCommunication group), no inferential statistics were applied in paper III. All demographic data and clinical characteristics at baseline, as well as trends in treatment response, are therefore reported in median and range. Treatment response i.e. changes in physical performance measures (balance and gait), well-being, executive function and voice intensity, from pre- to postintervention, was calculated as median differences in respective outcomes.

The DT effect on gait speed and accuracy on respective cognitive task was calculated as suggested by Kelly et al.[145]

$$DTE(\%) = \frac{Dual\ task - Single\ task}{Single\ task} \times 100$$

Feasibility outcomes with a numerical value, such as attendance rates and blinding rates, were compiled and reported descriptively. Recruitment rate was calculated as the

number of people eligible for inclusion divided (n=13) by the number of people reporting interest in participating (n=42). Closed questions in both the MRI feasibility questionnaire and the intervention follow-up questionnaire were coded and collated. Open questions were instead categorized as appropriate, but not coded.

4.5.4 Paper IV

The main aim of the study was to explore DT effects on all 16 gait parameters, as well as three outcomes on auditory Stroop (accuracy, reaction time and SDRT). The main outcome, the DT effect, was calculated as suggested by Kelly et al.[145]; see paragraph *4.5.3 Paper III* for equation. To assess whether there was a significant difference in performance between single s DTs, a Wilcoxon signed rank test was conducted (non-parametric statistics were used, as many of the gait variables were non-normally distributed).

For the secondary aims, unadjusted and adjusted linear regression were applied. Dual task effects (on gait speed, step time variability and cognitive performance) were used as dependent variables. Potential factors associated with DT effect variables were selected first on clinical reasoning, and thereafter on correlation ($p<0.2$) in univariate linear regression. Multicollinearity cutoff was set at $r>0.6$. Independent variables were entered into the regression models using backward selection. For more information on handling of univariate and multivariate outliers, see manuscript for paper IV.

Lastly, prioritization was calculated by subtracting the DT effect on gait variables speed and step time variability from the DT effect on cognitive performance. A negative value thus indicated gait task prioritization (posture first strategy), and a positive value indicated cognitive task prioritization (posture second strategy). In order to determine if the mean prioritization value was significantly different from zero, a single sample t-test was run. Univariate linear regression was used to assess the potential of group differences between the PD MCI group and the PD non-MCI group, with regards to the DT effect variables and prioritization (DT effect variables as dependent variable and cognitive status as independent variable). These models were also rerun adjusted for sex and age. A p-value <0.05 was considered statistically significant for all analyses.

5 RESULTS

5.1 PERCEPTIONS OF BALANCE AND GAIT – PAPER I

From the thematic analysis of the interviews in paper I emerged 13 subthemes that represented five main themes: Remaining in control over the body; Adapting behavior to deal with uncertainty; Directing focus to stay one step ahead; Resilience as a defence; and Exercise beliefs and reservations. Together, these main themes formed the overarching theme Focus and determination to regain control over shifting balance; see Figure 6 for an overview.

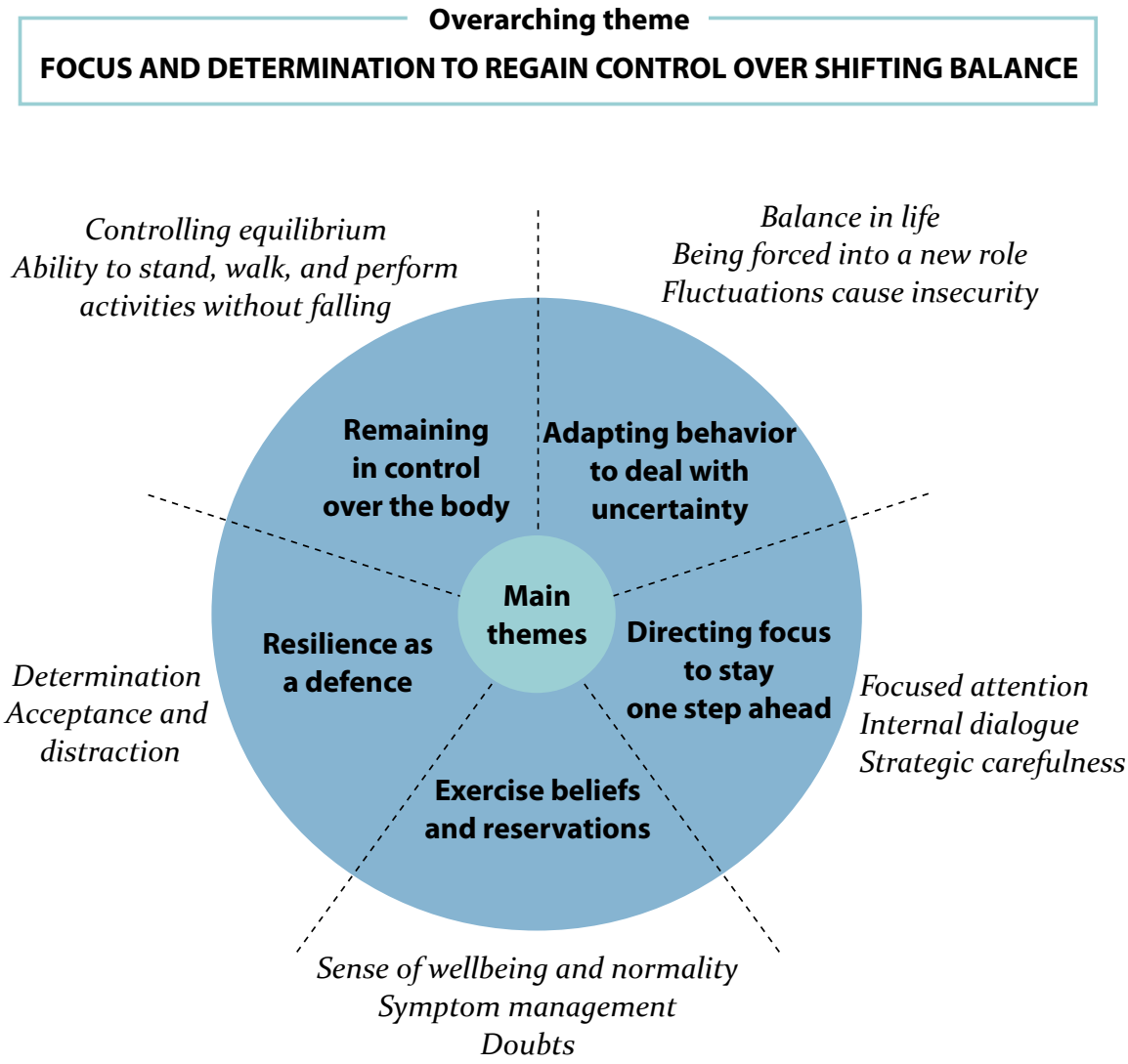

Figure 6. Overview of the overarching theme, main themes and subthemes (italics) emerging from the thematic analysis

5.1.1 Remaining in control over the body

Participants described the concept of balance in terms of being able to control one's equilibrium through a combination of automatic and voluntary processes. To have equilibrium was described as being in an effortless state where one did not have to plan for balance challenging movements. Having "good" balance meant feeling a sense of normalcy, where one wasn´t mistaken for being under the influence of alcohol and where movements could be performed in a "normal" manner.

5.1.2 Adapting behavior to deal with uncertainty

Having impaired balance repeatedly meant having to adjust or even quit doing activities one would like. This connection between balance as a physical function, and the consequences it had on one's sense of freedom and independence, meant balance was also talked about in relation to mental well-being and the interplay between body and mind.

5.1.3 Directing focus to stay one step ahead

Participants described becoming more aware of and careful in balance challenging situations. Not only were they more thoughtful when planning their movements, but also more attentive while performing them. They expressed having to concentrate on one task at a time and put an increasing amount of effort into it so as not to fall. One recurring strategy described was self-talk as a way to communicate with one's body when performing goal-directed actions.

5.1.4 Resilience as a defence

Even though having impaired balance forced participants to change some aspects of their everyday life, they did express a determination not to refrain from activities they enjoyed or from spending time with loved ones. Not adapting too much and not feeling sorry for themselves also meant that they did not let the diagnosis or balance impairment define who they were.

5.1.5 Exercise beliefs and reservations

Belief in exercise varied. Some used exercise or physical activity as a means to take their mind off of the disease. Others expressed exercise as necessary symptom relief, and some also believed that challenging activities was positive for the brain. Not all, however, believed that exercise could improve symptoms. Some believed that since the brain is affected by PD, symptoms were less likely to be managed with exercise. Others simply had previously had unsatisfying results from exercise, which had led to doubt.

5.2 EVIDENCE FOR EXERCISE-INDUCED NEUROPLASTICITY – PAPER II

The final result of our extensive database searches was that a total of 13 articles were included in the systematic review. These studies had been performed in various countries (Brazil, Canada, Germany, Israel, Italy, Spain and USA) and settings (three inpatient and ten outpatient). The sample sizes were small, rendering a total of 151 intervention group participants and 63 controls. Methods used to explore neuroplasticity were divided into three domains and included neurochemical (plasma and serum levels of brain-derived neurotrophic factor, as well as BDNF-TrkB signalling), brain function (fMRI, EEG, PET and TMS) and brain structure (MRI). Quality assessment according to the modified Downs and Black checklist revealed that a majority (nine) of these studies were of "fair" quality, while three were of "poor" quality, and one was rated as "good" quality.

5.2.1 Narrative synthesis

The narrative synthesis revealed positive effects of exercise on neuroplastic changes within the brain function and brain structure domains. Within the neurochemical domain, results were less clear, with three studies showing positive effects and one study no effects. See Table 4 for narrative synthesis.

5.2.2 Meta-analysis

Three studies within the neurochemical domain provided aggregable data and were therefore synthesized. Due to missing r-values, all studies were assigned the same r-value, and analysis was repeated three times with different values (0.25, 0.60 and 0.80). Overall effect sizes ranged from 0.91 to 1.84, but the confidence intervals included zero in all analyses, which indicated that these were non-significant. See paper II, Figure 2 for meta-analyses and forest plots.

5.2.3 Overall evidence synthesis

The GRADE analysis revealed the level of evidence in exercise-induced neuroplasticity in PwPD to be very low.

Table 4. Narrative synthesis of neuroplastic outcomes from pre to post intervention.

Reference	Method	Specification of signaling type or brain area/s	Change in direction*
		Neurochemical	
Angelucci et al[146]	Serum BDNF		—
Fontanesi et al[147]	TrkB signalling in lymphocytes	pY-TrkB (145 kDa)	↑
		pY-TrkB (95 kDa)	—
		NR1	↑
Frazzitta et al[148]	Serum BDNF		↑
Zoladz et al[149]	Serum BDNF		↑
		Brain function	
Batson et al[150]	fMRI	Connection between anterior and posterior aspects of Default Mode Network	↑
		Connection between basal ganglia and premotor cortex	↑
Duchesne et al[151]	fMRI	Temporal lobes	↑
		Left ventral striatum	↑
		Left hippocampus	↑
		Cerebellum (lobules 8 and 9 bilaterally, and right crus)	↑
Maidan et al[152]	fMRI	Middle temporal gyrus	↑
Shah et al[153]	fMRI	Connection between active motor cortex and ipsilateral thalamus	↑
Carvalho et al[154]	EEG	No significance given to area	↑
Fisher et al[111]	TMS	CSP-duration in both hemispheres	↑
Fisher et al[155]	PET	Dorsal putamen	↑
del Olmo et al[156]	PET	Right cerebellum	↑
		Right parietal lobe	↑
		Right temporal lobe	↑
		Brain structure	
Sehm et al[157]	MRI	Right hemisphere of cerebellum**	↑

*Change in direction as interpreted by respective authors as to whether the change in neuroplastic marker was positive (↑) or unchanged (—). No negative changes were reported.

**As compared to healthy control group

Abbreviations: BDNF, Brain Derived Neurotrophic Factor; pY, phosphotyrosine; TrkB, Tyrosine receptor kinase B; fMRI, Functional Magnetic Resonance Imaging; EEG, Electroencephalogram; TMS, Transcranial Magnetic Stimulation; CSP, Cortical Silent Period; PET, Positron Emission Tomography

5.3 FEASIBILITY OF EXPLORING EXERCISE-INDUCED NEUROPLASTICITY – PAPER III

5.3.1 Process feasibility

A total of 42 people responded to the advertisement and were screened for eligibility. Fourteen could be included, but one person chose to withdraw before randomization, rendering a recruitment rate of 31%. Of the 26 excluded during the initial telephone screening, 13 were excluded based on brain imaging safety reasons (incompatible implants or claustrophobia). See Figure XX for flow chart, and paper III, Table 3 for demographic and clinical characteristics of the included participants.

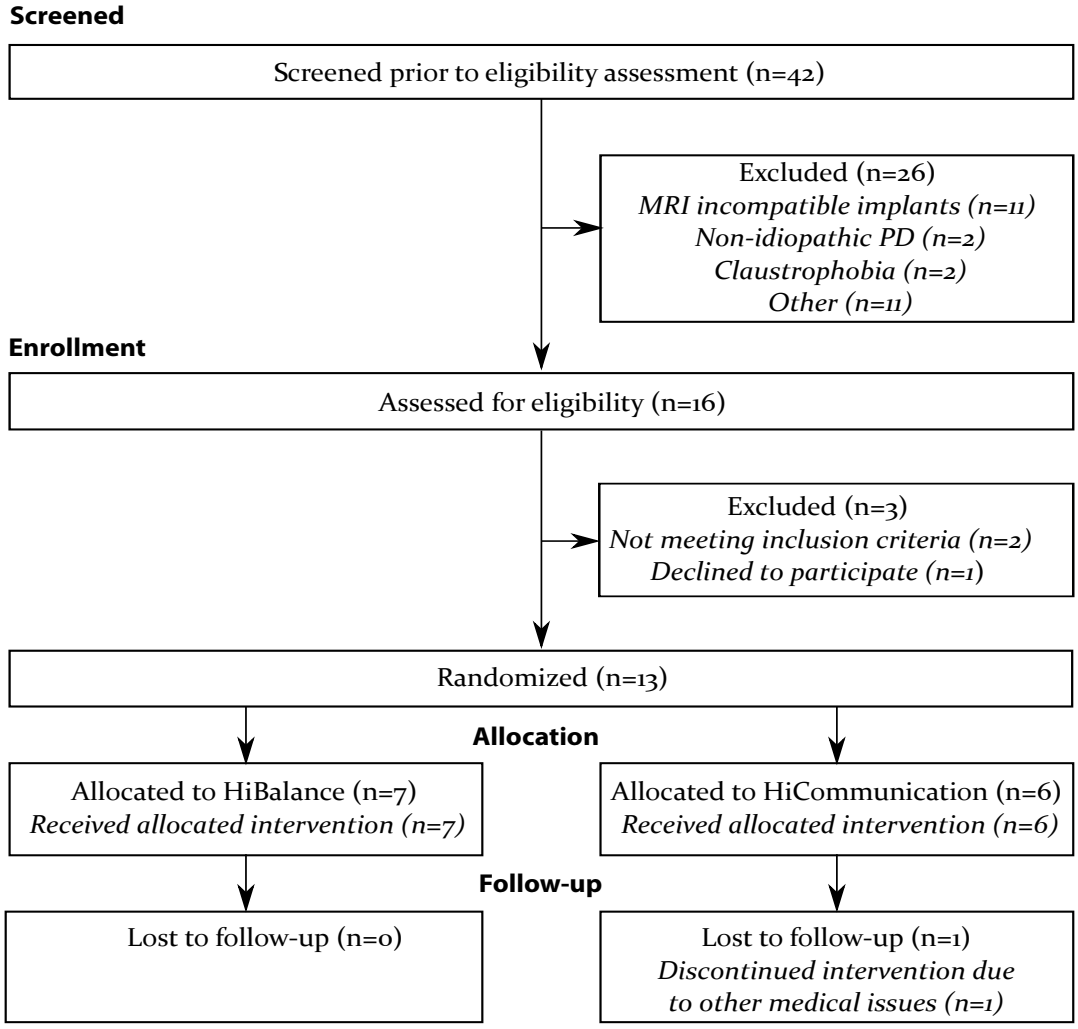

Figure 7. Flowchart of the study process in paper III.

Participant acceptability of both training groups as well as the three assessment sessions pre- and post-training, was overall good based on attendance rates (84.3% and 89.0%, respectively), home exercise diaries, follow-up questionnaires and MRI questionnaires. Brain imaging sessions brought forth a number of unforeseen challenges. Although a rigorous screening protocol was set in place, it turned out that two people could still not undergo the MRI examination because they reported anamnestic information of metal splinters in their eyes right before the session. With a number of participants that

were able to undergo brain imaging, we encountered issues that affected performance during task fMRI such as sleepiness, diplopia, physical discomfort or emotional distress. Structural images (T1) were of acceptable to good quality, and head motion was deemed to be at an acceptable level. Participants complied with blood sampling, but due to logistical problems several post-intervention blood samples were unfortunately lost. Blinding was successful in a majority of cases for one of the assessors but broken in half of cases for the other assessor.

5.3.2 Scientific feasibility

The focus when exploring trends in treatment response was on physical performance, well-being, executive function and voice intensity. These results should, however, be interpreted with caution, as no inferential statistics were applied and are reported descriptively as median difference only. No improvement in balance performance as measured by Mini-BESTest was shown in either group. There was a median increase of 0.05m/s in usual gait speed in the HiBalance group, whereas there was no change in the control group. Health-related quality of life as measured by the PDQ -39 summary index improved (median decrease of 8.4%) in the HiBalance group but remained unchanged in the control group (median increase of 1.7%). Results on tests of executive function were ambiguous with some results in favour of the HiBalance group and others in favour of the control group. Lastly, voice intensity improved in the control group (median increase in sound pressure level by 2.5%) but remained unchanged in the HiBalance group (median difference of 0.0%). There were two non-injurious falls during the group training sessions, and two non-injurious falls were reported during performance of home exercises in the HiBalance group.

5.4 DUAL TASK PERFORMANCE – PAPER IV

A total of 93 participants were included in the analysis for the primary purpose of paper IV, and 65 of these were then further analysed for secondary purposes. See paper IV, Table 2 for descriptive characteristics of included participants.

5.4.1 Dual task effects on gait and cognition

Different domains of gait were diversely affected when adding the cognitive DT. Whereas all variables within the pace and variability domains exhibited DTCs, there was no significant deterioration of variables within the asymmetry domain. Three outcomes concerning cognitive performance were assessed. Accuracy was not affected by doing the task during walking as opposed to sitting, whereas reaction times increased significantly and a measure of intraindividual variability, i.e. standard deviation of reaction time (SDRT), revealed high DT costs. See Figure 8 for a compilation of DT

effects on all variables within each gait domain as well as on the auditory Stroop task. For absolute values of single and DT performance, see paper 4, Table 3.

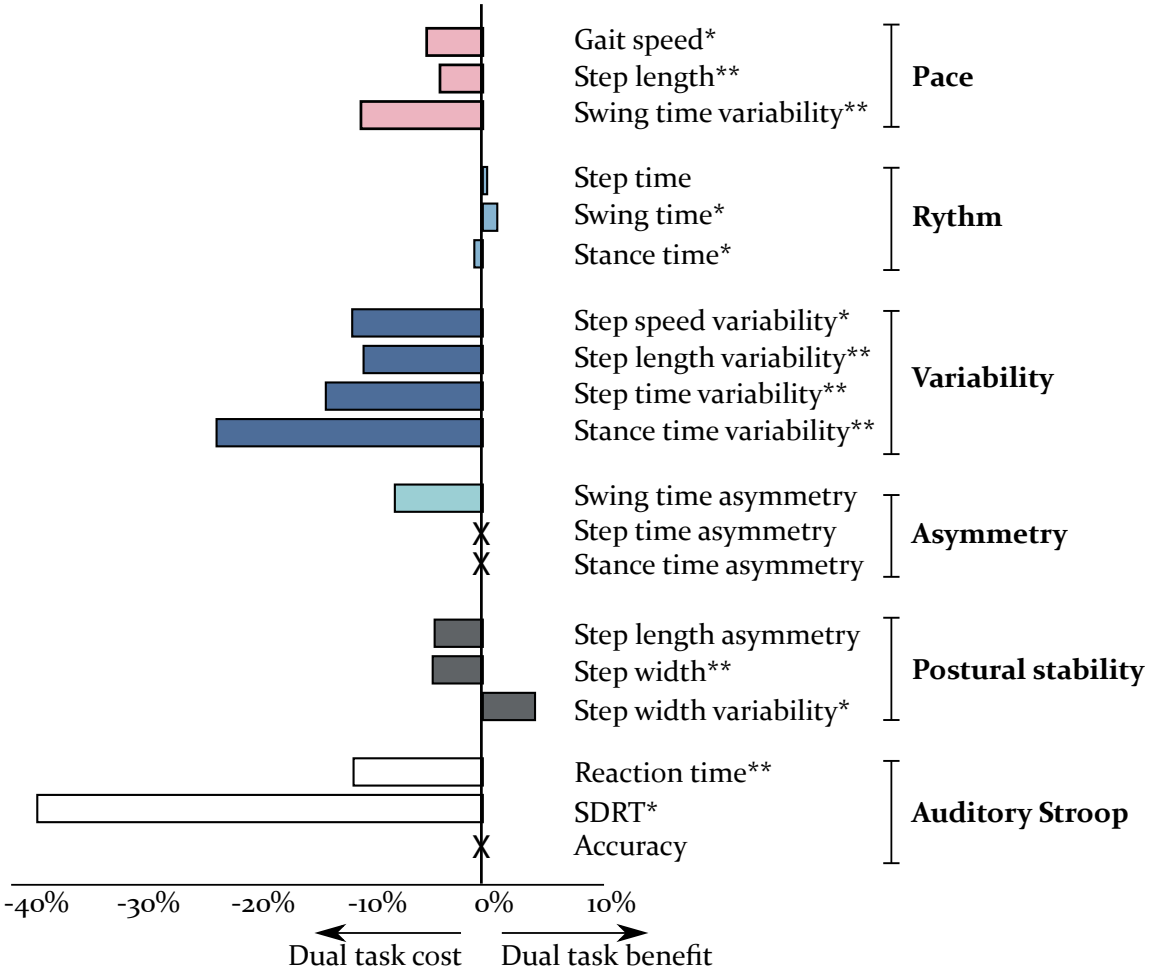

Figure 8. Overview of dual task effects on gait variables and the auditory Stroop task. Asterisks indicate those variables where the difference in performance between single and dual task was significant (** p<0.001, *p<0.05).

5.4.2 Factors predicting dual task performance

Three different models with different DT effect variables as dependent variables were carried out. All models attained statistical significance (p<0.05). Together, the independent variables cognitive status (PD MCI or PD non-MCI) and Timed Up and Go cognitive (TUG-cog) predicted 20.9% and 15.7% of the variance in DT effect on gait speed and DT effect on step time variability, respectively. The same independent variables with the addition of MDS UPDRS subscore I could predict 13.9% of the variance in DT effect on cognition.

5.4.3 Role of cognitive status in dual task walking

The participants who were classified as having PD MCI had significantly higher DTC on both gait speed and step time variability compared to PD non-MCI (mean difference

8.1% [95% CI 13.6 – 2.6; p=0.005] and 30.4% [95% CI 51.3 – 9.5; p=0.005], respectively). These results remained statistically significant after adjusting for sex and age (7.8%, 95% CI 13.7 – 2.0; p=0.009, and 32.6%, 95%CI 54.7 – 10.4; p=0.005, respectively). There was no across-group difference with regards to DT costs on cognitive performance (p=0.108). Further analysis revealed that cognitive status influenced prioritization during DT walking. PwPD in the non-MCI group prioritized gait speed over cognitive performance (p=0.003), while the PD MCI group instead prioritized cognitive performance over gait speed (p=0.044). The same pattern of prioritization with regards to step time variability was seen in the PD MCI group, whereas in the PD non-MCI group there was a lack of prioritization of one task over another. Across group analysis of both prioritization variables revealed statistically significant differences between the groups, supporting the finding that these populations prioritize differently. See Fig. 9 for scatter-graphs of DTE on gait speed and step time variability and on cognitive performance for PD non-MCI and PD MCI, respectively.

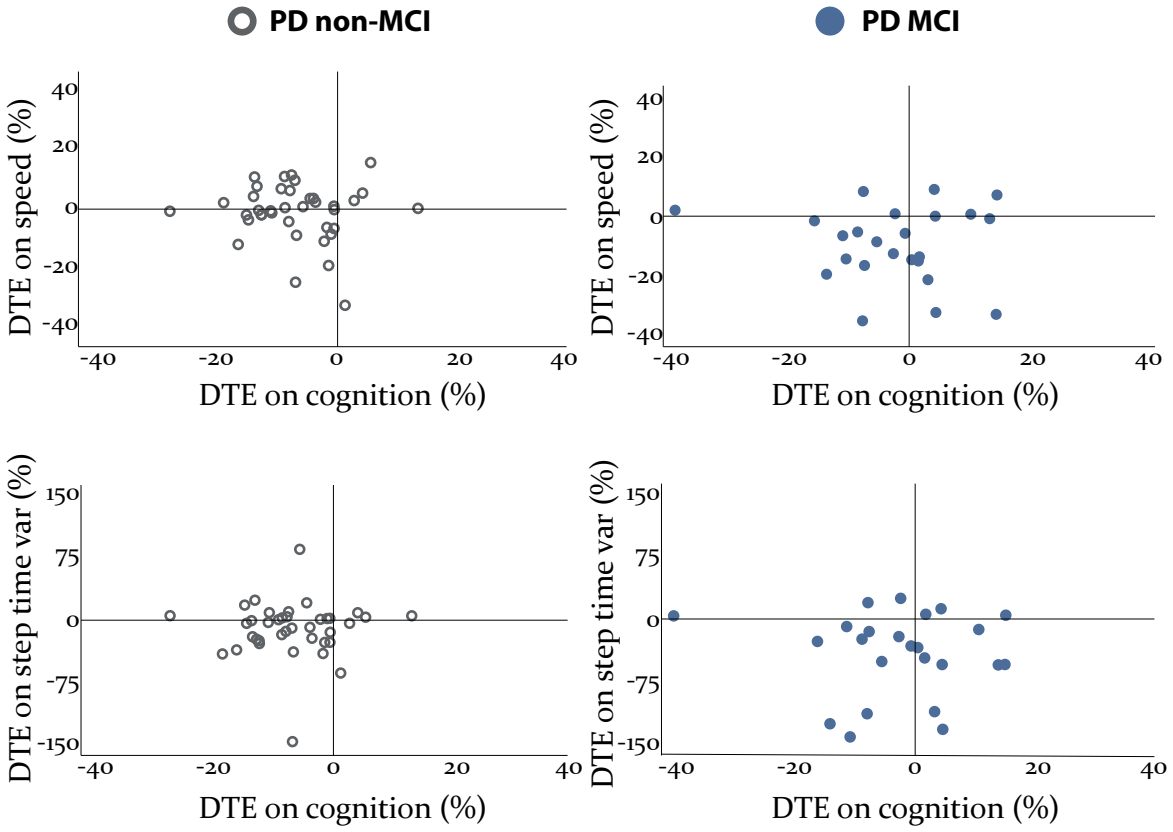

Figure 9. Patterns of dual task effects (DTE) between cognition and gait speed (upper two graphs) and step time variability (lower two graphs) for PD non-MCI (left) and PD MCI (right). In each graph the upper left quadrant indicates a gait-priority trade-off, the lower right quadrant a cognitive-priority trade-off, the upper right quadrant a mutual dual task benefit and the lower left quadrant a mutual dual task cost.

6 DISCUSSION

6.1 SUMMARY AND DISCUSSION OF MAIN FINDINGS

This thesis intended to explore perceptions and performance of balance and gait in PwPD. It further aimed to establish the current evidence for exercise-induced neuroplasticity and to evaluate feasibility aspects of investigating exercise-induced neuroplastic changes among PwPD. The results in this thesis describe how PwPD perceive the concept of balance as having multiple layers, both pertaining to physical equilibrium and to the interplay between body and mind. Having poor balance touched many aspects of everyday life, physically, emotionally and socially. Balance was described in the context of control, and how living with impaired balance in a sense meant losing control in everyday life. In PwPD, all aspects of gait except asymmetry was worsened when walking with an added task. Dual task walking appeared to be more compromised in people with PD MCI compared to PD non-MCI as shown in higher DT costs on gait speed and step time variability. Analysis of prioritization revealed that PD MCI consistently used a posture-second strategy whereas PD non-MCI tended to use a posture-first strategy. Current evidence for neuroplasticity in PD suggests that both brain structure and function can experience a positive alteration as a result of physical exercise, whereas studies on neurochemical adaptations points in disparate directions. The overall level of evidence for exercise-induced neuroplasticity in PwPD is still however very low. A proposed design for a large scale RCT investigating whether ten weeks of highly challenging balance training has the ability to induce neuroplastic changes in PwPD proved feasible and acceptable. Adjustments to the experimental set-up of the MRI paradigm, DT gait analysis and the blinding process will improve the design further.

6.1.1 The meaning of balance

During the interpretative stage of the interview analysis, it became clear how the meaning of balance was inherently intertwined with concepts of control. Whereas "good balance" mainly involved the ability to stay upright, impaired balance was instead talked about in a sense of losing control of everyday life, and a reduced sense of freedom and independency. In other words, balance was perceived both as bodily equilibrium and as the interplay between body and mind. Participants described how disease progression had led to a perceived loss of control and a feeling of being restricted from engaging in life as one would have wanted to, a description supported by other qualitative inquiries in PD.[158] Being able to uphold meaningful interactions and activities are two important factors for maintaining a sense of normalcy and social identity, but this can be challenging in PD.[159] Sustaining ones self-identity when being

diagnosed with PD entails making new meanings and taking action based on these meanings.[159] This thesis was particularly focused on the meaning of balance, and interviewees described various ways by which they struggled both physically and psychologically to maintain a sense of normalcy despite their impaired balance. Through this process of reconstructing life a person with a chronic illness can once again gain control over their body and their life.[160] The term locus of control (LOC) was coined by Rotter almost six decades ago, and concerns whether a person believes that an event is contingent on their own actions (internal), or luck, chance or a powerful other (external).[161] In PwPD, the belief that health is controlled by external factors is higher than in healthy controls.[162] As the disease progresses, the less likely PwPD are to believe that health lies within their own control. Within the context of our findings, we did not pose questions as to how feelings of control had changed over time, but we did ask whether they believed that they could affect their balance. Some participants expressed that they believed that by exercising and staying active they could influence their balance, whereas others believed that external factors such as medication or surgery was the sole remedy. In our sample, participants with negative previous experiences of exercise tended to express less belief in their own ability to affect balance. Given that exercise and physical therapy is an important part of managing PD symptoms it is of utmost importance that we understand the process by which PwPD initiate and maintain exercise behavior. According to the Common-Sense Model of Self-Regulation, this process is intrinsically dependent on our beliefs in whether our symptoms can be cured or controlled.[163] If we believe that an action leads to a desired result, we are more likely to initiate it.[164] Communication regarding previous exercise experience and on beliefs in anticipated results may be key to motivating our patients to initiate rehabilitation programs.

6.1.2 Walking while performing a secondary task

Several of the participants who were interviewed for this thesis described using a form of self-talk during balance-challenging situations. This was a strategy to stay focused on the task at hand, while at the same time managing and anticipating the next step. Walking was not relaxed, but instead required an increasing amount of effort. In PwPD, automatic movements, such as walking, become increasingly difficult as a result of dopamine loss in the basal ganglia. Instead of relying on automaticity, they need to exert to strategies that involve the use of goal-directed movements.[36] In other words, the self-talk as described in the interviews, allowed them to circumvent habitual, or automatic, walking behavior and perform complex walking and balance tasks in a goal-directed mode instead. It has been suggested that this loss of automaticity may be particularly evident during DT walking, and that the cost that performing a second task simultaneously, has on walking can be used as a proxy measure for attention and automaticity.[165] Findings from our gait analysis showed that the introduction of a

cognitive task to be performed while walking had significant costs across all domains of gait except asymmetry. Onset symptoms in idiopathic PD are commonly unilateral in nature which may lead to gait asymmetry being more prominent early in the disease process.[166] In paper IV we excluded those with unilateral symptoms, i.e. H&Y 1, which could explain why no DT effects were found in the asymmetry domain. Interestingly, within the variability domain there were not only significant DT costs across all variables, but compared to the other gait domains, they were also the highest. When gait shifts from an automatic mode into being more consciously controlled, it has been suggested that variability may be particularly affected.[42] The difficulties with consciously controlling variability in gait have been highlighted both in healthy people,[167] and in PD,[168] where studies have shown that despite instructions during DT walking to specifically concentrate on "consistent" or "safe" walking, variability stayed unchanged or even worsened. In paper IV performance of the cognitive task also deteriorated while walking, something which was shown by significant costs on reaction times and intraindividual variability (SDRT). Accuracy was not affected when walking and was high both in single and DT conditions. This may have reflected a ceiling effect. As part of the findings from paper III, we did shorten the interstimulus intervals in order to reduce the risk of such a ceiling effect for the larger RCT (from which baseline data have been used for paper IV) and given the range in RT it would have been difficult to shorten them even more. One thing to consider though is that we did not adapt the difficulty level of the auditory Stroop task to each individual, something that could be considered for future trials in light of these results.

Subgroup analysis revealed that cognitive impairment intensified DT costs further, as shown by greater proportional reduction in gait speed and increased step time variability in the PD MCI group, compared to the PD non-MCI group. This was an interesting finding as other studies comparing these groups either found no differences,[69] or only found differences during the OFF stage of the medication cycle.[169] A possible reason for the discrepancy between findings in the current thesis, and previous research may lie within differences in the PD MCI criteria used. We utilized a comprehensive neuropsychological test battery, and classified participants according to a level II criteria as suggested by the MDS task force,[134] whereas it is not unusual within this research area to use a less comprehensive and less varied test battery, or simply a cut-off from a single test of global cognition. Identifying cognitive impairment in PD is complex, something recently highlighted in a study in which up to 45% of PwPD who scored high (≥26) on MoCA actually exhibited cognitive decline on two or more neuropsychological tests.[170] This group would have been classified as PD MCI according to the MDS task force level II criteria.[134] By using different diagnostic criteria, research groups may therefore end up with groups who are, by definition, not comparable when it comes to PD with and without MCI. If the end goal is to synthesize data between

studies and provide clinicians with recommendations, a prerequisite is to make sure we draw conclusions from groups of comparable cognitive function.

This thesis also evaluated whether prioritization differed according to cognitive status. Indeed, we found that participants with PD MCI consistently prioritized the cognitive task over gait (posture-second strategy), whereas the PD non-MCI group tended to prioritize gait over cognitive performance (posture-first strategy). Once validated in other studies, such information may provide us with important clues as to whether interventions should be tailored differently according to cognitive status. It may also have a direct clinical application with regard to fall risk assessment as it has been suggested that using a posture-second strategy may predispose of falls.[53] Although the value of evaluating DT performance as part of a fall-risk assessment has been questioned previously,[171] several prospective studies have found cognitive impairment to be a main source of fall-risk in the PD population.[172-175] Both the European and the Swedish guidelines for physical therapy in PD recognizes the importance of being aware of any cognitive impairments when assessing and choosing an intervention in clinical care.[176, 177] As physical therapists are seldom trained in cognitive assessments, the European guidelines recommend that such information should be provided by a physician.[177] A survey study among Swedish physical therapists however revealed that collaborations with other professionals including physicians depended greatly on work setting .[178] Also, comprehensive neuropsychological test batteries such as the ones used in this thesis are seldom performed as a part of standard physical therapy rehabilitation. Given the complexity and range of cognitive impairments in PD and the consequences these may have for the person in question, it may however be time that we advocate for more detailed cognitive evaluations in clinical care.

6.1.3 Exploring exercise-induced neuroplasticity

Some of the interviewees in this thesis voiced opinions on how exercise was good for the brain, and even expressed positive thoughts on the brain's capacity for regeneration. Others were more skeptical, viewing changes to the brain as something that were out of their control. Our interviewees diverse thoughts on this topic also mirror the current evidence for exercise-induced neuroplasticity in PD. Although a majority of the studies published to date point to an ability of brain structure, brain function and levels of BDNF to alter in a positive direction after a period of physical exercise in PwPD, much work still remains in this research field. Researchers who endeavor to study the effects of exercise on neuroplasticity are however faced with some fundamental challenges. One is the question of causation.[179] Even if we can show that a certain type of exercise improved some measure of behavior, and that behavior was correlated to some change in brain structure, we still don't know exactly what caused these structural changes. However in order to improve neurorehabilitation through interventions that are

designed to facilitate neuroplastic changes, causation may not matter.[179] It does however speak to the importance of evaluating behavioral changes, as well as correlating them with the neuroplastic outcomes, something not always done in the studies included in paper II. The very point of exploring behavioral and neural signals that drive neuroplasticity is to be able to augment functional outcome.[8] Without a measure of behavioral change to correlate with, information on changes in neural structure and function after a period of training is rather uninformative from a neurorehabilitative standpoint. In an ideal setting, the therapist would have information on both impaired and preserved abilities at both the behavioral and neural levels. The therapist could then create a strategy for rehabilitation which involved recruiting residual brain structure and function to drive behavioral improvement.[8] We need an intervention that adheres not only to basic training principles (specificity, progressive overload and varied practice)[83, 84] but also to key elements that harness neural activity (intensity, repetition and timing).[8] The methods used to explore neuroplastic changes should not only be found acceptable by participants, but also cover behavioral changes complemented by one or more levels such as molecular or neural structure and function.[179] This ideal setting is however far from how rehabilitation in PD or other neurological populations is currently conducted, and many questions remains to be answered before such implementation can take place.

Given the complexity and need for multidisciplinary involvement when conducting research on exercise-induced neuroplasticity it is highly important to find feasible methods. Conducting a pilot trial in preparation of a large scale RCT provides an opportunity to increase the value and methodological rigor.[180] Although many of the studies in paper II were stated as pilot trials, few if any reported feasibility outcomes, nor have they progressed to large scale RCTs. All of them however reported effect, which given the small sample sizes, it can be questioned whether they were powered to do so. Properly piloting a trial design ahead of investing in a large RCT is ultimately also a question of avoiding research waste.[181] If a design is found not to be feasible, then researchers avoid wasting costs and resources, and more importantly participants avoid wasting their time and commitment. The pilot trial in this thesis (paper III) primarily served to improve the design of the EXPANd trial,[116] but the transparent reporting allows for other researchers to replicate feasible elements and avoid disadvantageous ones. As mentioned previously, we need RCTs with data aggregable for meta-analyzing in order to move this body or research forward and to be able to provide guidance to clinicians as to how rehabilitation can be tailored for PwPD.

6.2 ETHICAL CONSIDERATIONS

Ethical considerations in research pertains to three key concepts: *autonomy, beneficence and justice.* [182]

In interview studies, there are a several important aspects of these concepts to consider. Regarding autonomy in the paper I, each participant signed a written informed consent. Participants were excluded if they scored <21 on MoCA in order to minimize the risk of including individuals with compromised autonomy. Beneficence pertains to confidentiality and the importance of keeping the identities of participants anonymous.[182] I have kept this in mind during manuscript writing, in order to make sure that it will not be possible to reveal the identity of the participants from either the quotations, the descriptive table or any other part of the paper. The last key concept, justice, concerns equal share and fairness, and in qualitative research more specifically the need to recognize the vulnerability of the participants.[182] The roles as interviewer and interviewee can cause a power imbalance, and these differentials needs to be acknowledged.[183] With respect to this, interviews were conducted at a time and location of the participants' choice in order for them to feel as comfortable as possible.

When conducting a systematic review, it is of equal importance to keep the ethical considerations in mind. As Vergnes and colleagues points out, there is a theoretical possibility that reviews and meta-analysis publish original research that does not respect fundamental ethical principles. [184] Since the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist does not include any item for ethical consideration, it is of great importance for review authors to include a summarizing discussion about ethics in the articles included [185]. All studies included in the systematic review, paper II, had been approved by their respective local ethics committees. However, according to the declaration of Helsinki, human subjects should be informed of the aims, methods et cetera, of the paper. Since we have performed a meta-analysis, the aim of our review was not the same as the authors of each clinical trial, which means that subjects signed consent to the original study without knowing the aim of our paper.

Due to logistical shortcomings and the handling process, several of the blood samples that where drawn from participants in order to assess levels of BDNF, were lost. This was not only a logistical problem that needed to be addressed before the definitive RCT, but also an ethical issue. In order to minimize the risk of this happening again, we therefore organized a more stringent handling of the blood samples for the RCT whereby a core facility was engaged in the project. All blood samples for the RCT have thereby been stored safely, as well as collected and preprocessed in the same manner.

There were ethical issues to consider with respect to the MRI environment. Each patient was informed of potential hazards and assessed carefully with respect to their risk in the MRI environment. When there was any uncertainty, a clinical radiologist was consulted. The most dangerous risks are from ferromagnetic objects and from implanted electromechanical devices, such as pacemakers or deep brain stimulators

that cannot function in the magnetic field. Considering possible claustrophobia during the MRI-scan, every potential participant was instructed to tell us immediately if this was the case by pressing the alarm button. Following the scan, a specialist in neuroradiology and a neurologist screened all subjects for anomalies of pathological significance and each medically responsible in the respective project was contacted when action was needed. All participants were informed in advance that their images would be screened and that they would be informed in case of pathologies.

6.3 METHODOLOGICAL CONSIDERATIONS

6.3.1 Mixed methods

In the increasingly complex, dynamic and interdisciplinary world of research, we need to be able to complement methods with one another. Communication and collaboration between researchers in different disciplines has the possibility of providing exceptional research, and a prerequisite to this is understanding methods used by the other.[186] This thesis utilizes methodological plurality in that it includes both qualitative and quantitative inquiries of various designs. I have used interview data to explore perceptions of balance and gait as experienced by PwPD and complemented this with performance data from a cross-sectional investigation of these symptoms. I have assessed the feasibility of exploring exercise induced neuroplasticity in a Swedish setting and complemented it by systematically reviewing all available evidence for neuroplastic training effect in various settings worldwide. Since the data from the different papers has not been aggregated, the thesis as a whole can therefore be considered as a having a mixed methods approach with a segregated model.[187] Using qualitative and quantitative data together may provide more complete knowledge,[186] and could therefore be considered as a primary methodological strength of this thesis.

6.3.2 Trustworthiness – Paper I

The credibility of a qualitative study relates to how well the collected data and the analytic process addresses the intended focus.[188] As the focus in paper I was on the concept of balance, and how people with PD perceive this, we purposefully strived to include participants who we thought would have different perspectives and viewpoints concerning balance. One example is how we strategically included people without experience of organized exercise, a group previously underrepresented in research. This, along with a diversity in demographics, self-reported health and physical function, constituted our maximum variation sampling.[110] Another way of ensuring credibility of the findings in paper I was the use of investigator triangulation during the analytic process.[189] Initial meaning unit identification was done by myself, and then validated by two additional authors (BL and KSR). Coding and interpretation were performed through discussions with all authors during several team debriefing meetings. Involving

different researchers in the analytic process is also a way to address dependability. Dependability relates to whether the research findings are consistent and repeatable. The interviews in this thesis were conducted within a period of five months during which only minor changes were made to the order of the questions. It is however possible, if not probable, that mine and the other authors' backgrounds as physical therapists may have influenced the analytic process and interpretation of the findings.

In order to increase conformability, we adhered to a transparent reporting in the published article whereby a sample of questions from the interview guide was provided, as well as examples of the analytic process from meaning units to subthemes. Throughout the results section we also provided citations that we thought best mirrored the content of each theme.

In qualitative research, the findings are not meant to be thought of as facts, but rather as descriptions, perceptions or theories that are applicable within a specified setting.[190] It is the responsibility of the author(s) to provide enough detail on both the participants and the research process so that the reader can make a "transferability judgment", i.e. assess whether the findings are transferable to his or her own setting. With this in mind we provided rich descriptions of the participants, not only with regards to demographic information, but also pertaining to self-reported measures on health as well as performance measures of gait, balance and motor function. We also described details on recruitment, setting and the interview situation.

Preferably, the subjective experience that interviewees describe is reflected upon and interpreted by the researcher using different theories and philosophies. This way of perceiving and interpreting the same phenomena from different angles increases objectivity, also referred to as reflexivity.[191] In paper I we have used various theories, mainly from the psychological research field, in the interpretive process. Our use of theories such as the Common sense model of self-regulation,[163] or Locus of control,[161] enabled us to relate the described experiences in a broader context.

6.3.3 Experimental validity – Papers II-IV

6.3.3.1 Introduction to the concepts

The research literature abounds with definitions and descriptions on the concept of validity. The following paragraphs will focus on experimental validity, and specifically on internal and external validity. Internal validity concerns the degree to which the methods and design of a study allows the researcher to conclude that there is a causal relationship between treatment and outcome. In a study with poor internal validity, the likelihood is high that the results are attributable to factors other than treatment.[192] External validity instead relates to within what context the findings from a study can be

applied, and more specifically to generalizability and applicability. Generalizability concerns whether the findings can be extended to the population from which the sample is drawn, whereas applicability concerns whether inferences drawn from the study sample can be extended to specific patients of any population.[193]

6.3.3.2 Paper II

Synthetic knowledge acquired from systematic reviews is theoretically of the highest form, at least in terms of achieving results of high internal validity.[194] We did however not exclude papers based on high risk of bias or poor quality, hence the synthesized knowledge in paper II includes results from studies of which some had poor internal validity. While this may be considered a limitation, as of present, there are too few high-quality studies published in this area to allow for credible conclusions. Therefore, the broader inclusion approach used in this paper can be considered to reveal valuable information with regards to this novel treatment outcome. We chose to include all types of evaluative methods for neuroplasticity and various types of physical exercise interventions (i.e. at least two training sessions). All decisions on inclusion, both at title/abstract stage, and at full-text stage, were done by two authors blinded to each other's decisions. Quality assessment was done by one author (HJ), and decisions were checked by a second author (EF).

In systematic reviews, there is a lack of reporting on external validity and whether results can be generalized or applied to other populations and settings.[195] This is unfortunate as it makes clinical decision making based on the results problematic. During the write-up of paper II, several issues were encountered that rendered statements and conclusions on external validity difficult. Overall, the information on the population from which the sample was drawn in the different studies was incomplete or inconsistent. There was even a lack of information on the studied sample, especially when authors had analyzed a subgroup of a larger study. Paper II is not intended to support clinical decision making per se, but rather for use by researchers interested in evaluating neuroplastic effects of training. As this research area is still in its infancy, future meta analytic results, preferably based on larger RCT's will be better equipped to make clinical recommendations.

6.3.3.3 Paper III

One of the primary purposes of conducting feasibility studies is to reduce the threats to internal validity for the definitive trial.[196] In the pursuit of this we monitored the proposed design in order to detect when and where possible risks of bias may occur. We used a random assignment to parallel groups which should control for many of the threats to internal validity, except experimental mortality (attrition).[192] We had one drop-out from the control group, but this was unrelated to PD or to the intervention.

Given the vulnerability of small sample sizes, the drop-out may however have skewed the control group results in a false-positive direction. A diagnosis of idiopathic PD was verified either through confirmation from the participant's neurologist, or through medical journal transcripts in order to reduce the risk of misclassification bias. Participants performance on balance, gait and motor function was assessed by the same evaluator at both pre- and posttests. By doing so we minimized the risk of observer changes being more influential on the study results than the true treatment effect.[192] Another aspect with regard to the assessments is that all participants were assessed in their ON medication state and at the same time of day at pre and post-test sessions. This is important as PwPD may suffer from motor fluctuations leading to big differences in performance while in an optimally medicated state and when the medication is starting to wear off.[27] During clinical testing of balance and gait, the order of the tests was also randomized in order to control for fatigue.

In pilot and feasibility trials, the main focus in regard to external validity lies in providing enough information for the reader to judge whether methods and findings can be applied to a future trial or other studies.[114] Although the setup of paper III may not be replicable in its entirety in other settings or populations, large parts of our feasibility results may be of use to other research groups planning similar projects. We had a recruitment rate of 31% (13 out of 42 people who initially reported interest). Half (13 people) of those excluded during initial telephone screening were so based on reasons related to the MRI environment (incompatible implants and/or claustrophobia). We did not perform any analysis of those who were excluded before the eligibility assessment, other than taking note of reason for exclusion and sex. A more thorough collection of background data on these people could have provided useful information in regard to the population from which our sample was drawn and improved our ability to generalize the results. Even though the sample size of paper III does not allow for generalization of effect to routine clinical practice, it is still worth discussing inclusion criteria. In papers III-IV, we included people with mild to moderate PD who were 60 years of age or older, similar to previous HiBalance evaluations.[82, 85] Because of the MRI environment, we did however exclude people with duodopa pump or deep brain stimulation, a factor that may have led to inclusion of a somewhat healthier sample. These treatments are however usually offered as adjunct therapy options during the advanced stages of the disease.[27] Had these participants not been excluded already during the telephone screening, there is therefore a probability that they had been excluded during the eligibility assessment.

6.3.3.4 Paper IV

One of the major threats to internal validity in paper IV is the absence of a control group. Without a group of healthy controls, we cannot with certainty say that our

results are unique to PwPD. Further, since exposure and outcome are measured at the same time, causality is often unclear in cross-sectional studies.

As almost identical inclusion and exclusion criteria were used for paper III and paper IV, several of the issues pertaining to generalizability in paper III is also true for paper IV. In addition, for the secondary purposes in paper IV we excluded almost a third of the sample as they could not with certainty be classified as either PD MCI or PD non-MCI. This is a falsification of reality as this group very much exist in the real world. In reducing the risk of misclassification bias we instead compromised our ability to generalize the results, resulting in a trade-off between internal and external validity.[197]

6.4 CLINICAL IMPLICATIONS

The results of the interviews imply that a main key when choosing assessment method and training intervention, as well as motivating our patients lies in posing the right questions. We need to understand how people with PD make sense of balance and gait impairments and to what extent they believe that change is within their own control. We also need to be aware of the extent that a person uses cognitive or physical adaptations to influence balance in everyday life, as this will give us an indication as how to best challenge them during training.

As previously established, when evaluating DT effects during walking, we need to consider changes in performance on both gait and the secondary task. With both these pieces, we as clinicians can lay the puzzle to understand how a patient is affected when performing two tasks and then help translate it to real life contexts.

People with PD MCI as compared to PD non-MCI may have a different pattern of DT interference, as well as a different type of prioritization between tasks. This can have clinical implications since using a posture-second strategy may place people with PD MCI at greater risk for falls. Performing a neuropsychological test battery may therefore help guide rehabilitation and assessment of locomotor symptoms.

Gait speed is easily assessed in the clinic and should continue to be a main outcome in the PD population. However, with accelerometers and other body-worn sensors for step detection being increasingly affordable and assessable, clinicians can and should when possible also evaluate other aspects of the gait cycle, especially during DT gait assessment. In doing so, we would be able to provide our patients with a more nuanced evaluation.

6.5 FUTURE RESEARCH

Many of the findings presented as well as each methodological deficiency noted in this thesis represents an opportunity for improvement and future research.

There is still a paucity of qualitative research in PD. We should aim to understand how PwPD make sense of their plethora of symptoms, not just balance, if we wish to improve communication and motivational strategies for rehabilitation. Different qualitative efforts may help explore how symptoms are experienced, how this experience changes over time and to what extent they feel that improving their symptoms lies within their own control.

Despite efforts in this thesis, and by other research groups, much of the variance in DT effect is still unexplained for. More work is needed here to elucidate which factors can predict the ability to DT. Future studies can also help confirm or refute whether there is in fact a difference in task prioritization between people with PD MCI compared to PD non-MCI. Larger sample will also allow the investigation of whether there are differences across different cognitive profiles.

The reliability of using DT effect variables to evaluate training effects are still uncertain and need more investigation.

Research into exercise-induced neuroplasticity is still in its infancy, and much more work is needed before we can conclude which type of training and which dose is optimal for PwPD. Given the high costs of this type of research, along with a great need for adequately powered studies, collaborative efforts between research groups would help move this body of research forward. Researchers should strive to collect data using comparable interventions and aggregable outcomes. Transparent reporting of feasible elements, and perhaps even more important - disadvantageous ones, should be made readily available to other researchers.

7 CONCLUSIONS

Among people with Parkinson's disease, balance was perceived as a multilayered concept entailing both bodily equilibrium and the interplay between mind and body. The meaning of balance was intertwined with concepts of control, and whether one could control the body in everyday life. Participants described how they exerted influence over balance by directing focus and attention to the task at hand during balance-challenging situations. Exercise was seen by some as a means to improve balance, whereas others with previously bad experiences of exercise did not believe that they had any control over the progression of their balance impairments. Regardless of whether participants believed in their own ability to affect balance, several expressed how they had developed a psychological resilience to face the challenges of impaired balance.

Although a majority of studies published on PD indicate that various types of exercise may have the possibility to induce positive neuroplastic changes in the human brain, the concerted evidence as of today is very low. More high-quality randomized controlled trials, using scientifically sound methodology and transparent reporting are needed in order to drive this research field forward.

Our proposed design for a future randomized controlled trial investigating the effects of the HiBalance program on markers of neuroplasticity in PwPD proved feasible and acceptable. Overall participant acceptability of all three pre- and post-assessment sessions, as well as both the HiBalance and HiCommunication interventions were good as shown via follow-up questionnaires, attendance rates and home-exercise diaries. Some elements of the design will however need modifications, including strengthening of the blinding procedures, introduction of an expectancy questionnaire, improved logistical handling of the blood samples, and changes to both MRI paradigm and the DT gait assessment.

When walking while simultaneously performing a cognitive task, our sample of people with mild to moderate PD exhibited DT costs across all domains of gait except asymmetry. They also increased their RTs and SDRTs on the cognitive task, whereas a high accuracy was maintained from single to DT performance. Subgroup analysis revealed that people with PD MCI used a posture-second strategy as opposed to the PD non-MCI group who tended to use a posture-first strategy. These findings provide preliminary evidence to suggest that DT training and assessment should be planned and instructed differently according to cognitive status in PwPD.

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”Det bor en annan inuti,
under min fjäderdräkt.
Jag har hört dess skri:
”Släpp mig fri!
Släpp mig fri!”

Det är otäckt.
Jag tror inte ens att vi är släkt.”

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