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BALANCE CONTROL IN OLDER ADULTS WITH PARKINSON'S DISEASE
- EFFECTS OF MEDICATION AND EXERCISE

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Aim: To investigate the effects of dopaminergic medications on turning while walking in older adults with mild to moderate Parkinson's disease (PD). A further aim was to develop a training program targeting balance impairments related to PD, to verify the progression of this program and the specific effects on balance and gait, as well as the transfer effects on everyday living.

Methods: This thesis contains an experimental and a clinical part. In the experimental part, quantitative motion analysis was used to evaluate pre- and unplanned walking turns. Nineteen individuals with PD were tested after overnight withdrawal of dopaminergic medication and approximately one hour after taking their usual dose of medication, and were compared with 17 healthy control subjects. In the clinical part, a training program with highly-challenging balance exercise and dual-tasking was developed through workshops and pilot testing. Thereafter, training progression of dynamic exercises throughout this program was evaluated with accelerometers in two training groups (n = 6 and 4). In a randomized controlled trial, 100 individuals with PD were randomized, either to a training group that received a 10-week highly-challenging balance exercise intervention with dual-tasking or to a control group (usual care). The efficacy of this intervention was evaluated before and after the intervention which included specific effects; balance, gait with and without performing a concurrent cognitive task, and transfer effects which were concerns about falling, level of physical activity and activities of daily living.

Results: Dopaminergic medication had a positive increasing effect on turning distance, whereas no effects on body rotation were found. Compared with the healthy control group, individuals with PD demonstrated lower turning distance and body rotation, and turned with a narrower step width. The objective evaluation of training activity revealed that training progression was accomplished in two independent training groups. The randomized controlled trial demonstrated significant improvements in balance control and gait performance in the training group, compared with the control group. The training group also improved their performance of the cognitive task while walking; however, no group differences were found for any gait parameters during dual-tasking. Significant differences, in favor of the training group, were found for the level of physical activity and activities of daily living, while no group difference was found for concerns about falling.

Conclusions: Compared with the performance of the healthy control group, dopaminergic medication does not normalize turning performance. These residual turning impairments were accompanied by difficulties alternating step width during turning, which could be important to address in the rehabilitation of individuals with PD. Highly-challenging balance exercises, including dual-task, for a 10-week period was progressive and improved balance and gait performance in older adults with PD, compared with usual care. Positive transfer effects on activities of everyday living were also revealed, indicating that appropriate training programs could promote physical activity and daily activities in individuals with PD.

SAMMANFATTNING

Syfte: Att utvärdera effekterna av sedvanlig Parkinsonmedicinering för gående vändning hos äldre personer med mild till måttlig Parkinsons sjukdom (PS); samt utveckla ett balansträningsprogram specifikt riktat mot besvären vid PS, att undersöka progressionen av detta program, och att studera programmets effekter avseende balans- och gångförmåga, samt dess generella effekter avseende aktiviteter i det dagliga livet.

Metod: Denna avhandling innehåller en experimentell och en klinisk del. I den experimentella delen användes kvantitativ rörelseanalys för att studera planerad och oplanerad gående vändning. Nitton deltagare med PS testades först efter att ha varit omedicinerade i cirka 12 timmar och sedan cirka 1 timma efter intag av ordinarie medicin, och jämfördes därefter med 17 friska kontrollpersoner. I den kliniska delen utvecklades först ett 10-veckors träningsprogram med utmanande balansövningar och dual-task till följd av workshops och en efterföljande pilotstudie. Därefter undersöktes progressionen av dynamiska balansövningar under interventionen med accelerometrar i två träningsgrupper (n = 6 respektive 4). I den randomiserade kontrollerade studien lottades 100 deltagare med PS till en träningsgrupp som deltog i ett 10-veckors program med utmanade balansövningar och dual-task, respektive en kontrollgrupp som erhöll sedvanlig behandling. Utvärdering skedde före och efter interventionen avseende specifika effekter; balanskontroll, samt gångförmåga med och utan en kognitiv uppgift, respektive generella effekter; oro för att falla, grad av fysisk aktivitet och aktiviteter i det dagliga livet.

Resultat: Gående vändning under inverkan av Parkinsonmedicin resulterade i en positiv effekt avseende ökad gångsträcka av vändningen, dock förblev rotation av kroppen oförändrad. I jämförelse med den friska kontrollgruppen, påvisades deltagarna med PS lägre uppnådd gångsträcka och grad av kroppens rotation, samt smalspårig stegbredd vid vändning. Progressionen av träningsprogrammet bekräftades i båda träningsgrupperna. Träningsgruppen, i jämförelse med kontrollgruppen, visade signifikanta förbättringar av balans- och gångförmåga, samt utförandet av den kognitiva uppgiften under dual-task. Däremot förbättrade träningsgruppen inte gångförmågan under dual-task. Deltagande i träningen medförde dessutom signifikanta förbättringar avseende fysisk aktivitet och aktiviteter i det dagliga livet i jämförelse med kontrollgruppen, oron för att falla påverkades dock inte.

Konklusion: I jämförelse med prestationen i den friska kontrollgruppen, normaliserade inte Parkinsonmedicinering förmågan att gå och vända. Dessa kvarstående besvär var förknippade med svårigheter att förändra stegbredden under vändning vilket kan vara viktigt att beakta i rehabiliteringsprogram för personer med PS. Utmanade balansträning med dual-task övningar under 10-veckor visade sig vara progressiv och ledde till förbättrad balanskontroll och gångförmåga. Träningen ledde även till positiva effekter för aktiviteter i det dagliga livet, vilket indikerar att resultatet av utmanande balansträning kan öka fysisk aktivitet och förbättra aktiviteter i det dagliga livet.

LIST OF SCIENTIFIC PAPERS

I. Conradsson, D. Paquette, C. Lökk, J. Franzén, E.
*Pre- and unplanned walking turns in Parkinson's disease
- effects of dopaminergic medication*
Manuscript

II. Conradsson, D. Löfgren, N. Ståhle, A. Hagströmer, M. Franzén, E.
*A novel conceptual framework for balance training in Parkinson's disease-
study protocol for a randomised controlled trial*
BMC Neurology, 2012,12:111

III. Conradsson, D. Nero, H. Löfgren, N. Hagströmer, M. Franzén, E.
*Monitoring the progression of dynamic balance exercises in Parkinson's
disease: a pilot study*
Manuscript

IV. Conradsson, D. Löfgren, N. Nero, H. Hagströmer, M. Ståhle, A. Lökk, J.
Franzen, E.
*The Effects of Highly Challenging Balance Training in Elderly With
Parkinson's Disease: A Randomized Controlled Trial*
Neurorehabil Neural Repair. 2015 Oct 29(9):827-36

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of daily living
APA	Anticipatory postural adjustments
ANOVA	Analysis of variance
BETA-PD	Balance, Elderly, Training and Activity in Parkinson's disease
BoS	Base of support
CI	Confidence intervals
C7	Seventh cervical vertebrae of the column
CNS	Central nervous system
CoM	Center of mass
DT	Dual-task
ES	Effect size
FES-I	Fall Efficacy Scale International
HY	Hoehn and Yahr scale
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile range
LEDD	Levodopa equivalent daily dose
Mini-BESTest	Mini Balance Evaluation Systems Test
PD	Parkinson's disease
PIGD	Postural Instability and Gait Difficulty
ST	Single-task
VAS	Visual analogue scale
UPDRS	Unified Parkinson's Disease Rating Scale

DEFINITION OF CONCEPTS

Activity	Execution of a task or action by an individual.[1]
Automatic control	Movements controlled without the attention of the individual.[2]
Balance control	The act of maintaining postural stability and postural orientation.[3]
Body functions	Physiological functions of body systems.[1]
Fall-related psychological issues	An umbrella term which covers the negative psychological issues that could arise from falls or near-fall events, *e.g.* fear of falling, concerns of falling and loss of balance confidence.[4]
Dopaminergic medication	Pharmacological agents targeting the neurotransmitter imbalance within the basal ganglia circuits.
Dual-task	Simultaneous performance of two tasks with different goals, in which one could be referred to as the primary and the other as the secondary task.[5]
Exercise	A subset of physical activity that is planned, structured and repetitive with the objective to improve or maintain physical fitness components.[6]
Executive control	Movements controlled through the attention of the individual.[2]
Executive function	An umbrella term referring to a set of cognitive processes (*e.g.* working memory, inhibition, set shifting and fluency) that control goal-directed behavior.[7]
Level of physical activity	The sum of all activities a person does as part of her/his regular day.
Motor learning	A set of processes associated with practice or experience, leading to relatively permanent changes in movement capability.[8]
Participation	Involvement in life situations.[1]
Physical activity	Any bodily movement produced by skeletal muscles that result in energy expenditure.[6]
Progressive overload	A principle implying that training needs to provide a challenging overload to the physiological system through a certain level of intensity and regularity.[9]
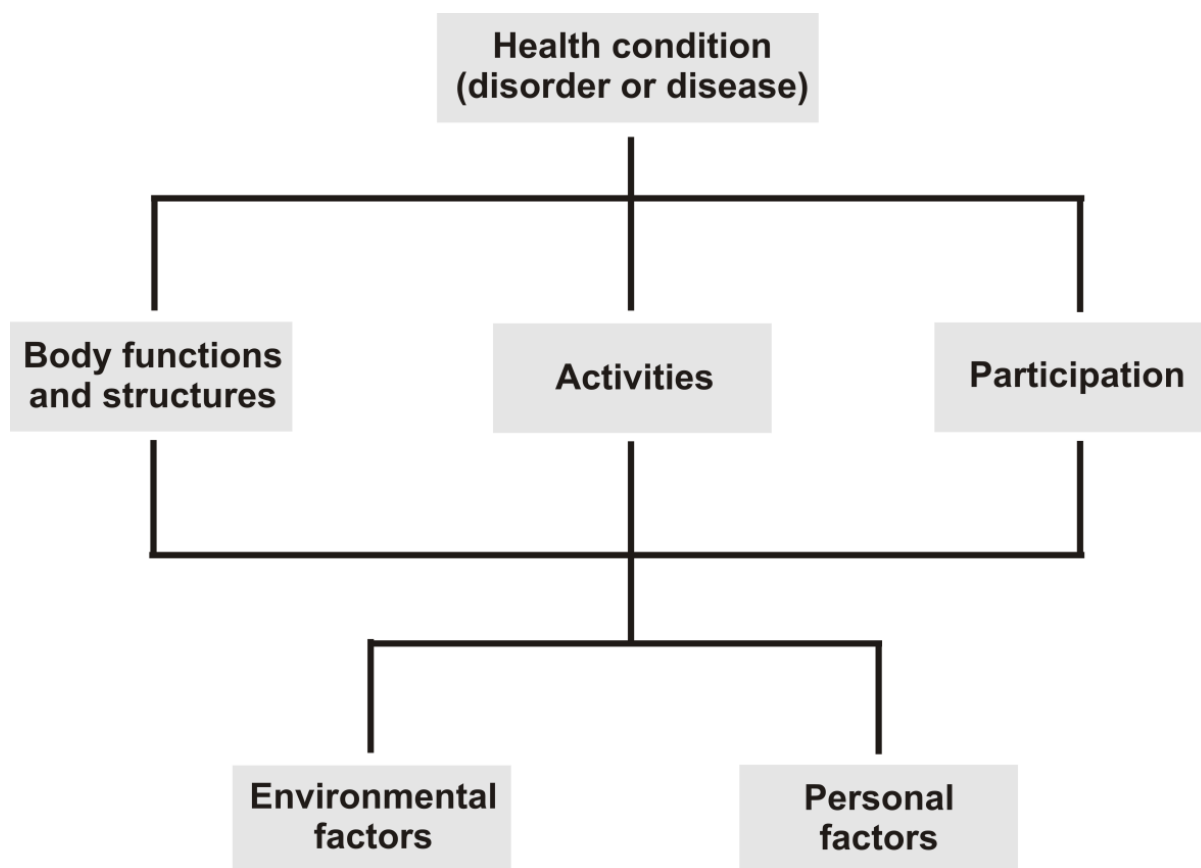
Figure 1. Schematic description of the interactional components of the ICF model.[1]
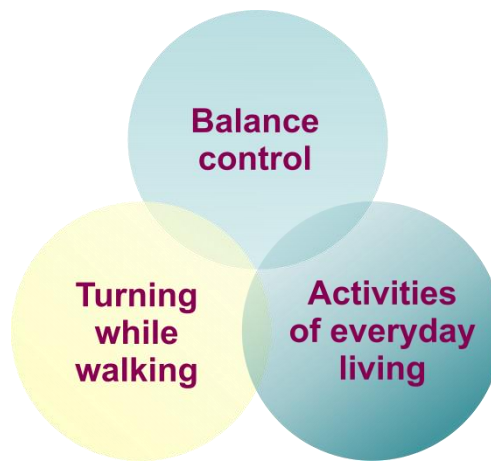
Figure 2. The main concepts in this thesis.

1 INTRODUCTION

This thesis is part of a larger research project, the BETA-PD (Balance, Elderly, Training and Activity in Parkinson's disease), with the overall goal of developing and establishing evidence-based rehabilitation programs for older adults with Parkinson's disease (PD). This thesis is underpinned by three overlapping concepts; balance control, turning while walking and activities of everyday living (Figure 2). As balance control forms the foundation of daily activities performance, declining balance control in individuals with PD may gradually constrain activities of everyday living. In particular, notwithstanding the problems these individuals face in daily life, impaired capacity to turn while walking is a common problem that, for many, is a trigger to falls. Dopaminergic medication has a dramatic clinical effect on the symptoms of PD; however, the effects of medication on balance control remain uncertain. Therefore, in order to sustain independency, it is important to develop training interventions that target the disease-related balance impairments of PD.

Within this thesis, the International Classification of Functioning, Disability and Health (ICF) is used as a framework to conceptualize, specifically, impairments and activity limitations related to balance impairments in individuals with PD. Methodologically, this thesis is divided into two parts: an *experimental part* (*Study I*) to determine the effects of dopaminergic medication on turning impairments, and a *clinical part* (*Study II-IV*) to develop an exercise program for addressing balance impairments in PD, and to evaluating the progression and effects of this program. Combining experimental and clinical studies enables the exploration of different treatment effects on the relevant ICF functioning domains of disability in PD.

1.1 PARKINSON'S DISEASE

Parkinsonism is an umbrella term that includes several medical conditions which partly share the same clinical manifestations.[10] The focus in this thesis is on idiopathic PD, which is the most common type of Parkinsonism.

Parkinson's disease, with a prevalence of approximately 1.2 million in Europe[11] and 22 000 in Sweden,[12] is the second most common neurodegenerative disease. The incidence of PD is more common among males,[12,13] and most people typically receive the diagnosis after the age of 60 years.[14] Given the tendency that people live longer and that the risk of PD increases with age,[13] the number of people with PD is expected to double by 2030.[15]

1.1.1 Clinical manifestations and disease progression

The primary pathophysiology of PD is the progressive degeneration of dopamine-producing cells in the substantia nigra.[10] The diagnosis is mainly based on clinical examination, given that bradykinesia is present (*i.e.* slowness of initiation of voluntary movements with progressive reduction of speed and amplitude of repetitive actions) and in combination with at least one of the following symptoms: rigidity, resting tremor or postural instability.[10,16] Importantly, in addition to these motor features, up to 70% of individuals with PD experience non-motor symptoms,[17] such as olfactory dysfunction, sleep disorders, constipation, depression and cognitive impairments.[18-20] Furthermore, PD is a progressive disease with gradually increased impairments and activity limitations which is commonly classified according to the original Hoehn and Yahr scale (HY, see Table 1).[21] However, it is estimated that only 4% of individuals with PD reach the late phase of the disease (*i.e.* HY 5), and PD is commonly not the cause of death.[22]

Table 1. Hoehn and Yahr scale

1:	Unilateral involvement only usually with minimal or no functional disability
2:	Bilateral or midline involvement without impairment of balance
3:	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
4:	Severely disabling disease; still able to walk or stand unassisted
5:	Confinement to bed or wheelchair unless aided

1.1.2 Pharmacological treatment

All treatment for PD is symptomatic and aims to optimize activities, participation and quality of life.[23] The first-choice therapy for PD is pharmacological treatment in that dopaminergic medication targets the neurotransmitter imbalance within the basal ganglia circuits. The most common dopaminergic agents are the dopamine precursor levodopa (L-dopa) which is transformed into dopamine in the brain and the dopamine agonists that stimulates the dopamine receptor in the striatum.[24] A common approach is to treat young-onset individuals with dopamine agonists and older patients with levodopa.[24,25] The rationale behind this approach is based on the tradeoff between positive effects on motor symptoms and negative side effects of these drugs.[24] Whilst levodopa causes dyskinesia in the long-term, which might not be relevant for older individuals, the risk of dyskinesia is decreased with dopamine agonists owing to more continuous receptor stimulation.[25] Still, dopamine agonists lead to

other side effects such as sleep disorders, orthostatic problems, impulse control disorders and hallucinations.[25,26] Despite the pharmacological advances made, the lack of consensus regarding the optimal treatment approach throughout the progression of PD continues to persist.[26,27] Importantly, despite optimal medical management, individuals with PD still experience activity limitations, falls and fall-related injuries.[28]

1.2 BALANCE CONTROL

1.2.1 Definitions

Balance control (or postural control) is defined as the act of maintaining postural stability and postural orientation. Postural stability is the ability to control ones center of body mass (CoM) relative to the base of support (BoS), whereas postural orientation refers to the ability of maintaining an appropriate posture of the body, *i.e.* the relationships between the body segments and the body and environment, respectively.[3,29]

Within the framework of the ICF, balance control could be conceptualized within the activity domain since the preferable output of balance control refers to the safe performance of activities. Still, whether or not we succeed in executing activities in a safe manner relies on several body functions. Accordingly, managing balance disorders requires a dynamic approach where the focus of therapists alternates between body functions and activities.

Furthermore, if balance control is considered to be a complex skill that is influenced by several subdomains as in this thesis, addressing a single activity or body function will most likely not be able to sufficiently detect or treat the impairment causing instability.[3,30] Instead, one could argue that the multifaceted nature of balance control needs to be considered while managing balance disorders.

1.2.2 Subdomains of balance control

Balance control is a complex and task-specific skill that relies on the interaction between several physiological systems, environmental factors and the nature of the performed task.[3] As such, the central nervous system (CNS) has to rely on different control strategies for different activities. Figure 3 illustrates a theoretical model by Horak, covering six different domains influencing balance control.[3] Three of these domains describe varying strategies used by the CNS to control balance (*i.e.* movement strategies, orientation in space and control of dynamics), while the remaining three (*i.e.* biomechanical constraints, sensory information and cognitive processing) could be considered as body functions within the ICF.
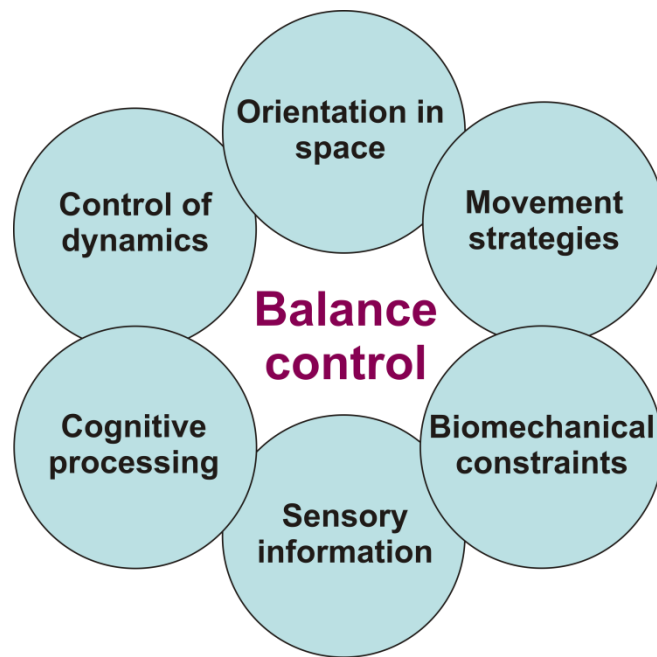
Figure 3. Subdomains of balance control according to Horak.[3]

1.2.2.1 Movement strategies

Importantly, there are no static conditions of the human body, and even quiet standing requires fine-tuned adjustments to maintain balance.[31] In more challenging situations, the CNS uses either reactive or proactive responses. First of all, in the case of unexpected perturbations, such as after a slip or trip, reactive responses (ankle, hip or step strategy) are used to control CoM.[31] But also voluntary movements have a destabilizing impact on the body due to changes in body configuration (*i.e.* displacement of COM).[31] Anticipatory postural adjustments (APA), or feed-forward control, is a strategy used to predict and stabilize CoM disturbances by performing small, unconscious movements before and during voluntary movements.[29]

1.2.2.2 Orientation in space

Another important control strategy is the ability to control the orientation in space, *i.e.* the ability to orient the body in respect to gravity. For most activities, vertical alignment of the body with respect to the support surface serves as an internal reference for the CNS. The sensitivity of this system is remarkable in that, healthy individuals can detect and adapt to a changing support surface of less than one degree without visual guidance.[32]

1.2.2.3 Control of dynamics

Control of dynamics incorporates the complex control of moving CoM during dynamical and changeable conditions (*e.g.* walking). Contrasting to quiet stance, dynamic tasks require the CNS to control CoM at the boundaries or outside the boundaries of BoS.[33] Inevitably, this threatens the lateral stability of the body, which requires precise regulation of step width and trunk control for sustained balance control.[34]

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1.2.2.4 Biomechanical constraints

Numerous biomechanical constraints, such as size and quality of the base of support, postural alignment in the sagittal and frontal plane, muscular weakness and joint range of motion, affect balance control.[3,35,36] Altogether, these factors influence the ability of the body to control postural perturbations using the control strategies described earlier.

1.2.2.5 Sensory information

For precise control of our movements and posture, sensory information from somatosensory, visual and vestibular systems needs to be integrated and transformed into one single reference frame by the CNS.[37] It has been estimated that healthy individuals mainly rely on information from the somatosensory system (70%), followed by vestibular (20%) and visual information (10%) for stability while standing on a firm surface in a light environment.[32] However, if the sensory environment changes, the CNS re-weight the dependency on the different sensory systems[37] which is important for the ability to adapt to different sensory environments (*e.g.* changing support surface or lights).

1.2.2.6 Cognitive processing

There is a growing body of research revealing the interaction between cognition and mobility.[2,38,39] Human movements are believed to be controlled by a balance between automaticity, *i.e.* movements controlled without the attention by the individual, and executive control, *i.e.* movements controlled through the attention by the individual.[40] Gait incorporates both control mechanisms; it has thus been used as a model to study cognitive-motor interaction.[2] Although human walking is modulated by spinal networks,[41] evidence from brain imaging studies has revealed that areas also related to higher cognitive control are activated during walking.[42,43] In healthy individuals, walking is considered to be a highly automated skill since minimal use of executive control is needed to coordinate the walking pattern.[2] The automatic control of walking is critical for safe ambulation, since executive control may then be allocated to other important aspects of the environment (*e.g.* an approaching obstacle) or to other tasks (*e.g.* reading items on a shopping list). With disease or injury, evidence suggests that the control of walking shifts from being highly automatic to executively controlled with the attention on 'how' the body is moved.[2] Unfortunately, executive control of walking has shown to cause an overload to limited cognitive reserves, which could potentially lead to unstable walking and increased risk of fall.[39]

The most widely used behavioral approach to address the impact of cognition on motor performance is the assessment of dual-tasking (DT). DT is defined as the simultaneous performance of two tasks with different goals, in which one could be referred to as the primary and the other as the secondary task.[5] In the DT paradigm, the primary task is performed as a single-task (ST, *e.g.* walking) as well as a DT (*e.g.* walking while performing a cognitive task). Different theoretical models have been applied to explain DT interference,[44-46] the bottleneck and the capacity-sharing theories as the most commonly referred to. The bottleneck theory, postulates that the concurrent performance of two tasks

using the same neural network will delay performance of one of the tasks until the network is available again.[47] Thus, according to the bottleneck theory, it is not possible to perform two tasks concurrently if they occupy the same neural networks. Conversely, the capacity-sharing model suggests that it is possible to perform two tasks simultaneously, however, the amount of available capacity is restricted and performance degrades if the total capacity is exceeded.[48]

1.3 BALANCE IMPAIRMENTS IN PARKINSON'S DISEASE

Balance control is negatively affected from the early stages of PD and worsen as the disease progress.[49] As PD causes impairments of several physiological systems, balance impairments in individuals with PD cannot be explained by one single function but are rather the result of impairments of multiple systems.

1.3.1.1   Movement strategies

Balance impairment in individuals with PD is traditionally associated with poor or absent reactive responses following external perturbations.[50] As an example, the quality of the balance reactions in the backward direction is actually used as disease severity criterion.[51] However, APA is also impaired in PD; thus leading to instability and decreased movement quality, for instance during postural transfers[52,53] and gait initiation.[54,55] Degeneration of the basal ganglia also leads to inflexible adaptation of motor commands, which is important for task and context-specific adjustments of movement.[56,57]

1.3.1.2   Orientation in space

Individuals with PD have demonstrated compromised perception of verticality of the body which increases the risk of falling.[58,59]

1.3.1.3   Controls of dynamics

Impaired gait occurs early on in PD, and comprises two types of disorders.[60] Firstly, the continuous gait disorder that often includes decreased velocity, reduced arm swing, as well as short shuffling and variable steps.[60] Secondly, individuals with PD might also demonstrate episodic gait disorders, such as festination and freezing. The latter is characterized by the inability of generating walking steps despite having the intention to walk.[61]

1.3.1.4   Biomechanical constraints

Several biomechanical constraints characterize PD, *e.g.* decreased joint range of motion, 'stooped' posture, narrow foot stance and axial rigidity.[50,62,63] These impairments degrade the ability of the body to control postural perturbations[50] and restricts the functional limits of stability, *i.e.* the area in which the CoM can be moved with maintained stability and without changing the BoS.[64]

1.3.1.5 Sensory information

Dysfunction of the basal ganglia influences the re-weighting and integration of sensory information which degrades the ability of adapting to different sensory environments.[37] For individuals with PD, this problem is accompanied by impaired proprioception,[37,65] overestimation of the amplitude of movements[66] and over-reliance on vision for balance control.[67]

1.3.1.6 Cognitive processing

Dual-tasking leads to degraded balance and gait performance in individuals with PD,[46,52,68] resulting in vulnerability to falls during many daily activities.[69,70] Considering walking, most previous studies have demonstrated a decrement of ≥20% in walking velocity between ST and DT in PD,[46] compared with only 5-10% in healthy individuals.[71] Furthermore, it is likely that non-motor symptoms, in particular impaired executive functions (*i.e.* cognitive abilities that control goal-directed behavior),[72] interfere with balance control in individuals with PD.[44,45,72] Both the bottleneck and capacity-sharing theories have been applied to explain DT interference in individuals with PD.[45,46]

1.3.2 Turning while walking

Locomotion in everyday life is rarely performed during steady state walking; in fact, up to 50% of the steps executed each day incorporate turning steps.[73] In this thesis, turning is conceptualized within the 'control of dynamics' domain of balance control, and is defined as movements that lead to a change in direction of the body with respect to the longitudinal axis. In particular, this work accentuates turning that takes place while walking and which according to Patla *et al*, this task incorporates re-orientation of the body towards the new path and adaptation of the ongoing step cycle.[74]

Walking turns have been divided into two strategies, either step strategy (turning to the opposite side of the stance leg, *e.g.* turning right with the right foot and the left foot is on the ground) and spin strategy (turning towards the stance leg, *e.g.* turning right with the left foot and the right foot is on the ground).[75] From a balance control point of view, the step strategy offers greater stability owing to a wider base of support compared with the spin strategy.[75,76] Turning is a complex task that integrates spatial awareness and dynamic control of CoM,[74,75,77] which is especially apparent during community ambulation since turning is frequently executed unexpectedly with limited time for planning (*e.g.* negotiating obstacles and navigating crowded environments).[78,79]

1.3.3 Turning impairments in Parkinson's disease

Turning impairments is a common feature of gait disturbance which is, for many, a trigger to freezing of gait and falls.[80-82] Turning deficits in PD often appear before any changes in linear walking can be observed,[83] and are characterized by impaired axial coordination[84-86] and the requirement of a greater number of steps.[86-88] Even if turning difficulties increase with disease progression, more than 50% of subjects with mild to moderate stage of PD report turning

problems.[82,89] In a recent study by Mancini *et al.,* the authors demonstrated that for individuals with PD, an average turn in daily living included three turning steps, resulting in a turning angle of approximately 90°.[90] Laboratory studies have also shown that turning impairments in PD became more prominent while turning 120° compared to 60°.[85,91] As cognitive distraction and stressful situations (*e.g.* tasks with limited time for planning) degrade dynamic balance control in individuals with PD,[61] these aspect could be important to consider in the assessment of turning.

1.4 EFFECTS OF BALANCE IMPAIRMENTS

For individuals with PD, balance impairments have a negative impact on several domains of activities of everyday living, including limitations in activity and restrictions in participation according to the ICF.

1.4.1 Falls and fall-related psychological issues

Among the negative effects of balance impairments in individuals with PD, falls are the most alarming due to the devastating consequences of these events. In fact, compared with healthy individuals, elderly with PD have shown a nine times increased risk of injurious falls[82] accompanied with high mortality and costs in the general older population.[92,93] Furthermore, among individuals with PD, falls commonly occur while tripping, turning, reaching and rising,[81] with impaired balance control as one of the critical factors of the etiology of falls.[94] Regardless of whether a person experience falls or not, or if physical injury occurs, falls or near fall events often lead to fall-related psychological issues, such as fear of falling, concerns about falling and loss of balance confidence.[4,95] Although these psychological constructs are similar, they are believed to represent unique information with regard to their impact on falls, activity and participation.[4] For individuals with PD, cross-sectional studies have revealed that fall-related psychological issues are associated with impaired balance performance, dependency in daily activities, fatigue and poorer quality of life.[96-98] Furthermore, fall-related psychological issues have shown to be a barrier to exercise[99] and an independent predictor for future falls.[100]

1.4.2 Activity limitations

For individuals with PD, the wide variety of symptoms, including balance impairments, induces different limitations in activity, such as transfers, walking, eating and communicating.[101,102] Activity limitations in PD are also linked to other negative features, such as decreased quality of life[103] and decreased physical activity.[104] Physical activity is an important aspect to consider in the management of individuals with PD due to the risk of inactivity that is precipitated by a decline in physical functioning (*i.e.* decreased muscular strength, joint range of motion, aerobic capacity), and increased risk of co-morbidity (*e.g.* cardio-vascular diseases).[105,106] In this thesis, the term level of physical activity is used to address the habitual physical activity (*i.e.* the sum of all activities a person does as part of their regular day).[107] Previous studies in individuals with PD have shown about 30% lower levels of physical activity, compared with healthy individuals of the same age.[108,109] Higher

disease severity and impaired gait performance have been associated with lower physical activity levels in this population.[108,109] Older individuals with PD are at risk of inactivity, not only because of increased age, but also due to the motor and non-motor symptoms of PD contributing to sedentary behaviour.

1.5   TREATMENT FOR PARKINSON'S DISEASE

1.5.1   Effects of dopaminergic medication on balance impairments

The effects of dopaminergic medication on balance-related tasks are commonly addressed by evaluating the task performance in an 'OFF' and 'ON' medication state.[110] In particular, OFF testing is commonly performed after overnight withdrawal of medication, whereas ON testing is performed approximately one hour after taking the prescribed medication. Importantly, this is a pragmatic approach where the performance of a certain task is compared between a condition when medication wears off and symptoms recur (OFF) and a second condition when the individual experience a favorable response to medication (ON).

Although dopaminergic medication has a dramatic clinical effect on PD,[24] the effects of medication on balance control remains uncertain.[28] One reason for this uncertainty is the divergent effects that dopaminergic medication has on impairments as well as different domains of balance control.[111] First of all, regarding body functions, medication has showed to improve bradykinesia of the limbs in individuals with PD,[112,113] while axial rigidity and proprioception remained ineffectively addressed by medication.[62,65] Secondly, several studies have demonstrated that dopaminergic medication led to faster walking velocity owing to longer steps[111,114-116] as well as improved performance on clinical balance tests.[115,117] In contrast, other important domains of balance control, such as postural adjustments[118,119] and postural sway,[111,120,121] have showed to be negatively affected by medication.

Previous studies on the effects of medication on turning in individuals with PD investigated in-place turns[62,122-124] and walking turns.[111,125] Independent of the type of turn evaluated, the studies have demonstrated inconsistent results, varying from no improvement[62,122,124,125] to slight improvements.[111,123] Furthermore, those studies focused mainly on global performance measures (*e.g.* turning duration). Therefore, limited knowledge exists regarding the effects of medication on specific features influencing turning performance, *e.g.* how turning is initiated and the manner in which the walking pattern is regulated while turning. As such, information concerning the effects of and features not addressed by medication is needed to first understand the medication effects, or non-effects, and secondly to guide training interventions.

1.5.2 Balance training

1.5.2.1 Exercise modalities

Exercise is defined as 'a physical activity that is planned, structured and repetitive with the objective to improve or maintain physical fitness components'.[6] According to the *European Physiotherapy Guideline for Parkinson's disease*, training interventions addressing balance impairments in PD could be divided into three broad and partly overlapping categories: 1) *Exercise*: that target balance-related impairments directly, *e.g.* through walking or transfer exercise, or indirectly through strength and aerobic exercise; 2) *Movement strategies:* the application of cognitive strategies (*i.e.* cueing, attention and sequencing) to daily activities in order to compensate for deficits in movement automaticity, and 3) *Practice*: entails repetitive motor execution to improve the fluency of motor skills, either of original motor skills or through motor learning of novel skills.[23]

1.5.2.2 Effects of balance exercise

Although there is a growing body of research demonstrating that balance impairments in individuals with PD improves by use of different exercise modalities, no current evidence that suggests the effectiveness of one specific training modality over the other is available.[23,126,127] Furthermore, it remains unclear whether or not the positive effects of exercise on balance related outcomes (*e.g.* clinical balance tests) are further transferable to activities of daily living.[126,128] Based on a meta-analysis of exercise interventions targeting balance performance in PD, it was recommended that future exercise interventions should focus on more challenging aspects of balance exercises and consist of a higher training dose.[127]

1.5.2.3 Dual-task exercise

The focus of this thesis is on balance exercise within the *practice* domain, which aims to optimize motor learning by gradually increasing task and context complexity as well as cognitive engagement.[23] The most common approach in the management of PD within this domain is integrated DT training, *i.e.* two tasks (*e.g.* a motor and a cognitive task) are practiced at the same time.[45,129] Exercise that contains DT has several potential benefits for individuals with PD such as the concurrent training of motor and cognitive impairments (*e.g.* executive functions) under conditions that realistically resemble activities of everyday living.[45] Based on the often cited recommendations in PD evidence-based rehabilitation, a recent shift from emphasizing avoidance of DT[130] to recommending DT exercise as safe and effective in the mild to moderate stage of PD (H&Y 2-3) has been proposed.[23] Still, evidence on DT training in PD is limited. To date, we have previously showed that DT training is feasible in older adults with PD[131] and other pilot studies have indicated improved gait performance after DT-training in PD;[129,132-134] however, hitherto no randomized controlled trial confirmed those effects.

1.5.2.4 *Validity of balance exercise programs*

Training interventions targeting balance impairments are often based on frameworks that include theoretical principles that underpin and guide the practical execution of training. Similar to the description by Nilsen, a framework often includes a structure or plan consisting of various categories, *e.g.* concepts, constructs or variables, and importantly, frameworks do not provide explanations; they only describe empirical phenomena by fitting them into a set of categories.[135]

The transferability of a framework into practice could be considered to be an important aspect of internal validity. If uncertainty exists regarding the transparency between the framework of a training intervention and its practical implementation, it may be impossible to conclude whether certain characteristics of training were responsible for the efficacy of the intervention. Such uncertainty also compromises the comparison between clinical trials when synthesizing evidence.[136]

To prevent balance impairments and to promote motor learning in PD, it is recommended that training follows the principle of progressive overload, *i.e.* provide a challenging overload to the physiological system at a certain level of intensity and regularity.[137] In practice, this denotes that training should reflect the limits of individual capacity with a gradual increase of training load over time.[137] However, the transferability of this principle to practice is problematic, partly due to the complex nature of this intervention. To exemplify this complexity, no established criteria exist on how to monitor and progress balance training,[138] contrasting for example strength and aerobic exercises. Instead, the adaptation of balance exercise commonly relies on the trainer's ability to assess the performance of exercise and accordingly adapt the level of difficulty.[138] In contrast to such a subjective approach, it would be valuable to apply objective measurement to certain characteristics of balance training.
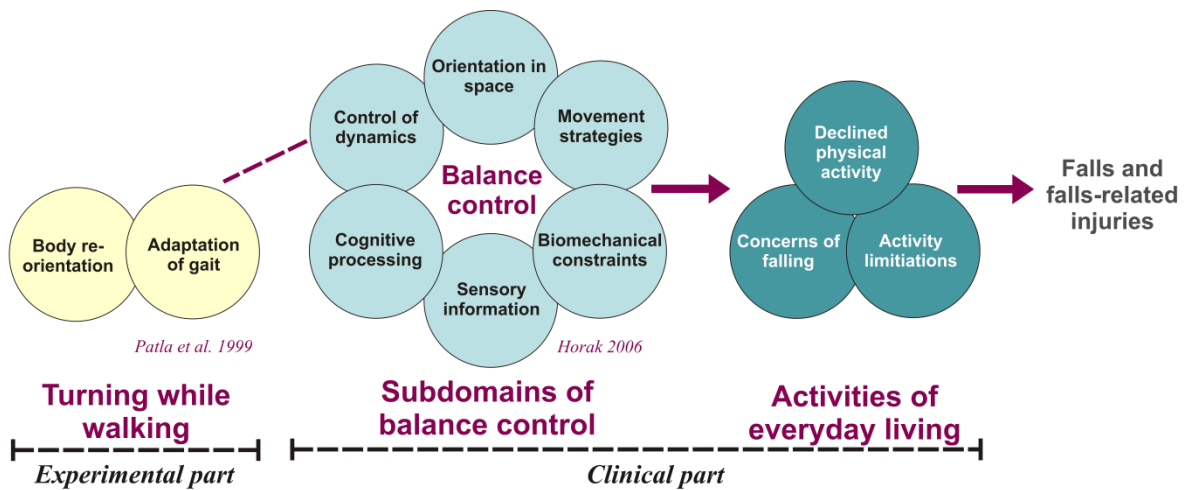
Figure 4. The main concepts in this thesis and their hypothesized interaction.

1.6   RATIONALE

Deterioration of balance control is a critical component in the downward spiral of activity limitations,[101,102] decreased physical activity,[104,108] concerns of falling[97,98] and falls in individuals with PD (Figure 4).[97,98] Falling occurs predominantly during dynamic transfers, and individuals with PD are at especially high risk of falling while performing turns.[80,81] Dopaminergic medication, the primary option of PD treatment, improves overall mobility in individuals with PD, but little is known about the precise effect of this treatment on walking turns.

The provision of appropriate exercise interventions for individuals with PD is one way to combat balance impairments and sedentary behavior in this group. Exercise interventions have not only the potential to postpone functional decline, but can also prevent adverse events related to inactivity.[105,106] In relation to training interventions, the mild to moderate stages of the disease are of specific interest since mobility impairments and falls are present and individuals are still independent ambulators. Owing to the preserved motor learning abilities in the mild to moderate stages of PD,[139] individuals are recommended to engage in exercise which challenges both motor and cognitive functions (*e.g.* DT-exercise).[23] Although pilot studies have showed positive effects of DT-exercise in PD,[129,132-134] no randomized controlled trial has yet confirmed these effects. Furthermore, although balance training programs are required to be progressive and highly-challenging, it remains unclear whether these principles can be achieved in the practical execution of training.

This thesis aims to address current gaps in the literature by investigating the efficacy of a highly-challenging balance intervention program in individuals with PD as well as the ways in which dopaminergic medications affect turning impairments in this group. In doing so, study findings can be expected to inform the development and implementation of effective training interventions which target disease-related balance impairments in PD and the sustenance of independent living among these individuals.

2 AIM

The aim with the *experimental part* was to investigate the effects of dopaminergic medications on turning while walking in older adults with mild to moderate PD. The *clinical part* aimed to develop a training program targeting balance impairments related to PD, to verify the progression of this program and the specific effects on balance and gait, as well as the transfer effects to everyday living.

Specific aims

Study I: To investigate the effects of dopaminergic medication on the initiation and performance of preplanned and unplanned walking turns in older individuals with mild to moderate PD compared to a healthy control group.

Study II: To develop a novel progressive balance training program that emphasises highly-challenging and varied balance exercises, including DT, specifically related to PD impairments.

Study III: To explore the intended progression of a 10-week balance program, including DT, in two independent training groups of older adults with mild to moderate PD.

Study IV: To investigate the short-term effects of a 10-week training program with highly-challenging balance exercises, including DT, compared with usual care in older adults with mild to moderate PD. In particular, the aim was to evaluate if this program led to specific effects on balance and gait, and whether these effects would also transfer to everyday living (concerns about falling, physical activity levels and activities of daily living).

3 METHODS

3.1 DESIGN

The *experimental part* contains a cross-sectional study (*Study I*), while the *clinical part* contains a study protocol (*Study II*), a longitudinal observational study (*Study III*) and a randomized controlled trial (*Study IV*).

3.2 SAMPLE SIZE AND POWER

For Study I, the sample size was based on previous studies that included approximately 20 individuals with PD and controls, respectively, to assess the effects of dopaminergic medication on turning, balance control and gait.[115,123] For the Randomized controled trial (Study II and IV), the sample size estimation was based on a pilot study[131] and similar intervention studies in PD.[132,140] The power calculation was performed separately for the three main outcome measures: balance performance assessed with the Mini Balance Evaluation Systems Test (Mini-BESTest); gait velocity measured during ST and DT conditions; and concerns of falling evaluated with the Falls Efficacy Scale–International (FES-I). In order to achieve 80% power with a 2-sided alpha level of 5%, the number of subjects required per group and the hypothesized effect size (ES) were 24 (ES = 0.83) for Mini-BESTest, 27 (ES = 0.83) for gait velocity and 32 (ES = 0.71) for FES-I. Altogether, by taking into account an anticipated dropout rate of 15%, a sample size of 40 in each group was needed (total n = 80). However due to long-term follow-up of the training program (not included in this thesis), the group size was increased to 50 subjects (total n = 100). Due to the exploratory nature of study III, no power calculation was considered necessary prior to this study.

3.3 PARTICIPANTS

3.3.1.1 *Recruitment*

All participants in the three studies were recruited for and derived from the BETA-PD study. Community-dwelling individuals with Parkinson's disease were recruited via advertisements in local newspapers, the Swedish Parkinson Associations, Karolinska University Hospital and outpatient neurological clinics in Stockholm County. Approximately 70% of the participants with PD were recruited via advertisements, 10% from the health care system and the remaining 20% were unknown. Data for all studies were collected between spring of 2012 and spring of 2013. An overview of the recruitment procedure, sample size and the dropout rates for all studies is provided in Figure 5. Furthermore, the participants' characteristics for the different studies are presented in Table 2.

3.3.1.2 *Inclusion and exclusion criteria*

Inclusion criteria were: a clinical diagnosis of idiopathic Parkinson's disease (Queens Square Brain Bank criteria);[16] a H&Y-score of two or three;[21] ≥60 years of age; the ability to independently ambulate indoors without a walking aid; ≥3 weeks of unchanged dopaminergic

medication and signs of impaired balance control (*e.g.* instability during postural transfers and gait impairments) during baseline clinical assessment. This approach attempted to simulate the real-world in that individuals with such disease profiles would be considered for physiotherapy in clinical practice.

Exclusion criteria were: cognitive deficits as indicated by a Mini-Mental State Examination score of <24,[141] and other medical conditions that would substantially influence balance performance or participation in the intervention. Specific exclusion criteria for study I were visual impairments, severe tremor and medication-induced dyskinesia affecting walking. In study I, healthy individuals (matched for age- and gender) were recruited through advertisement and senior training groups in Huddinge, Stockholm, to serve as a control group. The control subjects had no visual impairments or any medical condition affecting gait or balance performance.

3.3.2 Study I

In this experimental study, 20 individuals with PD and 20 healthy control subjects were assessed for eligibility. One individual with PD was excluded due to severe medication-induced dyskinesia and three in the control group due to visual impairment, imbalance due to vertigo and gait problems. Data from 19 individuals with PD and 17 healthy controls were analyzed.

3.3.3 Study III

A sub-group of individuals with PD that have been allocated to the training group in study IV was recruited to this study. This group represented two training groups, with the first that trained as part of the south cohort (n = 6) and the second as part of the north cohort (n = 4).

3.3.4 Study IV

Participants that have met the criteria for inclusion were divided into two geographic cohorts (south and north). After baseline testing, the participants in each cohort were randomized in blocks of four to either a training-group or control-group. The random sequence for group allocation was performed by one of the study coordinators (DC) using web-based software (http://www.randomization.com). Opaque envelopes, both sealed and numbered, were used to ensure that both testers and participants were blinded to the group allocation. Masking of the test leaders was not possible after baseline assessments because some also served as trainers during the balance training intervention. However, during the 10-week follow up assessments, we ensured that participants were never assessed by a test leader who had been involved in their training. A total of 100 participants with PD were randomized, and 91 participants completed the 10-week follow up. The dropout rate and reasons for discontinuing participation in the study were similar in both groups (Figure 5).
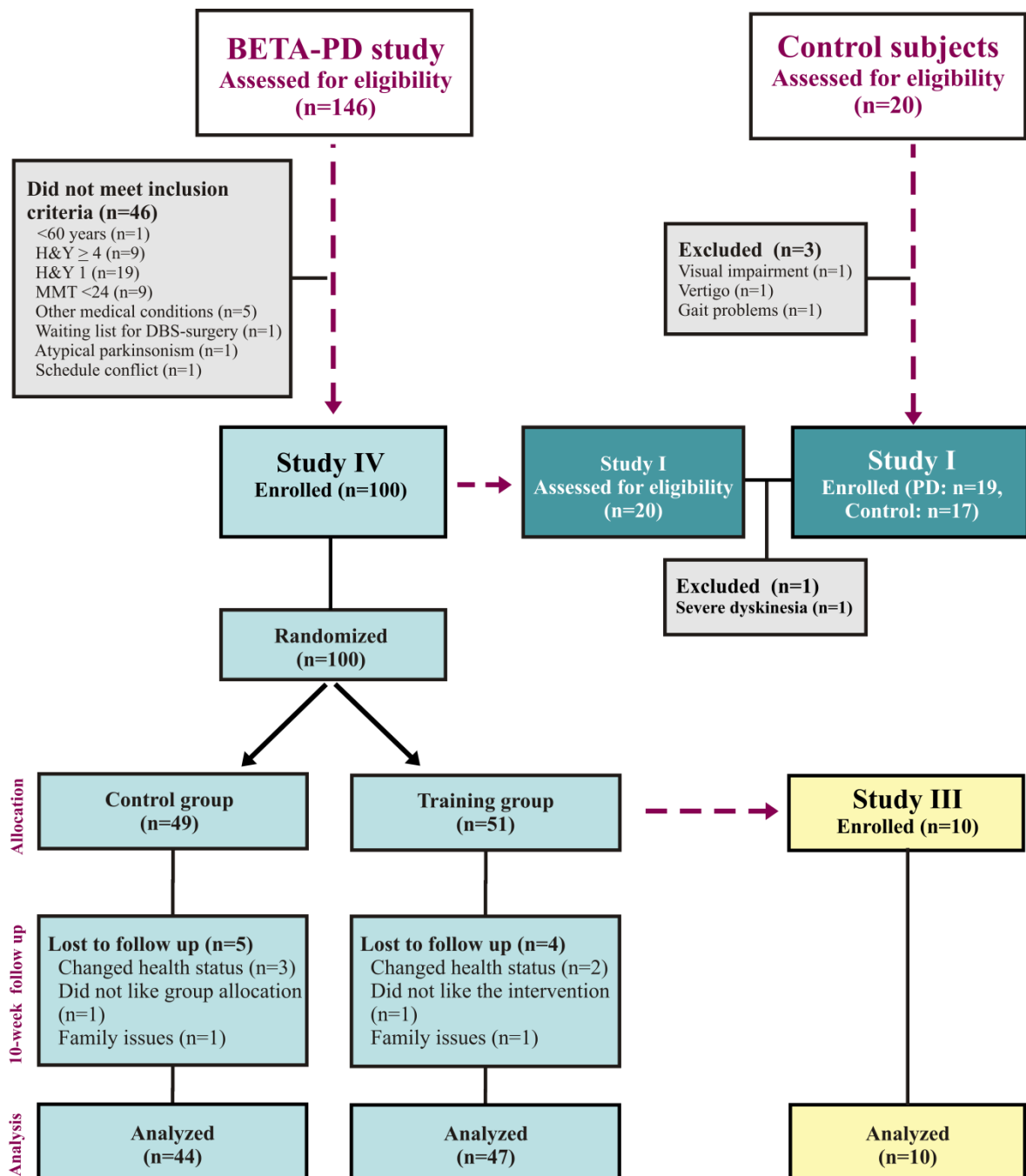
Figure 5. Flowchart illustrating the recruitment, enrolment and sample sizes for Study I, III and IV, as well as the randomization, follow-up and reasons for withdrawal from Study IV.

Abbreviations: PD = Parkinson's disease; H&Y = Hoehn and Yahr; MMT = Mini Mental State Examination.

Table 2. Background characteristics of the participants. Continuous data presented as mean (standard deviation) and min-max; nominal data is presented as numbers (percentages).

| | Study I | | | | Study III | | Study IV | | | |
| | PD (n=19) | | Healthy controls (n=17) | | PD training (n=10) | | PD training (n=47) | | PD control (n=44) | |
Variable	Mean (SD)	Min–Max	Mean (SD)	Min–Max	Mean (SD)	Min–Max	Mean (SD)	Min–Max	Mean (SD)	Min–Max
Age, yrs	72 (4)	65–82	72 (5)	65–87	71 (6)	63–83	73 (6)	61–87	74 (5)	65–87
Body weight, kg	75 (11)	58–92	76 (9)	61–94	83 (12)	57–101	76 (14)	48–102	77 (14)	45–101
Body height, cm	173 (6)	158–182	176 (9)	159–187	173 (9)	160–187	172 (9)	156–190	171 (9)	148–187
UPDRS motor	35 (8)	18–49	-	-	40 (7)	31–50	36 (10)	17–62	37 (11)	14–57
PD duration, yrs	5 (4)	1–17	-	-	4 (2)	1–7	6 (5)	1–25	6 (5)	1–21
LEDD,[a] mg/day	636 (228)	200–1102	-	-	479 (387)	0–1298	581 (295)	0–1487	645 (404)	225–2666
Gait speed, m/s	1.24 (0.13)	0.83–1.39	1.47 (0.14)	1.23–1.73	1.18 (0.21)	0.80–1.53	1.19 (0.21)	0.73–1.55	1.16 (0.18)	0.67–1.52
Average steps/day	5886 (3637)	774–14130	-	-	4632 (3496)	781–10696	4842 (3046)	376–13436	4695 (3397)	149–14495
	Numbers	%	Numbers	%	Numbers	%	Numbers	%	Numbers	%
Gender, male	12	63	10	59	7	70	28	60	23	51
H&Y stage, 3	4	21	-		4	40	27	57	25	57
Recurrent fallers,[b] yes	11	58	0	0	6	60	25	53	24	55
<5,000 steps/day	9	47	-	-	6	60	25	54	26	59

Abbreviations: PD = Parkinson's disease; H&Y = Hoehn and Yahr; UPDRS = Unified Parkinson's Disease Rating Scale; LEDD = Levodopa equivalent daily dosage.

[a] Daily levodopa dose equivalency calculated in accordance to Tomlinson *et al.* (2010).[142]

[b] Participants who had experienced ≥ 2 falls during the previous 12 months were classified as recurrent fallers.

3.4 DATA COLLECTION

According to the wide disability spectrum associated with balance impairments in PD [49,143,144] a multi-dimensional battery of outcomes were measured to explore different domains of balance impairments and treatment effects. Table 3 provides a classification of outcomes measures used in this thesis within the ICF.[1]

Table 3. Classification of outcome measures within the International Classification of Functioning, Disability and Health (ICF).

		ICF		
Instruments	**Domains**	Body functions	Activity	Participation
Study I				
Motion analysis system	Turning characteristics (onset, strategy and performance). Spatial gait parameters during straight walking and turning.	•	•	
UPDRS-motor	Motor symptoms	•		
PIGD	Balance control	•	•	
Medication-VAS	Self-perceived mobility impairments		•	
Study III				
Accelerometer	Training activity		•	
Study IV				
Mini-BESTest	Balance control	•	•	
MFE-test	Balance control		•	
Electronic walkway	Temporal and spatial gait parameters during ST and DT conditions	•	•	
Cognitive task	Executive functioning	•		
FES-I	Concerns about falling	•		
UPDRS ADL	Activities of daily living		•	
Accelerometer	Physical activity level		•	•

Abbreviations: FES-I = Fall Efficacy Scale International; Mini-BESTest = Mini Balance Evaluation Systems Test; MFE = Modified Figure-of-Eight test; ST = single-task; DT = dual-task; UPDRS motor = the motor section of the Unified Parkinson's Disease Rating Scale, part III; UPDRS ADL = the activities of daily living (ADL) section of the Unified Parkinson's Disease Rating Scale, part II; PIGD = Postural Instability and Gait Difficulty four-item sub-score; VAS = visual analogue scale.

3.4.1 Severity of Parkinson's disease

The motor section of the Unified Parkinson's Disease Rating Scale motor score (UPDRS-motor) was used to assess motor symptoms (*i.e.* tremor, rigidity, bradykinesia, postural instability and gait).[21,145] The UPDRS-motor section contains 27 items which are summarized as a sum-score (maximum score equals 108 points), where a higher score indicates more severe symptoms. The UPDRS-motor has proven to be valid and reliable in several studies [51]. From the UPDRS-motor assessment, disease severity of PD was classified according to the original H&Y staging scale,[21] with the use of disease duration (years) and daily levodopa equivalency daily dose (LEDD)[142] as additional proxies for disease severity.

3.4.2 Turning while walking

3.4.2.1 Test procedure

The PD group was tested twice, first after overnight withdrawal of medication (OFF, average off time = 16 hours, range: 12-22 hours) and approximately one hour after taking their usual morning dose of dopaminergic medication (ON). The mean LED (min-max) intake following OFF testing was 194 milligram (50-380) which on average represented 31% (17-71%) of their daily dosage.

Since it was not feasible for many participants to attend assessments over two days, both test sessions were performed on the same day. Before each test session (OFF and ON), the UPDRS-motor was administrated by a physiotherapist trained to assess motor impairments under both medication conditions. After OFF and ON testing, participants rated how well their medication was working using a 100 mm visual analog scale (*i.e.* 0 mm equals worst possible effect while 100 mm equal best possible effect).[122]

The control group also underwent a protocol comprising two sessions. First, turning was assessed at comfortable walking velocity, and thereafter the same protocol was then repeated where the walking pace was matched to a comfortable pace of the PD participants. For the majority of the control subjects, the matched velocity was achieved by instructing controls to walk slower than their comfortable speed. The test leader also paced the control subjects by using a handheld stopwatch and by counting the number of steps over a two-meter distance. This matching approach was applied because walking velocity alone can influence movement characteristics during straight walking[146] and turning.[84,147,148]

Experimental setup
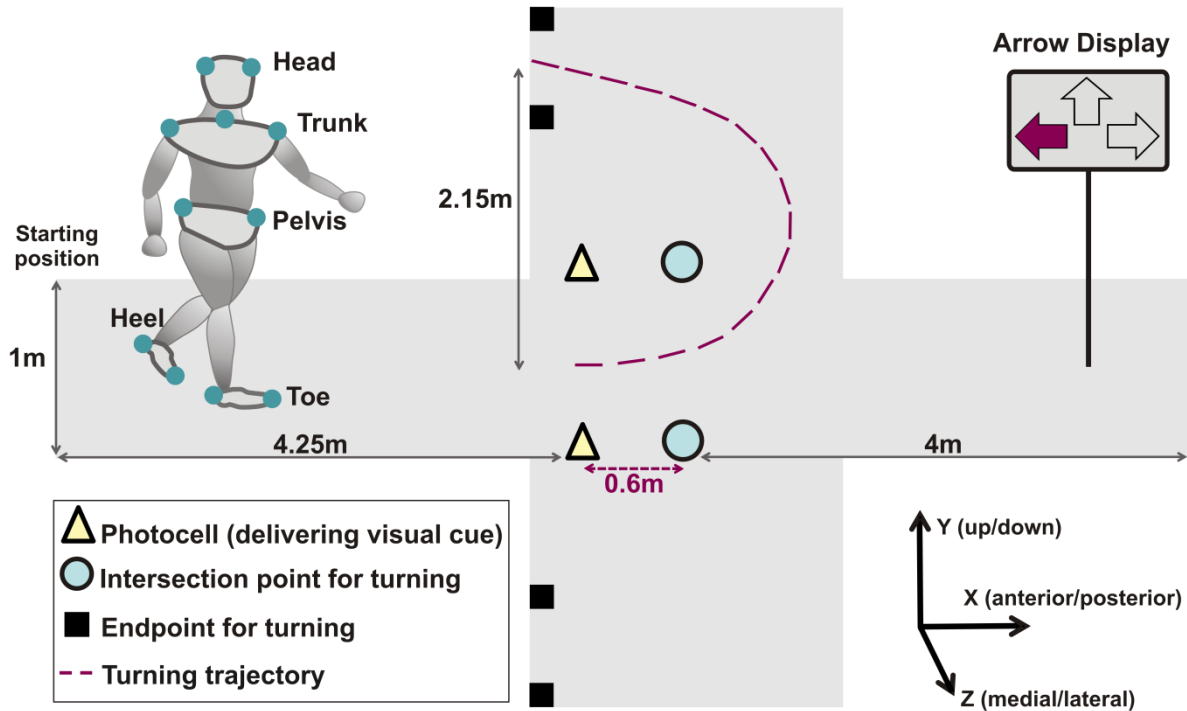
Figure 6. Schematic drawing of the walking alley, position of the reflective markers and the global reference system used. The walking direction (straight, right or left) was provided with a visual signal before walking initiation during preplanned turns and 0.6 meter prior to the intersection point during unplanned turns.

3.4.2.2   Preplanned and unplanned turning

Prior to data collection, practice sessions were held to familiarize participants with the procedure. The PD and control group performed two different turning conditions (preplanned and unplanned) in a randomized order.

For both turning conditions, the participants walked along a 9-meter T-shape walking alley where the turning position was delineated by two poles forming an intersection (see Figure 6). For both preplanned and unplanned turns, they performed one of three tasks, presented randomly: walking straight, or walking and turning 180° to the right or to the left. Subjects were instructed to walk and turn to the new direction without stopping whilst, taking the closest path to the target (defined by two poles, located 2.15 meter laterally and 1.0 meter behind the intersection). The subjects started each trial 4.85 meters from the turning intersection, thus providing a sufficient distance to reach a steady-state straight walking velocity before turning.[149] For the preplanned condition, the walking direction was provided by a visual signal before they initiated walking (*i.e.* while standing at the starting position) denoting that planning of the walking direction takes place prior to trial being executed. In contrast, for the unplanned condition, the same visual signal was provided 0.6 meter prior to the intersection point (*i.e.* during steady-state walking).[150] Consequently, for the unplanned

condition, participants had approximately one step length to plan and initiate turning. The pre- and unplanned turning condition each contained a total of 15 trials per subject (*i.e.* five trials each for straight walking, right and left turning). During testing, the participants were allowed to rest when needed.

3.4.2.3   Measurement of movement

Movements were recorder at 100 Hz using an eight-camera motion analysis system (Elite 2002, version 2.8.4380; BTS, Milano, Italy). Spherical retro-reflective markers (1cm in diameter) were positioned on the seventh cervical vertebra (C7) and bilaterally on the head, acromion, posterior superior iliac spine and heel (Figure 6). As spatial references, two markers were also positioned on the two poles forming the intersection. Three-dimensional trajectories of the markers were acquired using a tracking system (Tracklab-BTS, Milan, Italy) in accordance with a global reference system: y-axis (up/down), z-axis (medial/lateral) and x-axis (anterior/posterior) (Figure 6). Data were processed and filtered (Butterworth low-pass filter: 7-Hz cutoff frequency) using MATLAB software (MATLAB, 7.4.0, MathWorks, Natick, MA, USA, 2013).
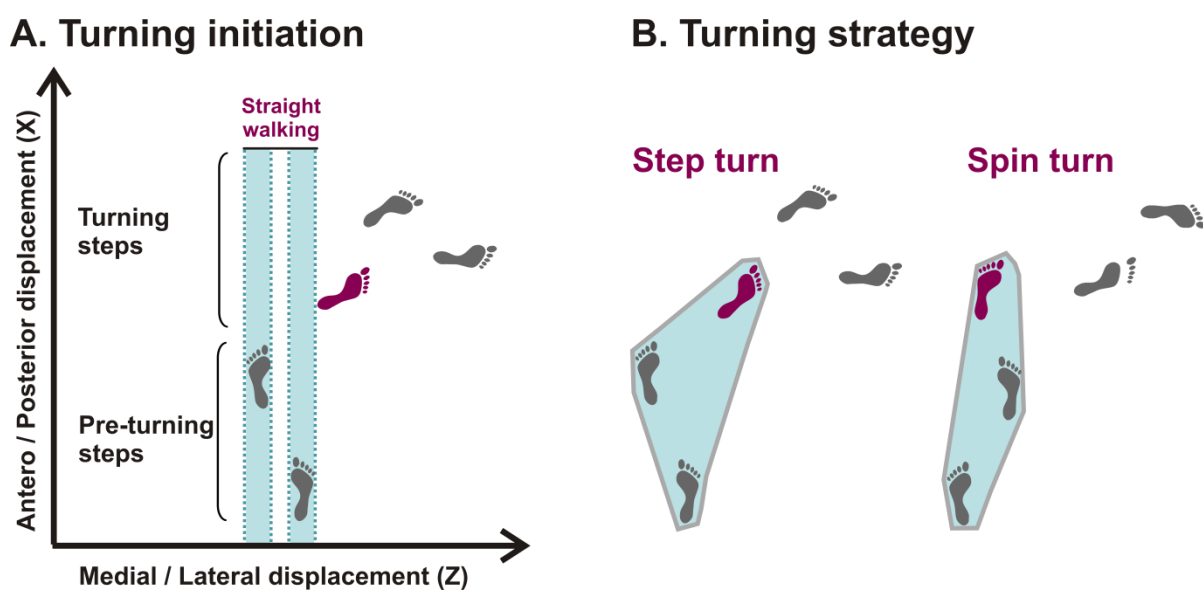
Figure 7. Representative footstep adjustments of two pre-turning steps and three turning steps.
A) The first turning step (*i.e.* plum color) was identified as the first heel strike that exceeded two standard deviations in medio-lateral displacement of straight walking. **B)** Representative footstep adjustments for step turns (*i.e.* first turning step equal the turning direction) and spin turns (*i.e.* first turning step opposite to the turning direction) are also illustrated. Notable is the wide and narrow base of support for the first turning step of a step and spin turn, respectively.

22

3.4.2.4 Turning outcomes

Three turning steps were analyzed, which is typical for turns in daily living (approximately 90°).[90] As shown in Figure 7a, heel strikes for two steps leading into and three steps exiting the turns were collected. Heel strike events were determined based on the velocity profiles of the heel markers (y-axis). The pre-turning steps were used as a baseline to determine onset of the first turning step,[148] and for the calculation of step length and width of the turning steps.[151] The turning steps were identified as the first heel strike that exceeded two standard deviations (SD) in medio-lateral displacement of five straight walking trials (computed for each participant) in the designated turning direction (see Figure 7a). To discriminate between preparatory turning steps and the actual turning step, the succeeding turning step also needed to exceed two SD from the straight walking trial average.[148] A turn was defined as a step turn if the first turning step was performed in the direction to turning or as a spin turn if the first turning step was the opposite to the direction of turning (see Figure 7b).[75] The outcomes for turning are explained in Table 4.

Table 4. Outcomes for walking turns.

Outcomes	Description
Turning strategy	The percentage of turning trials using the step strategy, *i.e.* the number of trials using step turns divided by the total number of trials.
Body rotation	The yaw angular displacement profile of the pelvis segment was calculated and the magnitude of pelvis rotation at the third turning step was retained for analysis.
Turning distance	The cumulative linear displacements in metres of the C7 marker [z and x-axis] for three turning steps.
Turning velocity	The first derivative of the tangential displacement of the C7 marker was calcutated and the mean velocity of three turning steps was analyzed.
Turning trajectory	The mean distance in metres between C7 and the markers positioned at the turning pole using three turning steps.
Spatial gait parameters	Step length and width of three turning steps were calculated in accordance to Huxham *et al*.[151]

3.4.3 Balance control

Balance control was assessed with the Mini-BESTest, which is a 14-item clinical test that covers four components of balance control (anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait).[152] Each item is scored on a three level ordinal scale from 0 (unable or requiring help) to 2 (normal) and the result is summarized as a total score (maximum score of 28 points).[153] The Mini-BESTest has shown to be reliable and valid for older adults with mild to moderate PD.[154,155]

The Modified Figure-of-Eight (MFE) test was also used to assess balance control.[156] During testing, the participants were instructed to walk two cycles in a figure of eight (marked with 40 mm-wide tape on the floor, each loop having an internal diameter of 1.63 m) as fast as possible, with every step touching the tape. The test was performed twice where the average time (seconds) and number of oversteps (*i.e.* steps not touching the tape) were used for analysis. The MFE-test has shown to be reliable and valid for older healthy adults.[156]

In addition, the Postural Instability and Gait Difficulty (PIGD) four-item sub-score was calculated from the Motor UPDRS (*i.e.* arising from a chair, standing posture, gait and pull test).[111]

3.4.4 Single and dual-task gait

Gait characteristics were assessed with a 9-meter electronic walkway system, GAITRite® (CIR Systems, Inc., Havertown, PA, USA), during normal walking and while performing an additional cognitive task (reciting every second letter of the Swedish alphabet), *i.e.* DT. The participants were instructed to walk at a normal pace under both conditions, and to place equal focus on the walking and the cognitive task during DT. Each gait condition was performed six times, and an average value was used for analysis. Gait outcomes were gait velocity (m/s), step length (m) and cadence (steps/min). The GAITRite® mat is valid and reliable for the assessment of spatial and temporal gait characteristics.[157,158]

To gain more insight into DT performance, the performance of the cognitive task during walking (DT) and as a ST while seated was also evaluated. For the performance of the cognitive task, percentage of errors (*i.e.* the number of errors / total number of letters recited) was used for analysis.

3.4.5 Concerns about falling

Concerns about falling, a subdomain of fall-related psychological issues,[4] were assessed with the Swedish version of the FES-I.[159] The FES-I is a questionnaire assessing how concerned people are about falling during 16 indoor, outdoor and social activities. Participants grade "how concerned" they are while performing the activities on a 4-point scale, *i.e.* from "not at all concerned" to "very concerned"). A total score is calculated (ranging from 16 to 64), and higher scores indicate greater concerns about falling.[159,160] The FES-I has shown to be valid and reliable for older individuals with PD.[161]

3.4.6 Falls

Fall frequency over the last 12 months was retrospectively reported, using structured questions. A fall was defined as an unexpected event in which the participants came to rest on the ground, floor, or lower level.[162] Fall data were descriptively presented, and individuals who experienced ≥2 falls during the previous 12 months were classified as recurrent fallers.[82]

3.4.7 Activities of daily living

Activities of daily living were assessed with the second part of the Unified Parkinson's disease rating scale (UPDRS-ADL).[145] The UPDRS-ADL is a 13-item questionnaire focusing on the effects of PD on various daily activities (*e.g.* speech, handwriting, getting dressed, freezing of gait, hygiene and walking). Concerning each item, an interviewer records the self-rated score on an ordinal scale ranging between 0 and 4 (0 = no problems; 4 = severe problems).[21] The result is summarized into a total score (0-52), where a higher score indicates more limitations. The UPDRS-ADL has shown to be valid and reliable for PD.[163,164]

3.4.8 Physical activity and training activity

Physical activity during daily living and balance training was measured using accelerometers (Actigraph GT3X+, Pensacola, FL, USA). The GT3X+ accelerometer records the acceleration in three axes: vertical, antero/posterior, and medio/lateral. Accelerometry data are stored in the units of gravity (g) and is subsequently transformed into an arbitrary unit (*i.e.* counts) in either axes or as a combined vector magnitude (VM).[165] Participants worn the accelerometer around the hip, attached slightly above the iliac crest with an elastic band. Data were sampled at 30 Hz and processed using the ActiLife 6 software (ActiGraph, Pensacola, FL). The ActiLife default filter was applied,[166] and data were summarized in 15-second epochs. The GT3X+ has been proven reliable and valid in assessing energy expenditure in healthy adults.[167]

Physical activity during balance training (Study III): The participants were equipped with accelerometers during all training sessions, *i.e.* data collection consisted of 30 sessions that lasted 60 minutes. The position of the accelerometer was checked by the physiotherapists before and during the training sessions. As proxies for training activity, the number of steps per session and the time (in minutes) spent walking at a velocity of >1.0 m/s, were used to reflect the volume (*e.g.* walking, stepping) and intensity of the dynamic exercises, respectively. The number of steps per session was derived from the vertical axis (using a default logarithm in the ActiLife software) and the time spent walking at a velocity of >1.0 m/s was based on VM cut-points developed for PD.[168]

Physical activity levels in daily living (Study IV): Participants were instructed to wear the accelerometer in their daily life for seven consecutive days, only removing it when showering, swimming, bathing and at night. Participants were also asked to record on a log sheet the exact times the device was worn (*i.e.* wear time). Physical activity data were validated by comparing the accelerometer data with self-reported wear-time. Participants with four or more valid days were included in the analysis since it has shown to be a valid and reliable indicator of free-living physical activity in adult and elderly populations[169,170] and PD.[171] In order for a day to be considered valid, we required data of at least nine hours (> 90 consecutive minutes of zeros was considered non-wear time).[169] As a proxy for the level of daily physical activity, the average number of steps per day was used.

Training and leisure activities in the control group (Study IV): After the intervention period, participants retrospectively reported whether they had participated in organized training and performed leisure activities that aimed at altering physical activity during the intervention period. The type of exercise/activity was reported, as well as their mean frequency per week.

3.4.9 Cognitive function

The Mini Mental State Examination score was used as a screening tool for inclusion, where individuals were excluded if they scored <24 points.[141]

3.5 TRAINING INTERVENTION

3.5.1 Development

The training program was developed, through discussions and workshops, by a group of researchers and physiotherapists, each with different expertise in the fields of PD, rehabilitation, and athletic training. This initial step led to a preliminary program, which feasibility was investigated in five older adults with mild to moderate PD in a University hospital setting.[131] Findings from this study supported the feasibility of highly-challenging group balance training in older adults with PD.[131] Still the participants found the program being too long; therefore to ensure a high level of motivation without decreasing the training dose, the length of the program was condensed from 12 to 10 weeks and the duration for each training session was increased from 45 to 60 minutes.[131]

3.5.2 Rationale

The rationale for the program relied on findings of preserved motor learning in mild to moderate PD[139] and was based on the motor learning principles of specificity, progressive overload and varied practice.

3.5.2.1 Specificity

Training need to be specific to the targeted function.[9] Accordingly, in the context of balance training, balance exercise needs to target functions, or impairments, of balance control associated with PD symptoms.

3.5.2.2 Progressive overload

Training needs to provide a challenging overload to the physiological system through a certain level of intensity and regularity.[9] To stimulate relearning of physiological systems important for balance control, it is important to consider the training stimuli with regard to intensity of the training, the difficulty level of balance exercises and the total training dose.

3.5.2.3 Varied practice

Training need to promote variation between exercise conditions.[172] To enhance motor learning, promote a multi-faceted repertoire of movement strategies and generalization of

balance skills to activities of daily living; it is essential to guarantee practice through a wide variety of balance exercise conditions.[9,172]

3.5.3 Applications of theoretical principles in practice

The training principles of specificity, progressive overload and varied practice were incorporated into a conceptual framework for balance training.[173] The practical application of each training principle for balance training and motor learning is outlined below.

3.5.3.1 Specificity

Inspired by King and Horak,[174] this framework comprises four specific balance components associated with balance constraints in PD (Table 5). In order to target a unique domain of motor control deficits in PD with each balance component, the principles and objectives of the different balance components were distinctively defined (Table 5). In addition, DT-exercises were gradually integrated into the program by adding concurrent cognitive (*e.g.* counting, remembering items/numbers) and/or motor tasks (*e.g.* carrying and/or manipulating objects) to the balance exercises.

3.5.3.2 Progressive overload

Based on previous recommendations,[127] balance training in elderly[175] and experience from a pilot study of balance training in PD,[176] a total training dose of 30 hours (*i.e.* three 1-hour sessions/week for 10 weeks) was considered feasible for elderly with PD as well as sufficient to accomplish the aims of motor learning. Training progression was promoted by the physiotherapists' ability to adjust the level of difficulty of the exercises and structure of the training program.

The physiotherapists adjusted the balance exercises based on the capacity of each training group as well as that of each participant. Specifically, the distribution between stationary and walking exercises was modified for the training group (*i.e.* walking exercises were considered to be more demanding), whereas the level of difficulty of balance exercises were adjusted for each individual (Table 5). The physiotherapists used two pragmatic principles for adaptation of balance training. For ST-exercises, the level of exercise difficulty was considered appropriate if the participants were forced to use reactive postural adjustments to control their balance. Similarly, the level of difficulty for DT-exercises was aimed at a threshold where there was consistent interference of the participants' motor performance (*e.g.* decreased gait velocity or increased stride variation).

Table 5. Balance training. Parkinson's disease specific balance components and the principles and objectives used for the practical application of each balance component, as well as the adjustments used for progression.

Balance components	Exercise principles	Exercise objectives	Exercise adjustments
Sensory integration Integration of sensory information (somatosensory, visual and vestibular) for estimation of body position	Walking tasks on varying surface with or without visual constraints	Improve interpretation of and reliance on somatosensory information	Increased surface unevenness and restricted field of vision (*e.g.* by carrying an object)
APAs Prediction and control of perturbation related to voluntary movements	Voluntary arm/leg/trunk movements focusing on movement velocity and amplitude, and postural transitions	Improve APA strategies regarding quality (timing, amplitude) and task-specific adaptation	Increased movement amplitude and velocity
Motor agility Coordination between body parts and movement adaptation, *e.g.* regulation of movement and quick shifts between tasks	Whole-body coordination during varying gait conditions and reciprocal movements. Quick shifts of movement characteristics (velocity, amplitude and direction) during predictable and unpredictable conditions	Improve whole-body coordination, ability to adapt movements and quick shifts between different tasks	Increased gait complexity (*e.g.* altering velocity, step patterns) and amount of unpredictability (*i.e.* unawareness of upcoming sequences/tasks) of walking and coordination tasks.
Stability limits Whole-body regulation relative to the BoS	Voluntary leaning tasks in standing with varying BoS-stimulating weight shifts in multiple directions through arm and trunk movements	Improve the ability to safely control CoM within BoS for increasing functional limits of stability	Changing the area or condition of the BoS and increasing leaning movement amplitude.

Abbreviations: PD= Parkinson's disease; APAs = anticipatory postural adjustments; BoS = base of support; CoM = centre of mass.

Considering the structure of the program, the intervention period was divided into three blocks (A, B and C) to promote appropriate progressive overload throughout the course of training (Table 6). Importantly, individuals with PD, compared with healthy individuals need more time to achieve motor learning.[139,177] Therefore progression of as well as variation in training was gradually increased throughout the 10-week program.

Block A (weeks 1–2): participants were introduced to the ST exercises of each balance component separately (no DT-exercises were practiced), with an emphasis on movement quality, the objectives of the exercises, as well as task-specific motor learning.

Block B (weeks 3–5): basic DT-exercises were introduced (*i.e.* cognitive or motor secondary task) and comprised approximately 40% of each session. While addressing each balance component separately during this block, the level of difficulty and task variation was increased.

Block C (weeks 6–10): the level of difficulty of all exercises was further enhanced by increasing the variation by combining several balance components during exercise. Additionally for DT-exercise, motor and cognitive secondary tasks were combined during the same exercise session, difficulty level was further increased, and the time spent on DT-exercises (approximately 60% of each session).

3.5.3.3 Varied practice

During the initial phase of training (Block A), the exercise for each balance component was trained separately in blocks, on a weekly basis, to encourage familiarity of the principles and objectives and promote task-specific motor learning. In the later phases of training (Blocks B and C), generalization of motor skills was facilitated by increasing training variation with regard to the characteristics of exercise in each balance component (*e.g.* variation in terms of body position, BoS and movement direction/velocity/amplitude) in Block B and by integrating exercises from different balance components in Block C.

3.5.4 Practical execution of balance training

Every training session started with a warm-up session of five minutes, consisting of varied walking tasks aimed at boosting the cardiovascular system. The following 50 minutes, including short resting periods, focused on highly-challenging exercise blocks (approximately 10 minutes per block) of standing and walking conditions. The balance components of stability limits and APAs were mainly addressed through stationary exercises, whereas the balance components of motor agility and sensory integration were mainly addressed by walking exercise conditions. The program ended with a 5-minute cool-down session of slow walking, axial stretching and breathing exercises. The number of exercise blocks for each training occasion and the distribution between standing and walking exercises were adjusted to the level of ability in each group.

Goal-oriented oral feedback addressing information external to the body, *i.e.* concerning the performance of the task in relation to the environment (rather than the position or motion of the body), has shown to be beneficial for individuals with PD.[178,179] Therefore, externally-oriented oral feedback was given as simple as possible to promote movement automaticity. Cueing strategies (visual or oral)[180] were only used when needed among participants experiencing severe freezing during training.

Importantly, no fixed scheme of predetermined exercises was used in the intervention. Instead, the training principles were used as a foundation for the application and adaptation of exercises to the participants' individual abilities. Consequently, this approach resembles clinical practice but also requires continuous evaluation, modification, and planning of the training. To ensure this, all the trainers involved in this study were physiotherapists (n = 10) educated in the framework of this training concept during two 4-hour sessions of both theory and practice.

After each training occasion, the individuals' performance of the exercises was briefly documented in terms of evaluating of both the appropriateness of exercises and the current level of difficulty. Adverse events (defined as an injury or medical event that restricted activities of daily living and participation in the intervention) and training adherence were monitored and recorded.

Table 6. Training program divided into three blocks (A-B-C). The content of balance training for each week is illustrated with regards to the balance components and dual-task.

Blocks	Week	Balance components	Dual-task
A	1	Motor agility/stability limits	
	2	Sensory integration/APAs	
B	3	Motor agility/stability limits	Cognitive
	4	Sensory integration/APAs	Motor
	5	Motor agility/stability limits	Cognitive
	6	Sensory integration/APAs	Motor
C	7		Cognitive / Motor
	8	Sensory integration/APAs/motor	Cognitive / Motor
	9	agility/stability limits	Cognitive / Motor
	10		Cognitive / Motor

Abbreviations: APAs = anticipatory postural adjustments.

3.6 CONTROL GROUP

The participants in the control group were encouraged to maintain their normal physical and daily activities and were not restricted from participating in ongoing rehabilitation programs. All participants were advised to keep up their normal level of exercise and activities throughout the intervention period.

3.7 ETHICAL APPROVAL

Ethical approval for this research was obtained from the Regional Board of Ethics in Stockholm (Dnr: 2006/151-31, 2009/819-32, 2010/1472-32, 2011/1665 22, 2012-1829-32). All studies were conducted in accordance with the Helsinki Declaration, and all subjects gave their written informed consent to participate.

3.8 STATISTICS

All statistical analyzes were conducted with STATISTICA software (Statsoft, version 12, Tulsa, OK, USA). Table 7 provides an overview of the descriptive and statistical methods applied in this thesis and across Study I, III and IV. The statistics tests applied in this thesis are detailed in text.

Table 7. Statistical methods.

| | Experimental part | Clinical part | |
	Study I	Study III	Study IV
Descriptive statistics			
Mean	●•	●	●•
Standard deviation	●•		●•
Standard error			●
95% confidence interval	●•		●•
Median	•	●•	●•
Interquartile range	•	•	●•
Min - max	•	●•	•
Frequency (n), percentage (%)	●•		●•
Statistical methods			
Independent t test			●•
Mann-Whitney U test	●		●•
Wilcoxon signed-rank test	●•	●•	●
Pearson's Chi-square test x^2			●
Fischer's exact test	●		•
Repeated measures ANOVA	●•		●
Two-way ANOVA	●•		
Tukey's HSD	●•		●
Cohen's d effect size	●•		●•
Logistic regression analysis			•

Abbreviations: ANOVA = Repeated measures analysis of variance; HSD = honestly significant difference. Black and grey dots indicate whether the statistical methods were applied in the manuscripts and in the thesis, respectively.

3.8.1 Study I

The responsiveness to medication on self-perceived mobility impairments, PIGD-score, straight walking and turning performance were expressed as Cohen's *d* effect sizes (ES).[181] Positive ES denote changes that are considered improvement.

Mobility, gait and balance performance: Self-perceived mobility impairments (by means of VAS rating) and the PIGD-score were compared during OFF and ON medication using Wilcoxon signed-rank test. Straight walking velocity and step length were compared between PD OFF and ON using repeated measures analysis of variance (ANOVA).

Turning strategy and performance: Data concerning turning direction and turning strategy were collapsed since no differences in turning performance between right and left turns, step and spin turns, or turning towards or away from the most affected side were found. Repeated measures ANOVA was used to evaluate the effects of medication (PD OFF and PD ON) and turning condition (preplanned and unplanned) on turning strategy and turning performance (*i.e.* body rotation, turning distance and velocity). Two-way ANOVA was used to evaluate the difference between groups (PD ON and controls) and turning condition (preplanned and unplanned).

Regulation of walking during turning: Data were split according to turning strategies (step and spin turns) and turning conditions (preplanned and unplanned). For this analysis a minimum of three valid trials per individual and turning strategy/condition were required. Repeated measures ANOVA was used to evaluate the effects of medication (PD OFF and PD ON, two levels) and steps (straight walking and turning step 1-3; four levels) on step width. Two-way ANOVA was used to evaluate the difference between groups (PD ON and controls) and steps (straight walking and turning step 1-3) on step width. In the thesis, step width normalized to straight walking is presented. Positive values reveal wider turning steps compared to straight walking, whereas negative values reveal narrower turning steps compared to straight walking.

The Greenhouse–Geisser correction was applied in the event of violations of sphericity, and Tukey's HSD test in cases where significant interaction effects were found. Significance level was set at $p \leq 0.025$ due to multiple analyses. Data are presented as mean and 95% confidence intervals (95% CI) or as median and interquartile range (IQR).

3.8.2 Study III

Training progression: Training activity of the two training groups was presented as the median value, quartiles and min-max for the training blocks (A, B and C). The analysis was performed in two steps. First, Wilcoxon signed-rank tests were used to compare the level of activity of all participants (n=10) between the blocks (i.e. A vs. B and B vs. C), with the significance level set at $p \leq 0.05$. Thereafter, training progression was addressed for each training group by calculating the percentage differences in training activity between the training blocks (*i.e.* A vs. B and B vs. C). To denote evidence of training progression, an

increase of ≥20% in training activity between the blocks was required. This cut-off was applied using a pragmatic criterion, since, to date; no scientific criterion for training progression exists.

3.8.3 Study IV

Training effects: The differences between pre- and post-test performance in the training and control group were used for analysis. The Mini-BESTest, gait variables, FES-I, UPDRS-ADL and average steps per day were normally distributed, whereas the performance of the cognitive task and MFE-test revealed skewed distribution. Depending on the distribution of data, between group differences were analyzed using Independent *t* test or Mann-Whitney *U* test and presented as the mean (95% CI) or median difference (IQR), respectively. Effect size between the two independent groups was computed using Cohen's d calculation.[181] We used both an intention-to-treat (last value carried forward data imputation) and a per-protocol approach. However, since the analyses revealed similar results, and given the small dropout rate, only the results of the per-protocol analysis are reported. Significance level was set at *p* ≤ 0.05.

Dropout and missing data analysis: The Mann-Whitney U test and Fisher's exact test were used to assess whether differences in age, gender, UPDRS-motor score, H&Y score, Mini-BESTest, comfortable walking velocity, UPDRS-ADL and FES-I were evident between subjects that dropped out compared with those who completed the study. Furthermore, due to the rather high proportion of missing data for physical activity (training group: 21%, control group: 27%), univariate logistic regression analysis was used to explore whether missing data were dependent on the observed values or missing at random.[182]

4 RESULTS

This section summarizes the main results of the *experimental* (*Study I*) and *clinical part* (*Study III* and *IV*) of the thesis. Detailed results of each study are provided in the publications and manuscripts.

4.1 EFFECTS OF DOPAMINERGIC MEDICATION ON TURNING WHILE WALKING

Data concerning pre- and unplanned turning for PD OFF, PD ON and controls are provided in Table 8. Figure 8 provides an overview of the effects of medication on motor symptoms, straight walking, and pre- and unplanned turning.

4.1.1 Balance control and gait

Participants with PD perceived greater benefits of medication on mobility in the ON compared with OFF medication state as supported by significant higher median ratings of the visual analogue scale (PD OFF: 65 mm, IQR: 46—82, PD ON: 82 mm, IQR: 64—92, $p = 0.005$). The median PIGD sub-score improved significantly after medication intake (PD OFF: 4, IQR: 3—5, PD ON: 3, IQR: 2—4, $p = 0.005$), as well as the mean straight walking velocity (PD OFF: 1.17 m/s, CI: 1.09—1.25, PD ON: 1.24 m/s, CI: 1.17—1.30, $p = 0.006$) owing to the increase in step length (PD OFF: 0.60 m, CI: 0.56—0.64, PD ON: 0.63 m, CI: 0.59—0.66, $p = 0.008$).

Table 8. Preplanned and unplanned turning in PD OFF and ON and controls.

	Preplanned turns			Unplanned turns		
	PD OFF	**PD ON**	**CON**	**PD OFF**	**PD ON**	**CON**
Step turns (%)	48	50	47	47	54	48
	(39—57)	(41—59)	(39—54)	(40—54)	(47—61)	(51—55)
Body rotation	77	80	99	100	103	113
(°) ‡	(68—86)	(72—88)	(92—105)	(94—107)	(97—109)	(108—118)
Turning distance	1.47	1.55	1.82	1.39	1.46	1.74
(m) † ‡	(1.37—1.57)	(1.46—1.63)	(1.74—1.89)	(1.29—1.49)	(1.36—1.55)	(1.67—1.82)
Turning velocity	0.46	0.47	0.45	0.18	0.19	0.22
(m/s)	(0.40—0.52)	(0.43—0.50)	(0.40—0.49)	(0.16—0.20)	(0.17—0.22)	(0.20—0.25)

Data represent mean values (95% confidence interval). Abbreviations: PD = Parkinson's disease; CON = control

† Significant medication effect (PD OFF vs. PD ON)

‡ Significant group effect (PD ON vs. CON)

4.1.2 Turning strategy and performance

Independent of medication state (OFF and ON), for group (PD ON and controls) or type of turn performed (pre- and unplanned), the results revealed a nearly 50:50 distribution between the step and spin turns (Table 8). Medication significantly increased turning distance by 5% for pre- and unplanned turns ($p = 0.003$), whereas no significant effects on body rotation or

mean turning velocity ($p > 0.025$) were evident. No interaction effects were found between medication state and turning condition for any of the turning variables. These findings together with similar effects sizes for pre- and unplanned turns (Figure 8) suggest that the responsiveness to medication was similar for pre- and unplanned turns.
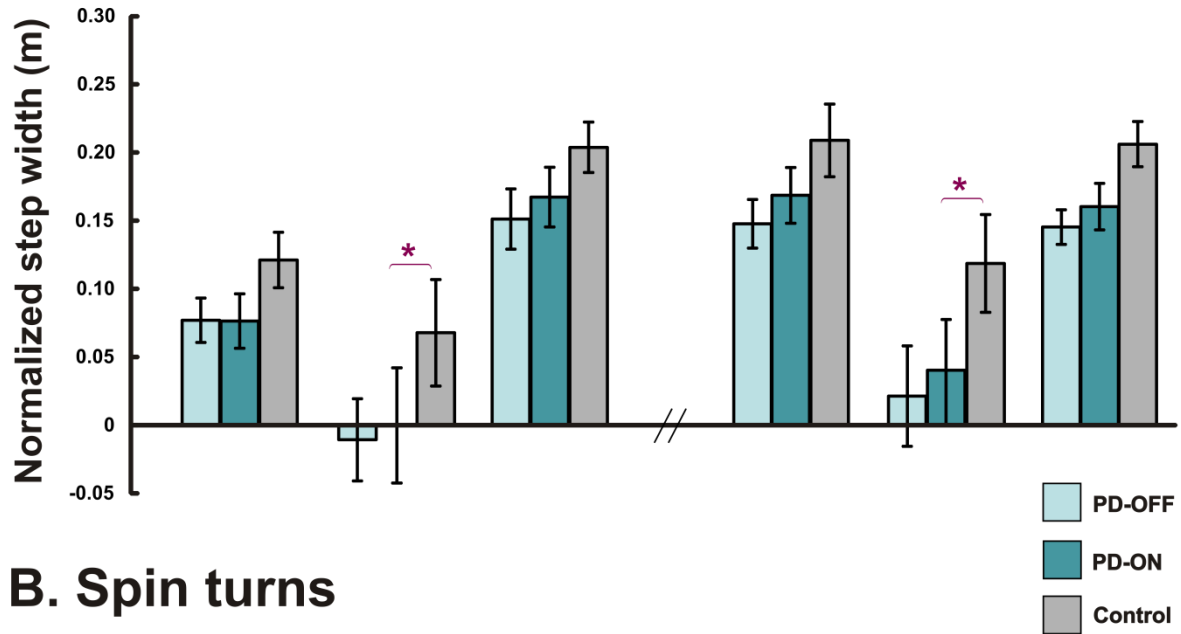
During pre- and unplanned turns, PD ON turned a significantly shorter distance (17-19%) and obtained significantly lower body rotation at the third turning step (10-24%), compared with controls (group; $p < 0.001$). Once again, no interaction effects occurred (*i.e.* group × turning condition), suggesting that the differences between PD ON and controls were independent of the type of turn performed (*i.e.* pre- or unplanned turns).
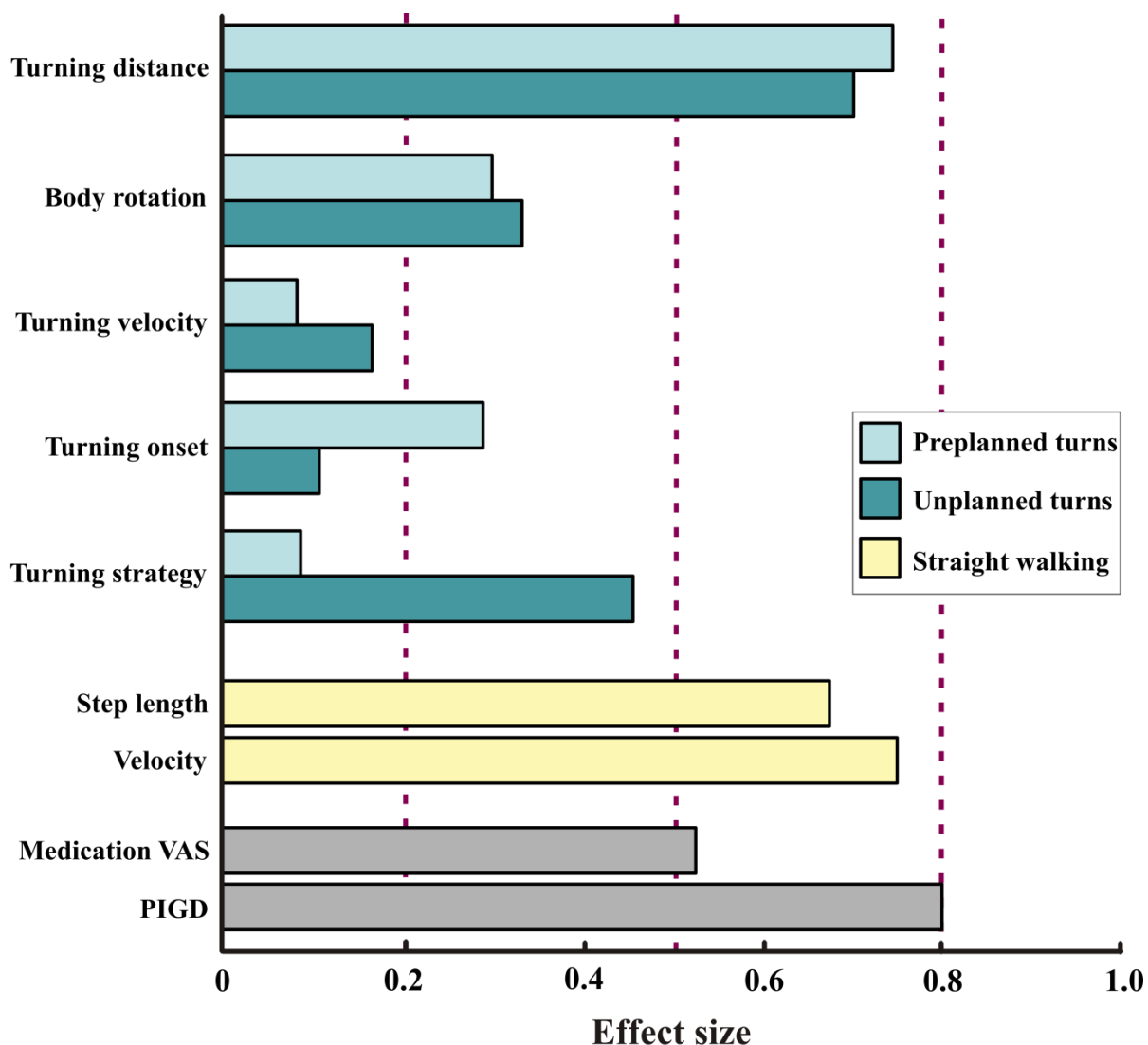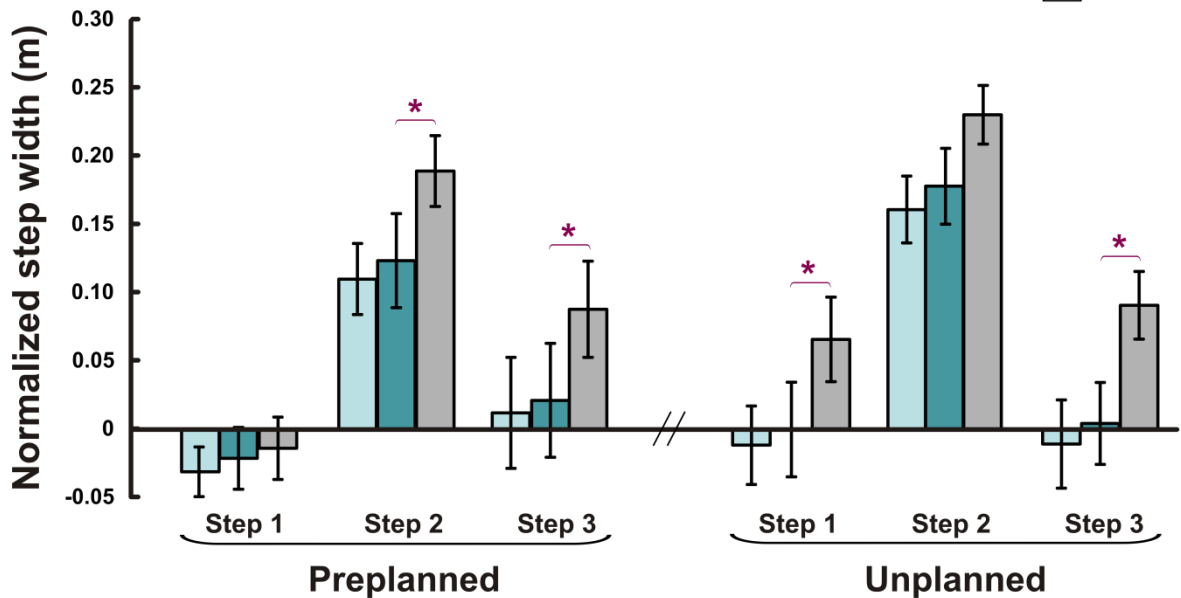

Figure 8. Effects of dopaminergic medication on balance control, gait and pre- and unplanned turns. Effect size (within groups: OFF vs. ON) was computed using Cohen's d. A value of 0.2, 0.5 and 0.8 were considered small, moderate and large effects, respectively. Abbreviations: VAS = Visual analogue scale; PIGD = Postural Instability and Gait Difficulty.

A. Step turns

B. Spin turns

Figure 9. Step width during pre- and unplanned turning while using A) step and B) spin turns.
Mean step width (meter) normalized to straight walking (*i.e.* the absolute difference between straight
walking and turning) for three turning steps for PD-OFF, PD-ON and controls. Error bars represent
95% confidence interval. *$p \leq 0.01$.

4.1.3   Regulation of walking during step and spin turns

There were significant main effects of medication on step width for the unplanned condition
using step turns ($p < 0.001$) and for the pre- and unplanned condition using spin turns ($p <
0.017$) (Figure 9a-b). These results reveal that subjects with PD turned, overall, with wider
steps during ON medication compared with the OFF state. Concerning the preplanned
condition using step turns, no effect of medication on step width was found ($p > 0.025$).

Furthermore, independent of the medication state, subjects with PD showed similar regulation of step width during turning, *i.e.* similar adjustments occurred compared with straight walking (medication × step: $p > 0.025$). Although both PD and controls demonstrated an alternation of step width while turning, *i.e.* wide - narrow - wide base of support for step turns and narrow - wide - narrow base of support for spin turns, this pattern was different in PD ON compared with controls (Figure 9a-b). In particular, there were no differences between the narrow steps and straight walking for PD ON ($p > 0.025$), while, overall, controls turned with wider steps compared with straight walking.

4.2 TRAINING PROGRESSION THROUGHOUT 10-WEEKS OF BALANCE EXERCISES

Training activity between Block A and B remained unchanged with regard to number of steps (median 860, IQR: 556─1316 vs. median 916, IQR: 712─1195, $p = 0.799$) and minutes spent walking >1.0m/s (median 19, IQR: 10─25 vs. median 19, IQR: 12─25, $p = 0.333$). In contrast, the comparison between Block B and C showed significant increases with regard to number of steps (C: median 1222, IQR: 882─1761, $p = 0.005$) and minutes spent walking >1m/s (C: median 26, IQR: 15-32, $p = 0.005$). Furthermore, by applying the criteria for progression (*i.e.* ≥20%) for each training group, similar results were found, *i.e.* a high level of progression occurred for both activity outcomes between Block B and C (Figure 10a-b).
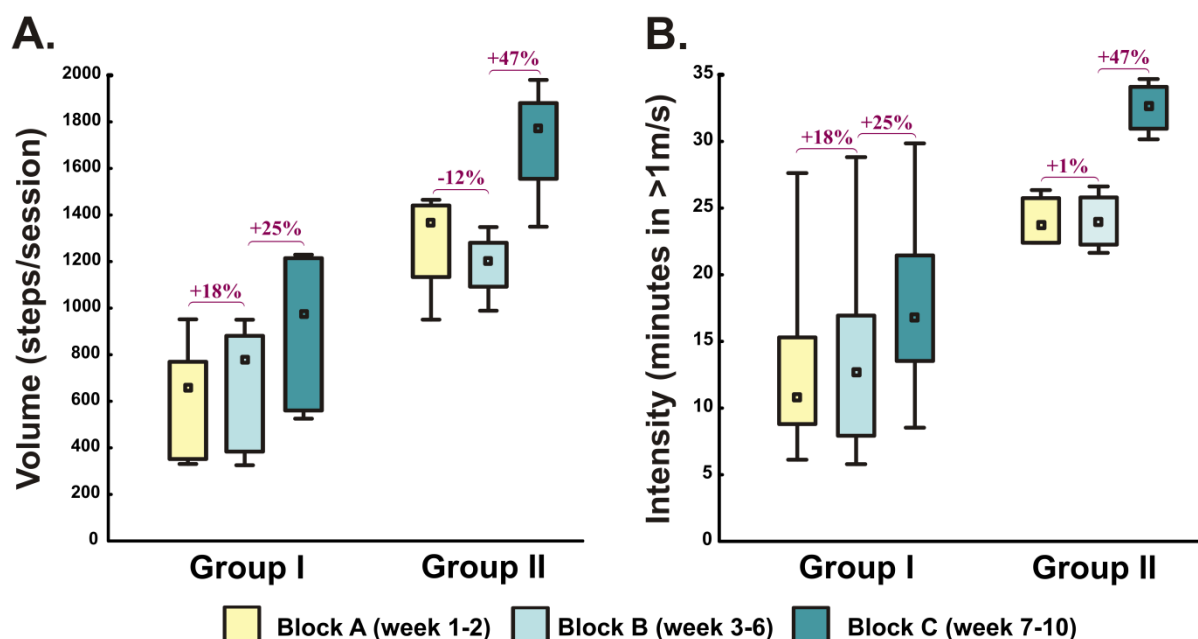
Figure 10. Training activity throughout the 10-week intervention. A) Volume and **B)** Intensity of dynamic exercises for training group I and II illustrated with boxplots for Block A (week 1-2), Block B (week 3-6) and Block C (week 7-10). The box plots represent median, quartiles and min-max.
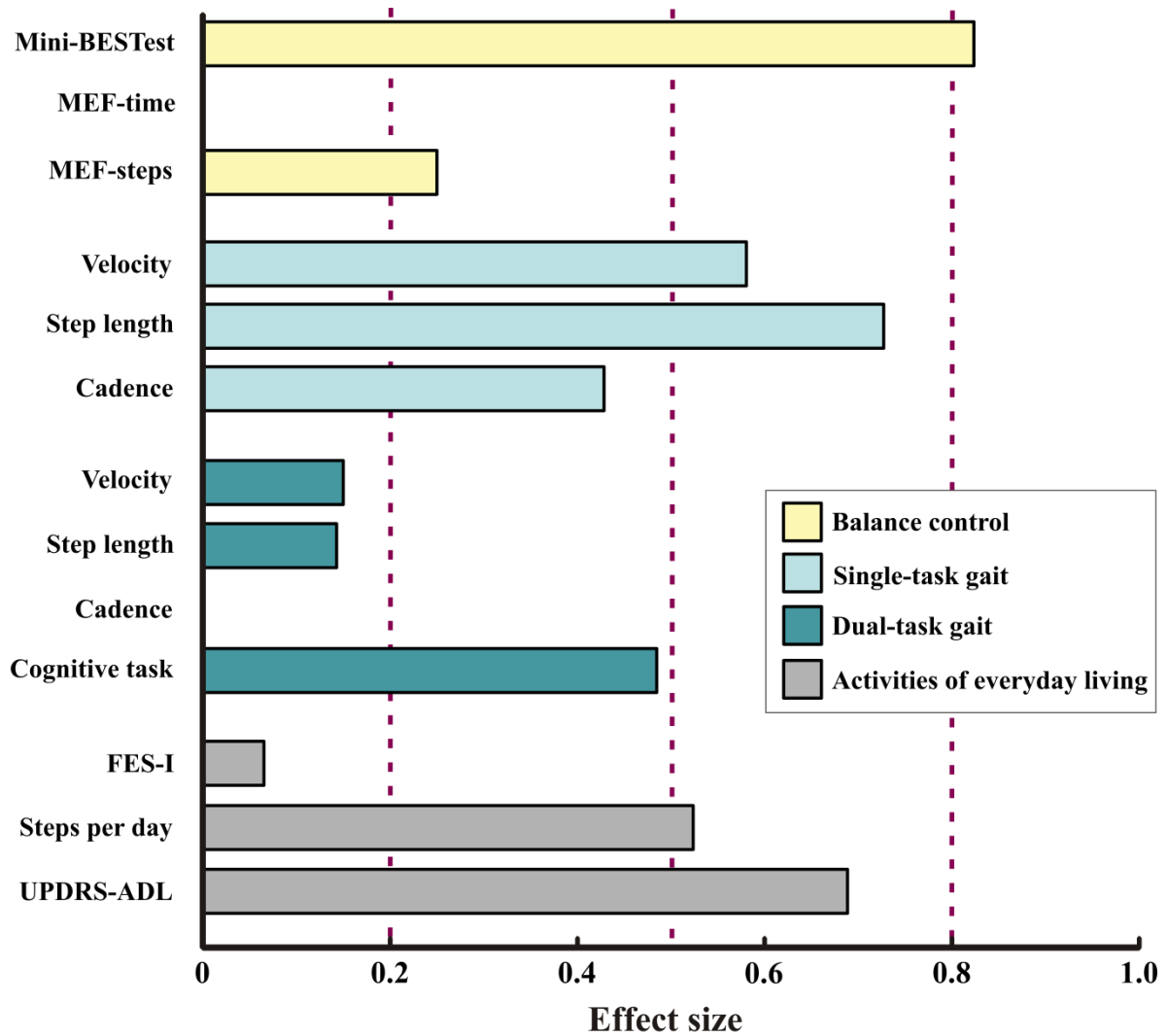
Figure 11. Effects of balance training on balance performance, gait and activities of everyday living. Effect size (between group: training vs. control) was computed using Cohen's d. A value of 0.2, 0.5 and 0.8 are considered small, moderate and large effects, respectively. Abbreviations: Mini-BESTest = Mini Balance Evaluation Systems Test; MFE = Modified figure of eight; UPDRS-ADL = Unified Parkinson's Disease Rating Scale; FES-I = Falls Efficacy Scale–International.

4.3 EFFECTS OF BALANCE TRAINING

The differences between pre- and post-assessment for all outcome variables in the training and control group are shown in Table 9, and effect sizes for the outcome variables are reported in Figure 11.

4.3.1 Balance control and gait

The results revealed a large improvement in the Mini-BESTest ($p < 0.001$) in the training group compared with the control group, whereas no effect was found for MFE ($p > 0.05$). Moderate improvements were also found for gait velocity ($p = 0.018$) and step length during ST gait ($p = 0.015$) but not for cadence ($p > 0.05$) in the training group compared with the control group. Contrasting ST gait, no group differences were found for any gait parameters

during DT ($p > 0.05$). However, an effect was found for the cognitive task performance while walking ($p = 0.006$), representing a 9% improvement in the training group. There were no differences between groups for the performance of the cognitive task while seated ($p > 0.05$).

4.3.2 Activities of everyday living

A moderate training effect was found for the average number of steps per day ($p = 0.033$), representing a 6% increase in activity in the training group (+282 steps/day, CI: -206─768) and a 12% decline in activity in the control group (-548 steps/day, CI: -1164─68). However, as indicated by the 95% CI´s, none of these within-group differences were significant. Furthermore, a moderate improvement in UPDRS-ADL ($p = 0.001$) was found in the training group compared with the control group, with no training effect evident for FES-I ($p > 0.05$).

4.3.3 Additional results

4.3.3.1 Training compliance and adverse events

The average attendance rate for the training-group was 90% (min-max: 66-100%). A total of 13 adverse events (all were falls during training) out of a total of 1380 training sessions were reported, resulting in an incidence rate of 0.9%. None of the fall events caused injury or pain that interfered with the participants' ability to proceed with the balance training or daily activities.

4.3.3.2 Training and leisure activities in the control group

During the intervention period, 59% of the subjects in the control group reported that they performed organized training weekly (mean frequency: two sessions per week). The most common training modalities were aerobic (n = 14), strength (n = 10) and balance training (n = 4). Furthermore, 84% of the subjects in the control group performed leisure activities aimed at altering physical activity, with a mean frequency of 6 sessions/week and mean dosage of 4 hours/week. The most common activity was brisk walks (n = 32).

4.3.3.3 Dropout and missing data analysis

As demonstrated in Table 9, age was the only variable that differed significantly between the subjects that dropped out (n = 10) and those who completed the study (n = 91). Accordingly, a significantly higher proportion of males dropped out of the study (78%) compared with those that completed the study (55%) ($p < 0.001$). Furthermore, no significant associations were found between baseline data (*i.e.* the variables included in Table 10) and incomplete physical activity data, thus indicating missing data at random.

Table 9. Treatment effects for the training group and control group.

	Training group (n = 47)				**Control group** (n = 44)				
		Mean	95% CI			Mean	95% CI		
	n	diff	LB	UB	n	diff	LB	UB	*P*-value
Balance control									
Mini-BESTest	47	3.0	2.3	3.7	44	0.9	0.0	1.7	**<0.001**
Single-task gait	46				44				
Velocity (m/s)		0.10	0.04	0.14		0.00	-0.03	0.05	**0.018**
Step length (m)		0.04	0.02	0.06		0.00	-0.01	0.02	**0.015**
Cadence (steps/min)		3	1	5		0	-2	2	0.108
Dual-task gait	45				42				
Velocity (m/s)		0.09	0.03	0.15		0.06	0.00	0.13	0.739
Step length (m)		0.04	0.02	0.06		0.03	0.00	0.05	0.469
Cadence (steps/min)		3	-2	7		3	-1	6	0.833
Daily activity									
FES-I	47	-2.8	-5.1	-0.5	44	-2.3	-4.6	0.1	0.772
Steps per day	37	282	-206	768	32	-548	-1164	68	**0.033**
UPDRS-ADL	47	-1.7	-2.6	-0.8	44	0.4	-0.5	1.3	**0.001**

	Training group (n = 47)			**Control group** (n = 44)			
		Median			Median		
	n	diff	IQR	n	diff	IQR	*P*-value
Cognitive task	45			42			
Single-task (% error)		0	19		0	17	0.634
Dual-task (% error)		-9	18		2	15	**0.006**
Balance control	44			39			
MFE Time (seconds)		-3	6		-2	5	0.506
MFE oversteps (n)		-3	6		-2	7	0.393

Treatment effects were calculated as the mean or median difference between pre- and post-test performances. Abbreviations: CI = confidence interval; LB = lower boundary, UB = upper boundary; n = numbers; Mini-BESTest = Mini Balance Evaluation Systems Test; UPDRS-ADL = Unified Parkinson's Disease Rating Scale; FES-I = Falls Efficacy Scale–International; IQR = interquartile range; MFE = Modified figure of eight.

Table 10. Dropout analysis. Baseline comparison between the participants that dropped out of the study and those completing the study.

	Drop-outs (n = 9)		**Completed the study** (n = 91)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	*P*-value
Age (yrs)	71 (5)	72 (69─75)	73 (6)	72 (69─77)	0.412
UPDRS-motor	40 (11)	40 (36─50)	36 (10)	36 (29─44)	0.2442
UPDRS-ADL	15 (5)	13 (12─18)	13.4 (4.7)	13 (10─17)	0.427
Mini-BESTest	18 (4)	19 (15─21)	19 (3.2)	19 (17─21)	0.687
Walking velocity (m/s)	1.18 (0.13)	1.14 (1.09─1.24)	1.17 (0.19)	1.21 (1.00─1.30)	0.933
FES-I	31 (10)	29 (27─34)	30 (10)	28 (23─35)	0.504
	n/total	%	n/total	%	
Gender, male	7/9	78	50/91	55	**<0.001**
H&Y, 3	4/7	57	52/91	57	1.000

Abbreviations: n = numbers; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = Activities of daily living; Mini-BESTest = Mini Balance Evaluation Systems Test; FES-I = Falls Efficacy Scale–International; H&Y = Hoehn and Yahr; SD = Standard deviation; IQR = interquartile range.

5 DISCUSSION

5.1 MAIN FINDINGS

This thesis intended to expand the current body of knowledge with regard to the effects of dopaminergic medication and exercise on balance control and activities of everyday living in older adults with mild to moderate PD.

Experimental part (Study I): The results revealed that dopaminergic medication increased turning distance in individuals with PD but did not result in more efficient turns with regard to the rotation of the body for pre- and unplanned walking turns. Compared with the performance in the healthy control group, dopaminergic medication did not normalize turning performance. These findings suggest that problem with alternating step width during turning is a critical feature in PD which could be important to address in the rehabilitation of individuals with PD.

Clinical part (Study II, III and *IV)*: In *Study II*, a 10-week of balance training framework emphasizing specific and highly-challenging aspects of balance control, including DT, was developed through workshops and pilot testing. Findings of the objective evaluation of training activity (*Study III*) revealed that training progression was possible in two independent training groups of older adults with PD throughout the 10-week program. *Study IV* showed that a 10-week highly-challenging balance exercise program improved balance and gait performance in older adults with mild to moderate PD, compared with usual care. Positive transfer effects to activities of everyday living were also revealed, indicating that appropriate training programs could promote physical activity and daily activities in PD.

5.2 EFFECTS OF DOPAMINERGIC MEDICATION ON TURNING WHILE WALKING

Numerous studies have demonstrated positive effects of dopaminergic medication on periodic gait (*i.e.* walking straight),[111,115,116,183,184] with this study being the first to evaluate the effects of dopaminergic medication on pre- and unplanned turns while walking in individuals with PD. Therefore, the experimental part of this thesis expands the current knowledge regarding the effects of medication on different features of pre- and unplanned walking turns.

The intention with the experimental part of this thesis was to capture realistic turning behavior by using a paradigm where the subjects were free to perform a step or spin turn without spatial restrictions. Irrespective of OFF or ON medication, subjects with PD demonstrated a nearly 50:50 distribution between step and spin turns for both pre- and unplanned turns. This was an unexpected finding since step turns are considered favorable for individuals with balance impairments (*e.g.* PD) as they are safer and considered biomechanically less demanding (*i.e.* wider BoS and less axial rotation).[76,148] This finding is somewhat contrary to previous studies in healthy older adults that have reported spin turns to be most common during preplanned turns,[148] whilst step turns have showed to be preferred when performing more challenging turns, *e.g.* unplanned turns [74] or 90° preplanned turns during fast walking.[148] Instead, the overall mixed preference between step and spin turns found in the present study could represent a consistently flexible repertoire of movement strategies unaffected by mild to moderate PD or older age.

Although the subjects with PD demonstrated significant effects of medication on balance and gait, medication only partially improved their turning performance. Specifically, dopaminergic medication increased turning distance but not the efficiency of the body rotation around the longitudinal axis. Although previous findings reporting similar effects of dopaminergic medication on the performance of in-place[62,123] and walking turns in individuals with PD,[111] the divergent medication effect found in the present study is novel. Indeed, while it is known that the ability to turn while walking involves an interaction between the forward progression of the body and the rotation of the body around the longitudinal axis.[185] According to the present results, the forward progression component appeared to be more responsive to dopaminergic medication. This notion is also supported by similar effects of medication found for turning distance and straight walking, both of which relate to the progression of the body while walking.

Similar to previous findings,[111,115,123] dopaminergic medication did not normalize turning performance, compared with the healthy control group, and these turning impairments in PD were accompanied with problems alternating step width during turning. Although being able to alternate between narrow and wide steps, the narrow steps of individuals with PD were equal to their step width during straight walking, while, in contrast, controls generally turned with wider steps than during straight walking. In individuals with PD, narrow step width has been demonstrated during balance reactions[50,186] and walking turns.[150] Narrow step width in PD could reduce medio-lateral stability[50,186] and the force production necessary to accelerate

the center of mass towards the turn direction.[150] Hence, it is likely that the narrower step width not only compromises turning performance in PD, but may also lead to instability and falls. This finding highlights the importance of targeting step width in individuals with PD during rehabilitation, *e.g.* by using reactive or proactive step training.[186,187]

Furthermore, the similar effect of medication on pre- and unplanned turns was an unexpected finding. Lower effects of medication on unplanned turns were expected since this turn requires rapid identification of a cue and quick modification of the walking pattern[150,188] as well as stresses impaired executive functioning in PD (*e.g.* planning, and selection of movements).[72] This assumption was based on the combination of challenging features of unplanned turns together with findings of limited effects of dopaminergic medication on executive functions[189,190] and the ability to shift between tasks in PD.[56] Unplanned turns on the other hand, were triggered by a light signal, which have been reported to facilitate movements in individuals with PD.[191,192] Accordingly, it is possible that the visual cue enhanced turning performance during unplanned turns; thus compensating for increased task complexity.

5.3   TRAINING EFFECTS ON IMPAIRMENTS AND ACTIVITY LIMITATIONS

The clinical part of this thesis served to investigate the short-term effects of a 10-week training program of highly-challenging balance exercises, including DT, in older adults with PD. This study adds novelty to the existing body of research by demonstrating the prospects of applying DT to balance training and its effects across the spectrum of balance-related impairments in individuals with PD.

The positive effects on balance control and gait in the training group are consistent with the results from recent meta-analyses of exercise interventions in PD.[126,193] Furthermore, the 3-point improvement in the training group on the Mini-BESTest is similar to the effects found in previous studies that have used this instrument to evaluate various exercise interventions on balance impairments in individuals with PD.[140,194,195] The training group also had a Mini-BESTest score of 22 points at post-assessment, which exceed the cut-off score (<19) that is associated with an increased risk of prospective falls in individuals with PD.[196] Enhanced balance control in the training group was also linked to improved gait velocity (0.10 m/s) and step length (0.04 m) during ST walking. These findings could have important implications since gait velocity is a vital indicator of health.[197] In fact, an increase of 0.10 m/s has been associated with decreased risk of mortality in older adults.[198]

We found further positive effects in the training group for level of physical activity and activities of everyday living, thus, emphasizing the notion that specific improvements in balance control could transfer into activities of everyday living. A few previous studies have demonstrated positive effects of balance training on objectively measured physical activity[199,200] and self-reported activities of daily living in individuals with PD.[194,201] Accordingly, the present study suggests that the promotion of activities in everyday living occurred in parallel to the improvement in balance control. Yet, these training effects were

rather small and should be cautiously interpreted. However, when dealing with a progressive disorder such as PD, such effects could be important in maintaining independency in daily activities, level of physical activity as well as promoting health.[105] No training effect on concerns about falling was found, and the uncertainty remains on how the experience of highly-challenging balance exercises influences patients' perception of their capacity. This unresolved question requires the application of a qualitative approach.

This study was the first randomized controlled trial to evaluate the effects of an intervention that included DT exercises in individuals with PD. The results revealed that the training group improved their performance of the cognitive task during walking, compared with the control group, whilst no differences between the groups were found for DT gait. This is a contradictory finding compared to previous pilot studies in PD that have demonstrated improved DT gait performance following DT exercise but not for the secondary task.[129,132,133] The cognitive task used in the present study was a reciting task (*i.e.* reciting every second letter in the Swedish alphabet) which could be considered a task related to working memory, *i.e.* the ability to temporarily process, store and manipulate information in conscious awareness).[7] As most of the DT exercises in the training program involved similar cognitive tasks (*e.g.* counting, remembering items/numbers), it is likely that the effects derived from the specificity of training. Furthermore, several plausible explanations exist while considering the underlying mechanisms for this DT improvement in the training group. First of all, improved ST performance might indirectly have improved DT performance by a more automatic control of the primary task (*i.e.* gait); thus, resulting in less overlap between the two tasks.[45] This view is supported by the large training effects found for ST performance in the training group. Alternatively, the positive effects found could be a consequence of improved efficiency of integrating the primary and secondary task.[45] Although the field of DT training for individuals with PD is nascent,[45] our findings indicate that DT performance might be improved in this population.

5.4 METHODOLIGICAL CONSIDERATIONS

5.4.1 External validity

One important aspect of external validity is whether the recruited sample is representative of the population being studied.[202] The sample of community-dwelling older adults with mild to moderate PD included in this thesis derived from the BETA-PD project.[203] As such, this sample was selected from the population based on their interest and appropriateness of participating in this intervention.

Several aspects regarding the criteria for inclusion and how the sample was recruited require consideration. First of all, similar to international data,[14] about 90% of the individuals with PD in Sweden, to date, is above 60 years of age and PD is approximately 1.2 times more common among males than females.[12] Accordingly, our sample matches the age dominance of the PD population as well as the ratio between males and females. Secondly, an inclusion criterion was 'signs' of impaired balance control at baseline clinical assessment. Despite the arbitrary nature of this criterion (*i.e.* no exact cut-off was used), this approach was applied from an ecological validity standpoint; an attempt to simulate the real-word setting in which individuals were included that would typically be considered for physiotherapy in clinical practice. Furthermore, 70% of the participants were recruited by advertisement, a method that could have led to a convenient sample of individuals interested in training and improving their physical status in general. Consequently, the risk of this approach is the possibility of attracting a 'too healthy' sample from the population and thereby failing to recruit more frail individuals that would benefit most from this intervention. The background characteristics of this sample (Table 2) revealed a group of independent ambulators with a mean walking velocity (about 1.2 m/s) and physical activity level (about 5000 steps per day) that were comparable to normative values of healthy older adults.[204,205] But on the other hand, data on fall-history revealed that about 50% in this sample had experience ≥ 2 falls the last year, which is in line with the increased fall-risk in this population.[206] Furthermore, the range in walking velocity and physical activity level, 0.67─1.55 m/s and 149─14495 steps per day, respectively, suggests varied physical capacities within this sample; ranging from frail to highly functional individuals. In accordance with the heterogeneous features of PD,[207] it is likely that the diversity in the present sample also exists in the population studied. However, emphasizing recruitment from the health care system (only 10% in this project) had probably been a useful strategy in order to better target individuals with a more frail disability profile.

The balance training intervention was conducted in the context of a university hospital setting and supervised by physiotherapists experienced in managing individuals with PD. This environment is resourceful not only owing to the experience of the physiotherapists, but also with regard to the accessibility of equipment and facilities that could promote this type of intervention. Although there might be similarities between different contexts, the results of this study regarding the effects of balance training should mainly be generalized to this context.

5.4.2 Internal validity

5.4.2.1 Assessment of balance control in relation to dopaminergic medication state

For all types of assessments of individuals with PD, it is important to take into account the influence of dopaminergic medication, such as changes in medication dose over time and the potential fluctuation in responsiveness to medication during the day.[22,101] To improve the reproducibility of the assessment, it was therefore important to standardize the time of the day when the assessment took place, as well as consider the time since last medication intake.

In the experimental part of this thesis, the responsiveness to dopaminergic medication on walking turns was assessed by comparing OFF and ON performance.[110] Although all subjects included in the present study were confirmed to be responders to dopaminergic medication by their neurologist, the level of responsiveness to medication at the time of testing was not an inclusion criterion, as in other studies.[115,123] Instead the responsiveness to medication in the present study was supported by significant benefits on balance and gait and participants' perceived benefits of medication. Another option could have been to use a stricter criterion for inclusion, such as including those demonstrating ≥20% improvements in the UPDRS-motor score after medication intake.[114,115] However, this approach would have excluded eight subjects (42%) in the present study. Although such a more stringent approach would likely have improved the validity of the OFF vs. ON comparison, it may have restricted the generalization of the results to the population of individuals with mild to moderate PD.

In the randomized controlled trial, all assessments of balance control were conducted during the ON state in order to restrict the impact of medication fluctuations. The participants were also instructed to maintain a stable medication dosage throughout the intervention period. Notwithstanding the recommendation, some participants changed their medication dose during the intervention; however, no significant differences were found in the proportions between the groups that increased or decreased their dosage.

5.4.2.2 Bias related to testing

Repeated measures is a threat to internal validity since testing itself could influence the variable of interest.[202] Repeated measures were used in both parts of this thesis; during the same day (OFF followed by ON) in the experimental part and before and after the 10-week intervention period in the clinical part.

For the evaluation of the medication effect, this approach may have led to an overestimation due to a practice effect where subjects with PD performed better during ON medication as they had more experience in the turning task, or an underestimation of the effect due to fatigue induced by repeated testing. Similar factors could have influenced the results in the randomized controlled, *i.e.* learning effects from being tested before and fatigue related to prolonged testing (each test session lasted approximately 3 hours). To address the risk of fatigue in both the experimental and clinical part, breaks were included in the test sessions and the participants were allowed to sit down and rest during testing. In addition, practice

sessions were held prior to formal testing in order to familiarize participants to the specific features of the test condition (*e.g.* performing pre-/unplanned turns or walking on an electronic walkway mat). To reduce the risk of systematic bias arising from a fixed order of testing, the order of the turning conditions (pre- and unplanned turns) was randomized in the experimental part as well as the order of the clinical tests in the clinical part.

In the clinical study, several co-workers served as both trainers of the balance training and assessors during data collection in this project. As most tests require knowledge about and experience in the particular test, the risk of inconsistent evaluations between raters cannot be ruled out. To minimize this risk, all assessors were registered physiotherapists that had taken part in written instructions and discussions concerning the standardization of instructions and scoring of the tests prior to assessment. To reach consensus, tests that were assumed to be 'bias prone' were also discussed between the assessors. Furthermore, the assessors were not masked to group allocation at the post-test assessment, which could have led to a favorable evaluation of the participants in the training group. However, during the follow-up assessments, participants were never assessed by a test leader who had been involved in their training. Although this strategy does not eliminate such testing bias, it was thus a pragmatic solution put in place given the numerous logistical challenges that come with a randomized controlled trial.

5.4.2.3 Balance training: predetermined exercises vs. a framework approach

There are different approaches available to execute a training program within a randomized controlled trial. One could use a fixed scheme of predetermined exercises for the trainers to follow or as in the present intervention, rely on the principles of a framework and the clinical reasoning of trainers (*e.g.* regarding the adaptation of exercise to individual capacities).

There are pros and cons with both approaches. Interventions with predetermined exercises commonly offer an exact recipe of what exercise to perform, which could be beneficial in terms of reproducibility but be less adaptive to individual capacities and learning profiles over time. On the other hand, the benefits of a 'framework' approach could be the prospect of adjusting the training to individual capacities and their achievements over time. In the present study, a framework based on four balance components and a structure for training progression was applied to address balance impairment in individuals with PD. Importantly, the content of training was adapted to the group and the level of difficulty of balance exercise was adapted to the individual. This strategy was applied since mild to moderate PD is a heterogeneous group[207] and thus less likely to benefit from a 'one-size-fits-all' treatment strategy. Furthermore, this approach was also used given its prospect of facilitating training progression over time, thereby promoting motor learning.[139] Using this strategy that somewhat mimic clinical practice; require continuous evaluation of the trainers in order to modify training. To achieve this, all trainers involved in this study were physiotherapists educated in the framework of this training intervention. The critique towards such a strategy typically highlights the unstandardized features and the risk of the intervention changing over time. Still, the results from Study III revealing a similar progressive pattern of training

activity in two independent training groups (*i.e.* different trainers and training facilities); thus, supporting the consistency of this intervention.

5.4.2.4   Laboratory vs. free-living assessments

Assessment of balance and gait mostly uses clinical and quantitative assessments in standardized controlled environments and the results are assumed to reflect the individual's performance in the "real-word" setting. The present experimental procedure aimed to assess walking turns as it occurs during everyday living, *i.e.* approximately 90° of turning performed across three steps.[90] In particular, two different type of turns were analyzed to address the predictable (*i.e.* preplanned) and unpredictable (*i.e.* unplanned) features of walking in daily living.[78,79] Similarly, in the clinical part, training effects on balance and gait were assessed in a laboratory environment with an electronic walkway system and clinical tests.

However, testing in controlled environments without the influence of fatigue and motor fluctuations, together with the subjects desire to perform optimally, may provide an overestimation of the actual performance. For example, recent studies using body worn sensors to monitor gait have showed a discrepancy between laboratory gait performance and walking in everyday living in older healthy adults.[208,209] Similar, in individuals with PD, the ability to turn in a controlled environment do not reflect their performance in their home environment.[210] Accordingly, laboratory assessments are believed to represent an individual's best performance rather than their usual performance.[208] Still, the positive effects of balance training on laboratory gait performance and free-living measures of physical activity are encouraging results that support the notion of a link between 'best' and 'actual' performance.

5.5   CLINICAL IMPLICATIONS

- As turning impairments were unsolved with dopaminergic medication, it is important to address these features in the rehabilitation of individuals with PD. Specifically, the findings suggest that exercises targeting the medio-lateral stability through appropriate step width modulation should be emphasized.

- Highly-challenging balance exercises for 10-weeks improve balance control and gait performance and reveal positive transfer effects on everyday activities in older adults with mild to moderate PD.

- Cognitive-demanding exercise, by application of DT, is not only feasible and safe in individuals with mild to moderate PD, but is also an ecologically valid approach to target motor-cognitive interference through training conditions that resemble everyday living.

- Based on a systems approach of balance control,[3] this exercise program was designed to target disease-related balance impairments in PD by applying the motor learning principles of specificity, progressive overload and varied practice. This approach is endorsed since the design of interventions is underpinned and guided by a framework that conceptualizes, for example, balance-related impairments, whilst the measurement of patient-specific outcomes is aligned to both the framework and the aims of the intervention.

5.6 FUTURE RESEARCH

- For diagnostic and evaluation purposes of PD, there is a great need of establishing ecologically valid assessments of the responsiveness of dopaminergic medication within the domains of body impairments and activity. The complexity of turning impairments in individuals with PD also requires further investigation, such as the impact of executive function deficits.

- The positive short-term effects of this balance training program are encouraging, but long-term promotion of balance control and an active lifestyle is of most importance. As such, future studies should investigate the long-term effects of highly-challenging balance training in individuals with PD.

- In the context of the heterogeneous features of mild to moderate PD,[207] it is crucial to explore whether certain disease characteristics of PD might be related to the response to cognitively-demanding DT exercise. For instance, as motor learning in PD is highly dependent on cognitive status,[211] individuals with cognitive decline may gain better effects from ST exercise. Similarly, individuals experiencing frequent episodes of freezing of gait could gain more from compensatory strategies (*e.g.* cueing).[45] However, these assumptions are not grounded in evidence and future studies are warranted in order to improve the management of balance related impairments in individuals with PD.

- In order to better understand the effects of different exercise modalities, it is crucial to improve the description of the active components of these interventions. For example, exercise programs that included movement of CoM, narrowing the BoS, and minimizing upper limb support were defined as highly-challenging in a meta-analysis in individuals with PD.[127] One could argue that such generic descriptions of balance exercise insufficiently distinguish between training programs. Therefore, it is suggested that future studies aim to develop standardized methods of describing the content of balance training.

6 CONCLUSION

- Independent of performing preplanned or unplanned walking turns, dopaminergic medication appears to improve the distance traveled during turning, but not the efficiency of turning with regard to body rotation in older adults with mild to moderate PD.

- Dopaminergic medication does not normalize turning performance, these findings suggest that problems with alternating step width during turning is a critical feature in PD which could be important to address in further rehabilitation programs.

- Training progression was possible throughout the 10-week program in two independent training groups of older individuals with PD. Interestingly, progression mainly occurred after habituation to challenging dual-task exercises and this finding could be useful while designing future interventions.

- Highly-challenging and progressive balance exercises for 10-weeks, including dual-tasking, improved balance and gait performance in older adults with PD when compared to usual care. Positive transfer effects to activities of everyday living were also revealed, indicating that appropriate training programs could promote physical activity and daily activities in older adults with PD.

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