

# **Gait and gait variability in individuals with Parkinson's disease – validity, reliability and long-term effects of intensive balance and gait training.**

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## **List of papers**

This thesis is based on the following papers which are referred to in the text by their numbers I-III.

### **Paper I**

Rennie L, Dietrichs E, Moe-Nilssen R, Opheim A, Franzen E. The validity of the Gait Variability Index for individuals with mild to moderate Parkinson's disease. *Gait and Posture*, 2017. 54: p. 311-317.

### **Paper II**

Rennie L, Löfgren N, Moe-Nilssen R, Opheim A, Dietrichs E, Franzén E. The reliability of gait variability measures for individuals with Parkinson's disease and healthy older adults - The effect of gait speed. *Gait Posture*, 2018. 62: p. 505-509.

### **Paper III**

Rennie L, Opheim A, Dietrichs E, Löfgren N, Franzén E. Highly challenging balance and gait training for individuals with Parkinson's disease improves pace, rhythm and variability domains of gait.

Submitted

Paper III is provisionally accepted subject to satisfactory revision.



## Abstract

**Introduction:** Parkinson's disease (PD) is a degenerative neurological disorder affecting the basal ganglia. Disturbances of postural control and gait are common. Structured exercise is advocated in PD management, and the High Intensity Balance (HiBalance) program was developed to target Parkinson-specific balance and gait impairments. When evaluating PD-gait, level of step-to-step variability is a much used outcome measure as an adjunct to mean gait characteristics. However, there is a lack of consensus regarding the methods used to estimate gait variability.

**Aims:** The overall aim of this dissertation was to evaluate the immediate and long term-effects of HiBalance program on gait variables associated with pace, rhythm, variability, asymmetry and postural control aspects of gait in individuals with PD. A further aim was to clarify valid and reliable methods for assessing level of variability in PD-gait.

**Methods:** A total of 129 subjects with mild to moderate PD, and 60 years or older, were included in three studies. Spatiotemporal gait variables measured during normal and fast walking on a pressure-sensitive mat were the main outcome measures in all studies, together with measures of functional balance and mobility. The Gait Variability Index (GVI) was calculated for 100 PD-subjects. The GVI displays the accumulated variability of nine spatiotemporal variables. A score of 100 signifies the reference mean normal, lower scores denotes higher gait variability. Construct validity was evaluated relative to functional balance and mobility scores and discriminatory ability (mild from moderate). For 29 PD-subjects, and 25 healthy older adults (HOA), gait variables were collected on two occasions for slow, normal and fast walking. Absolute and relative reliability was calculated for gait variability estimates for all speed conditions based 10 to 50 steps. The PD-training group (n=51) partook in 10 weeks of intensive balance and gait training, the PD-control group (n= 49) continued with care as usual. Data were collected at baseline, post intervention, and at 6 and 12 months. A linear mixed model was used to investigate group differences over all time points.

**Results:** The mean GVI for the PD cohort was 97.5 (SD 11.7). The associations between the GVI and functional balance and mobility scores were low ( $r=0.33$  and  $0.42$ ) and the index showed poor discriminatory ability ( $AUC=0.529$ ,  $SE=0.058$ ,  $p=0.622$ ). For individual gait variability variables lowest level of measurement error was seen when estimates were based on 40 steps. However, for slow PD-gait absolute reliability was poor. Immediate training effects of the HiBalance program were seen in the pace domain of gait with increased step velocity (normal speed:  $8.2$  cm/s,  $p=0.04$ ; fast:  $10.8$  cm/s,  $p<0.01$ ), increased step length (normal speed:  $3$  cm,  $p=0.05$ ; fast:  $2.3$  cm,  $p=0.05$ ) and reduced swing time variability (fast speed:  $-2.5$  ms,  $p=0.02$ ). In the rhythm domain reduced step time (fast speed:  $-19.3$  ms,  $p=0.02$ ), stance time (normal:  $-24.3$  ms,  $p=0.01$ ; fast:  $-29.6$  ms,  $p=0.02$ ) and swing time (fast speed:  $-8.7$  ms,  $p=0.04$ ) was seen. Relative to the variability domain, the training decreased step time variability (fast:  $-2.8$  ms,  $p=0.02$ ) and stance time variability (fast:  $-3.9$  ms,  $p=0.02$ ). No training effects were retained at 6 months.

**Conclusions:** The validity of using the GVI to estimate level of accumulated gait variability in PD-gait could not be confirmed. However, when investigating level of variability for individual gait variables, estimates should be based on at least 40 steps for normal and fast walking. The reliability of gait variability estimates for slow PD-gait could not be verified. Highly challenging balance and gait training improved pace, rhythm and variability aspects of PD gait in the short-term, but effects were not retained long-term. This could suggest that upholding gait function in the mild to moderate stages of the disease may require regular booster sessions of highly challenging balance and gait training at least bi-annually.

## Abbreviations

ANOVA	Analysis of variance
APAs	Anticipatory postural adjustments
AUC	Area under the curve
BETA-PD	Balance, Elderly, Training and Activity in Parkinson's disease
BoS	Base of support
CI	Confidence intervals
CoM	Center of mass
CoV	Coefficient of Variation
DBS	Deep brain stimulation
DT	Dual task
HiBalance	High intensity balance program
H&Y	Hoehn and Yahr scale
HOA	Healthy older adults
GABA	Gamma-aminobutyric acid
GVI	Gait variability index
ICC	Intraclass correlation coefficient
LEDD	Levodopa equivalent daily dose
Mini-BESTest	The Mini Balance Evaluation Systems Test
MLR	Mencephalic locomotor region
ms	Milliseconds
PD	Parkinson's disease
PMC	Pre-motor cortex
PPN	Pedunculopontine tegmental nucleus
RCT	Randomized controlled trial
SEM	Standard error of measurement
SRD	Smallest real difference
SD	Standard deviation
SMA	Supplementary motor area
SNpc	Substantia nigra, pars compacta
S <sub>w</sub>	Within-subject standard deviation
TUG	Timed Up and Go
UPDRS	Unified Parkinson's Disease Rating Scale



# 1. Introduction

Our ability to walk is a central function to us humans, and safe and independent mobility is essential when we interact and participate in society. Individuals with Parkinson's disease (PD), a neuro-degenerative disorder primarily affecting the basal ganglia, experience disturbances of continuous gait as well as transient episodes of freezing and festination. The importance of upholding gait function is central to those affected by PD. Independent walking was considered a prerequisite to an autonomous life and closely linked to social identity, emotional well-being, and integrity [1].

Physiotherapy and exercise are important adjuncts to pharmacological treatment in the management of PD for modifying long-term motor symptoms and secondary complaints [2]. With the aim of maximising functional ability, many exercise modalities have shown positive effects for individuals with PD [3]. However, balance training has been shown to be the most effective modality for improving balance, gait and mobility in individuals with PD with significant long term effects [4].

This thesis is part of a larger research project, the Balance, Elderly, Training and Activity in Parkinson's disease (BETA-PD) where the overall goal is to develop and establish an evidence-based rehabilitation program for older adults with Parkinson's disease (PD) that targets specific balance and gait impairments using motor learning principles. The main part of this thesis therefore investigates how intensive balance and gait training impacts relevant domains of continuous gait in this population, both in the short and long term (Paper III). Additionally, the thesis investigates valid and reliable methods of estimating level of gait variability in spatiotemporal variables (Paper I and II).

## 1.1 Parkinson's disease

Parkinson's disease is the second-most common neurodegenerative disorder that affects 2-3% of the population in those that are 65 years and older [5]. Neuronal loss in the substantia nigra, pars compacta (SNpc) which causes striatal dopamine deficiency, and intracellular inclusions containing aggregates of  $\alpha$ -synuclein, are the neuropathological hallmarks of the disease [5, 6]. The first clear medical description of Parkinson's disease was written in 1817 by James Parkinson [7] who accurately described the resting tremor and festinating gait, bradykinesia and postural instability by observing only six individuals [8]. The aetiology and underlying pathogenetic mechanisms of PD are still not fully elucidated. However, it is recognized that

the disease process begins years before diagnosis can be made, and a combination of genetic and environmental factors are acknowledged as causal. Multiple neuroanatomical areas are implicated in the course of the disease, and a broad range of symptoms manifests, motor as well as non-motor [5, 9].

### **1.1.1 Diagnosis and cardinal features**

The current gold standard for diagnosing PD is by most clinicians endorsed as a combined motor clinical- and pathologic syndrome, where typical motor symptoms show responsiveness to levodopa together with an absence of markers suggestive of other disease [10]. The most common and well-known symptoms which first presents are the cardinal features of motor: bradykinesia, muscular rigidity, and tremor (4-6 Hz), each with a unilateral, or at least asymmetrical, onset. A supportive feature is postural instability [11]. When motor symptoms present it is estimated that about 50% of dopaminergic neurons in the SNpc have degenerated [12]. With regards to pathological diagnostic criteria for PD, there is no generally accepted standard. However, a further confirmation of moderate to severe dopamine neuronal loss in the SNpc and  $\alpha$ -synuclein deposition (Lewy bodies) may give a definitive diagnosis post mortem [6, 11].

### **1.1.2 Epidemiology**

It is generally accepted that the global prevalence of PD range from 1 to 3 per 1000 in unselected populations [5, 13]. For Norway, it is estimated that approximately 10 000 individuals live with the disease, whereas the projected number is 22 000 individuals in Sweden, and 1.2 million individuals in the EU-area [14]. With regards to incidence rates, worldwide estimates range from 5 to 35 new cases per 100 000 individuals yearly [5]. Epidemiologic studies on Norwegian populations are few, but the ParkWest study published in 2009 [15] investigated the incidence of PD in the western region of Norway. An annual incidence rate of 13.5 per 100 000 inhabitants was reported.

Further, the prevalence and incidence of PD increases with age. Whereas PD is rare before the age of 50, the incidence is seen to increase 5-10 fold from the sixth to the ninth decade of life [16]. This increases the number of those affected by the disease from approximately 1% of the population above 60 years, to a prevalence of 4% in the highest age groups [13]. Given the tendency that people live longer and that the risk of PD increases with age, the number of

people with PD is expected to double by 2030 [17, 18]. Also of interest is the finding that PD is twice as common in men as in women in most populations [5]. This was also reflected in the Norwegian ParkWest cohort where the age standardised incidence of PD was 58% higher in men than women [15].

### 1.1.3 Disease progression and clinical symptoms

At the time-point of emerging motor symptoms and diagnosis, the disease can have been preceded by a premotor or prodromal phase of 5 to 20 years [6, 12]. In this earlier and undiagnosed phase of the disease, the person can have experienced several non-motor symptoms where impaired smell, constipation and sleep disturbances are common [6, 19] (see Figure 1). Following diagnosis, motor symptoms related to bradykinesia, rigidity and tremor additionally start to impact the movement ability of the individual, as well as postural instability. As the disease progresses, the person will experience a gradual increase in impairments and activity limitations commonly classified according to the Hoehn and Yahr scale (H&Y) (see Figure 2). Worsening postural instability, rigidity, bradykinesia and cognitive impairment, together with festination and freezing during gait become more prominent in the moderate to later stages, and are features associated with higher fall-rates [9]. 60.5% of individuals with mild to moderate PD are reported to fall at least once over the course of a year, with 39% reporting recurrent falls [20]. This signifies that around 70% of

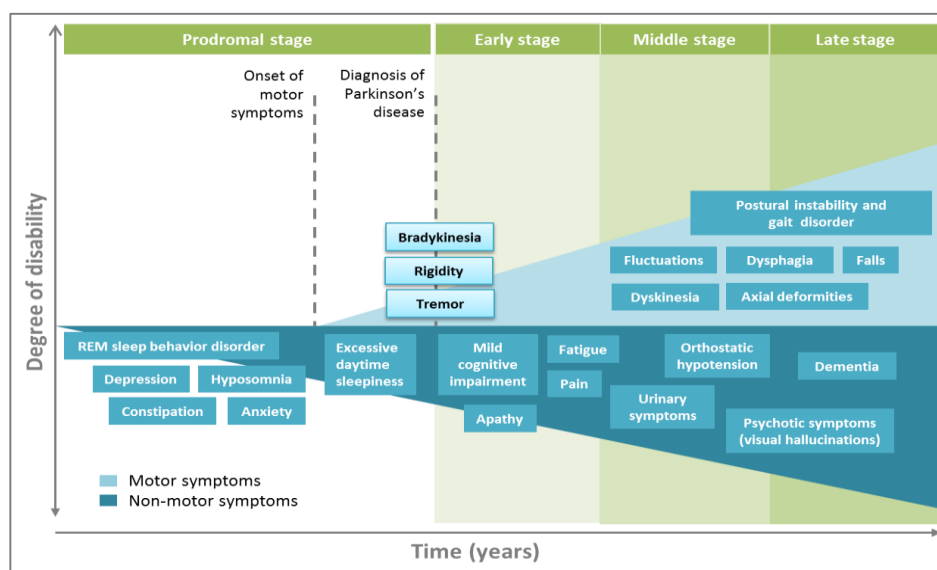


Figure 1: Development of motor and non-motor symptoms in Parkinson's disease (Based on Poewe et al [4])

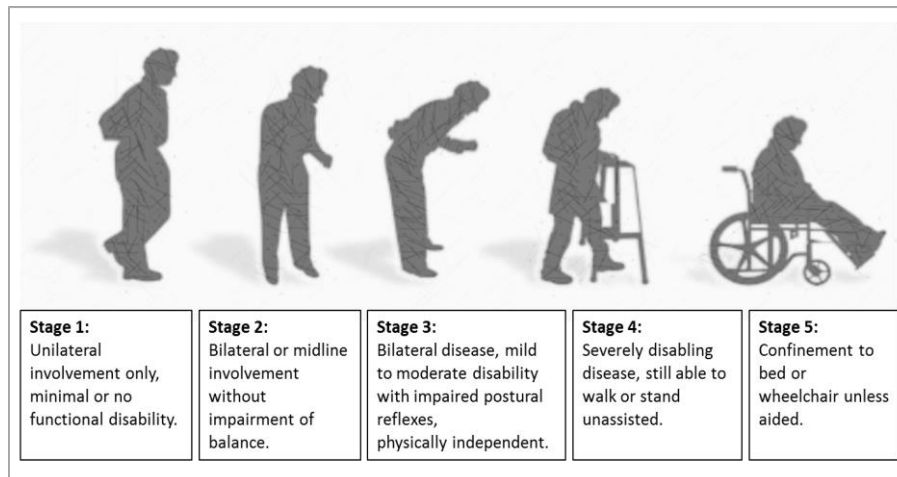


Figure 2: The Hoehn and Yahr staging of function in Parkinson's disease.

people with PD who fall do so recurrently, often resulting in injury [21], increased fear of falling [22], reduced activity levels and poor quality of life [23].

A theory that has contributed substantially to the understanding of the progressive stages of PD is the Braak hypothesis (see Figure 3). Braak and colleagues [24, 25] proposed that Lewy pathology seen in PD is caused by a pathogen that enters the body via the nasal cavity, which is subsequently swallowed and thereby reaches the gut. Neurons in both areas are infected, triggering a response resulting in the propagation of misshapen  $\alpha$ -synuclein (Lewy bodies) that are transmitted via the olfactory and vagal nerve towards the olfactory bulb and brain stem. Braak et al further theorized that the Lewy pathology further progresses towards the limbic and neocortices over time according to a specific pattern or stages [24, 26, 27]. Though not endorsed by all, the Braak hypothesis is viewed as an important contributor to the understanding of the progressive stages of PD, and is widely utilised as a tool in neuropathological diagnosis and as a framework for research [28].

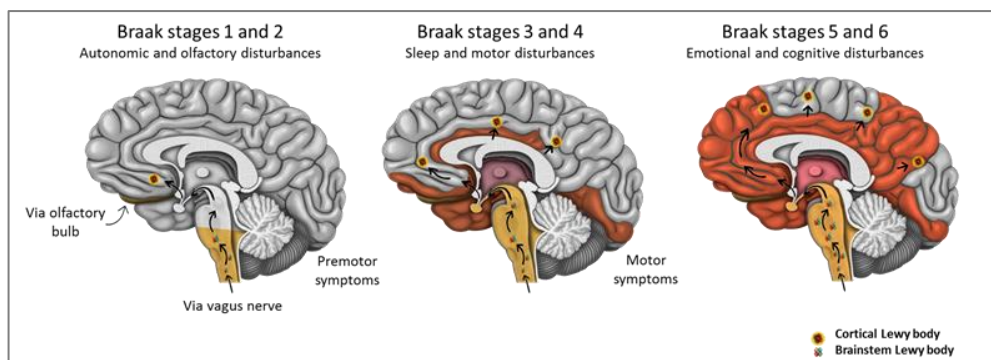


Figure 3: Illustration of the Braak stages in Parkinson's disease

#### **1.1.4 Management of Parkinson's disease**

Drugs that enhance intracerebral dopamine concentration or stimulate dopamine receptors remain the mainstay of treatment of motor symptoms in the management of PD. These drugs include levodopa (a dopamine precursor), dopamine agonists (which especially activate striatal D2-type dopamine receptors), monoamine oxidase type B inhibitors (inhibits the metabolism of dopamine), and less commonly, amantadine (antiglutamatergic properties and promotes the release of dopamine and prevents its re-uptake) [29]. A general consensus is that drug therapy should be initiated when symptoms cause the individual disability or discomfort, with the goal of improving function and quality of life [6, 29].

However, as the disease progresses into late-stage the beneficial effect of each levodopa dose becomes progressively shorter, where the brief levodopa serum half-life relative to the progressive loss of central dopamine storage is causal in this development. Other influencing factors are reduced gastric emptying and as well as competitive absorption of levodopa with large neutral amino acids in the blood [30]. These fluctuations in postsynaptic plasma drug levels renders the activation of dopaminergic receptors to be more and more pulsatile instead of continuous, affecting the movement ability of the individual further due to response fluctuations, wearing off, on-off fluctuations and dyskinesia [30, 31]. Interestingly, about 30% of those with idiopathic PD remain stable throughout the course of the disease and to a larger extent avoid dopaminergic drug-induced adverse motor and non-motor complications [6].

Gait and balance problems may persist, despite optimal dopaminergic medication [4, 32]. It is thought that the expression of these levodopa-resistant symptoms is related to abnormalities in other neurotransmitter systems including acetylcholine, glutamate, norepinephrine, and serotonin, which are recognised as contributors to the symptoms of PD [5, 6]. Therefore, the importance of physiotherapy and exercise in the management of PD is advocated, with mounting evidence for the positive effects of exercise on balance and gait function, as well as physical capacity and strength [33]. This is also reflected in the European physiotherapy guidelines for PD, where gait and balance is identified as one of four core areas that physiotherapist should focus on when assessing and treating individuals with PD [34].

## **1.2 Gait**

### **1.2.1 Neurological control of gait**

Human gait, or locomotion, is an extraordinary complex behaviour, and yet the most common of all human movements [35, 36]. Safe and effective gait is central to independence and longevity in older adults, and it has been shown that our general gait speed very well reflect our overall health, where decreasing gait speed is associated with level of frailty in older adults [37]. For the most part of our everyday life we mobilise in short bouts of walking, using less than 40 steps as we navigate through our indoor and outdoor environments. [38]. It is believed that an adult gait pattern is seen after the age of 12, and that this pattern is upheld through adult life [39]. However, with age degeneration of somatosensory functions, joint stiffness, pain and muscle weakness, as well as cognitive decline, are known to influence gait function [2, 40].

Humans use a symmetrical alternating gait pattern coupled with appropriate postural control to successfully progress the body in the desired direction [36]. Research in to the neurological control of posture and gait reveals a complex and integrated network involving all areas of the brain that work in unison to initiate, uphold and monitor movement output and postural control during locomotion [41]. As the individual intends to initiate gait the thought of doing so will have occurred in the frontal and parietal lobes, before being transferred to the supplementary motor area (SMA) and pre-motor cortex (PMC) where the desire to do so is converted to a motor plan [42]. At the same time information from the visual-, vestibular- and primary sensory cortex are utilised by the parietal and vestibular cortices to construct an internal model of self, relative to one's verticality [41]. This bodily information together with integrated information from the basal ganglia relaying memories of previous similar actions, is transmitted to SMA and PMC and applied for further refinement of the motor plan [41, 42]. This will include associating postural control programs, which are executed prior to the initiation of gait, to generate correct anticipatory postural adjustments via the corticoreticular and reticulospinal tracts [41]. Subsequently, appropriate motor programs are sent to the motor cortex (M1) initiating goal directed purposeful and skilled movements, such as gait [42].

Once initiated, locomotion is upheld by spinal inter-neuronal networks, termed central pattern generators, which produces rhythmic and synergetic muscle activation in the legs, trunk and arms [41, 43]. Simultaneously, postural control systems regulating tone and reflexes,

including head-eye coordination, are involved in achieving alignment of body segments relative to one another, and controlling the body's center of mass relative to the moving base of support during gait [36]. Responding to signals in proprioceptive and skin afferents, the spinal inter-neuronal networks modify the locomotor pattern in cooperation with descending signals from the brainstem structures and the cerebral cortex [44]. Information processing between the basal ganglia, the cerebellum, and the brainstem may enable automatic regulation of muscle tone and rhythmic limb movements [41].

### 1.2.2 Disturbances of continuous gait in Parkinson's disease

Gait is almost always affected in PD, and is related to disturbances of continuous gait as well as transient episodes of freezing and festination [45]. This is primarily related to the loss of dopamine release from the nigro-striatal pathway resulting in excessive inhibitory output from the basal ganglia [46] (see Figure 4). The altered output result in over-inhibition of the ventral thalamus which further reduces excitation of cortical motor structures such as the SMA and PMC [47]. As previously highlighted, these cortical areas are important for movement planning and scaling, and the reduced excitation may therefore cause failure in integrative sensory processing important for body alignment, anticipatory postural adjustments (APAs) and prospective motor programming [41, 45]. This in turn gives rise to the bradykinetic gait pattern and reduced automatic postural responses seen in PD [45].

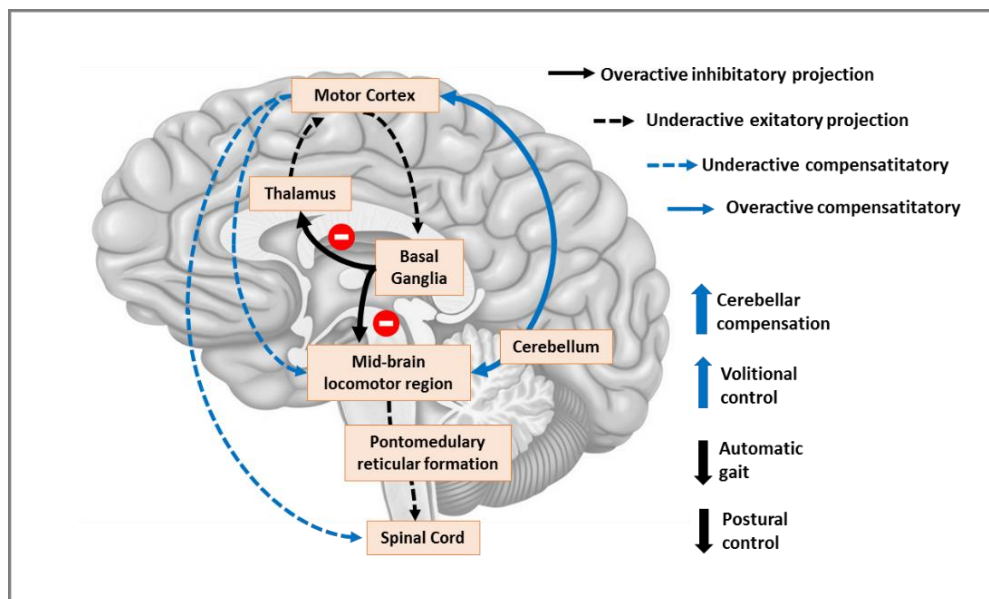


Figure 4: Framework for altered control of gait in individuals with PD (based on Peterson and Horak [45]).

The basal ganglia further exerts excessive inhibition through gamma-aminobutyric acid (GABA)ergic connections to the mencephalic locomotor region (MLR) and the pedunculopontine tegmental nucleus (PPN) in the midbrain [41, 45, 48] (see Figure 4). These are structures central for initiating and maintaining automated rhythmic locomotion (MLR) and regulating axial and limb muscle tone (PPN) via projections to the pontomedullary reticular formation in the brainstem and spinal cord [49]. The elevated inhibition of these structures in PD reduces the ability of the person to initiate and maintain locomotion, as well as leading to increased rigidity affecting both the neck, trunk and limbs [45].

Increased step-to-step variability is also a feature of gait in individuals with PD and is thought related to a compensatory shift from the basal ganglia and brain stem automatic pathways to more voluntary locomotor control [2, 45] as well as increased postural instability [50]. Higher levels of variability has been demonstrated for multiple spatiotemporal variables for this population when performing level ground walking, treadmill walking, walking backwards and walking while undertaking a cognitive task [51-53]. This is also a gait feature in newly diagnosed individuals [54] and level of gait variability was found to increase with disease severity [55]. Further, declining balance and mobility were associated with increased gait variability, which also has been shown to distinguish fallers from non-fallers in this patient group [56, 57].

### **1.2.3 Analysis of motor output during gait**

Walking in daily life involves initiating and terminating gait, ascending and descending hills and stairs, together with turning and navigating obstacles. However, most research that characterizes the normal locomotor pattern is done under continuous or steady-state (constant velocity) conditions [36]. The cyclic repetitive nature of continuous gait makes it ideal for investigating and understanding motor output and biomechanical aspects of gait, which in turn informs how injury and pathology alters gait function. Further, this test paradigm has been much used in research and clinical applications for evaluating and monitoring effects of orthotics, as well as surgical and exercise interventions with the intent of improving gait.

Traditionally all descriptions of gait, whether spatiotemporal, kinematic, kinetic or electromyographic, are done with reference to different aspects of the gait cycle, which is a crucial concept in gait analysis. Therefore, an understanding of the various periods and phases



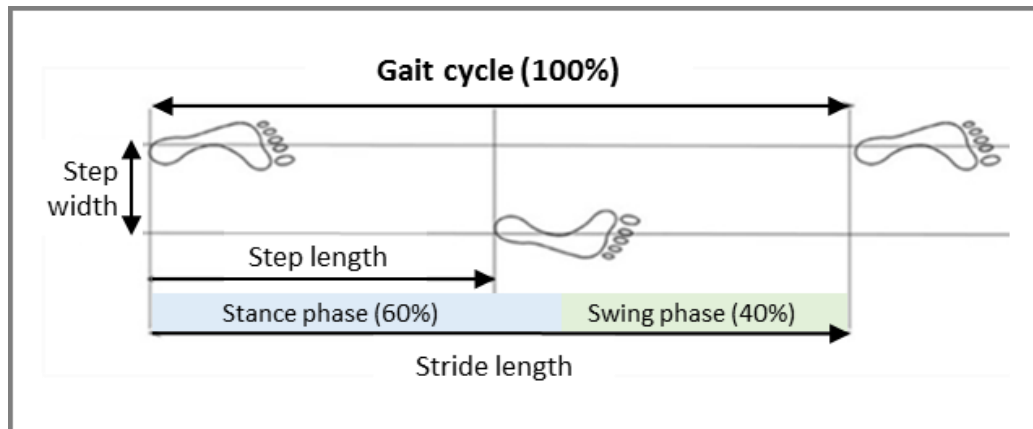


Figure 5: The gait cycle.

of the gait cycle is necessary for understanding descriptions of normal locomotion [36, 58] (see Figure 5).

By almost universal convention, the gait cycle starts at the instant one foot makes contact with the floor and continues until the next occasion when the same foot makes contact with the floor again, which constitutes a stride [58]. This is relative for each of the two lower limbs where the gait cycles for the left and right lower extremity are offset by 50% during normal symmetrical walking. This means that the contralateral initial foot contact occurs at 50% cycle of the ipsilateral limb [59]. This further denotes that one stride is the equivalent of one left and right step. The step or stride can be viewed both with respect to distance (spatially) and time (temporally), so that both the length and the time it takes to complete the step/stride is estimated. These aspects can further be combined to calculate step or stride velocity as a function of distance travelled in a given time. Another spatial gait variable that is often evaluated in gait analysis is step width, which is commonly calculated as the inter-heel distance between steps (see Figure 5).

It is further useful to divide the gait cycle into a number of phases in order to describe the processes that occur during walking. The simplest division is to split the cycle for a given limb into the stance phase, when the foot is in contact with floor, and the swing phase, when it is not [58]. In normal symmetrical walking the transition from stance to swing (toe-off) occurs at about 60% of the cycle, and it is worth noting that during the swing phase (40%), the contralateral limb is in single limb stance [59] (see Figures 5 and 6). This further denotes that for 20% of the stance phase both feet are on the ground, and is subdivided into first double support (from foot contact to opposite foot off), and second double support (from opposite

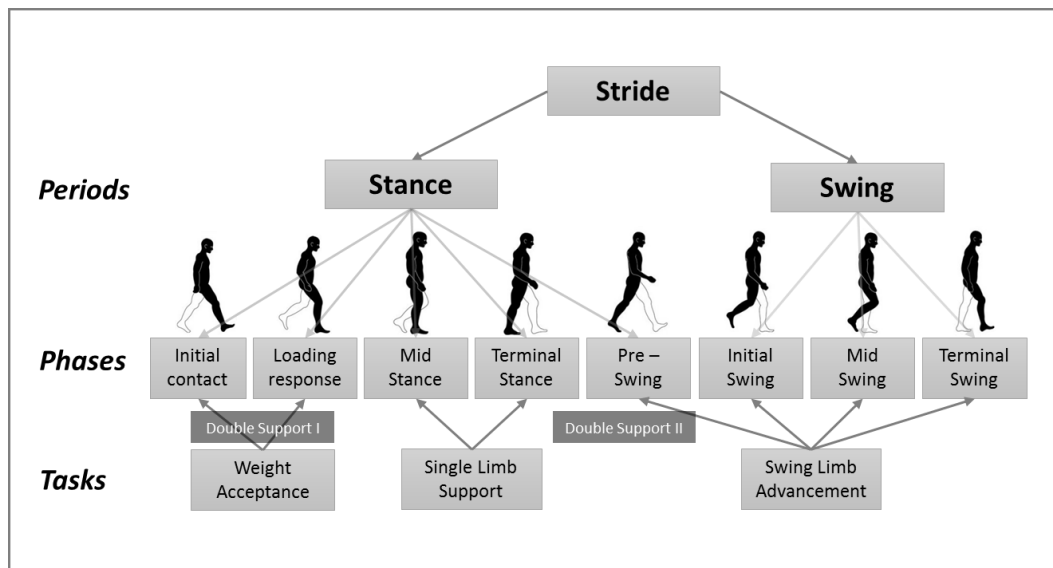


Figure 6: Divisions of the gait cycle

foot contact to foot off) [60] (see Figure 6). With increasing gait speed the double support phase becomes progressively shorter, until the transition is made into running, denoted by no double support at all [59]. These gait phases can either be depicted as percentage of the gait cycle, or with regards to duration in time (temporal).

Also in gait analysis it is common to specify the number of cycles taken in a specified time, where the common practice is to stipulate steps per minute. This is of course twice the number of strides per minute, and the difference is sufficiently large not to leave ambiguity as to which convention is being used [58]. Further, walking speed, the distance travelled in a given time, is related to both cadence and step length:  $\text{cadence} \times \text{step length} / 60$ , given that unit of gait speed is in meters per seconds, then cadence is in steps per minute and step length in meters. If measurements are in different units, the number 60 needs to be changed accordingly [58].

The output of the normal human gait pattern has been extensively described by measuring spatial and temporal characteristics, joint motions (kinematics), joint forces (kinetics) and muscle activity (electromyography) during gait [42, 58, 61]. Pronounced key features are as follows (see Figure 6): A well-positioned heel strike at initial contact, followed by the ankle first rocker and knee flexion for shock absorption and weight acceptance. Weight is shifted laterally and forwards onto the stance leg as the trailing leg is preparing for push-off into swing. The stance leg is thereby in single limb stance, and weight is progressed toward the forefoot as the knee and hip extends allowing the ground reaction force to act anterior to the

limb for support. Also, adequate hip abductor strength is paramount for stabilising the pelvis in this gait phase. In terminal stance, an efficient heel-rise together with full extension at the hip and knee on a rotating pelvis facilitates an efficient push-off, as well as giving optimal swing limb advancement of the contralateral limb. When in swing, adequate foot clearance is achieved through both an appropriate foot lift (ankle dorsiflexion) and adequate hip and knee flexion in the mid-portions of the swing phase. In terminal swing, prepositioning of the foot in preparation for the next heel strike is key and thereby starting the next cycle.

Previous reports have shown that the biomechanical consequences of hypokinesia/bradykinesia and rigidity on gait for individuals with PD are multiple. Smaller and slower steps affects step length and thereby gait velocity, whereas increased tone in neck, trunk and limbs contributes to the flexed postural alignment common in this population [45]. During gait the flexed posture results in a forward progression of the center of mass over the feet early in the gait cycle. Firstly, this reduces the person's ability to achieve a heel strike at initial contact, where instead contact is made with the foot flat or with the forefoot. Secondly, the person's ability to extend the knee and hip in mid-stance is decreased, as well as decreased ability to weight shift mediolaterally over the stance leg [36]. In terminal stance, hip rigidity interferes with the person's ability to extend the hip and knee together with plantarflexion of the ankle. This results in reduced ankle push-off power generation signified by decreased forward thrust of the body affecting steps length [62]. A more proximal strategy for forward propulsion ensues, to a pull-off gait strategy [63].

Dopaminergic treatment modulates bradykinesia and rigidity, and relative to gait, improves the ability to take longer steps and thereby generating higher gait velocities. However, decreased rigidity has mainly been seen in limb muscle tone, but not axial, and has been attributed to differing descending pathways from the PPN and the pontomedullary reticular formation. This pathway differentiation is likely implicated in why Levodopa is not effective for improving postural control [32, 45].

#### **1.2.4 Assessment of gait variability**

The study of gait variability concerns the quantification of level of step-to-step fluctuations over multiple cycles during walking. The method has over the past two decades offered a new way of quantifying level of consistency or motor control in locomotion, its changes with aging and disease, as well as a means of monitoring the effects of therapeutic interventions

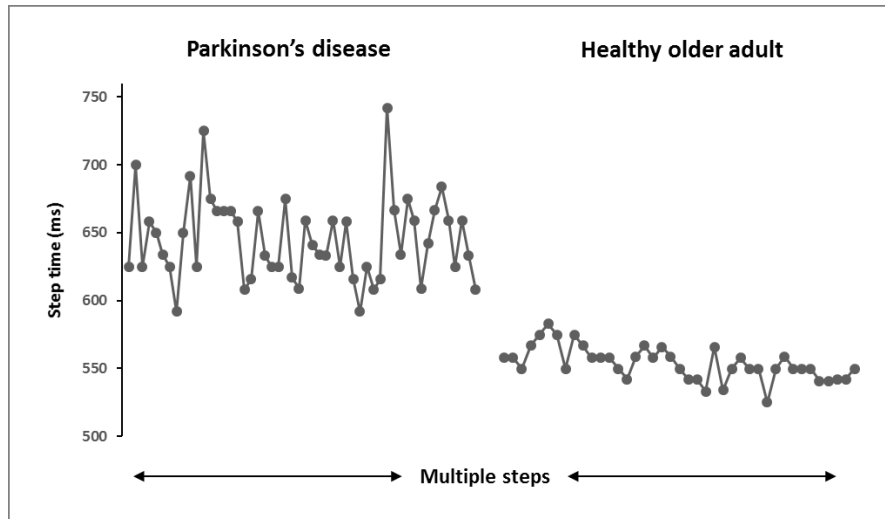


Figure 7: Increased step-to-step variability for individuals with Parkinson's disease as compared to healthy older adults.

and rehabilitation [64]. It has been demonstrated that step-to-step variability increases with age [65], and further with disease and pathology [66]. Figure 7 depicts the significantly higher variation in step times over multiple steps for an older individual with mild to moderate PD as compared to a healthy older adult.

To estimate the variability for a given gait variable (i.e step time), the variation relative to the mean over multiple steps is calculated. However, a review of the clinometric properties of gait variability highlighted the lack of consensus regarding the methods used [67]. It can be seen that most studies use either the standard deviation (SD) [65, 68, 69] or the coefficient of variation (CoV) [51, 70], but other methods such as fractal analysis have also been employed [64, 71].

Also, there is a lack of consensus regarding which gait variables are considered most informative [72]. It could be suggested that choice to some degree is related to the measurement instrument being employed. Using an instrumented walkway allows both spatial and temporal inter-step gait variables to be estimated, and step/stride length-, step width-, and stance time variability are most frequently reported [65, 68, 69, 73]. However, using pressure insoles or foot switches only allows calculation of temporal inter-step characteristics, together with spatial and temporal stride characteristics. Stride time- and swing time variability are often used [51, 54, 70, 74].

An important aspect when estimating gait variability is the amount of steps included in the calculation [75]. This varies between reports and is seldom specified. However, inferences can be made based upon the reported length of the capture area, together with number of runs made. On this basis, included steps can vary between 15-20 steps [69, 76], right up to 50 steps in others [65, 68]. Also, a study using force-sensitive insoles captured data over several minutes in a long corridor, allowing the accumulation of several hundred steps [55]. Importantly, studies that have assessed the reliability of gait variability estimates, both for continuous (on a circular track) and intermittent (back and forth) walking protocols at normal gait speed, suggest that at least 30 steps, and as many as 50 steps, should be included in the calculations to ensure consistent estimations [75, 77]. However, the reliability of gait variability measures at slow and fast gait speeds has not yet been reported.

Many investigations use the combined steps or strides from both the right and left leg in the gait variability calculations, and thereby increasing the amount of data used [65, 68].

Supporting this practice, Galna et al. [75] contended that using information from both sides avoids confounding step-to-step variability with variation originating from asymmetry, and thereby promoted estimating gait variability as the square root of the within-subject variance of the both left and right steps [75, 78].

Another recent method of interest is the Gait Variability Index (GVI) which was developed to be a generic tool, and therefore applicable to different diagnostic groups and disease severities [79]. The GVI displays the accumulated variability over the nine most commonly used spatiotemporal gait variables, and the level of gait variability for the individual is evaluated relative to a healthy adult reference population mean, set to the value of 100. Therefore, a  $GVI \geq 100$  indicates a similar level of gait variability as the reference population, and each 10-point reduction in the score denotes one standard deviation from the reference mean, signifying increased gait variability. The method is interesting as the GVI score is easily interpreted and could prove a valuable tool both in research and in clinical gait analysis. The index has previously been validated for individuals with Friedrich's ataxia and for healthy elderly [80], but has not been used relative to individuals with PD.

It was recently suggested that clinicians should challenge the motor control of gait by testing under various walking speeds to better expose a declining gait function [65]. Slow and fast walking is less conducive to the storage and recovery of elastic energy, and therefore mechanically less efficient, altering gait- and muscle activation patterns [81]. Slow gait speed

will place higher demands on postural stability through stabilizing muscle activation, due to increased time spent in single limb stands and increased mediolateral displacement of the center of mass (COM) [82]. Walking faster requires elevated muscle activity for propulsion and stability to drive increased joint range and motion for longer steps and higher cadence, as well as increased demands on eccentric muscle function for shock absorption [81, 83]. Level of gait variability at slower and faster gait speeds has been investigated in individuals with PD and in healthy older adults generally showing increased gait variability associated with slower gait speeds as compared to normal and fast [51, 65]. Further, the effects of dopaminergic treatment gait variability for individuals with PD are not clear, but it has been suggested that variability in spatial as compared to temporal variables are more responsive to medication [50].

### **1.2.5 Model of PD-gait**

Gait characteristics help to identify markers of incipient pathology, inform diagnostic algorithms and disease progression, and measure efficacy of interventions. [84]. However, a broad range of characteristics is used to describe gait performance, but there is no clear framework to guide selection [85]. Gait speed is frequently reported when measuring locomotion, however gait speed only represent overall performance and does not reflect the multidimensionality of a person's gait [84]. Therefore, conceptual models of gait have been developed to provide a simplified framework for selecting gait variables, with the approach to group characteristics into domains of gait [84, 86, 87].

It was recently shown that the gait of older adults with PD can be characterised by five independent domains reflecting the pace, rhythm, variability, asymmetry, and postural control aspects of gait (see Figure 8) [84, 85]. The model was developed using a strong theoretical paradigm extending on previous work [86, 87]. Sixteen core spatiotemporal variables were selected according to predefined criteria, and their associations with the individual domains were identified using principle component analysis [85]. Deterioration have been demonstrated in all gait domains for individuals with PD relative to healthy peers [45], also in the early stages of the disease [78] (see Figure 9). Reduced pace, rhythm and postural control are attributed to bradykinesia and increased rigidity, as well as poor integrative sensory processing [41, 45]. Shorter, slower and more irregular steps manifests in gait slowness [64], whereas wider steps with decreased step width variability indicate an inability to adapt to the dynamic balance demands of gait [76, 88]. Further, symptoms present asymmetrically,

especially in early stages after diagnosis, and are likely related to uneven loss of dopaminergic neurons in the SNpc [45]. Asymmetric timing of the stance and swing portions of stepping has been shown in the early stages of the disease [78].

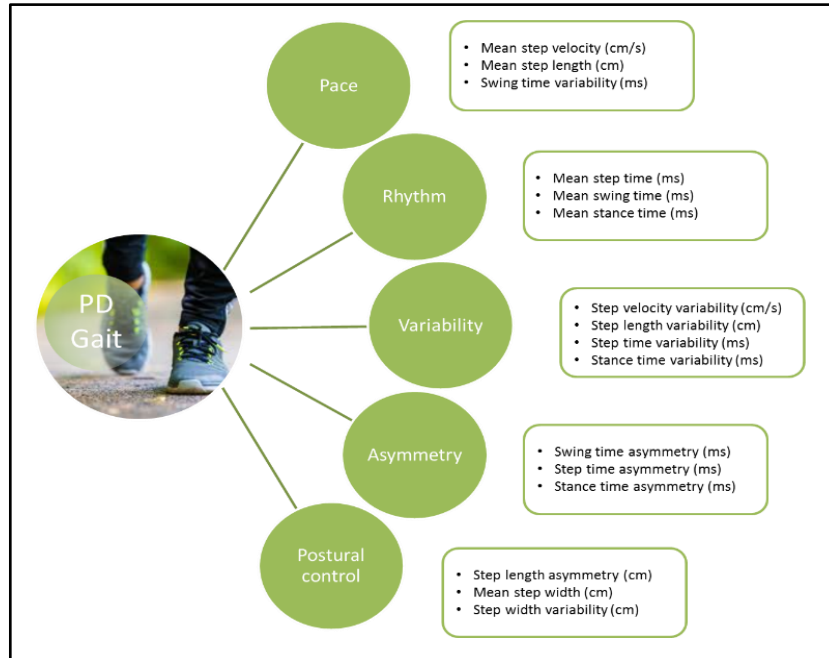


Figure 8: Conceptual model of PD-gait (based on Lord et al [83, 84]).

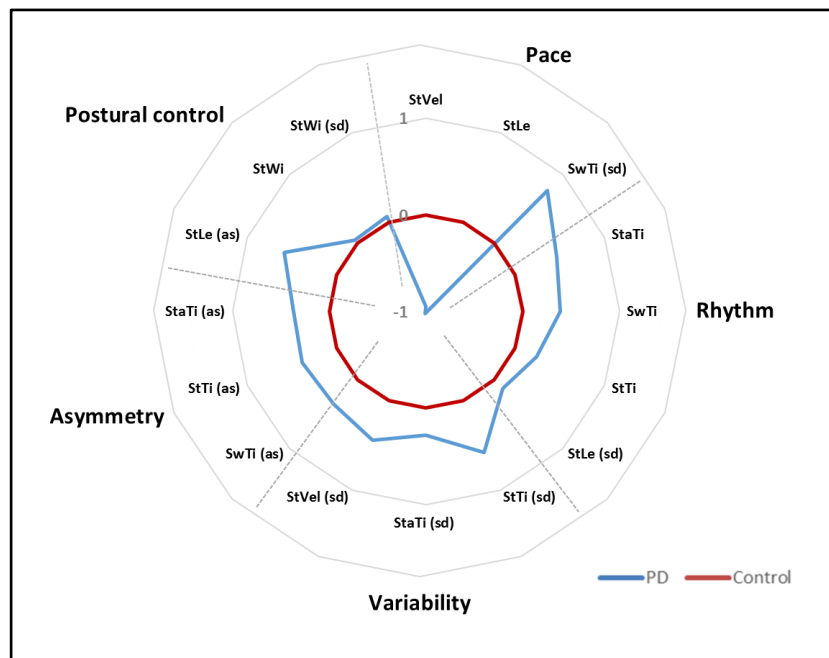


Figure 9: PD-gait disturbances as depicted in the radar plot showing deviations from healthy controls. Abbreviations: St = step; Sw = swing; Sta = stance; Vel = velocity; Le = length; Ti = time; sd = variability; as = asymmetry.

### **1.3 Effect of exercise on balance, gait and mobility in Parkinson's disease**

The Movement Disorder Society Evidence Based Medicine Panel recommend exercise and physical therapy as an efficacious adjunct to levodopa in the management of PD [89].

Training is thought important for modifying long-term motor symptoms and secondary complaints such as joint stiffness, muscle weakness, deconditioning and pain, and thereby maximizing functional ability [90]. Further, there is growing evidence that exercise can have positive effects directly on the brain, where studies in animal models, together with recent human clinical trials, have demonstrated neuroprotective effects, and neuroplasticity in the rodent brain [91-93], as well as increased brain growth factors and brain volume in humans [94].

Since impaired balance and gait are such a disabling aspect of the disease that respond poorly to drug therapies, there has been extensive research into the effects of physiotherapy and exercise on balance and gait performance with the intention to improve mobility and function, and to reduce falls and fall risk. Several reviews and meta-analysis summarising the research in this field over the past two decades have brought invaluable insights [3, 95-99].

Overall, the studies that have investigated the effect of exercise and task training on balance, gait and mobility, have mainly included individuals in the mild to moderate stages of PD that are stably on anti-parkinson medication [96, 98]. However, there is some diversity in the training interventions used, but they can broadly be divided into modes of balance, gait and strength training, with or without the use of dual task, functional task training and cuing.

Balance training mainly focused on different exercises incorporating leaning/ reaching tasks to challenge stability limits, standing on uneven surfaces (foam), in tandem or on smaller bases of support to improve somatosensory and vestibular function, as well as multi-directional stepping and the use of perturbations to promote motor agility and postural adjustments/ reactions [100-103]. Balance training also included Tai Chi [104, 105] and partnered dance [106, 107]. Gait training was conducted over ground and on treadmill where participants walked in multiple directions, with or without the use of body weight support and/or robotic assistive devices [108-111]. Strength training was included in some multi-modal interventions mainly focusing on lower limb strength where weight-bearing tasks such as sit to stand, heel raises, launches and squats were performed, with the use of weight vests and weight cuffs to ensure increase in loads [100, 112-114].



Programs were mainly group based and conducted in a facility with at least 50% supervision [105, 114], but some were also individual and based in the home with some contact with a trainer or physiotherapist (i.e once a week or month) [100, 112]. Further, the duration (number of weeks) and number of training hours per week varied greatly across studies. The majority of interventions were implemented over 8 to 13 weeks, where participants for the most part trained 2 or 3 times per week for 40-60 minutes per session [104, 114-116], but shorter training periods of 3 to 6 weeks was also used [117-119], as well as longer periods extending over 6 and 12 months [101, 107]. However, some of the short-duration interventions were more intensive, administering 4 -7 sessions per week over 4 to 9 weeks . However, it could be seen across the reviewed studies that the median training duration was 8 weeks with 18 hour of exercise (mean: 28 hours over 10 weeks).

All listed diversities between studies makes it challenging to compare results across investigations. However, Allen et al [96] (n=747) and Shen et al [98] (n=1881) showed in their meta-analyses that immediate effect of exercise and motor training on balance and gait related outcomes was significant but small (hedge's  $g = 0.30-0.33$ ,  $p < 0.01$ ). However, Shen et al (n=941) also estimated long-term effects (follow-up time ranged from 4 weeks to 12 months) which gave a Hedge's  $g = 0.42$  showing closer to moderate long-term training effects. In support of this, a current review on the long-term effects of physical exercise for individuals with PD concluded that balance training had the longest carry-over effects improving balance (10% improvement), gait and mobility (5-10% improvement), followed by gait training (10% improvement) and tai-chi (10% improvement) [4]. Ni et al [99] showed in their very recent meta-analysis (n=1656) that the effect of exercise (balance, gait and strength) on normal and fast gait speed, relative to non-exercise control, gave a Hedge's  $g$  effect size of 0.45 (95% CI: 0.24-0.66) and 0.43 (95% CI: 0.06-0.80) respectively.

This indicates that relevant balance, gait and strength exercises over the course of 8-13 weeks, and at least 4 weeks, significantly improves gait and balance related outcomes with small to moderate effects in individuals with mild to moderate PD, both short and long-term. The long-term improvement, are particularly interesting given the degenerative nature of PD, and could indicate the presence of exercise-induced neuroplasticity [120]. However, Allen et al [96] commented that many studies had used low challenge levels, and thereby urging future exercise interventions to implement more demanding balance exercises at a higher training dose to stimulate relearning of physiological systems important for balance control. Also of interest was the finding by Shen et al [98] that training at facilities led to better improvement

in balance and gait ability over the long-term than the community and home-based training. It was hypothesised that supervised facility-based training enabled participants to practice the training tasks at their optimal capacity. Lastly, many of the studies had few included participants, thereby reducing the statistical power, and there were few studies with follow-up periods extending past 12 weeks. This highlights the need for new evidence based exercise programs that elicits long-term effects for individuals with PD. It has also been commented that exercise-dependent neuroplasticity represent the neural basis of rehabilitation for individuals with PD, and is largely dependent on intensity, repetition, specificity, difficulty, and complexity of practice [90].

### **1.3.1 The High Intensity Balance (HiBalance) program.**

The HiBalance program was therefore constructed to be highly challenging and target specific and relevant balance components affected in PD. A key aspect of the program was not to use a fixed scheme of predetermined exercises. Rather, a framework based on motor-learning principles (specificity, progressive overload and variation) was used as a foundation for the application and adaptation of exercises to the participants' abilities. The intervention addresses relevant balance components such as sensory integration, anticipatory postural adjustments, motor agility and stability limits. Physiotherapy-led group sessions with 4-7 participants ensures varying training conditions and structured progression as well as participant safety. Especially exercises related to motor agility and sensory integration incorporated stepping and walking, where walking direction was varied throughout, and fast walking was used as an individual exercise. In addition, both motor and cognitive dual tasking was gradually integrated in conjunction with the exercises to further increase load and variation. The conceptual framework behind the HiBalance program has been well described in previous publications [121, 122].

The primary investigation into the impact of the training showed improved functional balance, self-selected gait speed and step length in the short-term, but not long term [123, 124].

However, gait speed only represent overall performance and does not reflect the multidimensionality of a person's gait [84]. As previously shown, the gait of older adults with PD can be characterised by five independent domains reflecting the pace, rhythm, variability, asymmetry, and postural control aspects of PD gait [85] (see Figure 8). The gait model offers a framework that facilitates a better understanding of underlying gait mechanisms and the

identification of contributory features to gait disturbance, and can be used to examine the effect of interventions [84].

## 1.4 Validity and reliability

Measurement of health outcomes is essential in scientific research and in clinical practice. Based on the scores obtained with measurement instruments, decisions are made about the application of subsequent diagnostic tests and treatments. Instruments used for health status measurements should therefore be both reliable and valid, otherwise there is a serious risk of biased results that might lead to wrong conclusions [125].

### 1.4.1 Validity

Validity is defined by the Consensus-based Standards for the Selection of health Measurement Instruments (COSMIN) panel as “the degree to which an instrument truly measures the construct(s) it purports to measure [125]. In general, three types of validity can be identified (see Figure 10). Content validity focuses on whether the content of the instrument corresponds with the construct that one intends to measure. Further, criterion validity refers to how well the scores of the measurement instrument agree with the scores of the gold standard, and lastly, construct validity denotes whether the instrument provides the expected scores, based on the existing knowledge about the construct. This is evaluated with regard to internal relationships, relationships with scores of other measurements or differences between relevant groups.

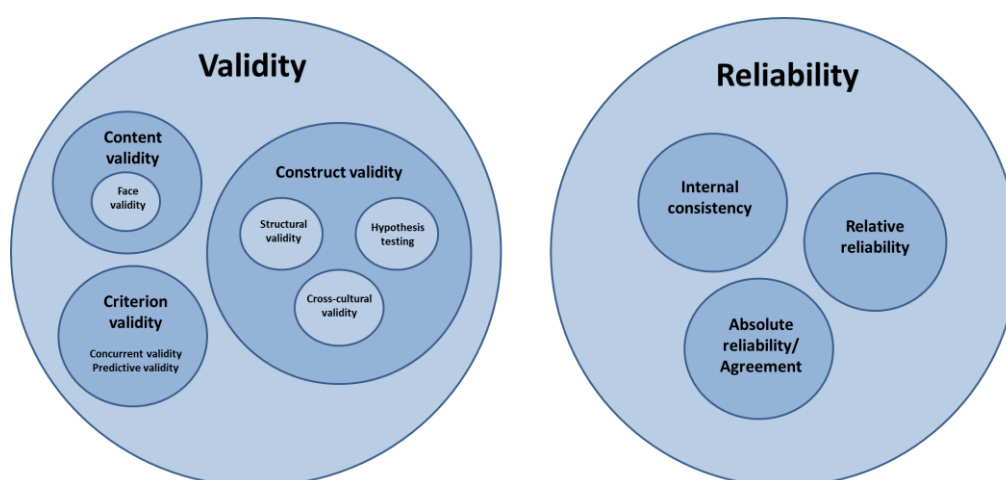


Figure 10: The concept of validity reliability as defined by the COSMIN panel [127].

In this thesis the method of hypothesis testing was used to explore construct validity of the GVI. The basic principle of this method is that hypotheses are formulated about expected differences between subgroups of patients (discriminative validity/ know-groups validity) and/or expected relationships in the measurement instruments evaluating related (convergent validity) or unrelated (divergent validity) constructs [125].

### **1.4.2 Reliability**

Reliability refers to the reproducibility of a measurement and concerns to which degree repeated measurements in stable study objects, often persons, provide similar results [126, 127]. This denotes that repeated measurements on the same subject will vary around the true value because of measurement error or variation [128]. This can be related to biological variation in the subject, the measurement instrument itself and the circumstances under which the measurement takes place [126]. Only by estimating the error or variability associated with repeated observations of a measurement method or instrument can we get closer to its true value [127]. Central to the concept of reliability is the difference between absolute reliability, or agreement, and relative reliability.

Firstly, agreement assesses how close the results of the repeated measurements are by estimating the level of measurement error [126, 127]. Agreement parameters are used to measure the change in health status, which is often the case in clinical practice [126]. A common design is to take two measurements of the same subject over a group of subjects. The measurement error is estimated by calculating the mean within-subject standard deviation ( $S_w$ ) over the group, which is also commonly termed the standard error of measurement (SEM) [127, 128]. The difference between a subject's measurement and the true value would be expected to be less than  $1.96 S_w$  for 95% of observations [128].

Another useful way of presenting measurement error is to estimate the smallest real difference (SRD), also called the minimal detectable change, as  $\sqrt{2} \times 1.96 S_w$  or  $2.77 S_w$ . This agreement value correspond to the upper and lower limits in the standard Bland Altman plot [127], and reflects the value that the difference between two measurements for the same subject is expected to be less than with 95% probability [127, 128]. Agreement parameters are expressed on the actual scale of measurement and provides useful information when there is a clear conception of the differences that are important.

Further, relative reliability assesses whether study objects, often persons, can be distinguished from each other despite measurement error [126, 127]. This means that the relative reliability depends on both the magnitude of measurement error (within-subject variability), and the heterogeneity in the population in which measurements are made, signified by the variability between individuals [127, 128]. Therefore, for discriminative instruments the measurement error needs to be small in comparison to the variability between persons that the instrument needs to distinguish. Relative reliability parameters are determined as a dimensionless value between 0 and 1, and are therefore less intuitive to interpret. A common statistic for establishing relative reliability is the intraclass correlation coefficient (ICC) [129].

## 2. Aims and research questions

The main aim of this thesis was to investigate the immediate and long-term effects of the HiBalance program on gait for individuals with mild to moderate PD. To get a more comprehensive picture, multiple gait variables (mean characteristics, variability and asymmetry) representing relevant domains of PD-gait were assessed, also for different gait speeds.

To enable a comprehensive evaluation of the training intervention, a further aim was to explore valid and reliable methods for estimating level of gait variability in multiple gait variables over slow, normal and fast gait speed conditions.

The main research questions addressed in the three papers included in the thesis were:

- What is the mean GVI score in a cohort of individuals with mild to moderate PD?  
**(Paper I)**
- Does the GVI score correlate with functional balance and mobility scores in a cohort of individuals with mild to moderate PD? **(Paper I)**
- Can the GVI scores distinguish those individuals with mild from moderate PD?  
**(Paper I)**
- Does gait speed influence the level of gait variability in spatiotemporal variables for individuals with PD and healthy older adults? **(Paper II and Thesis)**
- What is the effect of age and pathology on gait variability? **(Thesis)**
- Will absolute reliability (agreement) and relative reliability improve by the inclusion of more steps in gait variability estimates for individuals with PD and in healthy older adults, and is this different when walking in a slow, normal or fast manner? **(Paper II)**
- Does 10 weeks of intensive balance and gait training improve continuous normal and fast gait in individuals with PD, as represented by the pace, rhythm, variability, asymmetry and postural control domains of PD-gait? **(Paper III)**
- Are positive training effects retained 6 and 12 months after the training has ended?  
**(Paper III)**

## 3. Methods

### 3.1 Design

Data for this thesis were collected at two separate sites; the Balance and motion laboratory, Karolinska Institute, Stockholm, Sweden (Paper I and III), and the Motion laboratory at Sunnaas Rehabilitation Hospital, Nesodden, Norway (Paper II).

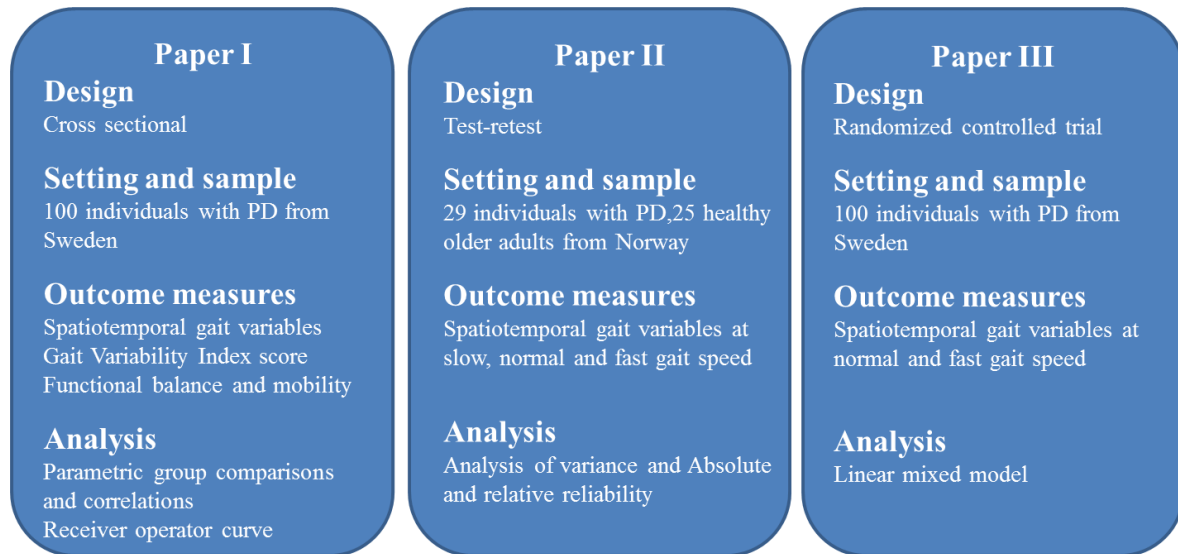


Figure 11: Overview of designs, settings and samples, outcome measures and the main analysis methods of the papers included in this thesis.

Paper I explored the construct validity of the Gait Variability Index (GVI) when used on gait data from individuals with PD. Cross-sectional data for this study were extracted from the BETA-PD randomized controlled trial (RCT) using the baseline measurements.

Paper II was a reliability study with a test-retest design. The absolute and relative reliability of gait variability data from individuals with PD and healthy older adults, sampled at slow, normal and fast gait speeds was investigated. Cross-sectional data for this study were collected at the Motion Laboratory at Sunnaas Rehabilitation Hospital, Norway.

Paper III was a pre-planned secondary analysis on gait data from the longitudinal BETA-PD RCT study, investigating the immediate and long-term effects of the HiBalance program on all domains of gait for individuals with PD sampled at self-selected normal and fast gait speeds.

## **3.2 Ethical approval**

Ethical approval for studies I and III were given by the Regional board of ethics in Stockholm, Sweden (Dnr. 2009/819-32, 2010/1472-32, 2011/37-32 and 2012/1829-32). Study II was approved by the Regional Ethics Committee for Medical Research and Ethics in South East Norway (Dnr: 2013/1621). These studies were conducted according to the Helsinki Declaration (ethical principles for medical research involving human subjects), where all participants gave their written consent after receiving written and oral information. The consent could be withdrawn at any time without justification.

## **3.3 Participants**

### **3.3.1 Inclusion and exclusion criteria**

All three studies used common inclusion and exclusion criteria for individuals with PD. To be included, participants needed to have a clinical diagnosis of idiopathic PD according to the UK PD Society Brain Bank criteria [130], be classified as H&Y stage 2 or 3, and be 60 years or older. Potential participants were excluded if they had a history suggesting atypical PD symptoms as defined by Hughes et al [130], a Mini-Mental State Examination (MMSE) score  $\leq 24$  [131], or other existing neuromuscular disorders or medical conditions that could influence their gait and balance function.

For Paper II, a group of healthy older adults was included on the basis of being 60 years or older, with no on-going or recent history of neuromuscular conditions or illness, and no previous joint replacements.

### **3.3.2 Sample sizes**

Sample size estimation for Paper I was done based on data from a previously published study where the GVI was validated for individuals with Friedrich's Ataxia [72]. However, the level of variability during gait in individuals with Friedrich's Ataxia is much more apparent relative to people with PD, and this sample size estimation was therefore viewed as informative but not definite. It was hypothesised that a doubling of the estimated sample size would be more accurate. Power was set at 80% with an alpha level of 5%. To detect a mean difference of 4 increments on the GVI between groups, representing differences in disease severity, a sample size of 40 was required, assuming a mean standard deviation (SD) of 6.0, producing an effect



size =0.56, which is only moderate. This led to the conclusion that that using the baseline data of the BETA-PD study with a sample size of 100 participants would be suitable.

In reliability studies an adequate sample size is important to obtain an acceptable confidence interval around the estimated reliability parameter. It has been put forward that a rule of thumb is to ensure that the number of subjects, times the number of measurements per individual should be at least 25 [132, 133]. On the other hand, Altman [134] stated that a sample size of 50 is needed to ensure that confidence intervals for the limits of agreement are not too wide. For ICC estimates one can calculate the number of subjects and measurements per subject necessary to reach a pre-specified confidence interval. To estimate an ICC value of 0.8 with a 95% CI of  $\pm 0.1$ , 50 subjects are needed when based on two measurements, whereas the number is reduced to 13 with an accepted 95% CI of  $\pm 0.2$  [135]. Considering all these aspects, together with evaluating the sample size used in similar reliability studies [75, 77], and the time and resources available to the project it was considered that a sample size of  $n=30$  would be adequate.

Paper III was a secondary analysis on gait data from the BETA-PD study. The sample size estimation done in the planning of the BETA-PD study where based on a pilot study [122] and similar intervention studies in PD [107, 136]. The power calculation was performed separately for three main outcome measures relative to balance performance, gait velocity and concerns of falling. With regards to gait velocity it was determined that in order to achieve 80% power with a two-sided alpha level of 5%, the number of subjects required per group were 27 with an hypothesized effect size of 0.83. In addition, a dropout rate of 15% was anticipated which projected an overall sample size of 40 in each group. However, due to long-term follow-up of the training program, the group size was increased to 50 subjects (total  $n = 100$ ).

### **3.3.3 Recruitment**

A flowchart of the recruitment process is shown in Figure 12. Recruitment for the BETA-PD RCT was done via advertisements in local newspapers, from Karolinska University Hospital and outpatient neurological clinics in Stockholm County, Sweden and through the Swedish Parkinson association. Participants with instability during postural transfers and gait impairments were identified based on a clinical assessment and offered to participate in the study. This approach aimed at using clinical reasoning by recruiting individuals who would be

assigned to balance training in clinical practice. Recruitment for the Sunnaas Rehabilitation Hospital cross sectional study was done in collaboration with the Norwegian Parkinson's Disease Association through advertisement on their web-site and via e-mail to its members in the municipalities of Oslo and Akershus, Norway. Relative to the recruitment process for both data collections, a screening interview of potential participants was conducted over the phone to identify other health complaints that could influence gait and balance, and further, to get a clearer picture of the persons' functional level with regards to gait and balance. Those found eligible were invited to undergo testing.

A control group of healthy older adults were recruited for the Sunnaas Rehabilitation Hospital cross sectional study. Recruitment was done for convenience among colleagues, friends and relatives of the staff at Sunnaas Rehabilitation Hospital, at a nearby senior centre and a nearby training studio.

It is also important to highlight that for Paper I, the already existing reference values embedded in the GVI macro and made available by Gouelle et al. [79] were used. These reference values represent level of variability found in matured adult gait, and not gait for healthy older adults. Characteristics of the participants in the different studies are shown in Table 1.

**Table 1.** Characteristics of the participants in Papers I-III

<b>Characteristics</b>	<b>Paper I</b> (Swedish cohort)	<b>Paper II</b> (Norwegian cohort)		<b>Paper III</b> (Swedish cohort)	
	PD (n=100)	PD (n=29)	HOA (n=25)	PD TG (n=51)	PD CG (n=49)
Sex (male/ female)	57/43 (57/43)	14/15 (48/52)	9/16 (36/64)	32/19 (63/37)	25/24 (51/49)
Age (years)	73.2 (5.6)	70.9 (5.5)	68.3 (4.9)	73.1(5.8)	73.0 (5.5)
Height (cm)	171.6 (8.9)	171.9 (10.9)	173.9 (9.9)	172.2 (8.9)	171.2 (9.0)
Weight (kg)	75.9 (13.8)	77.4 (17.3)	74.5 (9.8)	75.7 (13.5)	75.9 (14.0)
PD years	5.8 (5.0)	7.6 (4.0)	-	5.9 (5.1)	5.6 (4.8)
H&Y stage (2/3)	44/56 (44/56)	18/11 (62/38)	-	23/28 (45/55)	21/28 (43/57)
UPDRS motor	36.6 (10.5)	32.0 (6.9)	-	36 (10)	37 (11)

Continuous data presented as mean (standard deviation) and nominal data as proportions (percentages).

Abbreviations: PD = Parkinson's disease; HOA = Healthy older adults; TG = training group; CG = control group; H&Y = Hoehn & Yahr; UPDRS motor = the motor section of the Unified Parkinson's Disease Rating Scale, part III.

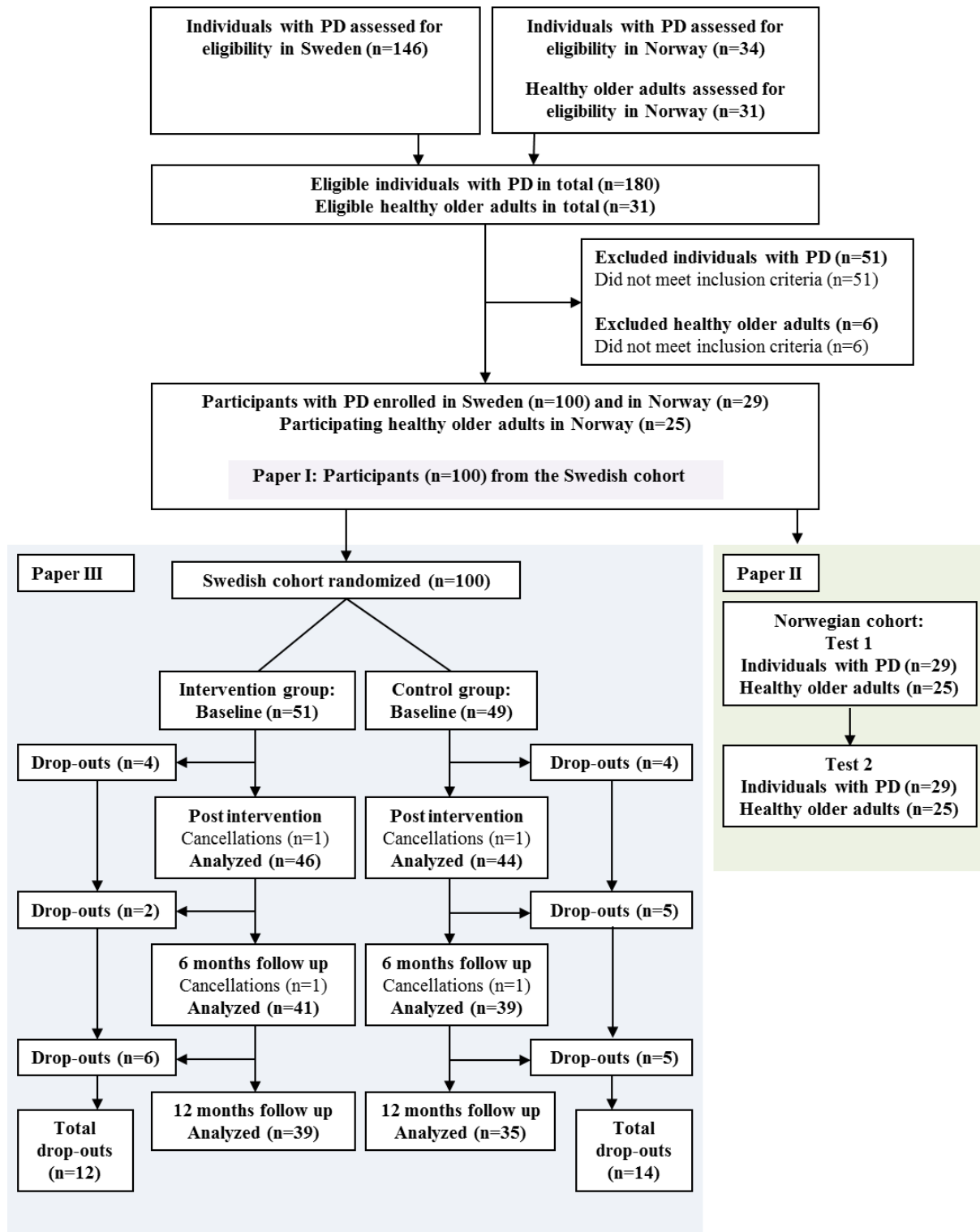


Figure 12: Flowchart illustrating the recruitment process and resultant sample sizes for all studies. Numbers relative to exclusion (total cohort) and drop-out rates (Paper III) are shown.

### 3.4 Data collection

Data for Paper I and III were collected from the spring of 2012 to the spring of 2015. Data for Paper II were collected from January to August 2015.

#### 3.4.1 Outcome measures

The main outcome measures used in this thesis related to disease severity, gait, balance, and mobility are presented in Table 2.

The motor section of the Unified Parkinson's Disease Rating Scale part III (UPDRS-motor) assesses motor symptom relative to tremor, rigidity, bradykinesia, postural instability and gait. The UPDRS-motor contains a 27 items scale which are scored, and them summarized in a

**Table 2.** Outcome measures

Instrument/ method	Domain	Variables	Paper I	Paper II	Paper III	Thesis
UPDRS- motor	Level of PD motor symptoms		x	x	x	
H&Y scale	Disability in functional mobility		x	x	x	
Electronic walkway	Pace, rhythm, variability, asymmetry and postural control domains of PD-gait (mean gait characteristics, gait variability and gait asymmetry)	Velocity (cm/s)		x		x
		Cadence (steps/min)		x		x
		Step length (cm)	x	x	x	x
		Stride length (cm)	x			
		Step width (cm)		x	x	x
		Step time (ms)	x	x	x	x
		Stride time (ms)	x			
		Swing time (ms)	x	x	x	x
		Stance time (ms)	x	x	x	x
		Double supt. time (ms)	x			x
		Single supt. time (ms)	x			
		Step velocity (cm/s)		x	x	x
		Stride velocity (cm/s)	x			
Mini- BESTest	Dynamic balance	Anticipatory postural adjustments	x			
		Postural responses				
		Sensory orientation				
		Stability in gait				
Timed Up and Go	Functional mobility	Time (s) for task completion	x			

Abbreviations: PD = Parkinson's disease; H&Y = Hoehn & Yahr; UPDRS motor = the motor section of the Unified Parkinson's Disease Rating Scale, part III; Mini-BESTest = Mini Balance Evaluation Systems Test.

total score (maximum score of 108 points). A higher score indicates more severe symptoms [137]. The UPDRS-motor assessment has been deemed valid and reliable [138]. From the UPDRS-motor assessment, disease severity of PD was classified according to the original H&Y staging scale [139]. Disease duration (number of years since diagnosis) and daily levodopa equivalency dose (LEDD) [140] were assessed as additional proxies for disease severity.

The Mini Mental State Examination score was used as a screening tool for inclusion, where individuals were excluded if they scored <24 points [131].

Gait was evaluated using a pressure sensitive electronic walkway (GAITRite, CIR Systems Inc., Clifton, NJ, USA). The mat contains pressure sensitive sensors arranged in a grid-like pattern, and a person's foot falls are registered as the individual walks over the mat forming the basis for the calculated spatiotemporal gait variables. The GAITRite system has been found to be valid and reliable when measuring gait in individuals with PD [141, 142].

Dynamic balance was evaluated using the Mini Balance Evaluation Systems Test (Mini-BESTest) which contains 14 items on 4 areas of dynamic balance: anticipatory postural adjustments, reactive postural control, sensory orientation and dynamic gait. Each item is scored from 0-2 (0=unable, 2=normal) [143] with a maximum score of 28 points [144]. The Mini-BESTest has been shown to be reliable and valid for older adults with mild to moderate PD [145-147].

Functional mobility was assessed using the Timed Up and Go test (TUG) which measures the time taken for a subject to rise from a chair, walk a distance of 3 meters, turn 180 degrees, walk back to the chair and sit down again. The subject wears shoes and uses his or hers walking aid [148]. Participants made a practice run prior to testing, and one valid attempt of the TUG was recorded. The TUG has been found reproducible and valid for individuals with PD [149].

### **3.4.2 Procedures**

For the BETA-PD study (Paper I and III) participants were interviewed regarding their current health status and general activity level prior to testing. Additionally, the Sunnaas-cohort (Paper II) was screened by a physician in rehabilitation medicine who cleared the participants

for testing. Participants used their regular medication and were tested in their medication “on” phase at the same time of day for each evaluations.

Data regarding disease severity, gait, functional balance and mobility for the BETA-PD study were collected at baseline, immediately after the training intervention (10 weeks), 6 months after the intervention had ended, and 12 months after the intervention had ended. This was done in a randomized order. Data for Paper II (Motion Lab, Sunnaas) were collected on two separate days no more than one week apart at the same time of day. The mean (SD) number of days between tests was 1.6 (1.4) for the PD group, and 3.3 (2.8) for the control group.

Spatiotemporal gait variables were sampled on a 10 meter pressure sensor mat (active zone 8.3 meters), where participants walked back and forth. After one completed run across the mat, the participant would stop and turn, before settling at a predefined starting point ready for a new run. To facilitate a steady state walking pace, a distance of 2.5 meters was available on each side of the mat for acceleration and deceleration (see Figure 13).



Figure 13. Test set-up for collecting gait variables at the Balance and Motion Laboratory, Karolinska, Sweden.

Paper I, II and III included gait data recorded at self-selected normal- and fast walking facilitated by giving the following instructions: “Walk at your normal comfortable pace” and “Walk as fast as you can, in a safe manner, without running”. The self-selected normal speed condition was always recorded first, and the fast walking conditions second. In study II a slow walking condition was added, where participants were instructed to: “Walk slowly, like you would do if you were taking a slow stroll without a specific place to go”. The slow walking trials were recorded after the normal and fast, and the same sequence was used for the second test session. Six valid trials were recorded for each walking condition, and the possibility of rest was given between walks.

### 3.6 Data processing and calculations

All gait data was organized in Access (Access®, Microsoft, USA). All recorded trials were quality assured with regards to correct labelling of left and right foot falls and full foot contact on the pressure sensor mat for included steps. Further, all trials for one speed condition and test point were compared and scrutinized with regards to outliers that could denote that the subject had used one or two trials in the beginning to get accustomed to the walking condition, or had experienced fatigue during the last runs. Those trials deemed uncharacteristic or atypical were discussed with a senior researcher before the decision was made to either include or exclude the specific trial. Specified gait variable values over multiple steps trials and test points for each individual were then exported to Excel (Excel®, Microsoft, USA) for further calculations.

In Paper I, GVI scores were calculated for all participants (n=100) based on the Excel macro (Excel®, Microsoft, USA) made available as supplemental material by Gouelle et al. [72]. The calculations include multiple individual step and stride values for nine spatiotemporal variables (see Table 2). The GVI calculation procedure considers left and right foot falls separately for any given gait variable  $i$  ( $V_i$ ) within any given trial  $j$  ( $V_{ij}$ ). The  $V_{ij}$  trial mean is given the dimensionless value of 100 percent, and the absolute difference between an individual  $V_{ij}$  step or stride value and the mean is expressed in absolute percentage points. The grand  $V_i$  mean and SD of the absolute difference values over all steps/ strides and trials is then computed. This result in nine mean values representing the magnitude of the variability, and nine SD values that provides an addition measure of consistency, giving 18 (absolute difference) values ( $v_n$ ) for each limb [79]. These 18 values are additionally adjusted in accordance to weighting coefficients ( $c_n$ ) determined by Gouelle et al [72] and for any given subject ( $\alpha$ ) the sum of the products was calculated as follows:

$$s^\alpha = \sum_1^{18} (v_n \cdot c_n) \quad (1)$$

The distance between a subject sum score and the mean sum score of the control group ( $\sigma$ ) is determined:

$$d^{\alpha,\sigma} = \|s^\alpha - s^\sigma\| \quad (2)$$

The natural logarithm of this difference is computed to give a raw index score:

$$GVI_{raw}^{\alpha} = \ln(d^{\alpha,\sigma}) \quad (3)$$

The subject's z-score is determined:

$$zGVI_{raw}^{\alpha} = \frac{GVI_{raw}^{\alpha} - \text{Mean}(GVI_{raw}^{\alpha})}{SD(GVI_{raw}^{\alpha})} \quad (4)$$

The z-score is used to determine the GVI score as follows:

$$GVI^{\alpha} = 100 - 10 \times zGVI_{raw}^{\alpha} \quad (5)$$

The overall GVI is the mean of right and left side.

In paper II and III the level of gait variability was calculated as described by Galna et al. [75] for 6 spatiotemporal variables (see Table 2). The calculation considers the combined standard deviation (SD) of left and right steps which was determined by taking the square root of the within-subject variance of the left and right steps as follows:

$$SD_{Left \& Right} = \sqrt{\frac{(\text{Variance}_{Left \text{ steps}} + \text{Variance}_{Right \text{ steps}})}{2}} \quad (1)$$

The  $SD_{Left \& Right}$  was calculated based on 10, 20, 30, 40 and 50 included steps, for each gait speed condition, for each test day in paper II. All estimates were based on 50 steps in paper III.

Gait asymmetry was estimated for swing time, step time stance time and step length by calculating the absolute difference between the left and right side (paper III).

### 3.5 Training intervention

The training intervention was implemented over 10 weeks, three times per week, where each session lasted 60 minutes. The one hour session started with a 5 min warm up, 50 min of highly challenging exercise, and 5 min cool down. The training was performed in smaller groups of 4 -7 participants and was led by two physiotherapists who had undergone specific training in the theoretical and practical framework of the HiBalance program.

A framework based on motor-learning principles such as specificity, progressive overload and variation was used as a foundation for the application and adaptation of exercises to the



participants' abilities. Specificity was ensured by training targeting four balance components associated with balance and gait constraints for individuals with PD. These are sensory integration, anticipatory adjustments, motor agility, and stability limits [121].

To ensure adequate progression and variation the following framework for the implementation of the training program was constructed (see Table 3). The program was divided into three blocks, where in block A (week 1-2) the participants were introduced to exercises within each balance component separately. In this period there was an emphasis on movement quality, the objective of the exercises, and task specificity. During block B (week 3-6) the level of difficulty and task variation for each balance components was increased.

Additionally, dual task-exercises were introduced, adding either a cognitive or a secondary motor task in conjunction with the balance exercise. In the last four weeks of the program, block C, variation in tasks and difficulty was further increased by combining exercises for all balance components. Additionally, the secondary motor and cognitive tasks were used interchangeably in the same session, and dual task exercises were used for longer parts of the session. Goal-oriented oral feedback was given with the intention of being as simple as possible and be externally oriented to promote movement automaticity.

To further optimise challenges to individual capacities, the physiotherapists individually adjusted the difficulty level of the exercises for each balance component. For *sensory*

**Table 3.** HiBalance 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.

<i>Blocks</i>	<i>Week</i>	<i>Balance components</i>	<i>Dual-task</i>
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

*integration* progressive overload was ensured by increasing surface unevenness and restricting the field of vision which could be achieved by i.e carrying an object. For anticipatory postural adjustments (*APAs*) increased movement amplitude and velocity was utilised. Targeting progression of *motor agility* the trainers would increase gait complexity through altering velocity or step patterns, and using verbal commands to facilitate planned and unplanned shifts between different gait conditions, reciprocal movements, and walking directions. For the planned condition the participant would be aware of the upcoming sequences or tasks, whereas they were not in the unplanned situation. With regards to *stability limits* strategies included changing the area, or condition, of the base of support and increasing leaning movement amplitude. Especially exercises related to motor agility and sensory integration incorporated stepping and walking, where walking direction was varied throughout. Fast walking was used as an individual exercise.

After the training period the participants in the intervention group were given physical activity on prescription, where the recommended activity was based on their interests, needs and abilities. The prescribed physical activity was followed up via a phone-call after three months by the physiotherapist asking the participants questions regarding compliance, performed activity type, frequency, and duration.

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. The control group where offered the opportunity to undertake the HiBalance program at the completion of the study period.

### **3.7 Statistical analysis**

All statistical analyses were conducted using SPSS 21.0 (Paper I and II) and SPSS 23.0 (paper III) (IBM SPSS Inc., Chicago, IL, USA). Significance level was set to  $p < 0.05$ .

Table 4 gives an overview of the descriptive and statistical methods used in this thesis across Papers I-III.

As part of this thesis, mean (SD) gait characteristics of the combined Norwegian and Swedish PD-cohorts are presented. Also, Cohen's *d* and Hedge's *g* were used to estimate standardized mean differences of mean characteristics, together with level of gait variability and asymmetry, relative to healthy peers.

**Table 4.** Statistical methods used.

Statistics applied	Paper I	Paper II	Paper III	Thesis
Mean	x	x	x	x
Standard deviation	x	x	x	x
95% confidence interval	x	x	x	x
Median	x	x	x	x
Interquartile range	x	x	x	x
Frequency (n)	x			x
Log transformation		x	x	x
Independent t-test	x			x
Paired t-test	x			
Cohen's d effect size	x			x
Hedges' g effect size				x
Pearson's correlation coefficient	x			
ROC curves	x			
Two-way mixed ANOVA		x		
Standard error of measurement		x		
Smallest real difference		x		
Intraclass correlation coefficient		x		
Linear mixed models analysis			x	

Abbreviations: ROC = Receiver Operating Characteristics

**Paper I:** The GVI total group mean (standard deviation) and GVI sub-groups H&Y 2 and 3 were determined. Despite bilateral involvement of symptoms in H&Y stage 2 and 3 there are substantial asymmetry of clinical symptoms from disease onset. Therefore both the overall GVI and the GVI score for the most affected side (mean, SD) were calculated.

Independent samples t-test was used to compare sub-groups H&Y 2 and 3 both with regards to overall GVI and GVI for most affected side. Further, paired samples t-test was used to determine if there was a significant difference between the overall and most affected side GVI scores.

Further, independent samples t-test and Cohen's d effect size were used to investigate if there were significant group mean differences between the PD cohort and the embedded control values for the 9 mean and 9 SD absolute difference values ( $v_n$ ). This would evaluate potential group differences in levels of gait variability for the individual gait variables that go into the GVI calculations.

The Pearson's correlation coefficient was used to investigate the correlation between GVI and the Mini-BESTest and the TUG. Due to a heteroscedastic distribution in the data, an inverse transformation was performed on the TUG scores ( $1/\text{TUG}$ ). The strength of all correlations were interpreted according to Munro (p. 358 [150]); 0.00-0.25 = little if any correlation; 0.26-0.49 = low correlation; 0.50-0.69 = moderate correlation; 0.70-0.89 = high correlation; 0.90-1.00 = very high correlation. Further, the ability of the GVI to distinguish between H&Y 2 and 3 was investigated using receiver operating characteristics (ROC) curve analysis. The strength of discrimination was interpreted according to Hosmer and Lemeshow (p. 473); 0.5 = no discrimination; 0.7-0.79 = acceptable; 0.8-0.89 = excellent; 0.9-1.0 = outstanding.

**Paper II:** Differences in mean gait and gait variability values between individuals with PD and healthy older adults across the slow, normal and fast gait speed conditions were investigated using a two way mixed ANOVA.

To establish to what degree gait variability measures were repeatable over two test occasions the absolute and relative reliability were determined based on  $SD_{\text{Left \& Right}}$  calculated from 10 and up to 50 included steps, for each gait speed condition.

Absolute reliability was assessed by estimating the measurement error for repeated measurements ( $S_w$ ), also termed the standard error of measurement (SEM) [135]. The latter term is used in this thesis. Firstly the mean within-subject variance ( $S_w^2$ ) was calculated as follows:

$$S_w^2 = \frac{1}{n} \cdot \sum_{i=1}^n S_{wi}^2$$

The SEM was computed as the square root of the mean within-subject variance as follows:

$$SEM = \sqrt{S_w^2}$$

The difference between a subject's measurement and the true value would be expected to be less than 1.96 SEM for 95% of observations [128].

Another useful way of presenting measurement error is estimating the smallest real difference (SRD) as:  $\sqrt{2} \times 1.96 \text{ SEM}$  or 2.77 SEM. The difference between two measurements for the same subject is expected to be less than 2.77 SEM for 95% of pairs of observations [128]. The

SEM was expressed both in absolute terms and as a percentage of the group mean (relative SEM<sub>%</sub>) to allow for comparisons across spatial and temporal estimates. The SRD was reported in absolute terms only.

Relative reliability was assessed using the intraclass correlation coefficient with a 2-way random effects model (ICC<sub>2.1</sub>). These were interpreted according to McDowell [151]: ICC <0.40 = poor, 0.40-0.59 = moderate, 0.60-0.74 = good, and >0.75 = excellent.

**Paper III:** To investigate the immediate and long-term effects of the HiBalance program on gait variables during normal and fast walking, a linear mixed model with a random intercept and random effect of time was used. The fixed effects of the model were group allocation and the interaction between group and time to estimate the time development between the training group and the control group.

## 4. Results

### 4.1 Summary of overall findings

Spatiotemporal gait variables were the main outcome in all three studies where mean gait characteristics and level of gait variability (paper I-III) and asymmetry (paper III) were estimated.

#### 4.1.1 Mean gait characteristics

A summary of the mean gait characteristics for the combined Swedish and Norwegian PD-cohorts for normal and fast gait speed, and the Norwegian PD-cohort for slow gait speed, relative to healthy older adults are presented in Table 8.

When comparing the Swedish and Norwegian PD-cohorts at normal and fast gait speeds, it could be seen that the Norwegian cohort walked slightly faster (normal speed mean difference: 8.6 cm/s, 95% CI [0.5-16.7],  $p=0.04$ ; fast speed mean difference: 11.9 cm/s, 95% CI [0.1-23.7],  $p=0.05$ ). This was due to taking longer steps (normal speed mean difference: 3 cm, 95% CI [-0.8-6.8],  $p=0.12$ ; fast speed mean difference: 3.6 cm, 95% CI [-1.6-8.8],  $p=0.17$ ) with a non-significant higher cadence (normal speed mean difference = 2.7 steps/min, 95% CI [-2.9-5.1],  $p=0.59$ ; fast speed mean difference: 4.3 steps/min, 95% CI [-0.8-9.4],  $p=0.10$ ). Apart from gait velocity, none of the mean gait variables was significantly different between the Norwegian and Swedish PD-cohorts for either speed condition confirming their comparability.

It can be seen that individuals with PD walk significantly slower than their healthy peers across all speed conditions, due to shorter step lengths and not lower cadence. Further, for the normal and fast gait speed condition only, individuals with PD had a significantly longer stance portion of the gait cycle, which was due to longer time spent in double support across speeds. Additionally, for normal speed only, significantly shorter swing times were seen.

**Table 5:** Group mean and standard deviation for investigated gait variables and gait variability variables for all speed conditions.

Gait Variables	<u>Slow gait speed</u>			<u>Normal gait speed</u>			<u>Fast gait speed</u>		
	PD <sub>(Nor)</sub> (n=29)	HOA <sub>(Nor)</sub> (n=25)	95% CI and p-value	PD <sub>(Tot)</sub> (n=129)	HOA <sub>(Nor)</sub> (n=25)	95% CI and p-value	PD <sub>(Tot)</sub> (n=127)	HOA <sub>(Nor)</sub> (n=25)	95% CI and p-value
Velocity (cm/s)	75.8 (21.0)	90.6 (16.6)	[4.3, 25.3] <0.01	118.9 (20)	145.6 (18.6)	[-34.8,-18.6] <0.001	157.9 (28.5)	187.1 (23.0)	[-41.2,-17.2] <0.001
Cadence (steps/min)	85.6 (14.9)	88.8 (11.1)	[-4.2, 10.5] 0.39	113.2 (9.7)	116.8 (10.3)	[-7.8, 0.6] 0.09	131.5 (12.3)	135.1 (12.1)	[-8.9, 1.7] 0.18
Step length (cm)	52.5 (10.0)	60.8 (6.1)	[-12.9, -3.8] <0.001	63.1 (8.9)	75.0 (7.3)	[-15.6, -8.2] <0.001	72.0 (10.7)	83.5 (7.9)	[-16.0, -7.0] <0.001
Step width (cm)	9.9 (4.5)	8.1 (2.6)	[-3.8, 0.3] 0.10	8.4 (3.0)	8.2 (2.5)	[-1.1, 1.5] 0.75	8.6 (3.0)	8.5 (2.4)	[-1.2, 1.4] 0.88
Step time (ms)	725 (149)	689 (99)	[-106.8, 33.9] 0.30	534 (48)	518 (44)	[-4.4, 36.5] 0.12	460 (46)	448 (40)	[-7.5, 31.5] 0.23
Stance time (ms)	974 (228)	898 (148)	[-183.7, 31.2] 0.16	687 (72)	640 (66)	[16.3, 77.7] <0.01	573 (70)	537 (56)	[6.7, 65.4] 0.02
Swing time (ms)	477 (85)	483 (53)	[-33.9, 44.2] 0.76	381 (36)	397 (27)	[-31.0, -1.0] 0.04	350 (33)	359 (28)	[-22.9, 4.9] 0.20
D.Supp. time (ms)	497 (169)	415 (101)	[-159,-3.8] 0.04	307 (64)	242 (46)	[38.4,-91.6] <0.001	225 (58)	178 (36)	[23.2, 70.8] <0.001

Abbreviations: PD<sub>(Nor)</sub> = Norwegian PD-cohort; HOA<sub>(Nor)</sub> = Norwegian healthy older adults; PD<sub>(Tot)</sub> = Combined Swedish and Norwegian PD-cohort; Dbl. Supp. time = Double Support time.

#### 4.1.2 Level of gait variability

Gait variability estimates for individuals with PD were compared to equivalent values for healthy adults (Paper I) and healthy older adults (Paper II). As the investigation in Paper I was done on gait data sampled at normal gait speed only, the results presented in Figure 10 are relative to self-selected normal gait. This overview indicates that individuals with PD show higher levels of gait variability as compared to controls for multiple spatiotemporal gait variables. However, the PD-gait variables showing the largest differences (effect size  $> 0.8$ ) from controls were firstly swing time variability, and this was relative to both healthy adults and healthy older adults. In addition, step and stride length variability and single support time variability was markedly higher in PD-gait as compared to healthy adults, whereas step time variability was markedly higher as compared to healthy older adults (see Figure 10).

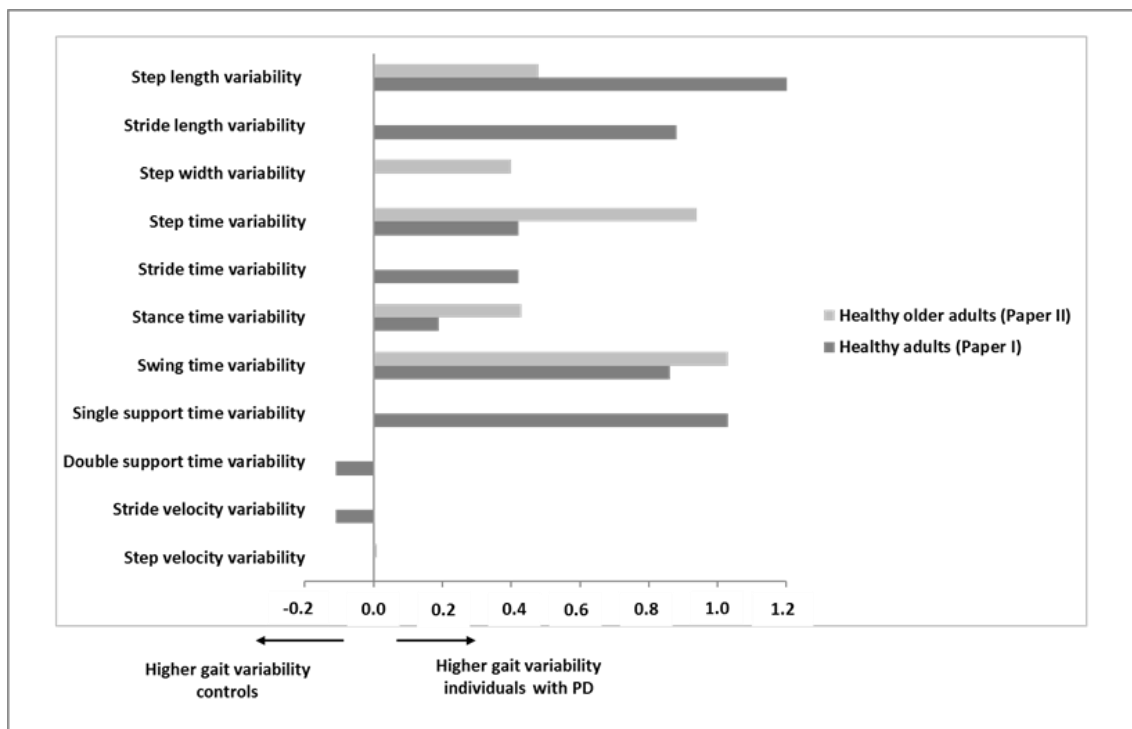
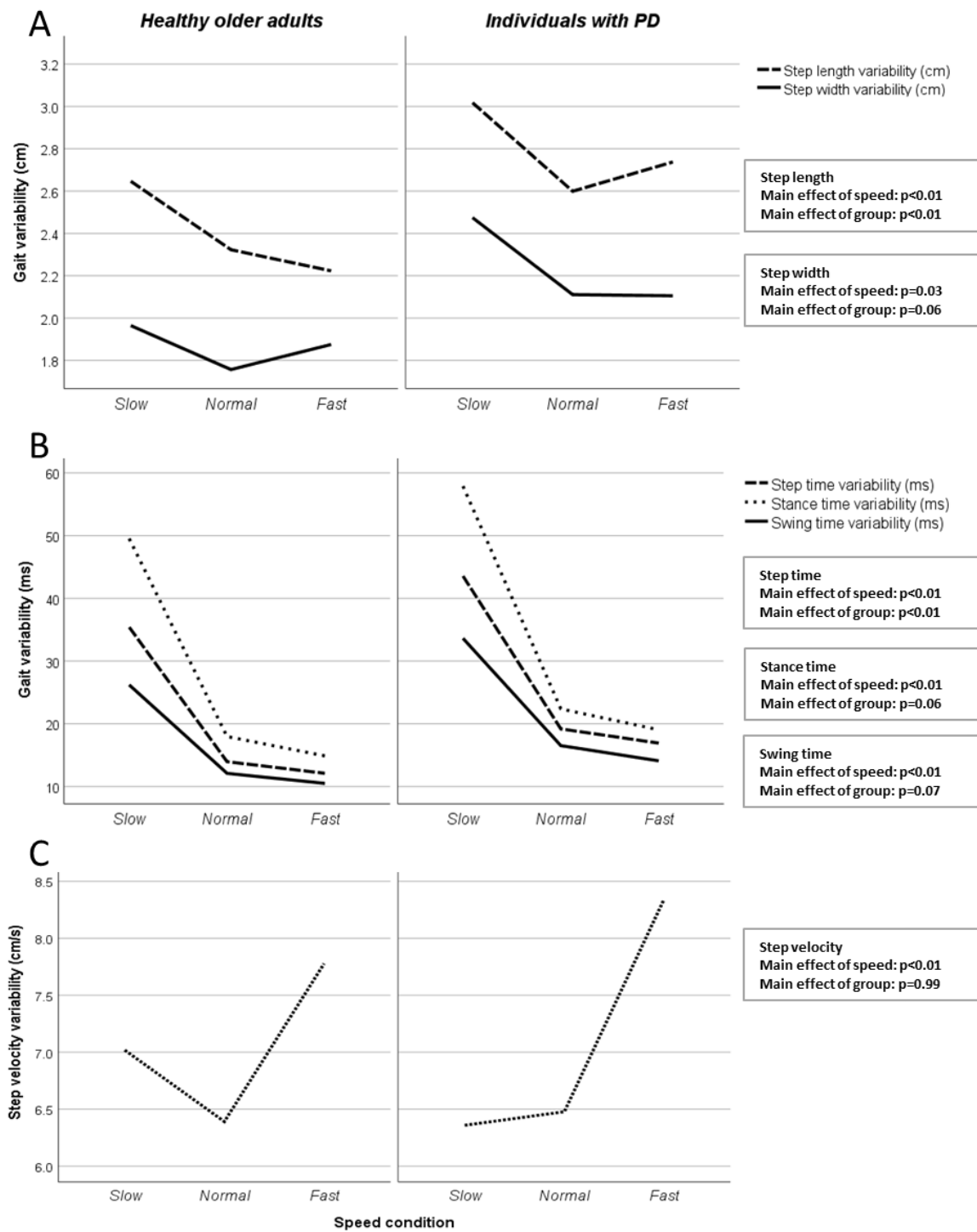


Figure 14: The mean standardized difference (effect size) in mean gait variability between individuals with PD ( $n=100$  in paper I,  $n=29$  in paper II) and healthy adults ( $n=246$  in paper I) and healthy older adults ( $n=25$  in paper II) for self-selected normal gait speed. Effect size estimates are based on  $d_{\text{cohen}}$  (non-parametric effect size). Abbreviations: PD = Parkinson's disease.



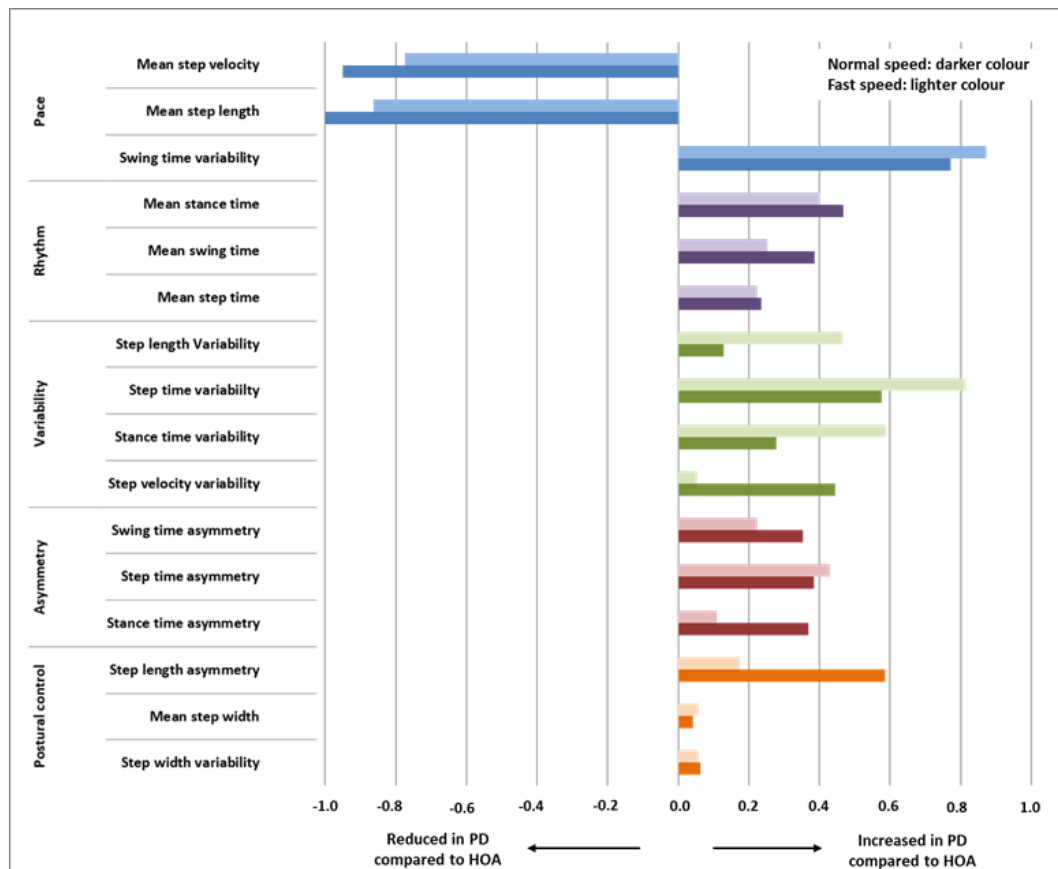
Further, a significant main effect of speed on gait variability was seen for all variables both for individuals with PD and for healthy older adults (see Figure 15). The mean estimates showed that the levels of gait variability was higher for the slow speed condition compared to normal and fast, and this was more marked for the temporal variables, in both groups (see Figure 15 B). The only exception to this pattern was seen for step velocity variability, where highest levels of variability was seen for the fast gait speed condition (see Figure 15 C). Also, individuals with PD showed significantly higher variability in step length and step time ( $p < 0.01$ ) relative to healthy older adults over the speed conditions (see Figure 15 A and B). It is worth noting that step width variability as well as stance- and swing time variability were close to significance level ( $p = 0.06$  and  $0.07$ ).



**Figure 15 A, B, and C:** Level of gait variability for slow, normal and fast gait in individuals with PD and healthy older adults. A: Spatial variables, B: temporal variables and C: step velocity. Abbreviations: PD = Parkinson's disease.

### 4.1.3 Effect of PD on domains of gait

Relative to domains of gait, it was of interest to compare differences in gait variables between individuals with PD and healthy older adults, both for normal and fast speed (Figure 13). The results show that the largest differences (effect sizes  $> 0.8$ ) were seen in the pace domain of gait (Figure 13, blue columns) for step velocity, step length and swing time variability. Small to moderate differences (effect sizes 0.2-0.6) were seen for the variability domain (green columns), whereas the other domains showed small differences. Exceptions from this could be seen for step time variability during fast gait where standardized mean differences between groups were large, and step length asymmetry during normal walking which was moderate.



**Figure 16:** An illustration of the standardized mean difference (effect size) in gait variables for domains of gait between individuals with PD and healthy older adults ( $n=25$ ) for self-selected normal ( $n=129$ ) and fast ( $n=127$ ) gait speeds. Effect size estimates are based on  $d_{\text{cohen}}$  (non-parametric effect size). Abbreviations: PD = Parkinson's disease; HOA = healthy older adults.

## 4.2 Summary of papers

### Paper I

*Aim:* To explore the mean GVI score in a cohort of individuals with mild to moderate PD, and to investigate construct validity of the index for this population.

*Methods:* 100 (57 males) subjects with idiopathic PD, Hoehn &Yahr 2 (n=44) and 3, and  $\geq 60$  years were included. Data on disease severity (UPDRS, H&Y), dynamic balance (MiniBESTest), mobility (TUG) were collected. The GVI was calculated based on spatiotemporal gait parameters measured at self-selected speed using a pressure sensor mat (GAITRite).

*Results:* The estimated mean GVI for the PD cohort was found to be within half a standard deviation from the reference mean of healthy adults indicating only a small, though significant ( $p \leq 0.04$ ) increase in gait variability for the PD cohort. This was true for the total GVI (combined left and right side) which was 97.5 (SD 11.7) and for the most affected side GVI score of 94.5 (SD 10.6). The GVI scores showed low correlation with dynamic balance ( $r=0.33$ ,  $p < 0.01$ ) and mobility scores ( $r=0.42$ ,  $p < 0.01$ ), and lastly showed poor ability in distinguishing moderate from mild disease severity (AUC=0.53, SE=0.06,  $p=0.62$ ).

*Conclusions:* The mean GVI was similar to previously reported values for older adults, contrary to consistent reports of increased gait variability in PD compared to healthy peers. The validity of the GVI could not be confirmed for individuals with mild to moderate PD in its current form due to low associations with validated tests for functional balance and mobility and poor discriminatory ability. Future work should aim to establish which spatiotemporal variables are most informative regarding gait variability in individuals with PD.

## **Paper II**

*Aim:* to evaluate the effect of (1) gait speed and (2) pathology on test-retest reliability in individuals with PD as compared to healthy older adults, and (3) identify the optimal number of steps for acceptable levels of reliability at slow, normal and fast gait speed conditions.

*Methods:* 29 (14 males) subjects with idiopathic PD, Hoehn &Yahr 2 (n=18) and 3,  $\geq 60$  years, and 25 age matched HOA were included. Spatiotemporal gait data was collected (GAITRite) during slow, normal, and fast walking on two occasions no more than one week apart.

*Results:* The investigated gait variability variables showed lowest levels of measurement error when estimates were based on at least 40 steps, with little benefit seen when including up to 50 steps. This was true across gait speed conditions for healthy older adults, but only for normal and fast gait speeds for individuals with PD. For individuals with PD the level of measurement error did not stabilise for estimates of step length-, stance time-, and step velocity variability for the slow speed condition, despite basing the estimates on an increasingly higher number of steps. Due to increased homogeneity in the variability estimates intraclass correlation coefficients (ICC) were low for healthy older adults, except for step width variability. In the PD cohort ICCs were good to excellent (0.6-0.8) for temporal- and step width gait variability across speeds.

*Conclusion:* Healthy older adults demonstrated reliable gait variability estimates across all speeds, whereas individuals with PD were reliable at normal and fast gait speeds only. Estimates should be based on at least 40 steps. Step width variability was overall the most reliable variable across groups and speed conditions.

### Paper III

*Aim:* To evaluate immediate and long-term effects of highly challenging balance and gait training on pace-, rhythm-, variability-, asymmetry-, and postural control domains of gait for individuals with Parkinson's disease (PD).

*Methods:* 100 (56 males) subjects with idiopathic PD, Hoehn & Yahr 2 (n=44) and 3, and  $\geq 60$  years were included. The training group (n=51) partook in 10 weeks of balance and gait training. Gait variables during normal and fast gait speed were collected at baseline, the completion of training, and at 6 and 12 months post intervention, using a pressure-sensitive mat (GAITRite). Group differences over all time points were investigated using a linear mixed model.

*Results:* Relative to the **pace domain** of the PD gait model the training group increased their mean step velocity immediately after the training by 8.2 cm/s ( $p=0.04$ ) for normal gait speed, and by 10.8 cm/s ( $p<0.01$ ) for fast gait speed, as compared to controls. This was achieved through increased step length (normal: 3.0 cm,  $p=0.05$ ; fast: 2.3 cm,  $p=0.05$ ). Swing time variability was also significantly reduced in the training group (-2.5 ms,  $p=0.02$ ) for fast gait speed. In the **rhythm domain** the training group significantly reduced mean stance time immediately after the training period (normal: -24.3 ms,  $p=0.01$ , fast: -29.6 ms,  $p=0.02$ ). This was mainly due to less time spent in double support (normal: -26.7 ms,  $p<0.01$ ; fast: -22.0 ms,  $p=0.04$ ), but also due to reduced swing time during fast gait speed only (-8.7 ms,  $p=0.04$ ). Mean step time was also significantly reduced for the fast speed condition (-19.3 ms,  $p=0.02$ ). Relative to the **variability domain** the training group showed significantly reduced step time variability (-2.8 ms,  $p=0.02$ ) and stance time variability (-3.9 ms,  $p=0.02$ ) for fast gait speed immediately after the intervention. Variability in step velocity and step length was similar in both groups. All variables associated with the **asymmetry and postural control** domains showed no significant differences between groups. None of the significant group differences were maintained at 6 and 12 month follow-ups.

*Conclusions:* Highly challenging balance and gait training improved pace, rhythm and variability aspects of PD gait in the short-term, but effects are not retained long-term.

## **5. General discussion**

### **5.1 Discussion of the main findings**

#### **5.1.1 Overall gait characteristics**

There is extensive reports documenting decreased gait speed in individuals with PD relative to healthy peers for self-selected normal gait [45], and this characteristic is further confirmed by the findings of this thesis. On the other hand, testing PD-gait relative to healthy controls during slow and fast walking is not so common, and the findings of this thesis showed that individuals with PD also walked slower than their healthy peers across speed conditions. This is in support of Morris et al. [152], who demonstrated decreased gait speed for individuals with PD relative to healthy controls for slow, normal and fast walking.

The slower gait speeds seen for the PD-cohort relative to healthy older adults in this thesis was due to them taking shorter steps, and not as a result of lower cadence (step frequency). This was true for all speed conditions (see Table 8). The shorter steps distinctive of parkinsonian gait is related to both the hypokinetic and bradykinetic movement pattern seen with the disease, resulting in slow movements with reduced amplitude [36]. However, reduced scaling of steps (hypokinesia) may be a more consistent contributor to slowed gait than slower steps [45]. This is supported by Morris et al. [152, 153] who examined the ability of individuals with PD to modulate cadence over slow to normal and normal to fast gait speed conditions. Their findings suggested that cadence control was unaffected throughout the entire gait speed range in PD, and it was concluded that regulation of stride length was the fundamental problem in gait hypokinesia. These findings are further supported by this thesis.

Also, the PD-cohort had significantly longer double support times as compared to healthy older adults, across all speed conditions (see Table 8). The double support phase of stance is typically found to be longer in individuals with PD [154], and it has been suggested that longer time spent in double support is a compensatory strategy to facilitate re-stabilisation after taking a step [50] reflecting decreased balance during gait. It can be seen that the mean double support time decreases in both groups when going from normal to fast gait, as can be expected with higher gait speeds (see Table 8).

### **5.1.2 Gait variability – effect of PD-pathology and age**

The results of this thesis showed higher levels of gait variability for individuals with PD relative to healthy controls in multiple spatiotemporal variables during normal self-selected walking (see Figure 10). Level of gait variability likely reflect disruptions in intrinsic motor or postural control during walking resulting from age- or disease-related decline in the central and peripheral nervous systems [69, 155]. The following section will discuss those gait variability variables that were most markedly different from healthy controls.

Firstly, swing time variability was consistently higher in individuals with PD as compared to healthy adults (Paper I) and healthy older adults (Paper II), and the mean difference between groups was considered large (effects sizes  $> 0.8$ ). This was also the case for single support time variability which was investigated in Paper I only. As previously mentioned, swing time and single support time are highly correlated, as the two events happen simultaneously, but on opposite legs interchangeably. It therefore stands to reason that the two variables show similar levels of variability in PD-gait as compared to controls.

In supporting of our finding, previous investigations have demonstrated higher levels of variability in swing time during normal walking in similar PD-cohorts as compared to healthy peers [51, 55]. This highlights that individuals with PD show decreased consistency in the time spent in single limb stance while swinging the opposite leg through to initiate the next heel strike, suggesting decreased motor control and stability during this demanding phase of gait. Higher swing time variability was also identified in newly diagnosed individuals [54, 78] suggesting it may be an early marker of gait deterioration at the onset of motor-symptoms. Viewing the effect of age relative to PD-pathology, our findings propose that this gait variable is more influenced by PD pathology rather than age. Consistently large differences were seen between the PD cohort and controls regardless if the PD group were compared to healthy adults (Paper I) or healthy older adults (Paper II). This is supported by Almarwani et al. [65] who found no significant difference in level of swing time variability (SD) between younger and older adults during normal walking.

Other variables showing large mean standardized differences relative to healthy controls were stride and step length variability when compared to healthy adults in Paper I. The variability in steps in the anterior-posterior direction has been shown to be closely linked to fluctuations in self-selected walking speed [45, 156]. Interestingly, the difference was reduced to moderate when compared to healthy older adults in Paper II (effect size = 0.5), which would suggest an



effect of age as well as pathology for this gait variable. It has been shown that levels of variability increase significantly in step length between younger and older adults [65], signifying that with increasing age there is a natural decline in the consistency of spatially controlling stepping during continuous walking. This could be related to the reduction in muscle power, loss of distal proprioception and vision seen with age [157, 158]. In addition, it has been suggested that step length is controlled by the cortico-basal ganglia circuit [159], and there is evidence that gait speed is specifically linked to the frontoparietal control network, which is critically involved in executive function [160]. Decreased executive function has been associated with decreased gait speed due to decreased stride length, together with increased stride length variability in elderly with mild cognitive impairment [161]. These structures are further impacted by PD, both due to the functional effects of dopamine depletion in the cortico-basal ganglia-thalamocortical loop, but also due to dysfunction in the cholinergic systems which impacts executive and attentional functions in individuals with PD [162].

However, for step time variability the picture was the exact opposite. The difference in level of variability between individuals with PD and controls increased from moderate to large relative to adults and older adults (see Figure 10). This would imply that the motor control of step time improves with age. However, other reports do not support this finding. Decker et al. [173] showed a significant difference in step time variability between younger and older adults when walking at normal gait speed on a treadmill, whereas Almarwani et al. [65] found no differences between groups for this gait variable.

However, it is interesting to consider if there with age is a shift from spatially to more temporal control of stepping, where healthy older adults become more reliant on regulating the timing of stepping due to mild deficits in executive function affecting spatial control. Lo et al. [160] investigated neural networks associated with gait variability, and showed that stride time variability was primarily linked to the dorsal attention network. Further, lower more automated brainstem and spinal cord pathways are also thought to be involved in the control of step timing [160]. It is therefore possible that the attention network was not so affected in this convenience sample of healthy older adults, rendering this control strategy open to this cohort. However, individuals with PD show significant deficits in both attention [162] and in the lower automated pathways [45], and this supports why PD-pathology results in marked increased levels of variability in this gait parameter. However, the same pattern

could be seen for all investigated temporal variability variables, suggesting that temporal control of gait is reliant on functional attention networks and the lower automated pathways.

Relative to the gait model developed by Lord et al. (see Figure 4) it is interesting to consider that three of the variables associated with the variability domain (step length-, step time- and stance time variability) were identified as showing moderate to high levels of variability in individuals with PD as compared to controls in this thesis. This supports the validity of the gait model and the variability variables that were found to be associated with the variability domain.

### **5.1.3 Gait variability – effect of gait speed**

All of the investigated gait variability variables in Paper II showed a significant main effect of speed over the three speed conditions. Further, it was seen that the estimated levels of gait variability was generally higher for the slow speed condition as compared to normal and fast, both in individuals with PD and for healthy older adults (see Figure 11 A-B), and that this finding was much more pronounced for the temporal as compared to spatial gait variables.

There is a sparsity of reports that have looked at the effect of gait speed on gait variability for individuals with PD, and to the best of our knowledge only two studies are relevant using similar cohorts and conditions as this thesis [51, 163]. Frenkel-Toledo et al. [51] showed a significant difference in stride time variability for comfortable walking speed as compared to slow walking, both for individuals with PD and healthy controls. However, no significant difference was found for swing time variability over the two speed conditions in either groups. The latter finding contrasts our result of higher swing time variability for the slow gait speed condition as compared to normal and fast, both for individuals with PD and healthy older adults (see Figure 11B).

A closer inspection revealed that the Norwegian PD cohort (paper II) and the healthy older adults in this thesis walked at a higher self-selected normal gait speed (PD: 1.26 m/s, HOA: 1.46 m/s) relative to the participants in the Frenkel-Toledo et al. study (PD: 1.12 m/s, HOA: 1.24 m/s). Additionally, the participants in this study walked markedly slower for the slow walking condition (PD: 0.76 m/s versus 0.93 m/s, HOA: 0.91 m/s versus 1.05 m/s). It can therefore be postulated that the participants in the Frenkel-Toledo et al. study did not walk sufficiently slow, and over a sufficient range, to elicit the marked increase in swing time variability seen in this thesis for either group. Though only investigating levels of gait

variability for healthy older adults, the results reported by Almarwani et al. [65] further supports the findings of this thesis. The authors reported higher levels of swing time variability, as well as for step-, stance-, and double support time, when healthy older adults walked slowly as compared to usual and fast, mirroring the results of this thesis by showing the same pattern of change in variability over gait speed conditions for temporal variables. The higher levels of gait variability seen for slow walking reflects that it is more challenging to walk slowly in a consistent manner, and this is related to the higher postural control demands with longer time being in single limb stance for this gait condition.

Whereas the previous investigation reported on differences in gait variability between normal and slow walking, Bryant et al. [163] investigated change in levels of gait variability between normal and fast walking for individuals with PD. They reported that walking fast significantly decreased the level of variability in stride length and stride velocity, whereas step time and double support time remained unchanged. The latter finding is supported by the results of this thesis where little change was seen in temporal gait variability between the normal and fast walking condition (see Figure 11B).

However, our results showed increased variability for step velocity with fast walking (see Figure 11C), whereas Bryant et al. [163] reported a lowering of the variability in stride velocity for this speed condition. Due to limited information in the report by Bryant et al. regarding the range of gait speeds seen in their PD-cohort, as well as the methods used for estimating level of gait variability, direct comparisons on the results of their study and this thesis are difficult. However, it can be seen that Bryant et al. reported level of variability in percent, suggesting the use of the CoV, whereas this thesis reported the level of variability as SD. It has been pointed out that the CoV is sensitive to the scale [72], as the SD is seen relative the mean of the variable. To exemplify why this could be relevant in explaining these conflicting findings consider the following: Two individuals show the same level of step velocity variability as indicated by a SD of 6.5 cm/s. However, one of the subjects walk with a mean step velocity of 120 cm/s, and the other 130 cm/s. The CoV of the first individual is 5.4% and the other 5.0% showing how with increasing gait speed the CoV lowers. It could therefore be suggested that a potential increase in step velocity SD for the fast walking condition, could have been masked by the resultant higher stride velocity in the Bryant et al. study, resulting in a lower CoV. For future studies it is important to be aware of these aspects when investigating level of gait variability over different gait speeds.

#### **5.1.4 Low validity of the GVI - potential issues**

It was the finding of Paper I that in a population of older individuals with mild to moderate PD, the mean GVI depicted only slightly elevated levels of total gait variability relative to healthy adults. In addition, when comparing our results to published GVI values for older adults ranging from frail to well-functioning [39], these were similar. This would imply similar levels of gait variability for individuals with PD to healthy older adults, and thereby poorly reflecting the higher levels of gait variability seen in several of the individual spatiotemporal variables that go into the sum score of the GVI. The index therefore appear unable to accurately portray level of gait variability in PD-gait, which also influenced the low correlation between GVI scores and mobility and dynamic balance scores, and low discriminatory ability between mild and moderate cases. This informed the conclusion that the GVI was not a valid tool for older adults with mild to moderate PD.

More in depth scrutiny of the method raised potential issues which could have influenced the seemingly low responsiveness of the GVI. Firstly, the issue of redundant variables was considered. The GVI was based on the summed step-to-step variability of multiple spatiotemporal variables, some of which are highly correlated and overlapping. This is exemplified by the stance phase of the gait cycle which can be further sub-divided into the time spent in double- and single limb support (see Figure 6). Relative to the GVI, all three variables are included by incorporating stance time-, double support time- and single support time variability. Further, the overall GVI was based on the combined values for the left and right side. This renders single support time- and swing time variability highly associated due to the fact that the two events happen simultaneously, but on opposite legs interchangeably. The norm is to report one of the two, however both are included in the GVI.

Another important issue was the finding that individual GVI scores could be well above the reference mean of 100. The reason for these higher values was related to the calculation method as follows: In order to determine a raw index score, the natural logarithm of the difference in total gait variability for the individual relative to the reference population mean was determined. This became problematic when the level of gait variability for the individual was close to that of the reference mean, as the natural log of values approaching zero will tend toward infinity (see equation 3 on page 38). This produced an artificially high z-score which resulted in GVI scores well above 100. Although there was no interpretational difference between a GVI of 101 or 130, both signifying normal levels of gait variability [79, 80], those

participants who had close to normal levels of gait variability got exponentially high GVI scores which elevated the group mean disproportionately.

However, a revised version of the GVI was published in 2018 as the Enhanced Gait Variability Index (EGVI) where identified shortcomings were addressed [164]. The potential for GVI scores above 100, together with a new found issue relating to determining the direction of gait variability (higher or lower than the reference mean), were both amended by adjusting the calculation method. Also, redundant variables were removed in the revised version. As part of a bigger collaboration, several clinical data-sets, including the data set from Paper I, were re-analysed with the EGVI as part of the publication [164]. This allowed us to explore if the new version would better display level of gait variability in spatiotemporal variables for individuals with PD, and thereby be more valid. As previous, an EGVI = 100 indicated that the person has a similar level of variability as the reference. However, with the amendments to the method EGVI values greater than 100 indicated higher levels of gait variability, whereas lower values showed lower levels of gait variability. As previous, each 10 point difference reflected one SD from the reference mean [164].

The results of the re-analysis indicated that 53% of the PD-cohort had higher levels of gait variability, 12% had lower, with 35% showing normal levels of gait variability. This diversity explains why the mean EGVI for the total group was only 107, displaying slightly elevated levels of gait variability. For the 53% who showed higher levels the mean EGVI was 114.2, and 116.6 for the most affected side only, which corresponds to approximately 1.5 SDs from the reference mean. However, when comparing these values to the mean EGVI estimated for healthy older adults, mean scores were still similar, suggesting comparable levels of gait variability between PD and healthy peers. Further, it was investigated if the higher gait variability sub-group would show improved association between the EGVI scores and functional balance and mobility scores. Strengthened correlations were seen with functional balance, which were now moderate and in accordance with the original hypothesis of Paper I. However, this was not the case with regards to TUG-scores. Lastly the ability of the EGVI to distinguish between those classified as mild as compared to moderate was not significantly improved from the GVI, even when only the higher variability sub-group was considered. It was therefore concluded that further investigation into the validity of using the EGVI on gait data from individuals with PD is warranted [164].

### **5.1.5 Reliability of gait variability measures – effect of gait speed**

The reliability of estimating the level of gait variability as the square root of the within-subject variance of the left and right steps was further investigated in this thesis. The work presented in Paper II sought to extend on existing knowledge by investigating how gait speed affected the reliability of gait variability measures relative to pathology and number of steps (amount of data) included in the estimates.

The results showed that best agreement was obtained when gait variability estimates were based on at least 40 steps for both individuals with PD and healthy older adults. However, stable agreement measures of gait variability were only established for the normal and fast gait speed conditions for individuals with PD, whereas healthy older adults were reliable across speeds.

The reason for the low agreement seen for several of the investigated gait variables at slow speeds for the PD cohort was due to decreased consistency in several gait variables for the slow walking condition. This suggests that slow walking was more challenging for the PD-cohort, and could be due to the fact that walking in a slow manner places higher demands on postural stability due to longer time spent in single limb stance and increased lateral displacement of the COM.

Scrutiny of the data suggested that especially three of the participants responded to the slow walking condition by inadvertently increasing their gait speed closer to normal over the course of the captured walking trials. Such fluctuations in speed would understandably increase variability in the more speed sensitive variables such as step length, stance time and step velocity, and thereby increased measurement error. In support of this it has been shown that variability of step length in the antero-posterior direction is closely related to fluctuations in self-selected gait speed [156]. Also relevant is the reported effects of dopaminergic treatment on steady state walking considering that the PD participants were tested in their medication-on state. It has been shown L-dopa mainly improves ability to take longer steps in individuals with PD [50], whereas the balance impairments characteristic for this group are found to be largely unresponsive [165]. This could suggest that individuals with PD are more able to modulate gait in the antero-posterior direction through the regulation of step length.

### **5.1.6 Effects of the HiBalance program on independent domains of PD-gait**

The work included in this thesis evaluated the immediate and long-term effects of intensive balance and gait training on relevant domains of continuous gait during self-selected normal and fast walking for elderly with mild to moderate PD. Our results showed immediate positive effects of the HiBalance program through improved pace and rhythm aspects of gait. Additionally, improvements in the variability domain were seen during fast walking. However, the postural control and asymmetry domains were not influenced by the training relative to either of the speed conditions. No positive effects remained at 6 and 12 month follow-ups.

The immediate effects of the HiBalance program on self-selected normal gait speed and step length has been previously reported [123]. There is much support showing that balance and gait training increases step length, and thereby increases gait speed, in individuals with PD [4, 103, 114]. These findings are strengthened by our results, where improvements in several of the gait variables associated with the pace and rhythm domains of continuous gait were found for the training group.

Improved normal gait speed in the training group as compared to controls was mainly due to increased step length, whereas improvements in fast gait speed was more so due to a significant reduction in step times, reflecting higher step frequencies. It has been reported that the ability to modulate step frequency remains intact in individuals with PD, both for self-selected normal and fast gait speeds [153]. It was therefore interesting to note that mean step time values seen for the training group after the intervention were similar to the values seen for healthy older adults in this thesis (see Table 8). This suggests that the HiBalance program improved the underlying ability in individuals with PD for higher step frequencies, restoring step time values to those seen for healthy peers during normal and fast walking.

Our results suggest that the improved pace and rhythm aspects of gait were related to better stability during the stance phase, which was more evident during fast walking. This was firstly denoted by the significant reduction in stance time seen in the training group after the intervention for both gait speed conditions, which was mainly due to reduced time spent in double support. Double-support times has previously been found to be longer in individuals with PD [154]. This is supported by the findings of this thesis where individuals with PD showed significantly longer double-support times as compared to healthy peers over all speed conditions (see Table 8). The prolonged time spent in double-support is regarded as a

compensatory strategy to facilitate re-stabilisation after taking a step [50]. This suggests that the HiBalance program improved stability during stepping in the training group, which in turn enabled longer steps. Also, the significant reduction in swing time and swing time variability during fast walking supports that the training improved stability and consistency during the swing and single support phases of gait, events that occur simultaneously, but on opposite sides. Improved stability during single limb support would positively influence the length of the contralateral step, whereas shorter swing times are associated with increased step frequencies.

Though not directly measured, it is interesting to consider if the significantly shorter double support times may indicate improved ankle (push-off) power generation during gait, which occurs in the late double support phase of stance [60]. Push-off is found to be reduced in individuals with PD [62], and is an important mediator of step length and step time [166]. One must therefore ask whether the reduction in double support times also could reflect a more effective ankle push-off during gait in the training group. Future studies should elaborate on how intensive balance and gait training might improve functional ankle push-off power in PD-gait.

Relative to the variability domain it could be seen that the training group significantly reduced the variability in step and stance time during fast walking relative to the control group, showing improved consistency in the timing of the step and the period of stance. Though not verified for fast walking, studies have found that stride time variability is increased in individuals with PD during normal gait speed [88, 163]. Further, increased step time variability was associated with a history falls in individuals with PD [57], which is also reported for stance time variability in older adults [69]. It is therefore relevant that intensive balance and gait training improved motor control of the step and stance portions during fast gait. Importantly, it has been demonstrated that step time variability in individuals with PD was not affected by gait speed relative to normal and fast walking [163]. One can therefore more convincingly state that the change in step time variability was a result of the training intervention and not due to the higher gait speed seen for the training group.

No impact of the HiBalance program was seen on gait variables associated with the asymmetry and postural control domains of gait. However, unilateral symptoms are more pronounced in the early and mild stages of the disease, and become more bilateral during the moderate stages [167]. It is therefore possible that asymmetry was not a prominent feature in



this cohort. Also, it has been found that gait variables in the asymmetry domain were more responsive to dopaminergic treatment compared to other domains in elderly with newly diagnosed PD, and that these were maintained over an 18 month period [78]. This could imply that the potential for improvement, above the effect of medication, was limited also in the mild to moderate stages.

With regards to the postural control domain, further scrutiny of step width and step width variability values at baseline showed that these were similar to values for healthy older adults as can be seen in Table 5 and in Figure 16 for normal and fast gait speed. This is contrary to previous reports showing increased step width and decreased step width variability for this population, also in those newly diagnosed [78, 88]. Reduced step width variability indicates an inability to adapt to the dynamic balance demands of gait [76]. This suggests that the PD cohort in this study did not display considerable deterioration in the postural control domain of gait, thus having little potential for improvement. Another factor to consider was that participants were tested in an open plan laboratory environment, which might not have been sufficient to challenge their postural control during walking. Future studies should therefore aim to test continuous gait in more challenging surroundings. Additionally, it was commented by Lord et al, [85] that the postural control domain of the gait model explained the least amount of total variance in their factor analysis, and suggested that there is a need for more appropriate measures to reflect this complex feature of dynamic locomotion.

### **5.1.7 Long-term effects of the HiBalance program**

No long-term effects of the HiBalance program were found for any of the gait variables related to the pace, rhythm and variability domains. This is in line with the previous main findings of the HiBalance program on overall gait performance [124]. To our knowledge, no other study has investigated long-term effects of intensive balance and gait training on the underlying domains of gait. However, a recent review of RCTs investigating the effects of balance training on balance, gait and mobility, showed that six out of nine included studies had investigated long term training effects (13-52 weeks) [4]. Of these, only one study could demonstrate significant training effects in overall gait speed 6 months after a multi-dimensional balance intervention, but not at 12 months [114].

Decreased retention of newly learned motor skills has been demonstrated for individuals with PD and is linked to the function of the striatal system [168, 169]. Implicated mechanisms are

insufficient neural activity during exercise resulting in failure to trigger efficient long-term potentiation cascade signalling, but also disturbance of sleep, an important mediator of long-term retention [170]. On the other hand, the degenerative nature of PD also plays a role where further degeneration of the dopamine producing cells in the substantia nigra will exacerbate the effects of cardinal symptoms. It is therefore challenging to delineate if loss of training effects were due to decreased retention and/or the result of aggravated symptoms. Galna et al [78] showed that over an 18 month period newly diagnosed and stably medicated individuals with PD mainly displayed gait deterioration relative to the pace and rhythm domains, implicating further nigro-striatal dysfunction, despite an increase in anti-parkinson medication over the period. This is firstly supported by the findings of this thesis, where the largest standardized mean differences between individuals with PD relative to healthy older adults were seen in the pace and rhythm domains (see Figure 13). Further, this finding could explain why the HiBalance program had the most impact on pace and rhythm aspects of gait in the short term. In addition, the loss of positive training effects within six months could reflect the susceptibility to deterioration in these domains of continuous gait for individuals with PD.

## **5.2 Methodological considerations**

### **5.2.1 Study sample**

A central aspect of external validity is whether the recruited sample is representative of the population being studied [150]. The present study sample consists of older community dwelling individuals with idiopathic PD in the mild to moderate stages of the disease, with good cognitive function. It therefore follows that the generalizability of our results pertain only to this group. However, it is important to highlight that the mean age of the sample, as well as the overall male to female ratio of 1.3, well reflect the general finding that PD is more common in those 60 years and older, and that there is a consistent male preponderance associated with the disease [5, 13].

An important consideration regarding the study sample is that the majority of participants were recruited by advertisement. This is a method susceptible to resulting in a convenience sample of individuals who are interested in training and physical activity, and thereby leaving out more severely impaired and/or less motivated individuals. It has been shown that symptoms such as depression and lack of motivation are common among individuals with PD [171]. Consequently, there is the possibility that more frail individuals that would have

benefitted most from the HiBalance intervention were not recruited. However, from a physical function point of view it can be seen that the mean normal gait speed of the sample was 118.9 with a SD of 20 cm/s (Table 5). This shows a range in gait speed for the sample from 80 – 160 cm/s, signifying varied physical capacity ranging from frail to highly functional individuals [37, 87] and arguably thereby reflecting the heterogeneous presentation of PD [172].

Relevant for the internal validity of the studies in this thesis, it is important to consider the influence of dopaminergic medication when assessing individuals with PD, such as changes in medication dose over time and the potential fluctuation in responsiveness to medication during the day [29]. This is particularly relevant for the repeated testing conducted in Papers II and III. Therefore, the time of day when assessments were performed were standardised, and coincided with the medication ON state in order to minimise the impact of fluctuations. Also, for the RCT (Paper III) the medication dose of the participants were registered, and despite an increase in total dose of anti-parkinson medication, no significant differences were found between training and control group over the trial period.

### **5.2.2 Methods**

There are some aspects of the methods used in these studies that are important to discuss. Firstly, with regards to Paper I, the adult gait reference values embedded in the published GVI calculation macro [72] were used for the GVI calculations. After deliberation, it was deemed important to continue with these reference values as adding to, or replacing these would change the basis for the estimated mean gait variability representing a GVI of 100, and thereby the following GVI calculations. This would make direct comparison with previously published GVI estimates invalid. Additionally, it was considered important to evaluate the index in its current form from a clinical application point of view.

However, it must be considered that potential differences in testing protocols between Gouelle et al. and this thesis could have influenced our results. Based on the available information it was determined that the reference data in the study by Gouelle et al. were collected at two different sites using slightly shorter GAITRite mats than the one used in this thesis. However, similar distances were used before and after the mat to ensure steady state walking and similar amount of steps were included in the gait variability estimates. We therefore considered it reasonable to calculate the GVI for individuals with mild to moderate PD relative to reference

values for adult gait, hypothesising that potential differences in gait variability would be more marked. Additionally, we had the opportunity to further distinguish gait variability associated with older age from that induced by PD by comparing our results to previously published GVI values for older adults [39].

Secondly, all gait data for this thesis were collected during intermittent walks, where the participants walked the length of the mat, before turning and getting repositioned for another run over the mat. This was done contrary to the finding by Galna et al. [75] that using a continuous (circular) walking protocol resulted in more reliable variability estimates in individuals with PD and healthy older adults for normal gait speed. However, it was considered that many clinical test-setups sample data during intermittent walking, and it was deemed more clinically relevant that the results of this thesis reflected this practice.

Further, it is important highlight that several of the co-workers involved in the BETA-PD project served as both assessors during data collection, and trainers during the HiBalance training program. This meant that the assessors were not blinded to group allocation (training or control) at the post intervention assessments, which could have led to tester bias in favour of the training intervention. However, participants were never assessed by an assessor that had been involved in their training. To further minimize the risk of varying evaluations between testers, all assessors were registered physiotherapists, and had taken part in written instructions and discussions concerning the standardisation of instructions and scoring of the tests prior to data collection. Also, if there were uncertainty about a result or score, this would be discussed among assessors to reach a consensus. Although this strategy does not eliminate testing bias, it was implemented as a pragmatic solution to the numerous logistical challenges that come with a RCT.

Also, relative to Paper III it must be considered that the RCT study was powered on the basis of finding a between-group difference for change in normal gait speed, and not potential changes in underlying gait variables at both normal and fast speed conditions. It is therefore the possibility that the analysis was under-powered, and especially for the long term follow-up data where a 24% (training group) and 28% (control group) loss of participants were seen during the course of the study. However, this was in part compensated by using the more robust method of linear mixed models.

## 6. Conclusions

The GVI was not found to be a valid tool for estimating level of gait variability in older individuals with mild to moderate PD in its current form. This was related to issues with redundant variables and to the calculation method itself, rendering the sum score of the GVI to poorly reflect known differences in levels of gait variability between individuals with PD and healthy peers. Further, the GVI was deemed insensitive to detect known associations between level of gait variability and disease severity, as well as functional mobility and balance in this group.

Levels of gait variability in older adults with PD were found to be highest for step and stride length and step time, swing-/single support time relative to healthy controls for normal gait speed. Decline in executive function and automatic processes used in gait and postural control are implicated.

Walking at a slow pace increased levels of gait variability in both spatial and temporal gait variables as compared to normal and fast gait speed. This pattern could be seen for both older adults with mild to moderate PD and for healthy older adults, and was most marked for the temporal gait variables. Walking slowly places higher demands on stability and postural control due to longer times in single limb stance with higher displacement of the COM in the medio-lateral direction during transitions between steps.

To ensure reliable gait variability estimates (SD) in spatial and temporal gait variables, calculations should be based on at least 40 steps. Reliable gait variability estimates could be estimated for older adults with mild to moderate PD during self-selected normal and fast, but not slow walking. This was related to problems with maintaining the slow walking condition for some of the PD-participants, where a strategy of reverting back to more normal gait speed was seen. Healthy older adults showed reliable gait variability estimates across all gait speed conditions.

The gait of older adults with PD can be characterised by independent domains of pace, rhythm, variability, asymmetry and postural control. Older adults with mild to moderate PD showed largest gait deviations in the pace, rhythm and variability domains relative to healthy peers, both for normal and fast gait speed.

10 weeks of highly challenging balance training significantly impacted pace and rhythm aspects of continuous gait in elderly with mild to moderate PD at self-selected normal and fast

gait speed. This was related to improved stability and control during stepping, facilitating longer steps at higher frequencies. Improved variability was also seen for fast walking suggesting improved motor control.

No significant changes were maintained at the 6 month follow-up and could reflect the susceptibility to deterioration of pace and rhythm aspects of gait related to further degeneration of the dopamine producing cells in the substantia nigra. Also, the dysfunction in the striatal system could be implicated in decreased ability for long term retention of newly learned motor skills for individuals with PD.

## **7. Clinical implications**

Instrumented gait analysis is an assessment tool that is more readily available to the clinician due to smaller and less expensive portable equipment with user-friendly software aiding data processing and real time presentation of results, making reporting less time consuming. The estimation of gait variability can give the clinician important information related to the motor control of gait, and is highly relevant for evaluating populations with pathology, disease and injury.

When sampling data for gait variability estimations, it is paramount to include sufficient data, and it is recommended that at least 40 steps be used in the calculations. Clinicians should further challenge gait by testing over a range of gait speeds. However, it is important to be aware that reliable gait variability estimates could not be obtained for older individuals with mild to moderate PD during slow walking, only normal and fast. Healthy older adult were reliable across speed conditions.

Highly challenging balance and gait training, performed in smaller supervised groups over 10 weeks, is an evidence based way of improving pace, rhythm and variability aspects of normal and fast gait for older individuals with mild to moderate PD in the short term. However, none of the positive training effects were retained at 6 months. This might suggest that upholding gait function in the mild to moderate stages of PD may require regular HiBalance booster sessions at least bi-annually.

## **8. Future research**

Gait variability is deemed an informative variable reflecting motor control in the analysis PD-gait, and the importance of testing gait over a range of speeds had been highlighted. Future research should aim to clarify if reliable gait variability estimates can be attained for individuals with mild to moderate PD during slow walking when tested in a continuous manner on a circular track. Further, it should be investigated if methods for statistically controlling gait speed from slow to fast can be applied when investigating gait variability in speed dependant variables.

The model of gait for individuals with PD it a useful tool for monitoring gait function, as well as evaluating effect of intervention. However, it was commented by Lord et al, [85] that the postural control domain of the gait model explained the least amount of total variance in their factor analysis. Future research should therefore aim to clarify which variables more appropriately reflect this complex feature of dynamic locomotion.

The HiBalance program was designed to be intensive and highly challenging to optimize the potential for neuroplasticity and long-term effects that were not achieved. It is therefore important that future studies aim to further clarify exercise intensity and dose, as well as the role of sleep, to optimize long-term retention of motor skills for individuals with PD while at the same time controlling for natural progression of the disease.



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