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GAIT AND BALANCE IN PARKINSON'S DISEASE- PSYCHOMETRIC PROPERTIES AND EFFECTS OF TRAINING

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Gait and balance in Parkinson's disease- psychometric properties and effects of training

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“It ain’t over ‘til the fat lady sings”

- Unknown philosopher

ABSTRACT

Aim: The overarching aims of this thesis were to: evaluate the psychometric properties of a new clinical balance tool in People with Parkinson's disease (PwPD) with mild to moderate disease severity; as well as to investigate the effects of a new gait and balance training regime, developed to target specific symptoms commonly observed in this population.

Methods: Paper one entailed the evaluation of a balance tool's (the Mini-BESTest) reproducibility in a clinical context, when used in PwPD. In order to investigate how the reproducibility was affected by different administrators, 27 PwPD performed the Mini-BESTest with two physiotherapists who administered the test separately. In order to evaluate how the reproducibility was affected between test occasions, the participants returned 7 days later to be reassessed by one of the physiotherapists. Paper two entailed the evaluation of the Mini-BESTest's validity by means of hypotheses testing, which included, for example, the test's ability to distinguish between PwPD and healthy controls; and between PwPD with mild and moderate severity. A total of 105 PwPD and 47 healthy controls participated in this evaluation. Papers III & IV evaluated, in form of a randomised controlled trial (RCT), if participation in 10-weeks of symptom-specific and challenging training affected gait and balance abilities, fall related concerns, physical activity and activities of daily living (ADL). In addition, the training effects on the abilities to walk while simultaneously performing an added task were also specifically addressed. One-hundred PwPD were recruited to this study and were randomised to either the training or control group (care as usual).

Results: The reliability of the Mini-BESTest was found to be good. However the measurement error on individual level was considered high, reflecting more than 10 percent of the total score. When the agreement is related to a group level (in this case, 91 individuals), the measurement error only reflected 2 percent of the total score. Moreover, the Mini-BESTest was able to adequately distinguish between PwPD and healthy controls, as well as between PwPD with mild and moderate disease severity, respectively. The findings from the RCT showed that the participants in the training group, when compared to the control group, improved balance, gait, ADL and showed tendencies towards increased physical activity, whereas fall related concerns were unaffected. During gait with an added task, the performance of the added task was improved while the gait remained unaffected.

Conclusions: The psychometric properties of the Mini-BESTest make it appropriate for research purposes. Although the measurement error on individual level is considered large, the clinical value of the test is considered to exceed its flaws. Specific and challenging training can improve gait and balance abilities amongst PwPD, effects that might influence improved physical activity. Future research should investigate the importance of the added cognitive task when performed during gait.

SAMMANFATTNING

Syfte: Det övergripande syftet med denna avhandling var att undersöka skalegenskaperna hos ett nytt kliniskt balanstest hos personer med mild till måttlig grad av Parkinsons sjukdom (PS), likaledes var målet att utvärdera effekterna av ett nytt gång- och balansträningskoncept, specifikt utvecklat för denna population.

Metod: Det första delarbetet bestod av utvärderingen av balanstestet Mini-BESTests reproducerbarhet då det används i klinisk miljö hos personer med Parkinsons sjukdom (PS). Tjugosju försökspersoner med PS deltog i studien. För att undersöka hur reproducerbarheten påverkades av olika fysioterapeuters bedömning utförde deltagarna Mini-BESTest under instruktion av två olika fysioterapeuter. För att även undersöka hur reproducerbarheten påverkades då testet utförs vid olika tillfällen, återkom deltagarna 7 dagar senare för att genomgå samma test med en av fysioterapeuterna. Delarbete två bestod av utvärderingen av Mini-BESTests validitet. Detta utfördes i form av hypotestester, bland annat rörande hur väl testet förmådde skilja mellan personer med PS och friska kontrollpersoner, samt mellan personer med olika grad av sjukdomen och olika fallhistorik. Till detta delarbete inkluderades 105 personer med PS, samt 47 friska kontrollpersoner. De två avslutande delarbetena utvärderade, i form av en randomiserad kontrollerad studie, hur medverkan i 10 veckors symptomspecifik och utmanande träning påverkade gång och balansförmåga, fallrädsla, fysisk aktivitet och aktiviteter i dagliga livet. Likaså utfördes en specifik analys av förmågan att dela sin uppmärksamhet mellan gång och en kognitivt utmanande tilläggsuppgift. Till denna studie rekryterades 100 personer med PS, vilka randomiserades till att ingå i en träningsgrupp respektive en kontrollgrupp (sedvanlig behandling).

Resultat: Balanstestet Mini-BESTest påvisade god reliabilitet, dock motsvarade mätfelet på individnivå drygt 10 procent av testets totalpoäng, vilket ansågs högt. Då mätfelet anpassades till gruppnivå (91 individer) motsvarade det dock mindre än två procent av totalpoängen. Vidare förmådde Mini-BESTest skilja mellan personer med PS och friska kontroller, liksom mellan personer med mild respektive måttlig grad av PS. Resultatet från den randomiserade kontrollerade studien visade att deltagarna i kontrollgruppen, i jämförelse med kontrollgruppen, förbättrade sin gång och balansförmåga. Tillika resulterade träningen i förbättrad förmåga att utföra aktiviteter i dagliga livet samt tendenser till ökad fysisk aktivitet, däremot påverkades inte fallrädslan. Under gång med en kognitiv tilläggsuppgift, förbättrades utförandet av den kognitiva uppgiften hos träningsgruppen, gångförmågan förblev dock oförändrad.

Konklusion: Mini-BESTests skalegenskaper på gruppnivå gör testet lämpligt att använda vid forskning. Mätfelet på individnivå bedöms vara stort. Detta till trots bedöms testets kliniska värde överstiga dess tillkortakommanden. Specifik och utmanade träning kan förbättra gång och balansförmågan hos personer med mild till måttlig PS, effekter som dessutom visar tendenser till ökad aktivitetsnivå i dagliga livet. Framtida studier bör undersöka vikten av den kognitiva uppgiften då den utförs simultant med gång.

LIST OF SCIENTIFIC PAPERS

I. Löfgren, N. Lenholm, E. Conradsson, D. Ståhle, A. Franzén, E. *The Mini-BESTest- a clinically reproducible tool for balance evaluations in mild to moderate Parkinson's disease?*
BMC Neurology 2014, **14**:235

II. Löfgren, N. Benka Wallén, M. Sorjonen, K. Conradsson, D. Franzén, E. *Investigating the Mini-BESTest's construct validity in elderly with Parkinson's Disease*
Submitted to Acta Neurologica Scandinavica

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

IV. Löfgren, N. Conradsson, D. Rennie, L. Moe-Nilssen, R. Franzén, E. *Training effects on automaticity and attention allocation in elderly with Parkinson's disease; a randomized controlled trial*
In manuscript

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of daily Living
APA	Anticipatory Postural Adjustments
BESTest	Balance Evaluation Systems Test
BoS	Base of Support
CoM	Centre of Mass
DT	Dual-task
DTI	Dual-task interference
ES	Effect Size
FES-I	Falls Efficacy Scale International
H&Y	Hoehn and Yahr
ICC	Intra Class Correlations
Mini-BESTest	Mini Balance Evaluation Systems Test
MMSE	Mini-mental State Examination
PD	Parkinson’s disease
PwPD	People with Parkinson’s disease
SEM	Smallest Error of Measurement
SRD	Smallest Real Difference
ST	Single-task
TUG	Timed Up and Go
UPDRS	Unified Parkinson’s Disease Rating Scale

1 INTRODUCTION

The maintenance of gait and balance functions is crucial for physical independence and successful aging in general, and in particular, the self-perceived quality of life of people with Parkinson's disease (PwPD).[1,2] Hence, the overarching theme of this thesis was the investigation of the effects of a new gait and balance training regime in PwPD, aimed at targeting related functioning problems. However, in order for conclusions to be valid in medical research, one needs to be able to rely upon the measurements used.

This thesis was divided into two parts. The first, psychometric part, constitutes the investigations of the psychometric properties of a clinical balance instrument (The Mini-BESTest) stated to measure the construct of dynamic balance. The second, intervention part, investigated the effects of a new gait and balance training regime (The HiBalance programme)[3] with regard to the following: (1) the overall gait and balance performance; and (2) the automaticity of gait and a simultaneously performed cognitive task.

2 BACKGROUND

2.1 PARKINSON'S DISEASE

2.1.1 Prevalance and pathophysiology

Parkinson's disease (PD) is the world's second most common neurodegenerative disorder. Although hereditary and environmental factors account for a slightly increased risk of diagnosis, the aetiology of PD remains largely unknown.[4,5] The estimated prevalence of PD is 5 million cases worldwide and 22 000 in Sweden. [4,6] Although PD also occurs at younger ages, the disease is most commonly diagnosed after the age of 60.[4] With the increased life expectancy worldwide it is estimated that approximately 9 million people will be diagnosed with PD in the next 15 years.[7]

The pathophysiology in PD is rather complex, however, a simplistic description of the main characteristic is the progressive process of neuronal degeneration in the substantia nigra pars compacta.[8] This leads to a substantial loss of dopaminergic neurons in the nigrostriatal pathway and, eventually, the basal ganglia. The major cause of the motor symptoms occurring in PwPD is related to this neuronal loss.[9,10]

2.1.2 Clinical manifestations, diagnosis and disease severity

The main clinical manifestations observed in PwPD are the cardinal motor symptoms: tremor; bradykinesia; rigidity; and postural instability.[11] Other common motor features include but are not limited to: impaired gait; speech impairments; dysphagia; and reduced facial expressions. In addition to the well documented motor symptoms, PD is also accompanied by a variety of non-motor symptoms.[12] These include the prevalence of cognitive impairments such as executive dysfunction.[13] Other common non-motor symptoms are impairments of the autonomic system, gastrointestinal disturbances, sensory symptoms, sleep disorders and neuropsychiatric symptoms, including depression.[14]

There is no definite test to diagnose PD. Hence, clinicians tend to base their conclusions upon the presence of a combination of the above-mentioned cardinal symptoms, and the response to Levodopa medication (i.e. the first hand treatment for PwPD).[15] It is possible, however, that, the clinical characteristics may overlap between PD and other Parkinsonian subtypes, which may alter the primary diagnosis; therefore the diagnosis may change with time if certain symptom patterns related to the progression of the disease are absent.

Since PD is a progressive disorder -meaning that symptoms tend to increase with time -the healthcare management of it may differ depending on the stage of the disease. One commonly used scale to categorise PwPD with regard to their severity of motor symptoms is the Hoehn and Yahr scale (H&Y).[16] This scale ranges from one to five, where a higher H&Y score signifies a more severe disease stage (Table I).

Table I. The Hoehn & Yahr Scale

1.	Unilateral involvement only, usually with minimal or no functional disability
2.	Bilateral or midline involvement without impaired balance
3.	Bilateral disease, mild to moderate disability with impaired postural reactions
4.	Severe disability, ability to walk or stand without assistance
5.	Restricted to bed or wheelchair, Assistance required for mobility

2.1.3 Effects of Parkinson's disease on everyday life

Among the symptoms observed in PwPD that have the most detrimental effects on health related quality of life are gait and balance impairments.[2] Indeed, up to 70 percent of PwPD fall every year and out of these, 40 percent fall multiple times.[17,18] Impaired gait and balance abilities are among the major contributors to increased fall risk[19], and are related to fall-related concerns as well as activity limitations.[2,20] Therefore such impairments may interfere with participation in daily life.[2]

2.2 GAIT AND BALANCE CONTROL

Within this thesis continuous steady state gait during less-demanding conditions and transient task-specific gait (for example negotiating obstacles and performing sudden turns) will be treated as two different constructs.[21,22] Operationally, the former and latter will be referred to as 'gait' and as 'dynamic gait', respectively throughout the thesis.

Gait refers to steady state gait during over-ground walking conditions and entails the detailed investigation of the overall performance of numerous repeated steps.

Dynamic gait entails the ability to perform specific tasks while walking and relies upon adaptability to the demands of those specific tasks. It is clinically evaluated with regards to the overall performance of different gait-specific tasks, and is considered to be related to the multi-dimensional construct of balance control.[23]

2.2.1 Gait

Gait is fundamental for a physically independent lifestyle, and is a strong predictor of overall health status.[24-27] Although walking may appear as a simple task, the recent description of a supraspinal locomotor network and its complex interactions highlights the complexity of gait.[28,29] Considering that PwPD exhibit deviant activity in all structures related to this network,[22] it is unsurprising that gait impairments is one of the main disabilities found in this population. Indeed, PwPD have been shown to walk slowly, with short, narrow, variable and asymmetric steps, compared to healthy people.[22]

The importance of investigating different gait parameters in PwPD can perhaps be highlighted by relating different aspects of gait impairments to common symptoms and their related structural characteristics. The *slowness* of gait, for example, may be related bradykinesia and/or rigidity.[22] These symptoms have been suggested to be caused by reduced excitability of cortical motor areas;[30] and impaired interactions between the basal ganglia and deep brain structures,[31] respectively. Moreover, whereas *gait asymmetry* among PwPD is likely related to the unilateral onset of the disease (and suggested to depend upon the asymmetric dysfunction of the basal ganglia),[32] *gait variability* (i.e. the step to step fluctuations) has no clear cut structural explanation.[22] Nevertheless, gait variability has been promoted as a particularly important characteristic with the potential to predict falls.[33,34]

Taken together, it is unsurprising that different aspects of gait have been thoroughly investigated over the years. On the other hand, a lack of unity regarding which gait parameters to investigate and what they represent has made it difficult to compare results across studies.[35] However, in recent years efforts have been made to identify discrete parameters related to independent domains of gait.[36,37] Each of these domains is theorised to contain important information regarding specific aspects of gait, while at the same time combine to represent the multidimensional construct of human gait.

One of these models has been validated for PwPD[35] and encompasses the following domains: Pace; Rhythm; Variability; Asymmetry and Postural Control (Figure 1). Indeed, in comparison to healthy controls, PwPD have shown impairments related to all of these domains.[22]

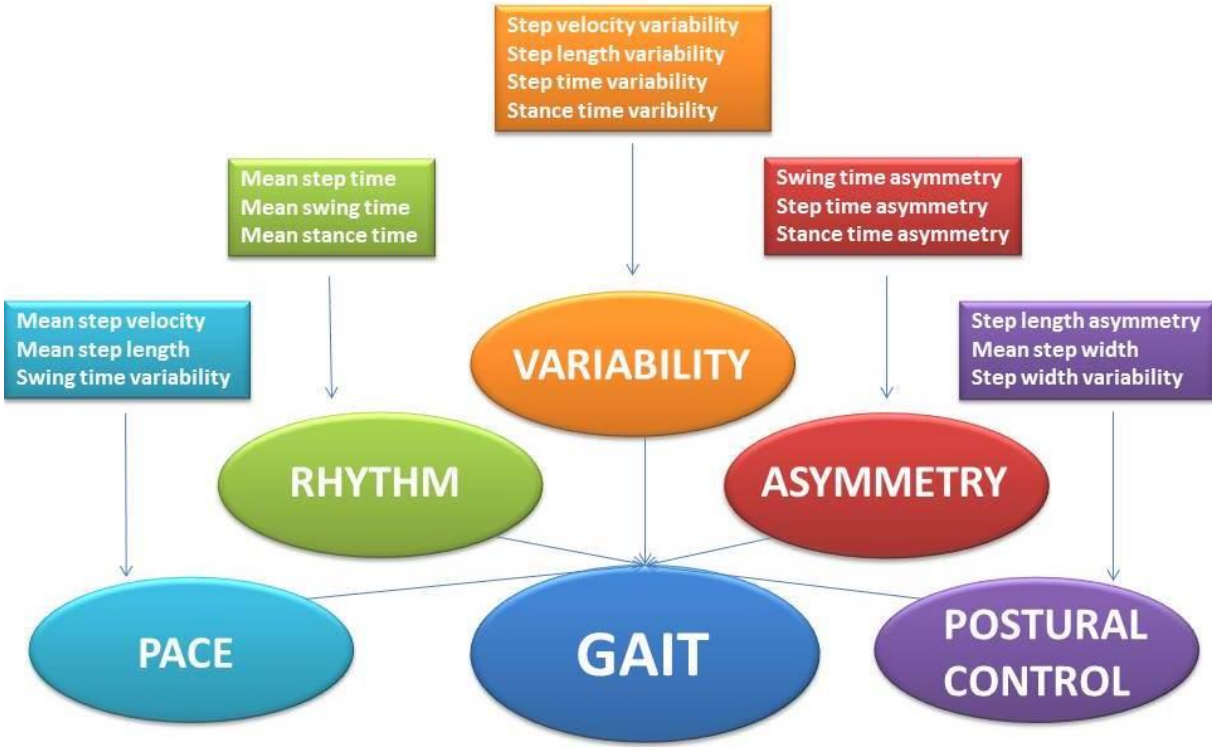


Figure 1. An illustration of the independent domains of gait and its related parameters, theorised to represent the multi-dimensional construct of gait.[37]

2.2.1.1 The concept of automaticity

Gait has for a long time been considered an automatic activity in healthy people.[38] The notion of gait automaticity is that it requires minimal attention, which instead can be directed elsewhere.[39] Automatic gait may be highly relevant for everyday life, especially when performing tasks or actions within a particular context such as when a person is crossing a street. Indeed, if this person would then be preoccupied by paying attention to the gait performance, he or she may not be able to detect potential hazards, such as approaching vehicles, curbs or other pedestrians.

2.2.1.2 Automatic versus controlled processing

The concept of automaticity relies upon the framework by Schneider and Shiffrin,[40] and has its theoretical roots within the cognitive research field (but has since been adopted by the locomotor research field).[39] This framework distinguishes between automatic and controlled processing.[41] *Automatic processing* was defined as "the activation of a sequence of nodes that nearly always becomes active as a response to a particular input configuration", and that is "activated automatically without the necessity for active control or *attention* by the subject". *Controlled processing*, on the other hand, was defined as "a temporary set of nodes that are

activated under control of, and through *attention*, by the subject". Whereas the automatic processing relies upon and require an appreciable amount of training to fully develop, controlled processing has the benefit of being applied in novel situations.[41] By translating this to activities, motor or cognitive, these two types of processing may be interpreted to complement each other. When sufficient amount of training have led to automatic processing, a task may be optimally performed with minimal attention, which instead can be allocated to a novel (or untrained) task which requires attention.

2.2.1.3 The dual-task paradigm

The most common way of investigating automaticity is by means of the dual-task (DT) paradigm.[42] This paradigm entails the concurrent performance of two tasks with distinct objectives. Each of these tasks is also performed separately, that is, as single-tasks (ST). From this, the difference in task-performance under DT and ST-conditions, termed DT-interference (DTI) could be approximated, which is considered an estimation of the degree of automaticity.[39] Moreover, the DTI can be presented as an absolute value (by subtracting the ST performance from the DT performance of the same task) or a relative value (by dividing the absolute DTI with the ST-performance).[43,44]

In addition to measuring automaticity, the DT-paradigm can also be used to assess DT-abilities per se, that is, without taking the ST-performance into account. Whereas the DTI is a relative measure, considered to represent automaticity; the absolute measures of DT-abilities can be considered to represent the abilities to perform certain tasks under dual-processing.

Within the field of gait research, the DT-paradigm refers to the examination of gait performance in combination with an added task. This added task may be of a more manual (for example, manipulating buttons) or cognitive character (such as counting backwards by 3s). However, in recent years cognitive tasks have been more commonly used, due to the increased understanding of the impact that executive functions may have on gait.[38]

2.2.1.4 Executive functions

Executive functions are defined as a set of cognitive processes that control goal-directed behaviours.[13] These processes have been found to have great impact on DT abilities. One of the prevailing models used to conceptualise the role of executive functions and its impact on automaticity and attention, is the supervisory attentional system model.[45] This model suggests that two basic tasks can be performed simultaneously without interference as long as they are automatic, whereas more advanced, non-automatic tasks need conscious attention that is coordinated from the supervisory attentional system. Relating this model to neurophysiology, it is widely accepted that the basal ganglia is responsible for automaticity, whereas the role of the prefrontal cortex is coinciding with that of the supervisory attentional system.[13]

2.2.1.5 Structural impact on automaticity in people with Parkinson's disease

PwPD frequently exhibit impaired automaticity of both motor and executive functions.[13,39,46] This is believed to be due to the basal ganglia dysfunction in this population, which in turn leads to a dependency of cortical attention (i.e. the supervisory attentional system) even for the performance of basic tasks (which are automatic in healthy people).[13] In addition, it has also been suggested that impaired motor automaticity in PwPD is related to impairments of the sensorimotor striatum, a structure that is responsible for automatic motor programming in healthy people.[46] This in turn suggests that PwPD need to rely upon controlled processing (which is limited in its capacity)[41] even for single-tasks. Hence, during DT-conditions, there might be a competition for attention, which may highlight the importance of prioritisation strategies among PwPD.

2.2.1.6 Prioritisation strategies during dual-task conditions

The concept of task prioritisation during DT-conditions refers to the idea that attention will be allocated to the "most important" task. Prioritisation strategies are commonly investigated by comparing the DTI of the two concurrently performed tasks, where the task with the least interference is considered to be prioritised.[44]

For a long time, the common comprehension was that a sound prioritisation strategy was to use the *posture first* strategy.[47] The idea of this strategy is that healthy people will always prioritise the motor task (for example gait or balance), rather than the added cognitive task during DT-conditions. PwPD on the other hand, have been considered to use the supposedly deviating *posture second* strategy during DT-conditions.[48] Although this may be true, recent evidence suggests that similar strategies are used by healthy people.[49] Moreover, two studies that investigated the abilities to actively allocate attention to either gait or the added task found similar patterns among PwPD and healthy people.[50,51]

Based on this, a new model of task prioritisation has emerged.[49] According to this model, task prioritisation during DT-conditions depends upon a balance between *postural threat* and *postural reserves* as perceived by the subject. The first, *postural threat*, refers to the perceived hazard of the task at hand, such as the risk of injury; and the second, *postural reserves*, refers to the physical abilities of the individual, for example gait and balance abilities. Moreover, this model states that healthy people, with sufficient postural reserves, will always prioritise the added cognitive task if the motor task is perceived to be of low threat. Conversely, a person with limited postural reserves will prioritise the motor task if the added task becomes too demanding, thereby competing for attentional resources. It may be interpreted that this model highlights the importance of the perceived difficulty level of either task, in relation to the individual's capacities.

2.2.1.7 Relation between dual-task deficiencies and falling

Both impaired automaticity and absolute DT-gait abilities have been related to increased risk of falling in elderly people.[52] Moreover, although single-task gait speed is an important indicator of overall health and survival, a recent review found that dual-task gait performance had an added value with regards to fall-prediction.[52] This review also recommended future studies to analyse the impact of the added task and the DTI of gait performance with regards to the future risk of falling.

2.2.2 Balance control

Balance control has been defined as a complex motor skill dependent upon the interaction multiple sensorimotor processes, with main functional goal of postural equilibrium and postural orientation.[53] Postural equilibrium (or stability) refers to the control of Centre of Mass (CoM) in relation to the Base of Support (BoS). Postural orientation refers to the active maintenance of an adequate posture and depends upon gravity, visual environment, support surface and internal references.[53]

Balance control is a prerequisite for the performance of a variety of activities. In humans these activities have been classified into three overarching categories: (1) the maintenance of a specific posture, for example sitting or standing; (2) voluntary movements, for example movements between postures; and (3) the reaction to an external disturbance, such as a trip, a slip, or a push.[54]

Relying upon the notion that balance control relies upon a set of different underlying systems,[55] Horak et al. recently presented a model for balance control.[23] This model encompasses six underlying domains, thought to represent the multidimensional construct of balance (Figure 2).

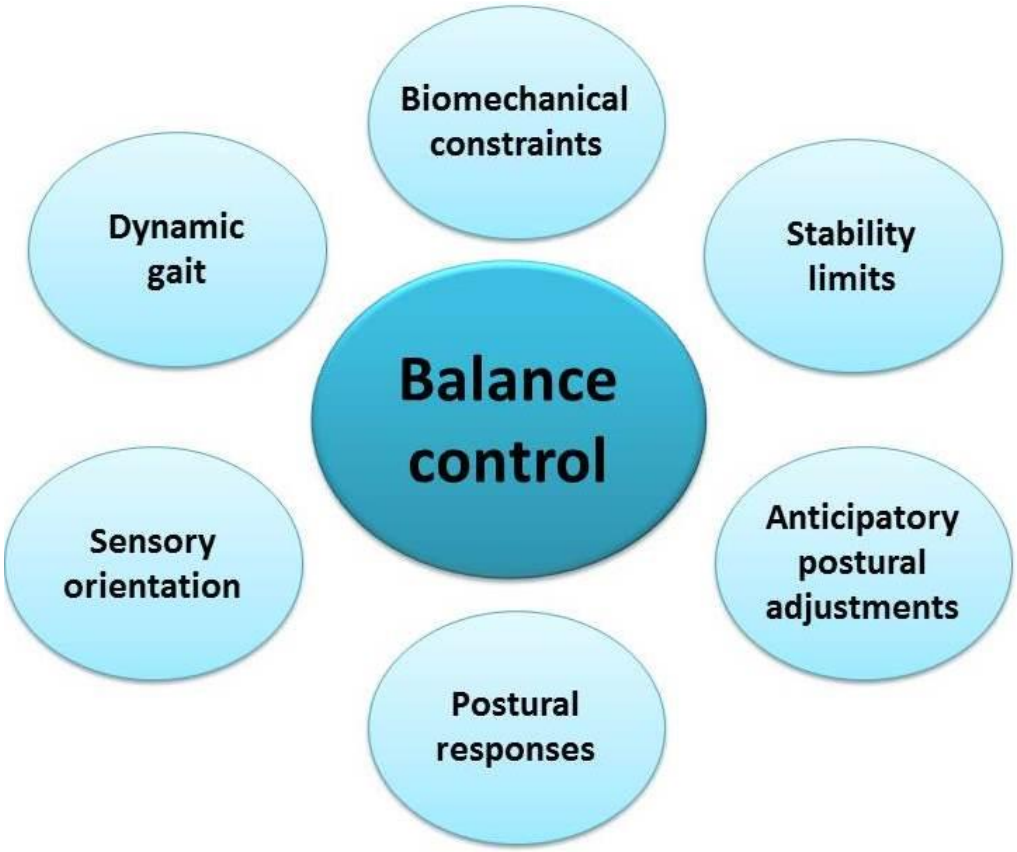


Figure 2. An illustration of Horak's model for balance control.[23]

2.2.2.1 Biomechanical constraints

Biomechanical constraints refer to constraints arising from the individual's biomechanical system, which may alter balance abilities. In PwPD, common biomechanical constraints are related to symptoms such as reduced lower limb joint torques, flexed spinal abnormalities and stooped posture.[56,57]

2.2.2.2 Stability limits

Stability limits refer to the relation between the CoM and the BoS. Generally, if the CoM falls outside of the BoS, an object or a person lose the control of balance.[54] Hence, the area making up the BoS may therefore be considered the theoretical stability area (i.e. the limits of stability).[58] Moreover, in clinical balance assessments, stability limits may be defined as the maximum possible displacement of the body's CoM without the necessity of taking a step, or worse, falling.[59] This is commonly assessed with regard to an individual's voluntarily inclined posture, which in addition to body biomechanics and segment properties, is affected by subjective and environmental factors.[58,59] As such, clinical assessments may be assessing *the functional limits of stability*, which might differ from the limits of stability.[58] In this thesis, *stability limits* refer to the functional limits of stability.

From an early disease stage, PwPD demonstrate impaired stability limits when compared to healthy people, with particularly pronounced deficiencies in the backwards direction.[59] Indeed, it has been proposed that the stooped posture in PwPD, resulting in a forward projection of the CoM, may be the results of a compensatory strategy, protecting them against backwards falling.[22,60]

2.2.2.3 Anticipatory postural adjustments

Anticipatory postural adjustments (APAs) refer to the onset of postural changes (for example activation of postural muscles) that occur prior to a self-initiated balance perturbation.[61] The APAs are affected by three main factors: (1) the expected magnitude and direction of the perturbation; (2) the voluntary action associated with the perturbation; and (3) the postural task.[62] For example, starting to walk from a standing position will be preceded by different APAs than when rising up to standing from a seated position, or when lifting a heavy suitcase.

People with PD have demonstrated slower APAs of smaller magnitude when compared to healthy people, which has been related to the cardinal symptom bradykinesia. Moreover, the deviant APAs in this population have also been found to be asymmetric[63] and variable.[64] Taken together, these findings have been implied to play a part in the delayed step initiation and freezing of gait among PwPD.[63-66]

2.2.2.4 Postural responses

Postural responses refer to the ability to respond to a sudden external perturbation (such as a trip, slip or push) that position CoM outside of the BoS. Therefore, adequate postural responses may be considered the ultimate attribute for the avoidance of falling. Postural responses are considered to be automatic, however they differ from spinal reflexes in the sense that the latter occur at shorter latencies, indicating different neural pathways.[67-69] Although the brainstem's involvement in the generation of postural responses is undisputed at large, recent findings suggest that the interaction between the basal ganglia and the cortex plays a role.[22,69-72] In addition, it has also been suggested that the neural circuitry may differ between postural responses in different directions.[72]

Taken together, this may suggest why PwPD show impaired postural responses at an early disease stage,[73,74] and perhaps also why impairments of postural responses in the backwards direction appear to be particularly pronounced in this population.[75-78]

2.2.2.5 Sensory orientation

Sensory orientation (or sensory integration) refers to the ability of using sensory information to generate adequate motor responses (such as stabilising the body) within the context of the current environmental challenges. This occurs through the central nervous system, where the respective information from the visual, vestibular and proprioceptive systems are integrated and weighed.[79] Moreover, this integration process is adaptive, meaning that the input from the different systems will have different impact depending on the situation.[80]

One common way to measure sensory orientation is by analysing, for example, the frequency and amplitude of body sway (i.e. the continuous movements of the CoM) during upright standing (with the feet in fixed positions). Increased body sway is then generally interpreted as challenges with the integration of sensory information, and tend to increase when visual input is restricted or when an individual stand on unstable surfaces.

PwPD exhibit a variety of somatosensory impairments, including tactile, thermal, proprioceptive, and nociceptive disturbances.[81] Such disturbances may combine to produce incorrect integration in the central nervous system, leading to impaired signalling necessary for the preparation and execution of motor responses. This may be an explanation to deviant postural behaviours among PwPD (in comparison to healthy people); such as exaggerated body sway, which, in turn, become particularly pronounced when visual input is restricted.[82,83] The latter finding has been attributed to an over-dependency of visual input, in particular considered to compensate for impaired proprioception in this population. Although, this visual dependency is important in its own right, it may be particularly detrimental when considering that PwPD are at risk of developing a variety of visual impairments throughout the course of the disease.[82]

2.2.2.6 Stability in gait

Stability in gait (or dynamic gait) refers to context specific adaptability during gait. This may include the ability to perform a sudden turn while walking (for example to avoid an approaching obstacle), the need to suddenly increase or decrease the walking speed (for example during a road crossing, before the traffic light changes) or lift the foot to clear an obstacle.

PwPD have difficulties adapting their gait.[84-86] This may contribute to the fact that PwPD experience falls during common everyday life situations that require the ability to adapt gait, for example during turning while walking.[74,87]

2.3 TREATMENT OF GAIT AND BALANCE IMPAIRMENTS

The treatment of gait and balance impairments in PwPD is recommended to include a combination of levodopa medication and training.[88] This is partly due to uncertainties regarding the effects of levodopa on certain aspects of gait and balance,[89,90] in combination with increasing evidence supporting the impact of training.[91-93]

2.3.1 Effects of levodopa on gait and balance control

The first hand treatment for PwPD is levodopa medication. In fact, responsiveness to this sort of medication has traditionally been a prerequisite to be diagnosed with idiopathic PD.[11] However, levodopa has mixed effects on gait and balance abilities.[89,90] Indeed, while levodopa appears to have a moderately beneficial effect on gait measures related to bradykinesia such as step velocity and step length during gait, it does not appear to affect gait measures related to rhythmicity, such as swing or stance time.[89] With regards to balance, small improvements were shown with regards to APAs, whereas sensory orientation (measured as postural sway) actually worsened with levodopa treatment.[89] In order to address these balance deficiencies, training interventions may prove highly important as a complement to levodopa treatment.

2.3.2 Effects of training

Up until recently, it was cast in doubt whether or not training interventions would prove beneficial with regards to, among others, gait and balance impairments in PwPD.[94] However, in the past few years, an increasing number of studies on this issue have contributed to the general perception that training can indeed prove beneficial for PwPD. [88,92,93,95] More specifically, recent findings suggest that training can improve functional outcomes as well as induce neuroplasticity and be neuroprotective in PwPD.[91,96,97]

2.3.2.1 Training effects on plasticity and neuroprotection

Recent evidence from animal models[98-100] as well as PwPD[101-106] suggests that exercise may have the potential to induce neuroplasticity and neuroprotection in this population. Findings range from increased cortical excitability[101] (which is related to, for example, the slowness of gait in PwPD)[22] to improved neurotrophic factors (suggested to reduce cell death, hence is considered to be neuroprotective).[91,103-105] Moreover, although most of the findings are related to high intensity aerobic exercises,[101,102,105] one study found that six weeks of balance training, consisting of one 45-minute session per week, induced grey matter changes in the parietal basal ganglia circuitry.[106] This may be highly relevant since this is an area that have been related to impaired automaticity in PwPD.[91]

2.3.2.2 Training effects on single task gait

Previous findings on ST-gait improvements following training in PwPD generally refer to improved gait speed, whereas for example, improved step length is more rare to achieve.[93] Nevertheless one training programme that compared extensive walking over six weeks, with Nordic walking and placebo training, found that both walking groups improved step length and step length variability in comparison to the placebo group.[107] These improvements were significantly larger in the Nordic walking group, as compared to the walking group. The authors argued that it was due to higher intensity walking in the Nordic walking group, which may indicate that ST-gait in PwPD might benefit from prolonged exposure to gait at higher intensity (or challenge) levels.

2.3.2.3 Training effects on automaticity and dual-task gait

It was earlier questioned if PwPD were even able to improve automaticity and DT abilities. Rather, it was earlier advised against DT-gait training in this population since such training was considered to put PwPD at risk of adverse outcomes.[108] However, it has since been shown that PwPD have the ability to obtain motor learning through DT-training, in fact their learning curves are similar to those of healthy people, albeit slower.[109] This is a finding that has been supported by recent pilot studies. Specifically, those studies indicate that DT-training can improve DT-gait abilities, [110-116] whereas the effects on ST-gait[112,116] are more uncommon. This in turn may indicate the potential of improving both DT-gait abilities and gait automaticity among PwPD. On the other hand, few studies have found improvements[112,113] on the added task, which is an area that has received little attention within this field.[117] Nevertheless, the above mentioned findings remain to be confirmed through randomised controlled trials in order to guide clinicians whether or not to expose PwPD to DT-training.

2.3.2.4 Training effect on balance control

Findings from recent meta-analyses show that training interventions can improve balance control in PwPD.[93,118] However, the diversity of studies make it difficult to convincingly pin-point specific training characteristics related to improved balance control.[118,119] Whereas the results from one of these studies indicate that highly challenging training may prove most beneficial for improving balance control among PwPD, it remains unclear to what extent specific balance tasks needs to be targeted.[118] On the other hand, aerobic exercises alone were found to have limited effect on balance improvements. In addition, no evidence was found to support home-based multi-component training programmes that included balance exercises. These findings may indicate that training, in addition to be highly challenging, needs to incorporate balance exercises in order to improve balance control among PwPD. In line with

this, a recent recommendation suggests that training interventions in PwPD needs to emphasise intensity, specificity and complexity.[92]

2.4 GAIT AND BALANCE ASSESSMENTS

In order to enable adequate assessments of gait and balance abilities, as well as the effects of training, outcome measures (i.e. tests) need to be appropriate. This means that the results produced by each of these measures need to capture the phenomenon (or construct) that the measure purports to capture. Take the construct of balance control for example, it is important that the results produced by a test that is used to assess an individual's balance control actually represents this individual's current abilities pertaining to the construct. This means, for example, that the test needs to produce different results if the test is assessed in two individuals with different abilities of the investigated phenomenon, or in an individual with changed abilities between two test occasions (i.e. if balance control have become improved or worsened). Similarly, if the test is assessed in a single individual at different occasions, given that the individual's abilities of this phenomenon has not changed between the occasions, the results produced by the test should not differ between the occasions (that is, the measurement error should be small).

2.4.1 Assessment of gait and balance in laboratory versus clinical settings

When investigating gait and balance abilities in research settings, advanced equipment is commonly used and tests are performed under highly controlled conditions. The assessment of gait for example, is commonly conducted by means of an electronic pathway or with sensors positioned at different segments of the subjects' body (e.g. to assess foot patterns or joint angles),[120,121] whereas balance control tends to be investigated by means of force plates (e.g. enabling the detailed analysis of body sway or APAs).[122] Although such measurement conditions are indeed affected by, for example, instructions, their measurement properties may be argued to be relatively robust. Such measures may disclose highly important information[123] but are rarely available in clinical settings, which may question its ecologic validity. Conversely, measures that are commonly used in clinical settings, and thereby have higher ecologic validity, tend to be more subjective in nature; hence, their measurement properties may lack robustness. Indeed, in clinical assessments, a variety of factors may threat the robustness of findings, not least related to the tester.[124,125] In accordance with this, the measurement error found in many clinical tests can be considered quite high,[126-128] often exceeding reasonable changes within treatment periods.[129-131] Nevertheless, the importance of clinical tests is difficult to argue against due to their efficiency in providing information regarding a specific symptom (or construct). Indeed, should every patient need to be investigated in a laboratory setting, very few patients would be examined at all. This may emphasise the importance of thoroughly investigating the psychometric properties of clinical

tests. Such information can then be used by clinicians in order to interpret their findings; and/or by test developers to improve the tests.

2.4.2 The Mini-Balance Evaluation Systems Test

The Balance Evaluation Systems Test (BESTest)[23] is a balance test that was based on Horak´s model of balance control, which relies upon the theory that the multidimensional construct of balance control encompasses six underlying domains (Figure 2); each of which should be investigated separately. The stated purpose with the BESTest was to enable clinicians to identify potentially deficient aspects of balance in patients, and direct treatment towards those domains. However, the BESTest was found too time consuming a test to use in clinical practice, since it was estimated to take around 30 to 40 minutes to administer. Therefore, the developers sought to develop a shorter, more clinically applicable version, which they named the Mini-Balance Evaluation Systems Test (the Mini-BESTest).[132] This test had evolved from statistical analyses (i.e. Rasch and principal component analyses) and was stated to measure a unidimensional and undefined construct named *dynamic balance*.[132,133] However, although this indicates that only the total score of the Mini-BESTest should be considered, the test clearly identified four underlying domains (*APAs*; *postural responses*; *sensory orientation*; and *dynamic gait*) and seemingly encouraged the sub scoring of these domains.[134]

2.5 PSYCHOMETRIC PROPERTIES

Within this thesis, the psychometric properties of the Mini-BESTest will be investigated with regard to reproducibility and validity, as conceptualised and defined by the COSMIN taxonomy (Figure 3).[135]

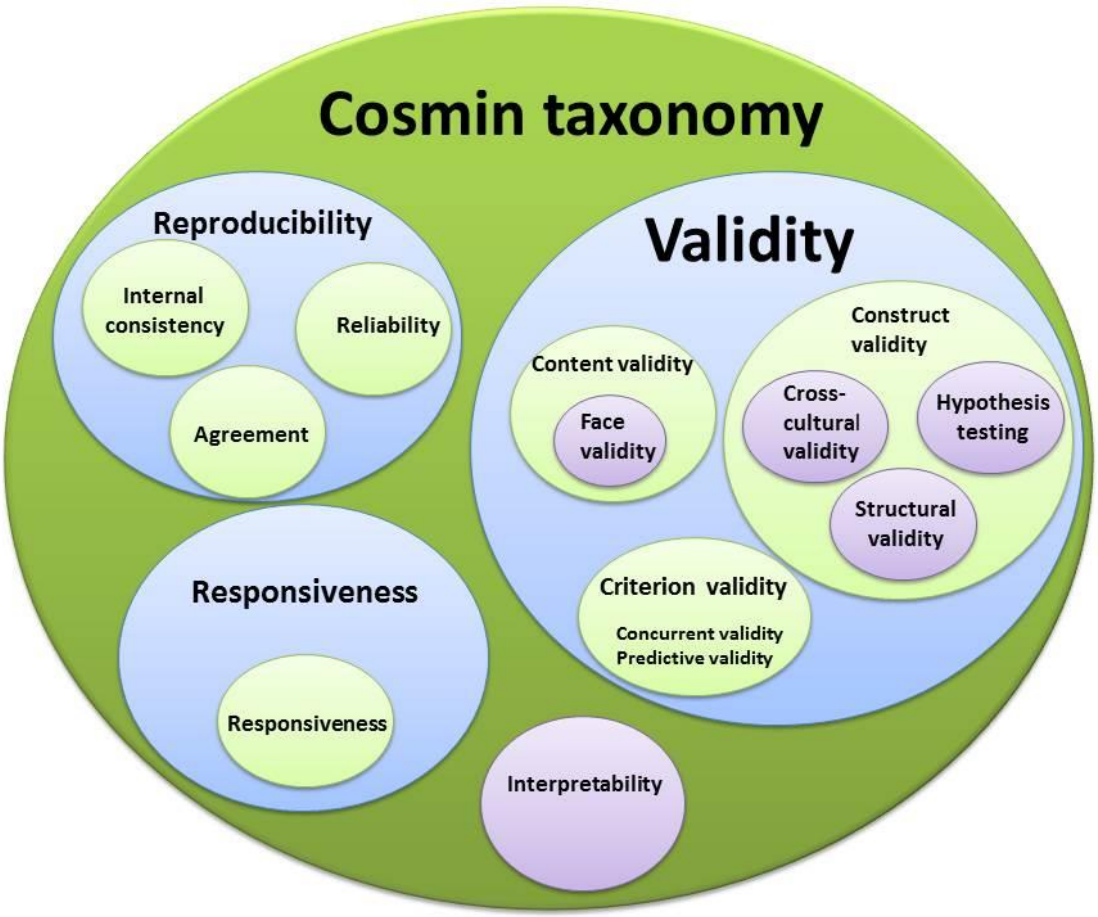


Figure 3. An illustration of the Cosmin taxonomy of psychometric properties.[135]

2.5.1 Reproducibility

Reproducibility concerns the degree to which repeated measurements in study objects provide similar results, and can be divided into parameters of *reliability* or *agreement*.[124]

Whereas reliability measures aim to distinguish study objects from each other despite measurement errors; measures of agreement assess the absolute measurement error of a test (i.e., the exact measurement error, presented in the same units as the investigated item).[124,136]

2.5.1.1 Reliability

Reliability is commonly investigated and reported by means of intra-class correlations (ICC), a measure that is highly dependent upon the variability in a sample (ICC= variability between subjects/ variability between subjects + measurement error).[125,137] Since reliability measures aim to distinguish between subjects despite measurement errors, this means that if there is large variability between subjects, a larger measurement error will be accepted, and vice versa. Hence, the reliability measure is only generalisable to samples with similar variability.[124] In addition, reliability measures have been proposed to be particularly important for assessment tools that are used for discriminative purposes, and less important for tools that are used for evaluative purposes.[138] Nevertheless, the reliability measure may, arguably, be considered to measure if the sensitivity of the tool exceeds the measurement errors, a quality that may be important for research as well as clinical practice.

2.5.1.2 Agreement

Agreement is a measure considered to be neglected in medical research[124]; but that have been proposed to be important for assessment tools that are used for evaluative purposes[124,138] (such as effects of training). In addition, agreement can be calculated both on an individual level[139] (that is, as the absolute measurement error of a single individual in the current population) and on a group level.[140]

Agreement is calculated as the square root of the sample variance. This is interchangeably referred to as subject within or smallest error of measurement (SEM), in this thesis the term SEM will be used. Moreover, the SEM can either be calculated as $SEM_{agreement}$ (including systematic differences) or $SEM_{consistency}$ (excluding systematic differences). Since systematic differences are likely to occur in clinical practice, particularly if different clinicians administer the same test at different occasions, $SEM_{agreement}$ is considered to increase the ecological validity and is therefore used within this thesis. Once the SEM is calculated, the Smallest Real Difference (SRD; also known as the smallest detectable change[140] or minimal detectable difference) can be calculated with the formula: $SRD=SEM \times \sqrt{2} \times 1.96$.[139] This is considered the absolute measurement error on an individual level ($SRD_{ind)}$ with a 95% confidence interval, hence is the score that needs to be exceeded in order to attribute potential changes to rehabilitation.

In summary, reliability and agreement are considered to be important for discriminative and evaluative purposes, respectively. However, since both purposes may be of interest in a clinical assessment tool, it may be relevant to investigate both.

2.5.2 Validity

The overall concept of validity refers to whether or not the result produced by an assessment tool is an adequate reflection of the construct that it intends to measure.[141,142]

The three overarching categories of validity are *content* validity, *criterion* validity and *construct* validity. While the content validity is primarily investigated when developing a new instrument, the two latter categories are generally used to investigate the validity of existing instruments. Out of these two, criterion validity is regarded to be more powerful than construct validity, and can be assessed by means of concurrent or predictive validity. However, the definition of criterion validity is "the degree to which the scores of an instrument are an adequate reflection of a *gold standard*".[135] Hence, if no gold standard exists for the construct of interest, the criterion validity cannot be investigated. In such a case, a more preferable option is to investigate the construct validity.

2.5.2.1 Construct validity

Construct validity is defined as "the degree to which the scores produced by a measurement instrument are consistent with hypothesis", for instance with regard to internal relationships, relationships with scores of other measurements or differences between relevant groups.[135]

There are three existing categories of construct validity: structural validity, hypotheses testing, and cross-cultural validity. This thesis will focus on hypotheses testing.

2.5.2.2 Hypotheses testing

The basic principle of hypotheses testing is that hypotheses are formulated about expected differences between subgroups of patients (discriminative validity/known-groups validity) and/or expected relationships with measurement instruments evaluating related (convergent validity) or unrelated (divergent validity) constructs.[135]

2.6 RATIONALE

Gait and balance disabilities are amongst the most debilitating impairments accompanying PwPD. Such symptoms have a major impact on the self-perceived quality of life and are related to increased fall frequency and activity limitations.[2,17-19] However, recent evidence suggests that adequately designed training interventions (i.e. emphasising intensity, specificity and complexity, hence are highly challenging),[92,118] have the potential to improve such symptoms.

Inspired by Horak's model of balance control, as well as by contemporary evidence with regard to motor learning and DT, we therefore developed the HiBalance programme. This procedure was conducted through workshops with clinicians and researchers, and resulted in four main balance components to be specifically addressed throughout the 10-week programme: *Sensory orientation*; *APA's*; *stability limits*; *and motor agility*. Moreover, since this research field specifically identified a need for highly challenging balance training programmes,[92,118,143] the exercises in the programme were to continuously evoke postural responses in order to ensure an adequate difficulty level. To further increase the challenge level, DT-exercises were introduced to the walking exercises during the mid-stage of the programme. Subsequently, the feasibility of the programme was investigated in a pilot study.[144] This was followed by input from trainers and participants, which brought about minor modifications and resulted in the final study protocol.[3]

Meanwhile, since balance control is best measured with a variety of balance tasks;[145] the arrival of a new and promising clinical tool, encompassing multiple items corresponding to balance deficiencies commonly observed amongst PwPD, warranted the investigations of its psychometric properties when used in PwPD with mild to moderate disease severity.

Therefore, this thesis is divided into two parts, where the first part investigates the Mini-BESTest's psychometric properties, with regard to reproducibility and construct validity, respectively. The second part constitutes the investigations of the effects of the HiBalance programme[3] with regard to overall gait and balance performance, and the automaticity of gait and a simultaneously performed cognitive task.

3 AIM

The overall aim of this thesis was to, in elderly PwPD with mild to moderate disease severity, investigate the psychometric properties of a clinical balance tool as well as the effects of the HiBalance programme with regards to: overall gait and balance performance, automaticity, and attention allocation during dual-task conditions.

3.1 SPECIFIC AIMS

Paper I

The aim was to investigate the inter-rater and test-retest reproducibility of the Mini-BESTest and its subcomponents in elderly with mild to moderate PD, under conditions similar to clinical practice.

Paper II

This paper aimed to investigate the Mini-BESTest's construct validity by means of hypotheses testing, in PwPD with mild to moderate disease severity.

Paper III

The aim was to investigate the effects of a highly challenging training programme on overall gait and balance performance and fall-related concerns.

Paper IV

The aim was to investigate the effects of highly challenging training on automaticity and attention allocation in elderly with mild to moderate Parkinson's disease.

4 METHODS

4.1 DESIGN

Paper I: test-retest design.

Paper II: cross-sectional design,

Papers III & IV: a randomised controlled trial with a repeated measurements design

4.2 RECRUITMENT

Recruitment for the HiBalance programme was performed through advertisements in local newspapers; oral presentations at the Swedish Parkinson's disease association; and outpatient neurological clinics.

Participants that showed interest to participate in the HiBalance programme, and those subsequently called to baseline assessments were later contacted to participate in paper I. Conditional to their participation was that they had not performed the Mini-BESTest within the last two months.

All participants that had been called to baseline assessments for potential participation in the HiBalance programme were asked for consent to use their results in paper II, given that they met the inclusion criteria. Figure 4 illustrates the recruitment of participants and sample sizes with regards to the respective papers.

4.3 ETHICAL APPROVAL

Ethical approval for these papers was obtained from the ethical board of ethics in Stockholm (Dnr: 2006/151-31; 2009/819-32; 2010/1472-32; 2011/1665-22; 2012-1829-32). These studies were conducted in accordance with the ethical principles for medical research involving human subjects, that is, the Helsinki declaration. Prior to entering the studies, all participants were informed of the purpose with each paper and that they would be able to withdraw at any time. In addition, the participants randomised to the control group were after the closure of the study offered to take part in the same training at the same facilities as had the training group.

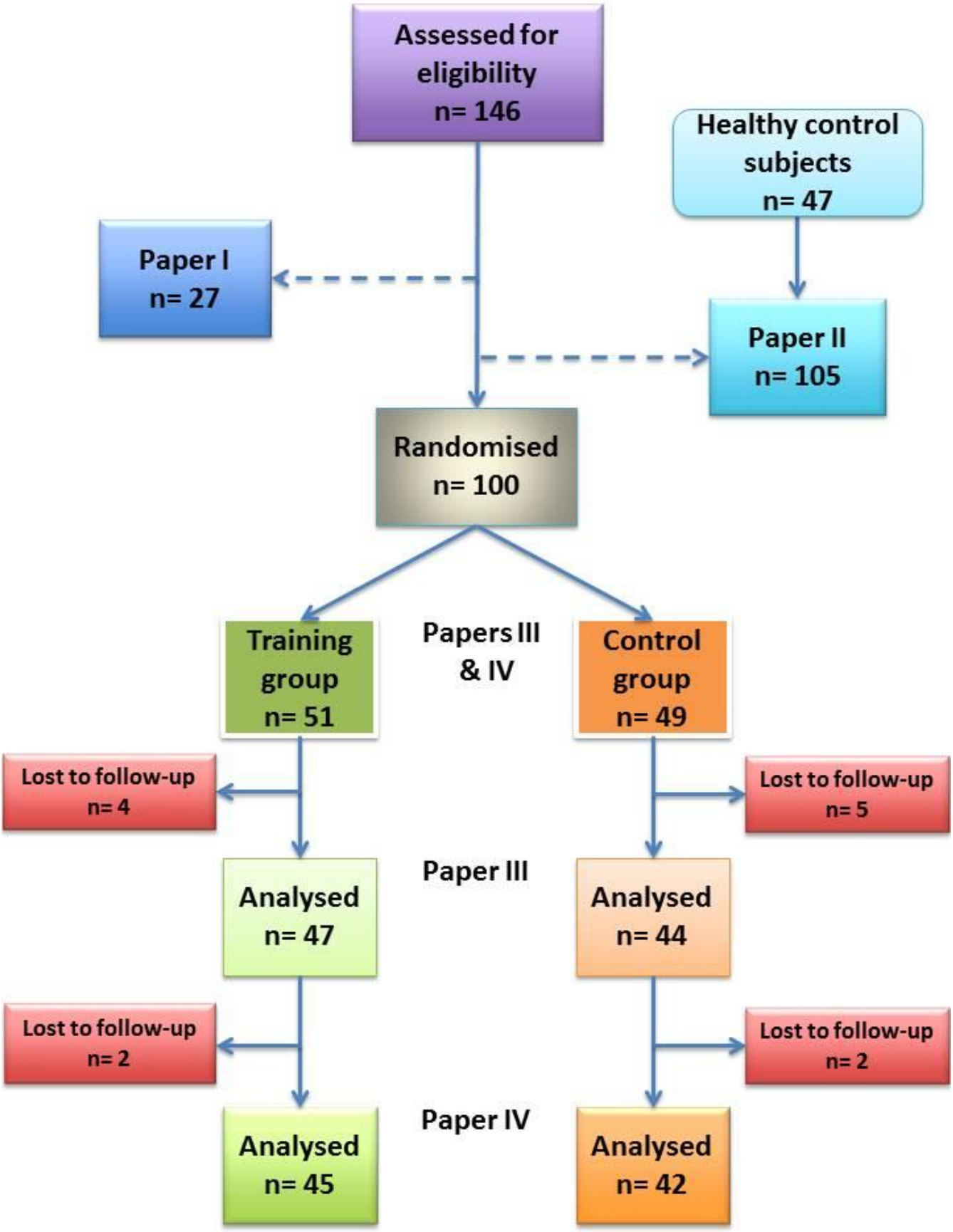


Figure 4. Flowchart, an illustration of the recruitment procedure and the sample sizes for each respective paper in this thesis.

4.4 INCLUSION/EXCLUSION CRITERIA

The inclusion criteria were: a clinical diagnosis of idiopathic PD;[146] H &Y stages 2 or 3;[16] ≥ 60 years of age; the ability to independently ambulate indoors without a walking aid; ≥ 3 weeks of unchanged dopaminergic medication; and observed signs of impaired gait or balance performance during the baseline assessments. The latter criterion was endorsed in an attempt to increase the ecological validity of the study, i.e. by including PwPD that would be considered for gait and balance training in clinical practice.

The exclusion criteria were as follows: a mini-mental state examination (MMSE) score <24; other medical conditions affecting balance control; and/or other personal circumstances that might interfere with adherence to the study.

Exceptions to inclusion criteria: Neither paper I nor paper II used *observed signs of impaired gait or balance* as an inclusion criterion.

Exceptions to exclusion criteria: Paper I did not use an MMSE score as an exclusion criterion, in attempt to increase ecologic validity.

4.5 SAMPLE SIZE ESTIMATIONS

Paper I: The sample sizes estimations were based upon the sample sizes of similar studies investigating the psychometric properties of the Mini-BESTest, which a typical range of between fifteen and thirty-two participants.[127,128,133,147] Despite initially aiming to include thirty-five PwPD, we ended up with twenty-seven due to late drop-outs and time constraints.

Paper II: The sample size estimations used in this study were based upon the Cosmin recommendations, for hypotheses testing.[148] Here a sample of at least one-hundred participants is considered excellent, and a sample of fifty is considered to be good. Keeping with the recommendation for excellence, one-hundred and five PwPD with a mild to moderate disease severity were included. However, for the recruitment of healthy control subjects, we aimed to include fifty people but had to settle with forty-seven included subjects.

Papers III & IV: The sample size estimations were based upon a pilot study on the training programme[144] as well as similar studies in PwPD.[114,149] Power (80% at a 5% alpha-level) was calculated for three outcomes: the Mini-BESTest; DTI of gait velocity; and the falls efficacy scale (FES-I). With an estimated dropout rate of 15%, and corrections for long term follow-up (not included in this thesis), a sample size of one-hundred PwPD was recommended (i.e. fifty PwPD per group). Hence, one-hundred PwPD were included.

4.6 PARTICIPANTS

The demographic characteristics of the participants in each paper are summarised in Table II.

4.7 ASSESSMENT TOOLS

A variety of assessment tools were used in this thesis, both as descriptors and as outcome measures. Table III summarises the tools used for each respective paper.

4.7.1 The Mini-BESTest

The Mini-BESTest[132] is a clinical tool, stated to measure dynamic balance. This test encompasses 14 items, divided into the four subcomponents: anticipatory postural adjustments, postural responses, sensory orientation, and dynamic gait. Items are scored from 0 (unable or requiring help) to 2 (normal) on an ordinal scale, with a maximal total score of 28 points. In accordance with recommendations,[134] the items single limb stance and compensatory stepping correction (lateral) were assessed for both the right and left sides, albeit only the score of the worst side was used to calculate the total score. The items of the Mini-BESTest are presented in Table IV.

Within this thesis, The Mini-BESTest- both its total score and subcomponent scores - is an outcome measure in papers I, II and III.

Table II. Participant characteristics with regards to the respective papers included in this thesis.

	n	Mild/ Moderate (%)	Male/ female (%)	Age (years)		UPDRS, motor		Time since diagnosis (years)	
				Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Paper I									
PwPD	27	59/41	67/33	73 (4)	66-80	35 (11)	11-63	6 (4)	1-15
Paper II									
PwPD	105	46/54	57/43	73 (6)	61-87	33 (12)	12-76	6 (5)	1-25
Healthy controls	47		57/43	71 (6)	60-88				
PwPD mild	48	100/0	54/46	72 (6)	63-83	30 (10)	12-75	4 (4)	1-17
PwPD moderate	57	0/100	60/40	73 (6)	61-87	35 (12)	16-76	7 (6)	1-25
PwPD fallers	46	44/56	52/48	73 (5)	63-84	34 (13)	12-76	6 (6)	1-25
PwPD nonfallers	59	48/52	61/39	73 (6)	61-87	32 (11)	14-75	5 (4)	1-19
Paper III									
PwPD training	47	43/57	60/40	73 (6)	61-87	36 (10)	17-62	6 (5)	1-25
PwPD control	44	43/57	51/49	74 (5)	65-87	37 (11)	14-57	6 (5)	1-21
Paper IV									
PwPD Training	45	42/58	60/40	73 (6)	61-87	32 (12)	12-75	6 (5)	1-25
PwPD Control	42	43/57	50/50	74 (6)	65-87	33 (12)	16-76	5 (5)	1-21

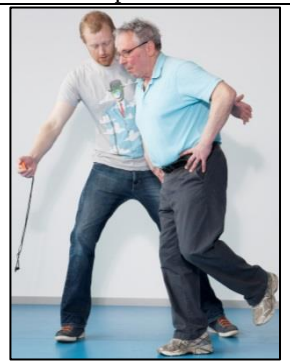
PwPD= People with Parkinson's disease; n=number; UPDRS, motor=Unified Parkinson's disease rating scale, part III; SD= Standard deviation; Mild= Hoehn and Yahr stage 2; moderate= Hoehn and Yahr, stage 3.

Table III. An overview of the measurement instrument used in this thesis

Instruments	**Paper I**	**Paper II**	**Paper III**	**Paper IV**
The Mini-BESTest	•	•	•	
UPDRS-motor	•	•	•	•
MMSE	•	•	•	•
The TUG		•		
The UPDRS-ADL		•	•	
GaitRITE			•	•
Cognitive task			•	•
Accelerometers			•	
FES-I			•	

The Mini-BESTest= a clinical multi-item tool stated to measure dynamic balance
UPDRS, motor= the Unified Parkinson's Disease Rating scale, part III, a test to assess severity of motor symptoms
MMSE=the Mini-Mental State Examination score, a test to screen for cognitive impairments
TUG= the Timed Up and Go test, a test to assess functional mobility
UPDRS-ADL= the Unified Parkinson's Disease Rating scale, part II, a test to assess disease related Activities of Daily Living
GaitRite®= an electronic walkway to assess gait during single- and dual-task conditions
Cognitive task= reciting alternate letters of the Swedish alphabet, performed as a single and dual-task, respectively
Accelerometers= Devices that can be used to measure an individual's acceleration
FES-I=Falls efficacy scale-international, a test to assess fear of falling

Table IV. Summary of the subcomponents and items of the Mini-BESTest.[a]

				
Subcomponents	***Anticipatory***	***Reactive postural control***	***Sensory orientation***	***Dynamic gait***
Items	1. Sit to stand	4. Compensatory stepping correction- forward	7. Stance (feet together); eyes open, firm surface	10. Change in gait speed
	2. Rise to toes	5. Compensatory stepping correction- backward	8. Stance (feet together); eyes closed, foam surface	11. Walk with Head turns- horizontal
	3. Stand on one leg, left and right[b]	6. Compensatory stepping correction- lateral, left and right[b]	9. Incline, eyes closed	12. Walk with pivot turns
				13. Step over obstacles
				14. Timed up & go with dual-task

[a] Maximal score 28 points. [b] Only the score of the worst side was used to calculate the total score.

4.7.2 The Unified Parkinson's disease rating scale

The Unified Parkinson's Disease Rating scale (UPDRS) was developed to enable comprehensive monitoring of PD related disabilities and symptoms.[150] This scale entails four parts: part I concerns mentation, behaviour and mood; part II concerns activities of daily living); part III investigates motor symptoms; and part IV focuses on complications.

Within this thesis the parts investigating disease related motor symptoms (III) and activities of daily living (II) are used.

4.7.2.1 UPDRS, motor (part III)

The UPDRS, motor, was used to assess the severity of motor symptoms commonly observed in PwPD. Such symptoms include: bradykinesia, rigidity, tremor, postural instability during transfers and gait. Moreover, the UPDRS, motor, also includes a retropulsion test,[151] that is, a test that assesses how PwPD react to rapid perturbation in the backwards direction. Here the number of steps required to regain balance control is commonly used[150] to distinguish between mild (H&Y$\leq$ 2) and moderate to severe (H&Y $\geq$ 3) disease severity, where the use of more than two steps is interpreted as postural instability.[151] The UPDRS, motor, contains 27 items, each contributing to the total score that amounts to 108. A higher score is interpreted as more severe motor symptoms.[152] The UPDRS, motor, have been found valid[150] and reproducible.[153] In this thesis, the UPDRS, motor, is used as a descriptor of disease severity.

4.7.2.2 Activities of daily living part (II)

The UPDRS, activities of daily living (ADL), measures disease related ADL. This is assessed by means of a questionnaire, and can either be administered via an interview or as self-report questionnaire (in this study an interview was performed).[150] Thirteen items are included in this questionnaire, including questions ranging from the self-perceived ability to eat and wash to the occurrence of falling and gait abilities. The score of each item is subsequently calculated to produce a total score that has a maximum of 52. A higher score is interpreted as more severe limitations of ADL. The UPDRS, ADL, has previously been found valid and reproducible.[154,155] In this thesis, the UPDRS, ADL was used as an outcome measure in papers II and III.

4.7.3 The Mini-Mental State Examination score

The Mini-Mental State Examination score (MMSE) is test of cognitive function, stated to cover areas such as orientation, registration, attention and calculation, recall and language.[156] This test, entailing 11 items, is evaluated based on a total score. The maximal score is 30 of which a score below 24 is considered an indication of cognitive impairment.[156] The Movement Disorder Society Task force has recommended MMSE to be used in PwPD.[157] In this study, a score of at least 24 was a requirement to be included in the randomised controlled trial.

4.7.4 The timed up and go test

The timed up and go test (TUG) is a clinical test evaluating the construct of physical mobility,[158] and has been found reproducible and valid in PwPD.[159] The test itself measures the time it takes for a subject to perform the following sequence: stand up from a standard arm chair, walk a distance of 3 meters, turn 180 degrees, walk back to the chair, and sit down again. In this thesis, the TUG test was performed during the performance of item 14 of the Mini-BESTest. The TUG is an outcome measure in paper II.

4.7.5 The GAITRite® electronic walkway system

For the assessment of gait during ST and DT-conditions the GAITRite® system was used (CIR Systems, Inc., Haverton, PA, USA). This is a nine metre (active zone: 8.3 meters) electronic walkway that is connected to a computer. The walkway has embedded pressure sensors that allow for the detailed investigation of specific gait parameters. The GAITRite® system has been found to be valid and reproducible when measuring gait performance in PwPD.[160,161]

For both ST and DT-conditions, (which was preceded by a practice session aimed at minimising the risk of learning bias) walking was performed by means of ordinary over-ground walking. Acceleration and deceleration distances of three 3 meters was given on each side of the walkway to ensure steady state walking when gait was measured .[162] When assessing gait, the participants were instructed to repeatedly walk at self-selected (normal) speed. This continued until six valid trials of each condition had been captured. However, the participants were not informed of this on beforehand in order to avoid bias. Moreover, in order to minimise the risk of fatigue affecting the results, all participants were required to sit down and rest in the midst of the gait assessments. During the DT-condition, the participants were instructed to pay equal attention to the walking and the added task at all times.

Within this thesis, both the ST and DT-gait performance, respectively, were used as outcome measures in paper III. The relation between ST and DT-gait (i.e. automaticity) was used as outcome measure in paper IV.

4.7.6 The added task during the single and dual-task conditions

The added task that was chosen for this intervention was a cognitive task which was influenced by the walking while talking paradigm.[163,164] This task, which has been found to predict falls in older people,[165] entailed the reciting of alternate letters of the Swedish alphabet at self-selected speed, and was performed under both ST (while seated) and DT-conditions (during gait) following a randomised sequence.

When the added task was performed during the DT-condition, the participants were instructed to start reciting as soon as they started to walk and to continue until they had stopped. Importantly, only the letters recited while the participants walked upon the walkway were recorded.

The participants performed the added task under the ST-condition until three valid trials had been recorded. Each trial lasted 15 seconds, starting when the participants initiated reciting. However, only the letters recited between the fifth and fifteenth seconds were recorded, in order to resemble the DT- condition. In order to minimise practice bias, the participants received different starting letters following a standardised scheme shortly before each trial started.[164] Moreover, the performance of the added task, both under ST and DT-conditions, was included in the above mentioned practice session.

Within this thesis, the performance of the added task under ST and DT -conditions, respectively, was used as outcome measures in paper III. Similar to gait, the relation between the ST and the DT performance (i.e. automaticity) was used as outcome measure in paper IV.

4.7.7 Falls Efficacy Scale International

The Falls efficacy scale international (FES-I)[166] is a self-report questionnaire assessing fall-related concerns with regard to specific daily activities. The FES-I entails 16 items, each of which are scored separately on a scale ranging from one to four. The score of each item sum to a maximum of 64, where a higher number is interpreted as a higher fall-related concerns. The FES-I has shown satisfactory psychometric properties when used in PwPD.[167]

In this thesis, the FES-I was an outcome measure in paper III.

4.7.8 Accelerometers

Accelerometers refer to devices that can be used to measure an individual's acceleration, for example while walking. In this study accelerometers (Actigraph GT3X+, Pensacola, FL, USA) were used to assess physical activity levels before and after the training intervention. Following the assessments in the movement laboratory, included participants were asked to wear accelerometers for seven consecutive days. The device was attached to an elastic band that was worn around the waist, with the accelerometers positioned at the hip. Data were sampled at 30Hz and subsequently processed by means of the ActiLife 6 software (ActiGraph, Pensacola, FL, USA). The Actigraph GT3X+ has shown appropriate psychometric properties with regard to the assessments of energy expenditure in old people.[168]

4.8 PROCEDURES

4.8.1 Paper I

To investigate inter-rater reproducibility two physiotherapists with different expertise and experience of the Mini-BESTest administered and rated the test performance of the included PwPD on the same day at a university hospital. The more-experienced rater (rater A) had administered and rated the Mini-BESTest more than 100 times, whereas the less-experienced rater (rater B) had administered the test approximately ten times before this study started. To synchronise their assessment of the Mini-BESTest, the two raters met prior to the study on two occasions to discuss the principles of the test, and to practice its administration and rating. However, during and after the test sessions the raters were blinded to each other's ratings. Participants were briefly interviewed, using a standardised protocol, regarding current health status including years since diagnosis. Disease severity was measured with the UPDRS, motor[154] and cognitive function was assessed with the MMSE. Subsequently, the participants performed the Mini-BESTest with each of the two test administrators, who were situated in separate rooms. Randomisation decided which administrator to start with. The test procedure took approximately one hour to complete.

For test-retest reproducibility, the more experienced rater (rater A) reassessed the participants seven days later. At the second test session, rater A performed a brief interview, including questions regarding pain, medication, activity, falls, and other possible incidents that might have influenced their balance performance since the previous session. Following this, the participants performed the Mini-BESTest at the same location and time of the day as they had performed the test the previous week.

4.8.2 Paper II

Included participants underwent an interview regarding current health status and were screened with the UPDRS, motor. Subsequently, the participants, in a randomised order, performed the Mini-BESTest, the TUG and the UPDRS, ADL. All participants completed every item of each test.

During each test session, the same assessor instructed and rated all tests independently. For practical reasons, four different physiotherapists served as test assessors. In order to standardise their instructions and ratings, all assessors took part in a training session prior to the commencement of the study.

4.8.3 Papers III &IV

The HiBalance intervention was performed at two geographical cohorts (north and south) in order to reduce travel times for the included participants. Randomisation, performed in blocks of four by, means of opaque envelopes (sealed and numbered) was separate for the respective geographical cohort. Therefore all participants were required to choose geographical cohort to be assigned to prior to taking part in the assessments, should they be included in the study. Following the baseline assessments, the included participants were randomised to the training group or control group.

Although the testers were blinded to group allocation at the baseline assessments, this was not possible at follow-up since some testers also served as trainers. In an attempt to decrease bias, testers that had served at trainers in one geographical cohort never assessed participants from that cohort during the follow-up assessments.

Participants that had been randomised to the training group participated in 10-weeks of highly challenging gait and balance training. The participants that had been randomised to the control group were encouraged to continue with their usual habits. They were neither discouraged nor encouraged to participate in organised training during the time of the study.

4.8.3.1 Training programme

The HiBalance training programme, a highly challenging gait and balance training that specifically targets well established impairments among PwPD, was performed in groups of 4-7 participants for 10 weeks (3 times á 60min/week). Each training session was supervised by 2 physiotherapists.

The core of the training programme consisted of 4 components specific to gait and balance impairments in PwPD: (1) *Sensory integration* (walking tasks on varying surfaces with or without visual constraints); (2) *Anticipatory postural adjustments* (voluntary arm/leg/trunk movements, postural transitions, and multidirectional stepping, emphasizing movement

velocity and amplitude); (3) *Motor agility* (inter-limb coordination under varying gait conditions and quick shifts of movement characteristic during predictable and unpredictable conditions); and (4) *Stability limits* (controlled leaning tasks performed while standing with varying bases of support, stimulating weight shifts in multiple directions).

The 10-week period was divided into 3 blocks (A; B; and C). In block A (weeks 1–2); participants were introduced to the ST-exercises of each balance component separately, in order to emphasise the quality of movement and the objectives of the exercises. In block B (weeks 3–6); DT-exercises were introduced and the difficulty level for each balance component was increased. In block C (weeks 7–10); the difficulty level and the variation was increased further by using exercises that combined the different balance components.

DT-exercises were gradually integrated into the program by adding concurrent cognitive tasks and/or motor tasks to the gait and balance exercises. The added tasks were mainly focusing on encouraging the continuous processing while walking under different circumstances. Examples of this included the silent counting of every step, or collaboration tasks (e.g. walking pairwise while exchanging words that starts with the same letter as the previous word ended with, or throwing balls to each other). The latter examples required the participants to continuously pay attention to their companion's performance and try to produce an adequate response, whether cognitive or manual. However, the DT exercises used during training were never the same as used at pre- and post-assessments (i.e. any task resembling alphabet reciting was prohibited).

Apart from the specific DT-exercises, the programme generally incorporated attentional demanding situations even during the ST-training (e.g. switching between tasks during gait in varied obstacles courses; spatial awareness in relation to obstacles; and collaborative tasks between participants).

Highly challenging training was defined as exercises where the participants intermittently needed to use reactive postural adjustments to maintain balance control during ST-exercises. Similarly, the difficulty level for DT-exercises was to achieve consistent interference of the participants' motor performance when compared to ST-performance (e.g. interfering with speed, movements' fluency or step to step fluctuations).

Since this training concept relied upon the continuous progression and adaptation of exercises with regards to the participants' abilities, it was dependent of educated and skilled trainers. Therefore, all the trainers involved in this study were physiotherapists (n = 10) that were educated in detail about the underlying theories that the programme was based upon, as well as its practical applications. In addition, the trainers documented the contents of each training session and were supported in the practical aspects of the training upon request.

4.9 DATA ANALYSIS

Table V summarises the statistical methods that have been used in this thesis.

Table V. A summary of the statistical methods used in the respective papers of this thesis.

	Paper I	Paper II	Paper III	Paper IV
Descriptive				
Mean	•	•	•	•
Median	•		•	•
Standard deviation	•	•	•	•
Inter quartile range			•	•
Range	•	•		•
95% Confidence Interval	•	•	•	•
Statistical methods				
Intra class correlations 2.1	•			
Cronbach's alpha?	•			
Smallest error of measurement ^{agreement}	•			
Smallest real difference^{ind}	•			
Smallest real difference^{group}	•			
Independent t-test	•	•	•	•
Mann-Whitney U test		•	•	•
Hedges g effect size		•		
Receiver operating curves		•		
Spearman's rho		•		
Spearman's correction for attenuation		•		
Williams T2 formula		•		
Repeated measures anova			•	
Tukey's HSD			•	
Cohens d effect size			•	
Wilcoxon signed rank test			•	•
Mann-Whitney U effect size			•	•

4.9.1 Paper I

Statistical analyses were performed with SPSS (version22, SPSS Inc., Chicago, IL). Reliability was investigated by means of ICC2.1 where one-way repeated measures analysis of variance (ANOVA) were used to calculate agreement between the raters (inter-rater reproducibility) and test sessions (test-retest reproducibility), regarding the total score of the Mini-BESTest as well as its subcomponents. To categorise the level of ICC agreement, we used Altman's classification: < 0.20 = poor; 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = good, 0.81–1.0 = very good.[169]

For parameters of agreement, first SEMagreement was calculated as follows: SEM= √within subject error variance.[140] Following this, the SRD_{ind}[140] was calculated with a 95%

confidence interval, resulting in the following formula: SRD = 1.96 × √2 × SEM.[139] To evaluate the proportion of the measurement error, the SRD% was clculated by dividing the SRD with the maximal total score of the Mini-BESTest (28 points). Similarly, the SRD_{ind} of each subcomponent was divided with its maximal total score (6 or 10 points).

Supplementary analyses specific to this thesis was later performed by calculating the agreement on a group level, i.e. SRD_{group} ,[140] to relate the absolute measurement error to the group of participants in paper III. The calculation used was: the SRD_{ind} /√91.[140] Moreover, in order to evaluate the magnitude of agreement, the SRD% on group level, i.e. $SRD_{group\%,}$ was divided with the maximal score, and the maximal score of each subcomponent, of the Mini-BESTest.

4.9.2 Paper II

Statistical analyses were conducted with STATISTICA software (Statsoft, version 12, Tulsa, OK, USA) and SPSS (SPSS Inc, version 17, Chicago,Illinois).

Independent t-tests were used to investigate the hypotheses that that Mini-BESTest scores (total score) would be significantly lower among: (1) PwPD compared to healthy controls; (2) PwPD with moderate disease severity compared to those with mild severity; and (3) recurrent fallers compared to non-recurrent fallers with mild to moderate PD.

Due to the lack of normal distributions, Mann-Whitney U Tests were used to investigate between-group differences regarding the subcomponents of the Mini-BESTest, where the hypotheses were identical to those regarding the total score. Level of significance was set to p=0.05.

Effect sizes (ES) were calculated in order to estimate the magnitude of between-group differences. Since there was a difference in group sizes, the Hedges g formula was used: M1-M2/SD*pooled.[170] The ES were categorized as: small (d=0.2); medium (d=0.5); and large (d≥0.8).[171]

The Spearman's rho test was used (due to a lack of normal distribution with regard to the respective scores of the TUG and the UPDRS, ADL) to determine how scores produced by the Mini-BESTest correlated with scores of similar (convergent validity) and different (divergent validity) constructs. The strength of the correlations was classified as follows: <0.40=poor; 0.41-0.60= moderate; 0.61-0.80= good; and 0.81-1.00= very good.[172]

The Williams T2 formula was used to investigate the statistical difference between the strength of the correlations for convergent and divergent validity.[173]

Moreover, the correlation between two measures is inevitably attenuated with regards to the reliability of each measure. This means that a measure can never produce a higher association with another measure compared to itself when assessed at two different occasions. Hence, to

obtain the true correlation, Spearman suggested a calculation based on the correlation between the two measures and the correlation obtained from test-retest measurements of each measure.[174,175] Since we had test-retest data for this population, we were able to estimate the true correlation between these measures.

Supplementary analyses were performed to investigate the potential occurrence of floor and/or ceiling effects of the Mini-BESTest as well as the subcomponents. Floor and ceiling effects, respectively, were determined to occur if at least 15 percent of the participants achieved the lowest or highest score available on the Mini-BESTest or the subcomponents.

4.9.3 Paper III

Statistical analysis was conducted using STATISTICA software (Statsoft, version 12, Tulsa, OK, USA). The Student *t* test, Mann-Whitney test, and the $\chi 2$ test were used to assess the homogeneity of the groups at baseline. To test for equality of variance and data normality, Levene's test was used, combined with a visual inspection of the normally distributed and residual curve. On fulfilment of these criteria, a 2-factor repeated-measures analysis of variance was performed to test for interaction effects between groups (training group vs control group) and with time (pre-test and post-test). In the case of significant interaction effects, Tukey's post hoc analyses were performed to assess differences between pre- and posttest. For outcomes with skewed data distributions, log-transformations were conducted, and if normally distributed afterward, an analysis of variance was used. For outcomes without normal distribution even after log-transformation (ie, performance of the cognitive DT), the Mann-Whitney *U* test was used to determine between-group differences (ie, calculated as the difference between pre- and posttest performances) and if significant, the Wilcoxon signed rank test was used to determine within-group differences between pre- and posttest in each group separately. Effect size between the 2 independent groups was computed using Cohen's *d* calculation. We used both an intention-to-treat (last value carried forward data imputation) and a per-protocol approach. However, since these analyses revealed similar results, and given the small dropout rate, only the results for the per-protocol analysis are reported. Significance level was set at $P \leq 0.05$.

Supplementary analyses were performed to investigate between-group differences with regards to the subcomponents of the Mini-BESTest. To test for equality of variance and data normality, the Kolmogorov-Smirnoff test was used, combined with a visual inspection of the normally distributed and residual curve. Due to lack of normal distributions, the Mann-Whitney U test was performed to assess between group differences at baseline. If no baseline differences occurred, the Mann-Whitney U test was also used to compare the groups at the follow up assessments. To obtain information regarding the magnitude of between-group differences at follow-up, non-parametric effect sizes were calculated based on the z-value obtained from the Mann-Whitney U tests, by using the following formula: $r=z/\sqrt{n}$. The

categorisation of the effect sizes were as follows: small effect=0.1; medium effect=0.3; and large effect=0.5.[176]

To investigate if effects of training were consistent with regards to the time and geographical cohorts, within-training group analyses were performed with regards to the difference between the baseline and follow-up assessments.

4.9.4 Paper IV

The gait parameters related to the gait model were calculated in accordance with recommendations,[37,43] that is: the mean and the variance of right and left steps were calculated separately. The mean gait parameters (step velocity, step length, step time, swing time, stance time and step width) were calculated as the mean of right and left step means. Asymmetry parameters were calculated as the absolute difference between the means of right and left steps. Variability parameters were calculated as the square root of the mean variance of the right and the left steps. This is a method that has been proposed to "clean" the variability parameters from variability that may derive from asymmetric gait.[161]

DTI was calculated as the absolute difference between the DT and ST-conditions (DT-ST). This was performed for all gait parameters; as well as for two cognitive parameters that were used to complement to each other: *cognitive performance and cognitive performance variability*. Cognitive performance entails the mean performance of the cognitive task and was calculated as the total mean of: the number of errors /the total number of letters recited per trial. Cognitive performance variability, which can be considered a measure of cognitive processing robustness,[177] refers to the intra-individual variability of the cognitive performance and was calculated as the standard deviation of the cognitive performance across trials.[178]

Statistical analysis was conducted using STATISTICA software (Statsoft, version 12, Tulsa, OK). To test for equality of variance and data normality, the Kolmogorov-Smirnoff test was used, combined with a visual inspection of the normally distributed and residual curve.

Due to lack of normal distributions, non-parametric statistics were applied. The Mann-Whitney U test was applied to analyse between-group differences (calculated as the difference between the baseline and the follow-up assessments). If a significant between-group difference was found, the Wilcoxon Signed Rank Test was used to analyse within-group differences. Effect sizes were calculated to obtain information regarding the magnitude of between-group differences. Since the data was not normally distributed, our calculations were based on the z values obtained from the Mann-Whitney U tests by using the following formula: $r=z/\sqrt{n}$. The categorisation of the effect sizes were as follows: small effect=0.1; medium effect=0.3; and large effect=0.5.[176]

In addition, specific to this thesis, the results of all gait parameters that are presented in forms of the relative measure DTI, are also presented as absolute ST and DT measures in order to increase the interpretability.

5 RESULTS

5.1 THE REPRODUCIBILITY OF THE MINI-BESTEST

For the reproducibility of the Mini-BESTest, both inter-rater and test-retest reliability was found to be good (ICC= 0.72; and 0.80, respectively), whereas the investigation of the proportional measurement error was considered high (SRD%=14.6; and 12.1, respectively).

Regarding the Mini-BESTests subcomponents, the inter-rater reliability was good for anticipatory postural adjustments (ICC=0.65), whereas it was moderate for postural responses, sensory orientation and dynamic gait (ICC $\leq$ 0.54). For inter-rater agreement, postural responses accounted for the largest proportional measurement error (SRD%=38.3) whereas it was lowest for sensory integration (SRD%=16.7).

For the test-retest reliability of the subcomponents, reproducibility was good for anticipatory postural adjustments, postural responses and dynamic gait (ICC $\geq$ 0.70) whereas it was moderate for sensory orientation (ICC=0.54). Conversely, for test-retest agreement, the proportional measurement error was lowest for sensory orientation and highest for postural responses (SRD%= 13.3; and 26.7; respectively).

Table VI illustrates the agreement of the overall findings of the Mini-BESTest's reproducibility in PwPD with mild to moderate disease severity (including the SRD_{group} findings, which are related to the sample size of the randomised controlled trial).

Table VI. Inter -rater and test-retest reproducibility for the Mini-BESTest and its subcomponents.

	Mean	SD	Range	Mean	SD	Range	$ICC_{2.1}$	Cronbach's alpha	SEM	SRD_{ind}	SRD_{ind}%	SRD_{group}	SRD_{group}%
Inter-rater reproducibility	Rater A			Rater B									
Mini-BESTest, total score	20.2	2.6	15-25	21.3	2.7	15-26	0.72	0.87	1.5	4.1	14.6[1]	0.4	1.5[1]
Anticipatory postural adjustments	3.6	1.2	1-6	4.1	1.0	2-6	0.65	0.83	0.7	1.9	31.7[2]	0.2	3.3[2]
Postural responses	4.2	1.0	3-6	3.7	1.1	1-6	0.43	0.63	0.8	2.3	38.3[2]	0.2	4.0[2]
Sensory orientation	5.7	0.6	4-6	5.9	0.5	4-6	0.54	0.70	0.4	1.0	16.7[2]	0.1	1.8[2]
Dynamic gait	6.7	1.4	5-10	7.7	1.1	5-9	0.48	0.75	1.1	2.9	29.0[2]	0.3	3.0[2]
Test-retest reproducibility	Session 1			Session 2									
Mini-BESTest, total score	20.2	2.6	15-25	20.5	2.9	14-26	0.80	0.88	1.2	3.4	12.1[1]	0.4	1.3[1]
Anticipatory postural adjustments	3.6	1.2	1-6	3.7	1.1	2-6	0.79	0.88	0.5	1.4	23.3[2]	0.2	2.5[2]
Postural responses	4.2	1.0	3-6	4.4	1.1	3-6	0.70	0.83	0.6	1.6	26.7[2]	0.2	2.8[2]
Sensory orientation	5.7	0.6	4-6	5.9	0.4	5-6	0.54	0.77	0.3	0.8	13.3[2]	0.1	1.4[2]
Dynamic gait	6.7	1.4	5-10	6.5	1.7	4-10	0.78	0.87	0.7	2.0	20.0[2]	0.2	2.1[2]

SD= Standard Deviation; ICC = Intra Class Correlation; SEM = Standard Error of Measurement (√within subjects error variance); SRD_{ind} = Smallest Real Difference on individual level (1.96 x √2 x SEM); SRD_{ind}%= [1]SRD_{ind}/maximal Mini-BESTest score x100; [2]SRD_{ind}/ maximal subcomponent score x 100; SRD_{group}= SRD_{ind}/√91; SRD_{group}%=[1]SRD_{group}/maximal Mini-BESTest score x100; [2]SRD_{group}/ maximal subcomponent score x 100.

5.2 THE CONSTRUCT VALIDITY OF THE MINI-BESTEST

The results showed that the Mini-BESTest scores were significantly worse among: PwPD compared to age matched controls (p=0.001; ES=1.17); and PwPD with moderate disease severity compared to those with mild severity (p=0.001; ES=1.09). However, there were no differences between PwPD with a reported history of recurrent falls as compared to non-recurrent fallers (p=0.096; ES=0.32).

In addition, the Mini-BESTest showed a moderate relationship with the TUG (rho=-0.586), and a poor relationship with the UPDRS-ADL (rho=-0.260).

5.2.1.1 Floor/ceiling effects of the Mini-BESTest and its subcomponents

No floor effects were found for the total score Mini-BESTest or any of the subcomponents. Nor were any ceiling effect present for the Mini-BESTest's total score (0%); APA's (6%); Postural Responses (7%); or Dynamic Gait (2%). However for Sensory Orientation, 48% of the PwPD obtained the maximal score possible. The distribution of scores for the Mini-BESTest and the respective subcomponents is illustrated in Figure 5.

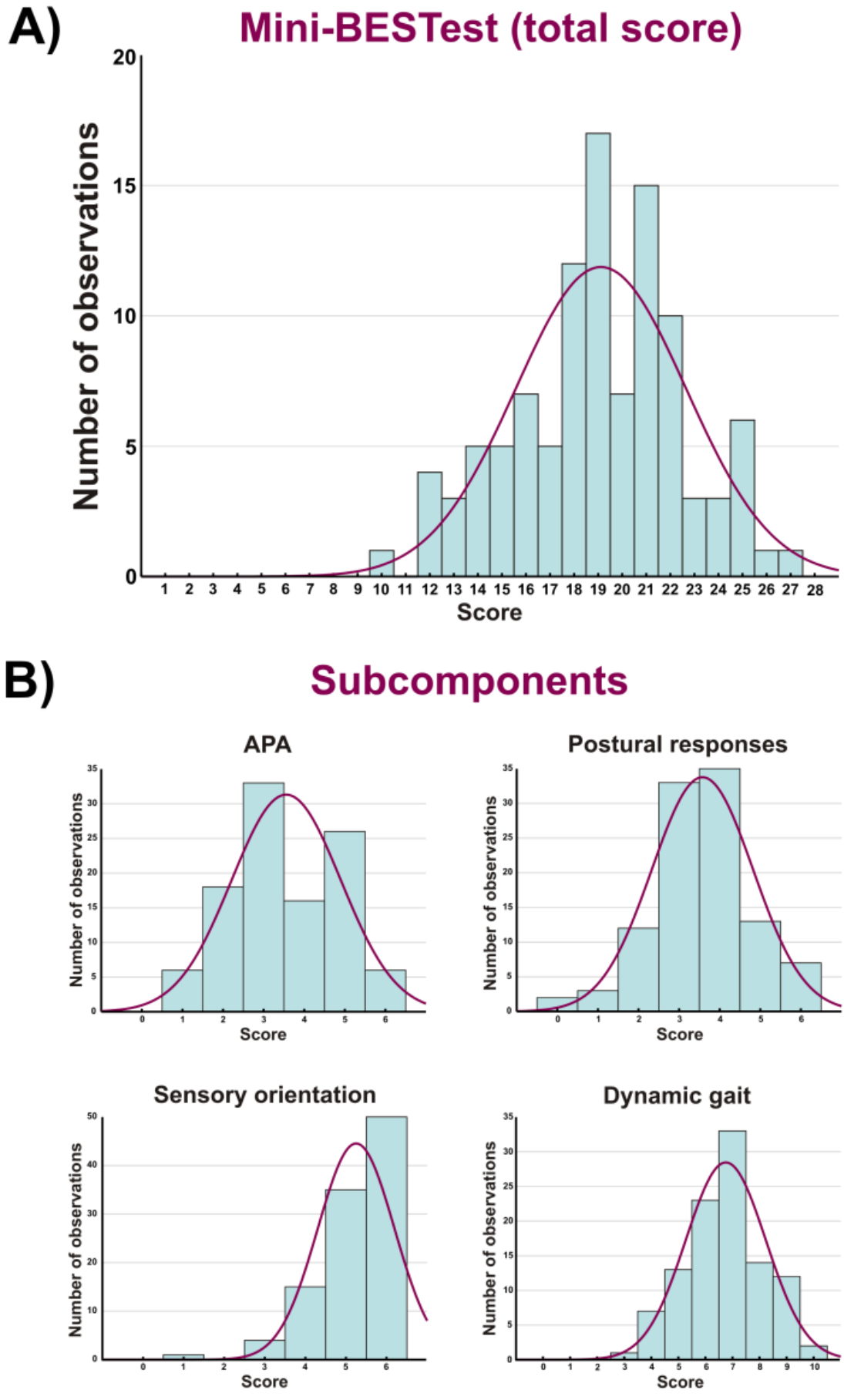


Figure 5. Illustrating the distribution of scores regarding (A) the Mini-BESTest (total score); (B) the respective subcomponents of the Mini-BESTest.

5.3 OVERALL EFFECTS OF GAIT AND BALANCE TRAINING

The results showed that the training group, in comparison with the control group, significantly improved the performance of the Mini-BESTest (p=0.001). The training group also improved velocity and step length during ST-gait (p=0.018; and p= 0.015, respectively) whereas cadence was unaffected (0.108). Although none of the aforementioned parameters were affected during the DT-condition (p≥0.469), the training group improved the performance of the cognitive task when performed as a DT but not when performed as an ST (p=0.006; and p=0.634, respectively). Moreover there were no between-group effects on fall-related concerns (FES-I; p=0.772). However significant between-group differences (p=≤0.033) were found for the UPDRS, ADL and the accelerometer measurements (i.e. total number of steps per day).

5.3.1.1 Within training-group effects with regards to training period

There were no differences between the training groups with regards to the three time periods that training had been undertaken, the median Mini-BESTest improvement for period 1, 2 and 3, respectively, was: 3, 4, and 2 points (p=0.189).

5.3.1.2 Within training-group effects with regards to geographical cohort

There were no between-group differences when comparing the participants that had participated in training at the two different geographical cohorts (p=0.850). The mean Mini-BESTest improvement was 3.1 points for the northern cohort and 3.0 points for the southern cohort.

5.3.1.3 Training effects on the subcomponents of the Mini-BESTest

The results showed that the training group, compared to the controls, improved the performance of APA and dynamic gait moderately (ES= -0.33) whereas the improvement of postural responses was small (ES=0.24). The performance of sensory orientation on the other hand was unaffected (p=0.159). These findings are illustrated in Table VII and Figure 6.

Table VII. Treatment effects of the Mini-BESTest's subcomponents between the training group and control group.

	Training group n=47			**Control group n=44**			
	Median (IQR)			Median (IQR)			
	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference	p-value
Anticipatory postural adjustments	3.0 (2.0)	4.0 (2.0)	1.0 (1.0)	3.0 (2.0)	3.5 (1.0)	0.0 (0.5)	**0.001**
Postural responses	3.0 (1.0)	4.0 (1.0)	1.0 (2.0)	4.0 (1.0)	4.0 (1.5)	0.0 (1.0)	**0.023**
Sensory orientation	6.0 (1.0)	6.0 (1.0)	0.0 (1.0)	5.0 (1.0)	6.0 (1.0)	0.0 (1.0)	0.159
Dynamic gait	7.0 (1.0)	8.0 (2.0)	1.0 (2.0)	7.0 (1.5)	7.0 (2.0)	0.0 (1.0)	**0.001**

IQR=Inter quartile range; Difference= Median difference between the baseline and follow-up assessments

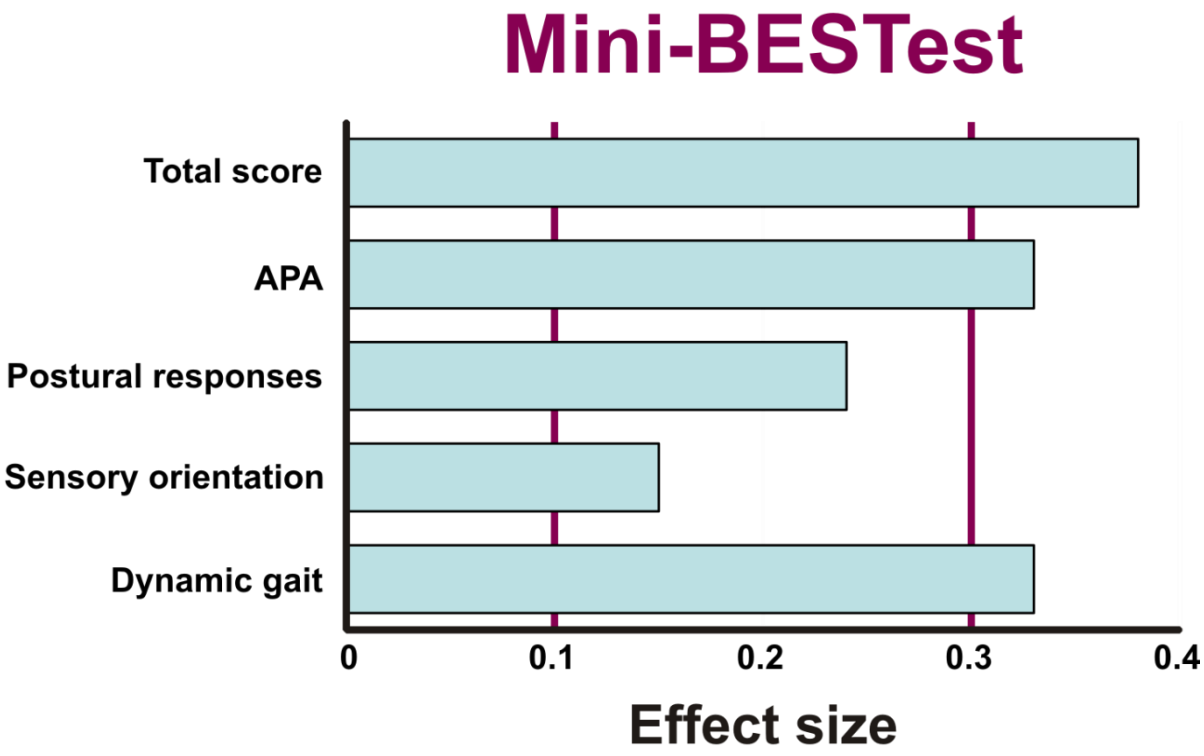


Figure 6. Illustration of the magnitude of differences between the training and control group with regards to the Mini-BESTest's total score and the subcomponents. An effect size of 0.1 equals a small effect, and an effect size of 0.3 equals a medium effect.

5.4 EFFECTS OF DUAL-TASK GAIT TRAINING ON AUTOMATICITY AND ATTENTION ALLOCATION

As shown in Table VIII there were no DTI differences between the groups with regards to any gait parameter of any gait domain ($P \geq 0.084$). However, the between-group differences of cognitive performance and cognitive variability ($p=0.018$; and $p=0.038$, respectively) revealed that the training group had improved both parameters significantly ($p=0.038$; and $p=0.032$, respectively). Figure 7 illustrates the effect sizes between the groups and their direction.

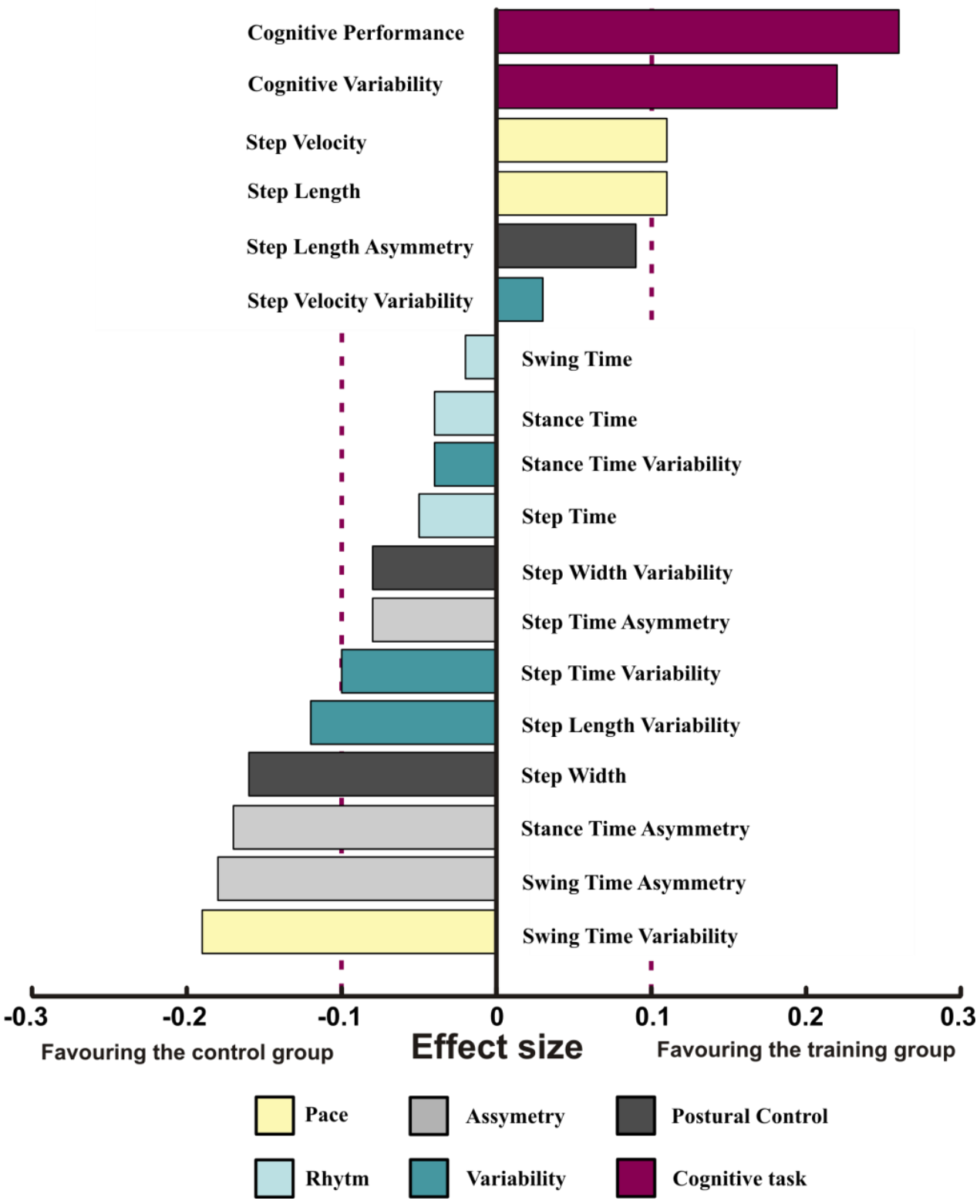


Figure 7. An illustration of the magnitude of dual-task interference differences (effect sizes) between the training group and the control group, measured as the difference between the baseline and follow-up assessments. The dotted line represents an effect size of 0.1 (small effect). The bars on the left side indicate that the control group has improved this parameter, whereas the bars on the right side indicate that the training group has improved this parameter.

Table VIII. Treatment effects with regards to dual-task interference for the training group and control group at baseline and 10-week follow-up.

	Training group (n=45)			Control group (n=42)				
	Median (IQR)			Median (IQR)			Effect size[a]	P-value Between group[b]
Pace Domain	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference		
DTI Step Velocity (m/s)	-0.173 (0.221)	-0.180 (0.250)	-0.001 (0.218)	-0.184 (0.310)	-0.167 (0.217)	-0.028 (0.218)	0.11	0.290
DTI Step Length (m)	-0.047 (0.070)	-0.035 (0.080)	-0.006 (0.056)	-0.044 (0.076)	-0.036 (0.052)	-0.018 (0.058)	0.11	0.298
DTI Swing Time Variability (ms)	7.8 (11.7)	6.7(11.4)	-0.9 (10.8)	10.0 (29.1)	8.9 (19.0)	2.9 (16.1)	-0.19	0.084
Rhythm Domain								
DTI Step Time (ms)	36.1 (65.5)	38.2 (65.7)	6.5 (49.4)	55.1 (114.1)	47.8 (108.8)	9.3 (64.2)	-0.05	0.662
DTI Swing Time (ms)	13.2 (36.2)	16.9 (43.9)	4.5 (40.8)	12.8 (59.1)	17.7 (61.6)	0.9 (39.2)	-0.02	0.842
DTI Stance Time (ms)	72.9 (109.6)	64.9 (95.8)	3.2 (69.9)	96.0 (171.9)	75.4 (168.0)	9.9 (117.3)	-0.04	0.731
Variability Domain								
DTI Step Velocity Variability(m/s)	0.026 (0.029)	0.018 (0.030)	0.002 (0.040)	0.017 (0.028)	0.022 (0.031)	0.002 (0.027)	0.03	0.802
DTI Step Length Variability (m)	0.008 (0.016)	0.007 (0.011)	-0.000 (0.016)	0.008 (0.011)	0.008 (0.014)	0.000 (0.018)	-0.12	0.246
DTI Step Time Variability (ms)	13.2 (19.3)	8.7 (16.7)	0.9 (18.9)	12.8 (33.1)	12.9 (28.3)	3.6 (22.8)	-0.10	0.352
DTI Stance Time Variability (ms)	18.2 (29.2)	11.4 (21.9)	3.2 (69.9)	21.1 (43.9)	16.7 (43.0)	9.9 (117.3)	-0.04	0.731
Asymmetry Domain								
DTI Swing Time Asymmetry (ms)	1.4 (9.3)	1.9 (12.5)	-2.5 (11.3)	3.6 (16.8)	3.5 (17.5)	0.3 (12.3)	-0.18	0.093
DTI Step Time Asymmetry (ms)	3.5 (16.5)	3.5 (13.8)	3.4 (16.6)	5.4 (26.4)	4.8 (21.4)	1.2 (19.9)	-0.08	0.462
DTI Stance Time Asymmetry (ms)	3.2 (12.7)	2.6 (11.4)	-0.5 (11.8)	8.1 (19.5)	3.0 (18.0)	3.6 (19.6)	-0.17	0.104
Postural Control Domain								
DTI Step Length Asymmetry (m)	0.002 (0.025)	0.001 (0.024)	0.007 (0.027)	0.000 (0.027)	-0.001 (0.029)	0.003 (0.021)	0.09	0.422
DTI Step Width (m)	0.009 (0.012)	0.009 (0.015)	-0.001 (0.013)	0.012 (0.015)	0.009 (0.010)	0.002 (0.014)	-0.16	0.138
DTI Step Width Variability (m)	0.001 (0.006)	0.002 (0.007)	-0.001 (0.008)	0.000 (0.005)	0.001 (0.006)	-0.000 (0.005)	-0.08	0.473
Cognitive Task								
DTI Cognitive Performance	8.8 (18.5)	4.4 (16.2)	5.1 (29.0)	5.9 (28.2)	7.5 (25.3)	-3.6 (25.6)	0.26	**0.018**
DTI Cognitive Performance Variability	1.9 (9.2)	-1.6 (10.7)	3.3 (11.0)	1.3 (12.6)	1.4 (8.5)	-0.6 (12.9)	0.22	**0.038**

Abbreviations: IQR= Inter quartile range; DTI = Dual-Task Interference; m/s=meters per second; m=meters; ms=milliseconds;
Cognitive Performance= the number of errors /the total number of letters recited per trial; Cognitive Performance Variability= the Intra-individual standard deviation of the cognitive performance across trials.

[a] Cohens r, non-parametric effect-size, computed using the following formula: r= z/√number of observations. [b]Mann-Whitney U test to determine between-group differences (i.e., computed as the difference between follow-up and baseline performance). Bold = statistical significance ($p < 0.05$).

5.4.1.1 Single-task gait

The analyses of the difference between the baseline and follow up assessments showed that in comparison to the control group, the training group improved parameters belonging to the pace domain (step velocity and step length) and the rhythm domain (step time and stance time). See Table IX.

5.4.1.2 Dual-task gait

The analyses of the difference between the baseline and follow up assessments showed that the control group significantly increased their step width in comparison with the training group ($p=0.046$). See Table X.

Table IX. Treatment effects with regards to single-task gait for the training group and control group at baseline and 10-week follow-up.

	Training group (n=45)			Control group (n=42)				
	Median (IQR)			Median (IQR)				
Pace Domain	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference	Effect size[a]	P-value Between group[b]
Step Velocity (m/s)	1.21 (0.279)	1.28 (0.250)	-0.109 (0.253)	1.18 (0.282)	1.18 (0.271)	-0.007 (0.161)	0.26	**0.016**
Step Length (m)	0.636 (0.143)	0.655 (0.094)	-0.027 (0.054)	0.623 (0.094)	0.639 (0.101)	-0.002 (0.061)	0.30	**0.006**
Swing Time Variability (ms)	14.2 (5.4)	13.5 (4.5)	1.5 (4.8)	16.0 (5.8)	15.0 (8.9)	1.1 (6.2)	-0.12	0.253
Rhythm Domain								
Step Time (ms)	534.3 (54.4)	521.4 (62.0)	13.0 (36.4)	532.6 (4.6)	532.7 (38.4)	-0.8 (34.5)	-0.23	**0.035**
Swing Time (ms)	382.6 (39.0)	381.5 (45.5)	-2.1 (27.0)	384.5 (46.4)	380.8 (34.1)	-0.2 (16.9)	-0.02	0.836
Stance Time (ms)	684.5 (68.4)	670.4 (77.8)	25.0 (62.4)	675.5 (75.0)	683.2 (65.0)	-1.2 (47.4)	-0.27	**0.013**
Variability Domain								
Step Velocity Variability (m/s)	0.048 (0.015)	0.051 (0.014)	-0.002 (0.022)	0.055 (0.016)	0.050 (0.018)	0.003 (0.023)	0.19	0.082
Step Length Variability (m)	0.024 (0.008)	0.023 (0.007)	0.001 (0.007)	0.024 (0.010)	0.025 (0.009)	0.000 (0.009)	-0.13	0.237
Step Time Variability (ms)	15.3 (7.4)	14.5 (5.2)	1.3 (5.8)	17.8 (6.2)	16.6 (8.8)	0.2 (3.7)	-0.09	0.395
Stance Time Variability (ms)	17.7 (8.7)	16.8 (4.6)	1.4 (6.4)	20.0 (8.7)	19.0 (8.5)	0.6 (7.5)	-0.05	0.645
Asymmetry Domain								
Swing Time Asymmetry (ms)	8.8 (12.9)	7.2 (11.0)	0.6 (9.1)	9.7 (12.7)	8.7 (13.3)	1.3 (12.0)	0.01	0.963
Step Time Asymmetry (ms)	14.0 (16.7)	10.3 (14.1)	3.6 (11.0)	13.5 (18.0)	12.9 (19.3)	0.8 (15.7)	-0.09	0.410
Stance Time Asymmetry (ms)	10.2 (12.0)	11.4 (13.2)	0.9 (9.6)	10.7 (11.6)	9.0 (13.4)	2.0 (11.5)	0.06	0.609
Postural Control Domain								
Step Length Asymmetry (m)	0.027 (0.027)	0.028 (0.035)	-0.001 (0.019)	0.027 (0.023)	0.030 (0.027)	-0.001 (0.020)	0.04	0.707
Step Width (m)	0.090 (0.031)	0.088 (0.036)	-0.001 (0.011)	0.076 (0.036)	0.076 (0.039)	0.001 (0.014)	0.06	0.609
Step Width Variability (m)	0.017 (0.009)	0.016 (0.007)	-0.001 (0.006)	0.018 (0.006)	0.018 (0.007)	-0.001 (0.006)	-0.10	0.368

Abbreviations: IQR= Inter quartile range; m/s=meters per second; m=meters; ms=milliseconds; [a] Cohens r, non-parametric effect-size, computed using the following formula: r= z/√number of observations. [b]Mann-Whitney U test to determine between-group differences (i.e., computed as the difference between follow-up and baseline performance). Bold = statistical significance ($p < 0.05$).

Table X. Treatment effects with regards to dual-task gait for the training group and control group at baseline and 10-week follow-up.

	Training group (n=45)			Control group (n=42)				
	Median (IQR)			Median (IQR)				
Pace Domain	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference	Effect size[a]	P-value Between group[b]
Step Velocity (m/s)	1.03 (0.289)	1.08 (0.272)	-0.061 (0.168)	0.93 (0.411)	1.03 (0.378)	-0.061 (0.290)	0.09	0.389
Step Length (m)	0.590 (0.133)	0.602 (0.133)	-0.027 (0.071)	0.573 (0.098)	0.596 (0.090)	-0.009 (0.099)	0.11	0.294
Swing Time Variability (ms)	22.8 (12.6)	21.1 (13.5)	2.1 (11.9)	28.0 (29.6)	24.5 (23.2)	1.8 (20.2)	0.09	0.422
Rhythm Domain								
Step Time (ms)	580.0 (67.0)	558.5 (100.0)	17.9 (53.4)	593.6 (162.8)	572.1 (111.3)	33.6 (75.8)	-0.03	0.802
Swing Time (ms)	399.2 (61.0)	393.3 (95.5)	1.3 (45.3)	403.8 (104.6)	406.4 (81.5)	-1.6 (45.9)	0.02	0.822
Stance Time (ms)	750.8 (151.7)	732.8 (162.6)	35.7 (79.8)	773.6 (255.0)	757.3 (167.3)	16.3 (123.9)	-0.05	0.656
Variability Domain								
Step Velocity Variability (m/s)	0.072 (0.030)	0.065 (0.033)	0.007 (0.037)	0.076 (0.028)	0.070 (0.028)	0.005 (0.026)	-0.00	0.990
Step Length Variability (m)	0.033 (0.016)	0.028 (0.016)	0.002 (0.012)	0.034 (0.017)	0.033 (0.018)	0.001 (0.016)	0.00	0.990
Step Time Variability (ms)	31.6 (20.8)	23.8 (20.8)	1.9 (17.0)	33.1 (40.1)	33.3 (28.7)	2.0 (23.2)	0.06	0.607
Stance Time Variability (ms)	41.8 (32.1)	28.0 (33.0)	2.9 (23.3.)	43.2 (49.5)	41.0 (50.2)	4.0 (28.6)	0.04	0.725
Asymmetry Domain								
Swing Time Asymmetry (ms)	11.8 (18.1)	12.0 (18.1)	-2.1 (18.9)	12.9 (27.4)	13.0 (21.5)	1.9 (19.3)	0.14	0.184
Step Time Asymmetry (ms)	16.9 (22.6)	13.2 (21.4)	2.3 (18.9)	22.6 (37.3)	20.7 (29.5)	0.5 (27.5)	0.02	0.862
Stance Time Asymmetry (ms)	13.0 (22.7)	16.1 (17.3)	-1.5 (16.6)	16.6 (25.6)	12.5 (25.8)	3.3 (14.8)	0.19	0.070
Postural Control Domain								
Step Length Asymmetry (m)	0.033 (0.028)	0.029 (0.031)	0.005 (0.025)	0.024 (0.041)	0.025 (0.036)	0.000 (0.022)	-0.09	0.379
Step Width (m)	0.096 (0.041)	0.103 (0.036)	-0.000 (0.016)	0.089 (0.050)	0.085 (0.039)	0.004 (0.014)	0.22	**0.046**
Step Width Variability (m)	0.018 (0.010)	0.017 (0.011)	-0.001 (0.006)	0.018 (0.008)	0.018 (0.008)	-0.001 (0.006)	-0.02	0.842

Abbreviations: IQR= Inter quartile range; m/s=meters per second; m=meters; ms=milliseconds; [a] Cohens r, non-parametric effect-size, computed using the following formula: r= z/√number of observations. [b]Mann-Whitney U test to determine between-group differences (i.e., computed as the difference between follow-up and baseline performance). Bold = statistical significance ($p < 0.05$).

6 DISCUSSION

6.1 OVERALL FINDINGS

The results derived from the psychometric part of this thesis were that the reproducibility of the Mini-BESTest was found to be good with regards to reliability, when assessed in a clinical setting. However, the measurement error of this instrument showed mixed results. Whereas it was considered acceptable when applied on a group level, it was consider high on an individual level. Moreover, since the results of the Mini-BESTest were in line with the hypotheses (except from its inability to distinguish between recurrent and non-recurrent fallers) the construct validity was found to be adequate in PwPD with mild to moderate disease severity.

The results from the intervention part showed that, compared to the control group, the training group significantly improved balance and gait performance during single-task conditions. On the other hand, the training programme did not improve any gait parameter during the dual-task condition, which also explains why the dual-task interference, i.e. gait automaticity, was not improved. Conversely, the performance of the added task was improved, both with regards to cognitive performance and cognitive performance variability during the dual-task gait conditions. Since this did not occur when this task was performed as a single-task, this suggests that these improvements were not due to a learning bias, and also explains why the dual- task interference was improved following training.

6.2 THE PSYCHOMETRIC PROPERTIES OF THE MINI-BESTEST

The Mini-BESTest was initially introduced as a more user-friendly version of the BESTest.[23] However, while the BESTest was a theoretically anchored test, the items included in the Mini-BESTest were predominately derived from statistical analyses.[132] This resulted in a theoretically somewhat ambiguous test[133] considered to measure the unidimensional and undefined construct of *dynamic balance*, indicating that only the total score of the Mini-BESTest should be considered. However, similar to the original BESTest, the Mini-BESTest clearly identifies four underlying domains and encourages the sub-scoring of these domains.[134] This could be interpreted as if each subcomponent may be investigated separately, which has been performed in recent studies.[75,179,180]

From a clinical perspective, although all items related to two of the subdomains of the original BESTest have been omitted, the Mini-BESTest still encompasses relevant items that other common multi-item balance tests (such as the Bergs Balance Scale[181] or the Tinetti balance assessment tool)[182] are lacking. Particularly the *postural responses* domain may be vital to assess in any individual with balance deficiencies, let alone PwPD. Although falling

is multifactorial[19] and its direct link to balance abilities is moderate,[183] it may be argued that the most devastating effects of impaired balance are the risks of injurious falls.[184] As such, the ability to react in order to regain balance following an irreparable perturbation appears to be essential for the avoidance of falling. Indeed, previous studies in PwPD have found items from the subcomponent postural responses to be significantly associated with falling.[75,180] Whereas the performance of this subcomponent did not differ between recurrent and non-recurrent fallers in this thesis (i.e. paper II); postural responses was the subcomponent that distinguished most clearly between PwPD with mild versus moderate disease severity, as illustrated by the large effect size (although closely followed by ApA's).

Postural responses also signify the subcomponent with the largest proportional measurement error. This has also been identified in a similar study albeit on another population.[127] Conversely, *sensory orientation* was the subcomponent with the lowest error. This may highlight a relevant issue when interpreting the results of clinical assessment tools. Namely that of the potential trade-off between *clinically relevant* tests that may be accompanied with a larger measurement error, while having the potential to provide important information; versus tests or items that are easier to reproduce but that may not be as relevant. Indeed, in this thesis it is evident that the subcomponent with the smallest measurement error, *sensory orientation*, provides little information of value due to its ceiling effect in this sample, (this is illustrated in Figure 5). This ceiling effect is likely the explanation to why sensory orientation was the only subcomponent unable to distinguish between PwPD with mild and moderate disease severity, a finding that limits its validity in this population. In summary, when investigating psychometric properties of clinical tools, it may be advisable to reflect upon the perceived clinical value in relation to the measurement properties, where it may be argued that a larger measurement error could be accepted for a tool with the potential to reveal important information, such as increased risk of falling.

The ceiling effect found for sensory orientation may be surprising since PwPD have frequently demonstrated deficient sensory integration[81,82] (which also was the reason to why the HiBalance programme specifically addressed this aspect of balance).[3] However, the answer to this is likely related to the fact that impaired sensory orientation is usually detected by means of posturography (i.e. body sway),[185] whereas in the Mini-BESTest, the body sway is disregarded of. This issue was actually brought up as a potential shortcoming when the BESTest was first presented.[23] Therefore, it is suggested that measures are taken to increase the sensitivity of this subcomponent when assessed in clinical practice.

The findings in this thesis show that the Mini-BESTest is by no means flawless. Nevertheless, the overall apprehension is that the test encompasses items of clinical relevance for PwPD, which similar multi-item tests are missing. Moreover, although the measurement error on individual level was considered high, it is similar to the measurement error of, for example, the Bergs balance scale.[126] Since the Bergs balance scale have been frequently reported to have a ceiling effect in this population,[126,128,186] it may be argued that the Mini-BESTest overall encompasses sensitive items, more relevant for PwPD, and therefore have a

higher clinical value. Therefore it is suggested for clinicians to use the Mini-BESTest in PwPD with mild to moderate disease severity, however when doing so, they need to relate their findings to the measurement error when evaluating the results.

Moreover, the reliability of the Mini-BESTest was considered to be good for the total score as well as for all subcomponents (except sensory orientation) when administered by the same rater. In contrast, when comparing the results between different raters, only the total score and the subcomponent APA were found to be good, despite the measures taken on beforehand (i.e. training sessions) to synchronise the interpretation pf performance. Similar results were found with regards to the proportional measurement error, which may highlight the challenges to interpret results found from assessments by different raters in clinical practice, particularly with regards to subcomponent scores. The difference with regards to the total score was marginal. Therefore, while it is always recommendable that the same clinician perform all assessments in a single subject to as large an extent as possible, this appear particularly important when evaluating rehabilitation periods with regards to the effects of the subcomponents.

Finally, the measurement error was considered large on an individual level, even when the same rater administers all tests. However, when transforming the measurement error on individual level to a group level error, the measurement error becomes reasonable. This, in combination with the overall adequacy of the construct validity of this test, makes the Mini-BESTest an appropriate outcome measure in future research; whereas, as of present, the Mini-BESTest cannot be recommended to identify fallers with mild to moderate PD.

6.3 THE HIBALANCE INTERVENTION

At large, the contents of the HiBalance programme corresponded to the subdomains of balance as presented by Horak et al.[23] Therefore it is encouraging that training not only improved the overall performance of dynamic balance (i.e. the Mini-BESTest), but that all the Mini-BESTest's subcomponents were improved beyond the measurement error, with the exception of sensory orientation. Indeed, the subcomponents APA's, dynamic gait, and sensory orientation were specifically addressed through the programme's training components. However, although postural responses were not addressed by means of a specific training component, the concept of being highly challenging relied upon the intermittent evocation of reactive responses throughout the entire intervention. It is therefore possible that this was not only an important factor for ensuring an appropriate difficulty level, but that it also was an important ingredient for promoting reactive abilities. Indeed, the recurrent postural responses during training, which consisted of taking compensatory steps in order to regain balance control, might have encouraged stepping strategies among the participant in the training group. This training characteristic, as well as its findings, corresponds with a recent study that promoted a stepping strategy during training in order to improve postural responses in PwPD.[187]

Another potentially important aspect of the results of training was how feed-back was delivered from the trainers. As stated in the study protocol,[3] feed-back was aimed to induce an external rather than an internal focus, that is, focus on the environment (for example, "step over those obstacles") rather than on the coordination of specific body parts (i.e. "walk with longer steps"). This approach was in line with the concepts of a recent model, the optimal theory, that highlights the importance of external focus and intrinsic motivation for optimizing motor learning.[188]

A particularly intriguing finding from this intervention was that the training group improved several aspects of ST-gait, whereas the DT-gait performance was unaffected in comparison to the controls (with the exception of the increased step width among the controls). Instead, the training group significantly improved the performance of the added cognitive task during the DT-condition (both with regards to cognitive performance and cognitive performance variability), but not during the ST-condition. These findings were in stark contrast to what has generally been found in pilot studies investigating the effects of DT-training in PwPD. Indeed, those studies have generally found improved gait during the DT-condition,[110,111,114] whereas improvements of ST-gait[112,116] or the added task are more uncommon.[112,113] There are likely several factors that contribute to the different results found here, but one factor may be embedded in the different design of the interventions. Unlike the majority of the previously mentioned studies, the HiBalance intervention did not focus entirely on DT-training, rather the ST-training played as large a part. It is possible that it is important to emphasise DT-gait more than ST-gait in order to achieve DT-specific gait improvements. Since a randomised controlled trial with such a design is underway,[189] it will be relevant to compare the results from our study with those upcoming findings in order to pinpoint potentially important training ingredients. Nevertheless, the rationale behind the mixture between ST and DT-training in this study was that although the importance of adequate DT-gait abilities have received increased attention in recent years, the importance of improving aspects of ST-gait, such as velocity cannot be overestimated due to its established impact on general health.[26,27] Hence, it was essential for the training programme that potential DT-improvements did not occur at the expense of ST-abilities. On the other hand, ST-step velocity has been found to be the strongest predictor for DT-step velocity.[190] In turn, this may indicate that improved ST-step velocity could have the potential to be accompanied by improved DT-step velocity. Although that possibly occurred to a limited extent in this study (since the DTI of step velocity was one of few gait parameters that showed a tendency to be improved in the training group, as compared to the controls, Figure 6), both the small magnitude of effect size and lack of significance undermines the impact of improved ST-velocity for DT-gait improvements.

It may be important to relate to the patterns of ST-gait and DT-gait, as well as to the results of the cognitive task when aspiring to interpret the DTI results. Although there is a lack of statistical significance with regards to the DTI gait results, as shown in Figure 6, the effect sizes as may reveal underlying patterns in the two groups. Indeed, the effect sizes are of small magnitude, nevertheless their direction may indicate a general tendency towards improved

DTI of gait in the control group, whereas the training group show the largest improvements for cognitive performance and cognitive performance variability. These subtle findings may be indicators of allocation strategies in the two groups, wherein the training group; a tendency might be discerned that the performance of the cognitive task was performed at the expense of DT-gait, and vice versa in the control group.

In order to optimise allocation strategies, it has been suggested for DT-training to emphasise a variety of allocation strategies during DT-training. Examples of this entail alternating between which tasks to prioritise: the motor task, the added task, or both.[51,113] This approach has been investigated in a pilot study among PwPD, which resulted in improvements of gait parameters related to the pace and variability domains, whereas the added cognitive task was unaffected.[114] In the HiBalance intervention, gait and the added tasks were always instructed to be equally prioritised. Therefore it was particularly interesting that the training group appeared to prioritise the cognitive task rather than the gait during the DT-condition at follow-up. This may seem extra puzzling since they also improved the balance and ST-gait performance. However, by relating these findings to a recently proposed model of task prioritisation during gait,[49] this can, arguably, be partly explicated. This model suggests that individuals with adequate postural reserves (for example balance or gait abilities) will always prioritise the added task when the postural threat (e.g. the perceived risk of physical harm, such as falling) is considered to be low. However, when the environment becomes more challenging, thereby increasing the postural threat, the attention is allocated from the added task towards the walking. At the follow-up assessment in this intervention, the training group performed at similar or higher levels than what has been reported for age matched, healthy people, both with regards to dynamic balance performance[191] and ST-gait velocity[25,36] (i.e. mean Mini-BESTest score=22.2 points; mean ST-gait velocity=1.28 m/s). Therefore it is possible that they did not perceive the DT-gait condition as a postural threat, but rather considered the added task as to be the more challenging situation and therefore allocated the attention there. Indeed, the training group had repeatedly performed DT-gait training in more environmentally challenging situations (e.g. walking on foam surfaces and negotiating obstacles etcetera), hence it would be understandable if they did not perceive the over-ground walking upon a flat GaitRITE mat as a postural threat.

In summary, the findings from HiBalance intervention are encouraging and add support to the existing studies showing improved gait and balance performance following training in PwPD.[118] However, more research is needed in order to establish if certain training characteristics might be superior to others; and in such a case, implement the successful training characteristics into clinical practice. Moreover, it may also be of relevance to investigate if individual traits in PwPD (for example cognitive abilities)[192,193] can predict the likelihood to benefit from training. In addition, although this thesis showed a tendency towards improved processing automaticity of the added task following DT-training, this finding needs to be supported by more evidence. Future studies also need to investigate if it is possible to improve gait automaticity following training, and if attention allocation strategies can be influenced in this population.

6.4 INTERNAL VALIDITY

Internal validity reflects to what extent research findings can be considered to be true reflections of reality, rather than dependent upon external factors. Among the threats to internal validity are: participant selection, group allocation, instrumentation and testing procedure.

6.4.1.1 Participant selection and group allocation

One major threat to internal validity is related to the group compositions. That is, do the groups differ with regards to important characteristics such as: age, gender, disease severity, medication, physical or cognitive function? The major advantage with performing a randomised controlled trial is that, if correctly handled, the randomisation of participants is likely to lead to an even distribution of important characteristics in all groups. In this study, block randomisation was used in blocks of four. This means that within each block two participants were allocated to the training group and two people were allocated to the control group. This is an adequate approach in the sense that it will ensure an even balance with the regards to the number of participants allocated to each group.[194] However, like all randomisation methods it also has some disadvantages. Indeed, although both the test assessors and the participants were blinded to group allocation until the included participant had opened the sealed opaque envelope, in theory, the use of fixed block sizes may enable the predictions of group allocation towards the end of each block.[195] Indeed, it has been suggested that there is a risk that the use of block randomisations might cause an imbalance between groups with regards to covariates. Nevertheless, block randomisation have been recommended for trials including up to 100 participants, and in this study no covariates were found to significantly differ between the groups (Table II).

6.4.1.2 Instrumentation and testing

In order to obtain internal validity with regards to the instrumentation used (i.e. the outcome measures), the psychometric properties needs to be acceptable. The psychometric properties of all outcome measures used in this thesis have been found acceptable. However, apart from the instrumentation, certain measures also need to be undertaken with regards to the standardisation of test assessors in order to increase the internal validity. In this study, all test assessors participated in training prior to the commencement of the study. This training included: theoretical discussions regarding the principles of the instrumentation, a synchronised view on how to rate the test performance, and practical training, including training on how to instruct the participants. Such measures were undertaken in order to minimise the risk of learning bias amongst the more inexperienced raters and discrepancies between raters and test occasions.[196] Moreover, during the assessments, a standardised scheme was followed in order to minimise learning bias amongst the participants. In addition, since the assessment sessions were quite extensive, there was a risk that fatigue might affect the performance of the tests performed towards the end of this session. Hence, all participants

were requested to take a seated rest midway through the test sessions. Moreover, to avoid a systematic bias, all tests were performed in a randomised order.

One threat to the internal validity of this intervention was that the test assessors were not blinded to group allocation at follow-up. Since randomised controlled trials pose a variety of logistic challenges, some test assessors also served as trainers. In an effort to limit this shortcoming, the participants were never assessed by an individual that had been involved in their training.

Finally, medication play an important part to reduce motor symptoms amongst PwPD, hence all participants were tested when optimally medicated (i.e. during the ON phase of the medication cycle). Since this population also commonly experience motor fluctuations of variable magnitude at different times of the day, all repeated tests were performed at the same time of the day. Although the participants were instructed not to change their medication dosage during the intervention, this nevertheless occurred among some participants. However, there were no significant differences between the training group and the control group with respect to change of medicament dosage.

6.5 EXTERNAL VALIDITY

External validity entails to what extent the findings from a specific study are generalisable to a broader spectra. With regards to the contents of this particular thesis, the sample, the trainers and the training programme is discussed in relation to external validity.

6.5.1.1 External validity of the sample

This study only included PwPD with a mild to moderate disease severity, hence the results found here can only be generalised to this specific population. Moreover, the recruitment process involved the advertisements in newspapers, where interested PwPD had to contact us. Therefore, it is likely that only PwPD motivated in participating in highly challenging gait and balance training were included. Since neuropsychiatric symptoms such as depression and lack of motivation are common among PwPD,[197-199] it is likely that the PwPD with such symptoms did not report interest for the study. Moreover, based on the MMSE,[156] we excluded participants with signs of cognitive impairment which limits the ecological validity of these findings, since PwPD with these symptoms constitutes a substantial portion of PwPD.[200] Indeed, although the included PwPD had a clinical diagnosis and a mild to moderate disease severity, their mean single-task gait velocity at baseline was well beyond one meter per second, which is a common cut-off to identify healthy older individuals.[25] Moreover, according to a recent categorisation of severity of balance problems based on the Mini-BESTest performance,[201] at baseline, the majority of the included participants had moderate balance deficits. On the other hand, nearly 50 percent of this sample could also be categorised as recurrent fallers.

6.5.1.2 External validity of the trainers

All trainers (n=12) of this intervention were trained physiotherapists currently working at a university hospital. The trainers' clinical experience from neurological rehabilitation ranged from 1 to 20 years. It was an equal distribution of male and female trainers. Since the results showed that there were no differences in improvements between the groups that had been supervised by the different trainers (i.e. during the different semesters and at the different geographical sites), this indicates that the results derived from this study were not dependent upon individual trainers. Moreover, it may indicate that the theoretical and practical training sessions undertaken prior to training were more important than the trainers' clinical experience.

6.5.1.3 External validity of the findings of the intervention

One aspect of external validity lays in the reproducibility of studies. Important for this training programme was that it was a mixture between controlled and uncontrolled ingredients. Whereas it was controlled in the sense that specific balance components were to be addressed following a structured scheme, it was uncontrolled in the sense that the trainers had the freedom to choose and design any kind of exercise within the specific domains. This kind of dynamic approach may be particularly beneficial for group training interventions since it might make it easier to adapt the training to the abilities of the specific group, both with regards to the difficulty level and the feasibility of the specific exercises. Indeed, within each geographical cohort, the group compositions were based upon the degree of the participants' gait and balance deficiencies (as perceived by the test assessors). Had the training instead used predetermined exercises (i.e. a "cookbook" approach) throughout the programme, it might have required participants with very homogenous symptoms in order to optimise the challenge level. This is seldom the case among PwPD given the heterogeneity of symptoms related to this disease.[202,203] However, the downside with the approach used in this intervention is that it may be difficult to replicate, which may reduce the external validity. On the other hand, the reasoning behind this approach was that it was similar to clinical practice and can therefore be argued to increase the ecological validity of the study. In addition, the within-training group analysis showed that there were no differences in improvements between the groups that had participated in training at different time periods (i.e. between 2012 and 2013), or at the different geographical sites. Since this training was performed by physiotherapists working at a hospital, different trainers were involved in the training at different time periods due to external reasons (for example change of responsibilities or jobs). Hence these findings may incline the arguments that the effects of training were more likely to depend upon the training programme, rather than on the trainers or the time that training took place.

6.6 IMPLICATIONS FOR CLINICAL PRACTICE

- Since the proportional measurement error of the Mini-BESTest is similar to other common multi-item balance tests-it is recommended to use for balance assessments in this population due to its higher clinical relevance.

- The Mini-BEST adequately distinguishes between people with Parkinson's disease with mild and moderate disease severity, but should not be used to identify fallers in this population.

- The subcomponents of the Mini-BESTest with, arguably, the highest clinical value also have the largest measurement error; therefore it is advisable to practice these items extra carefully before using the test in people with Parkinson's disease.

- The same person should administer the Mini-BESTest before and after a treatment period in order to decrease the measurement error, particularly when assessing the subcomponents; however it is advisable to have regular training sessions between administrators in order to synchronise the evaluation of patients.

- Challenging gait and balance training can be successfully conducted in groups of people with mild to moderate Parkinson's disease, thereby increasing treatment efficiency.

- When conducting dual-task gait training with an added cognitive task, it is important to consider the performance of both tasks, as well as the difficulty level of either task. In addition, it may also be of importance for clinicians to decide on beforehand what aspect of dual-task abilities is most important to improve (i.e. gait, the added task or both) and design training accordingly.

6.7 SUGGESTIONS FOR FUTURE RESEARCH

- Future studies needs to investigate if the Mini-BESTest's measurement error can be reduced when used in people with Parkinson's disease, for example by clearer instructions and increments.

- It needs to be established how to relate to the subcomponents of the Mini-BESTest, that is, if only the total score should be considered or if it has an added value to also investigate the subcomponents separately.

- Future studies needs to investigate if highly challenging gait and balance training have an added value over moderately challenging training in people with Parkinson's disease.

- It would be of value if future studies might identify individual traits that predict training outcomes in people with Parkinson's disease, such as cognitive status.[192]

- It needs to be investigated if training can affect strategies regarding the allocation of attention in people with Parkinson's disease, and if so, what strategies that are preferable.

- The added cognitive task used in dual-task interventions needs to be thoroughly investigated. That is, with regards to how well it reflects everyday function, what its potential improvement actually means, and what type task is ideally used (for example, which cognitive domains should the task represent and at what difficulty level).

- Future studies are also recommended to investigate if gait automaticity is possible to improve by means of dual-task gait training in people with Parkinson's disease.

7 CONCLUSIONS

- The Mini-BESTest can be recommended for use in research due to its validity, reliability and agreement on group level.

- The Mini-BESTest is not able to identify recurrent fallers with mild to moderate Parkinson's disease

- Highly challenging gait and balance training can improve balance abilities in people with Parkinson's disease with mild to moderate disease severity.

- Highly challenging gait and balance training in people with Parkinson's disease appears to primarily improve single-task gait abilities related to pace and rhythmicity.

- It remains unclear if highly challenging gait and balance training can improve absolute dual-task gait abilities in people with Parkinson's disease.

- Highly challenging gait and balance training including both single and dual-task conditions can improve the dual-task interference of cognitive performance as well as cognitive performance variability in people with Parkinson's disease.

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9 REFERENCES

1. Anton SD, Woods AJ, Ashizawa T, et al. Successful aging: Advancing the science of physical independence in older adults. *Ageing research reviews.* Nov 2015;24(Pt B):304-327.

2. van Uem JM, Marinus J, Canning C, et al. Health-Related Quality of Life in patients with Parkinson's disease-A systematic review based on the ICF model. *Neuroscience and biobehavioral reviews.* Feb 2016;61:26-34.

3. Conradsson D, Lofgren N, Stahle A, Hagstromer M, Franzen E. A novel conceptual framework for balance training in Parkinson's disease-study protocol for a randomised controlled trial. *BMC neurology.* 2012;12:111.

4. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *The Lancet. Neurology.* Jun 2006;5(6):525-535.

5. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Annals of neurology.* Dec 2012;72(6):893-901.

6. Lokk J, Borg S, Svensson J, Persson U, Ljunggren G. Drug and treatment costs in Parkinson's disease patients in Sweden. *Acta neurologica Scandinavica.* Feb 2012;125(2):142-147.

7. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology.* Jan 30 2007;68(5):384-386.

8. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology.* May 26 2009;72(21 Suppl 4):S1-136.

9. Poirier LJ, Sourkes TL. Influence of the Substantia Nigra on the Catecholamine Content of the Striatum. *Brain : a journal of neurology.* Mar 1965;88:181-192.

10. Bellucci A, Mercuri NB, Venneri A, et al. Review: Parkinson's disease: from synaptic loss to connectome dysfunction. *Neuropathology and applied neurobiology.* Feb 2016;42(1):77-94.

11. Jankovic J. Parkinson's disease: clinical features and diagnosis. *Journal of neurology, neurosurgery, and psychiatry.* Apr 2008;79(4):368-376.

12. Kakkar AK, Dahiya N. Management of Parkinsons disease: Current and future pharmacotherapy. *European journal of pharmacology.* Mar 5 2015;750:74-81.

13. Dirnberger G, Jahanshahi M. Executive dysfunction in Parkinson's disease: a review. *Journal of neuropsychology.* Sep 2013;7(2):193-224.

14. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *The Lancet. Neurology.* May 2009;8(5):464-474.

15. Rao G, Fisch L, Srinivasan S, et al. Does this patient have Parkinson disease? *Jama.* Jan 15 2003;289(3):347-353.

16. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* May 1967;17(5):427-442.

17. Canning CG, Paul SS, Nieuwboer A. Prevention of falls in Parkinson's disease: a review of fall risk factors and the role of physical interventions. *Neurodegenerative disease management.* 2014;4(3):203-221.

18. Allen NE, Schwarzel AK, Canning CG. Recurrent falls in Parkinson's disease: a systematic review. *Parkinson's disease.* 2013;2013:906274.

19. Fasano A, Plotnik M, Bove F, Berardelli A. The neurobiology of falls. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* Dec 2012;33(6):1215-1223.

20. Adkin AL, Frank JS, Jog MS. Fear of falling and postural control in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* May 2003;18(5):496-502.

21. Giladi N, Horak FB, Hausdorff JM. Classification of gait disturbances: distinguishing between continuous and episodic changes. *Movement disorders : official journal of the Movement Disorder Society.* Sep 15 2013;28(11):1469-1473.

22. Peterson DS, Horak FB. Neural Control of Walking in People with Parkinsonism. *Physiology.* Mar 2016;31(2):95-107.

23. Horak FB, Wrisley DM, Frank J. The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits. *Physical therapy.* May 2009;89(5):484-498.

24. Kikkert LH, Vuillerme N, van Campen JP, Hortobagyi T, Lamoth CJ. Walking ability to predict future cognitive decline in old adults: A scoping review. *Ageing research reviews.* Feb 6 2016;27:1-14.

25. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *The journal of nutrition, health & aging.* Dec 2009;13(10):881-889.

26. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *Jama.* Jan 5 2011;305(1):50-58.

27. Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign". *Journal of geriatric physical therapy.* 2009;32(2):46-49.

28. Jahn K, Deutschlander A, Stephan T, et al. Supraspinal locomotor control in quadrupeds and humans. *Progress in brain research.* 2008;171:353-362.

29. Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. *Movement disorders : official journal of the Movement Disorder Society.* Sep 15 2013;28(11):1483-1491.

30. Kaneda K, Nambu A, Tokuno H, Takada M. Differential processing patterns of motor information via striatopallidal and striatonigral projections. *Journal of neurophysiology.* Sep 2002;88(3):1420-1432.

31. Johnson MD, Zhang J, Ghosh D, McIntyre CC, Vitek JL. Neural targets for relieving parkinsonian rigidity and bradykinesia with pallidal deep brain stimulation. *Journal of neurophysiology.* Jul 2012;108(2):567-577.

32. Kumar A, Mann S, Sossi V, et al. [11C]DTBZ-PET correlates of levodopa responses in asymmetric Parkinson's disease. *Brain : a journal of neurology.* Dec 2003;126(Pt 12):2648-2655.

33. Hausdorff JM. Gait variability: methods, modeling and meaning. *Journal of neuroengineering and rehabilitation.* 2005;2:19.

34. Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. *Journal of the American Geriatrics Society.* Mar 1997;45(3):313-320.

35. Lord S, Galna B, Rochester L. Moving forward on gait measurement: toward a more refined approach. *Movement disorders : official journal of the Movement Disorder Society.* Sep 15 2013;28(11):1534-1543.

36. Hollman JH, McDade EM, Petersen RC. Normative spatiotemporal gait parameters in older adults. *Gait & posture.* May 2011;34(1):111-118.

37. Lord S, Galna B, Verghese J, Coleman S, Burn D, Rochester L. Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Jul 2013;68(7):820-827.

38. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Movement disorders : official journal of the Movement Disorder Society.* Feb 15 2008;23(3):329-342; quiz 472.

39. Clark DJ. Automaticity of walking: functional significance, mechanisms, measurement and rehabilitation strategies. *Frontiers in human neuroscience.* 2015;9:246.

40. Schneider W, Shiffrin RM. Controlled and automatic human information processing, I. Detection, search, and attention. . *Psychological Review.* 1977;84(1):1-66.

41. Schneider W. Controlled & automatic processing: behavior, theory, and biological mechanisms. *Cognitive Science.* 2003;27(3):525-559.

42. McIsaac TL, Lamberg EM, Muratori LM. Building a framework for a dual task taxonomy. *BioMed research international.* 2015;2015:591475.

43. Rochester L, Galna B, Lord S, Burn D. The nature of dual-task interference during gait in incident Parkinson's disease. *Neuroscience.* Apr 18 2014;265:83-94.

44. Plummer P, Eskes G. Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Frontiers in human neuroscience.* 2015;9:225.

45. Norman DA, Shallice T. *Attention to action: Willed and automatic control of behaviour.* Vol 4: Consciousness and Self-Regulation: Advances in Research and Theory IV; 1986.

46. Wu T, Hallett M, Chan P. Motor automaticity in Parkinson's disease. *Neurobiology of disease.* Oct 2015;82:226-234.

47. Shumway-Cook A, Woollacott M, Kerns KA, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Jul 1997;52(4):M232-240.

48. Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *Journal of the neurological sciences.* Oct 25 2006;248(1-2):196-204.

49. Yogev-Seligmann G, Hausdorff JM, Giladi N. Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Movement disorders : official journal of the Movement Disorder Society.* May 2012;27(6):765-770.

50. Kelly VE, Eusterbrock AJ, Shumway-Cook A. The effects of instructions on dual-task walking and cognitive task performance in people with Parkinson's disease. *Parkinson's disease.* 2012;2012:671261.

51. Yogev-Seligmann G, Rotem-Galili Y, Dickstein R, Giladi N, Hausdorff JM. Effects of explicit prioritization on dual task walking in patients with Parkinson's disease. *Gait & posture.* Apr 2012;35(4):641-646.

52. Muir-Hunter SW, Wittwer JE. Dual-task testing to predict falls in community-dwelling older adults: a systematic review. *Physiotherapy.* Mar 2016;102(1):29-40.

53. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age and ageing.* Sep 2006;35 Suppl 2:ii7-ii11.

54. Pollock AS, Durward BR, Rowe PJ, Paul JP. What is balance? *Clinical rehabilitation.* Aug 2000;14(4):402-406.

55. Horak FB, Henry SM, Shumway-Cook A. Postural perturbations: new insights for treatment of balance disorders. *Physical therapy.* May 1997;77(5):517-533.

56. Horak FB, Frank J, Nutt J. Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. *Journal of neurophysiology.* Jun 1996;75(6):2380-2396.

57. Jacobs JV, Dimitrova DM, Nutt JG, Horak FB. Can stooped posture explain multidirectional postural instability in patients with Parkinson's disease? *Experimental brain research.* Sep 2005;166(1):78-88.

58. Holbein MA, Redfern MS. Functional stability limits while holding loads in various positions. *International journal of industrial ergonomics.* May 1997;19(5):387-395.

59. Horak FB, Dimitrova D, Nutt JG. Direction-specific postural instability in subjects with Parkinson's disease. *Experimental neurology.* Jun 2005;193(2):504-521.

60. Schieppati M, Nardone A. Free and supported stance in Parkinson's disease. The effect of posture and 'postural set' on leg muscle responses to perturbation, and its relation to the severity of the disease. *Brain : a journal of neurology.* Jun 1991;114 (Pt 3):1227-1244.

61. Massion J. Movement, posture and equilibrium: interaction and coordination. *Progress in neurobiology.* 1992;38(1):35-56.

62. Aruin AS, Forrest WR, Latash ML. Anticipatory postural adjustments in conditions of postural instability. *Electroencephalography and clinical neurophysiology.* Aug 1998;109(4):350-359.

63. Boonstra TA, van Kordelaar J, Engelhart D, van Vugt JP, van der Kooij H. Asymmetries in reactive and anticipatory balance control are of similar magnitude in Parkinson's disease patients. *Gait & posture.* Jan 2016;43:108-113.

64. Lin CC, Creath RA, Rogers MW. Variability of Anticipatory Postural Adjustments During Gait Initiation in Individuals With Parkinson Disease. *Journal of neurologic physical therapy : JNPT.* Jan 2016;40(1):40-46.

65. King LA, St George RJ, Carlson-Kuhta P, Nutt JG, Horak FB. Preparation for compensatory forward stepping in Parkinson's disease. *Archives of physical medicine and rehabilitation.* Sep 2010;91(9):1332-1338.

66. Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB. Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. *Experimental neurology.* Feb 2009;215(2):334-341.

67. Chan CW, Jones GM, Kearney RE, Watt DG. The 'late' electromyographic response to limb displacement in man. I. Evidence for supraspinal contribution. *Electroencephalography and clinical neurophysiology.* Feb 1979;46(2):173-181.

68. Matthews PB. The human stretch reflex and the motor cortex. *Trends in neurosciences.* Mar 1991;14(3):87-91.

69. Jacobs JV, Horak FB. Cortical control of postural responses. *Journal of neural transmission.* 2007;114(10):1339-1348.

70. Rinalduzzi S, Trompetto C, Marinelli L, et al. Balance dysfunction in Parkinson's disease. *BioMed research international.* 2015;2015:434683.

71. Nonnekes J, Oude Nijhuis LB, de Niet M, et al. StartReact restores reaction time in HSP: evidence for subcortical release of a motor program. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* Jan 1 2014;34(1):275-281.

72. Nonnekes J, Scotti A, Oude Nijhuis LB, et al. Are postural responses to backward and forward perturbations processed by different neural circuits? *Neuroscience.* Aug 15 2013;245:109-120.

73. Hely MA, Morris JG, Rail D, et al. The Sydney Multicentre Study of Parkinson's disease: a report on the first 3 years. *Journal of neurology, neurosurgery, and psychiatry.* Mar 1989;52(3):324-328.

74. Kim SD, Allen NE, Canning CG, Fung VS. Postural instability in patients with Parkinson's disease. Epidemiology, pathophysiology and management. *CNS drugs.* Feb 2013;27(2):97-112.

75. Schlenstedt C, Brombacher S, Hartwigsen G, Weisser B, Moller B, Deuschl G. Comparison of the Fullerton Advanced Balance Scale, Mini-BESTest, and Berg Balance Scale to Predict Falls in Parkinson Disease. *Physical therapy.* Apr 2016;96(4):494-501.

76. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Movement disorders : official journal of the Movement Disorder Society.* Aug 2004;19(8):871-884.

77. Carpenter MG, Allum JH, Honegger F, Adkin AL, Bloem BR. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry.* Sep 2004;75(9):1245-1254.

78. Dimitrova D, Horak FB, Nutt JG. Postural muscle responses to multidirectional translations in patients with Parkinson's disease. *Journal of neurophysiology.* Jan 2004;91(1):489-501.

79. Peterka RJ. Sensorimotor integration in human postural control. *Journal of neurophysiology.* Sep 2002;88(3):1097-1118.

80. Mergner T, Siebold C, Schweigart G, Becker W. Human perception of horizontal trunk and head rotation in space during vestibular and neck stimulation. *Experimental brain research.* 1991;85(2):389-404.

81. Conte A, Khan N, Defazio G, Rothwell JC, Berardelli A. Pathophysiology of somatosensory abnormalities in Parkinson disease. *Nature reviews. Neurology.* Dec 2013;9(12):687-697.

82. Stylianou AP, McVey MA, Lyons KE, Pahwa R, Luchies CW. Postural sway in patients with mild to moderate Parkinson's disease. *The International journal of neuroscience.* Nov 2011;121(11):614-621.

83. Mancini M, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Chiari L. Trunk accelerometry reveals postural instability in untreated Parkinson's disease. *Parkinsonism & related disorders.* Aug 2011;17(7):557-562.

84. Galna B, Murphy AT, Morris ME. Obstacle crossing in people with Parkinson's disease: foot clearance and spatiotemporal deficits. *Human movement science.* Oct 2010;29(5):843-852.

85. Stegemoller EL, Buckley TA, Pitsikoulis C, Barthelemy E, Roemmich R, Hass CJ. Postural instability and gait impairment during obstacle crossing in Parkinson's disease. *Archives of physical medicine and rehabilitation.* Apr 2012;93(4):703-709.

86. Yang WC, Hsu WL, Wu RM, Lu TW, Lin KH. Motion analysis of axial rotation and gait stability during turning in people with Parkinson's disease. *Gait & posture.* Feb 2016;44:83-88.

87. Stack E, Ashburn A. Fall events described by people with Parkinson's disease: implications for clinical interviewing and the research agenda. *Physiotherapy research international : the journal for researchers and clinicians in physical therapy.* 1999;4(3):190-200.

88. Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* Oct 2011;26 Suppl 3:S2-41.

89. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease. *Movement disorders : official journal of the Movement Disorder Society.* Sep 2015;30(10):1361-1370.

90. Calabresi P, Ghiglieri V, Mazzocchetti P, Corbelli I, Picconi B. Levodopa-induced plasticity: a double-edged sword in Parkinson's disease? *Philosophical transactions of the Royal Society of London. Series B, Biological sciences.* Jul 5 2015;370(1672).

91. Hirsch MA, Iyer SS, Sanjak M. Exercise-induced neuroplasticity in human Parkinson's disease: What is the evidence telling us? *Parkinsonism & related disorders.* Jan 2016;22 Suppl 1:S78-81.

92. Abbruzzese G, Marchese R, Avanzino L, Pelosin E. Rehabilitation for Parkinson's disease: Current outlook and future challenges. *Parkinsonism & related disorders.* Jan 2016;22 Suppl 1:S60-64.

93. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy versus placebo or no intervention in Parkinson's disease. *The Cochrane database of systematic reviews.* 2012;8:CD002817.

94. Deane KH, Ellis-Hill C, Jones D, et al. Systematic review of paramedical therapies for Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* Sep 2002;17(5):984-991.

95. Bloem BR, de Vries NM, Ebersbach G. Nonpharmacological treatments for patients with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* Sep 15 2015;30(11):1504-1520.

96. Monteiro-Junior RS, Cevada T, Oliveira BR, et al. We need to move more: Neurobiological hypotheses of physical exercise as a treatment for Parkinson's disease. *Medical hypotheses.* Nov 2015;85(5):537-541.

97. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *The Lancet. Neurology.* Jul 2013;12(7):716-726.

98. Cohen AD, Tillerson JL, Smith AD, Schallert T, Zigmond MJ. Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF. *Journal of neurochemistry.* Apr 2003;85(2):299-305.

99. Wu SY, Wang TF, Yu L, et al. Running exercise protects the substantia nigra dopaminergic neurons against inflammation-induced degeneration via the activation of BDNF signaling pathway. *Brain, behavior, and immunity.* Jan 2011;25(1):135-146.

100. Real CC, Ferreira AF, Chaves-Kirsten GP, Torrao AS, Pires RS, Britto LR. BDNF receptor blockade hinders the beneficial effects of exercise in a rat model of Parkinson's disease. *Neuroscience.* May 1 2013;237:118-129.

101. Fisher BE, Wu AD, Salem GJ, et al. The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Archives of physical medicine and rehabilitation.* Jul 2008;89(7):1221-1229.

102. Fisher BE, Li Q, Nacca A, et al. Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *Neuroreport.* Jul 10 2013;24(10):509-514.

103. Zoladz JA, Majerczak J, Zeligowska E, et al. Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in Parkinson's disease patients. *Journal of physiology and pharmacology : an official journal of the Polish Physiological Society.* Jun 2014;65(3):441-448.

104. Marusiak J, Zeligowska E, Mencel J, et al. Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. *Journal of rehabilitation medicine.* Apr 2015;47(4):372-375.

105. Frazzitta G, Maestri R, Ghilardi MF, et al. Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study. *Neurorehabilitation and neural repair.* Feb 2014;28(2):163-168.

106. Sehm B, Taubert M, Conde V, et al. Structural brain plasticity in Parkinson's disease induced by balance training. *Neurobiology of aging.* Jan 2014;35(1):232-239.

107. Reuter I, Mehnert S, Leone P, Kaps M, Oechsner M, Engelhardt M. Effects of a flexibility and relaxation programme, walking, and nordic walking on Parkinson's disease. *Journal of aging research.* 2011;2011:232473.

108. Keus SH, Bloem BR, Hendriks EJ, Bredero-Cohen AB, Munneke M, Practice Recommendations Development G. Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research. *Movement disorders : official journal of the Movement Disorder Society.* Mar 15 2007;22(4):451-460; quiz 600.

109. Nieuwboer A, Rochester L, Muncks L, Swinnen SP. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. *Parkinsonism & related disorders.* Dec 2009;15 Suppl 3:S53-58.

110. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-Cognitive Dual-Task Training in Persons With Neurologic Disorders: A Systematic Review. *Journal of neurologic physical therapy : JNPT.* Jul 2015;39(3):142-153.

111. Ginis P, Nieuwboer A, Dorfman M, et al. Feasibility and effects of home-based smartphone-delivered automated feedback training for gait in people with Parkinson's disease: A pilot randomized controlled trial. *Parkinsonism & related disorders.* Jan 2016;22:28-34.

112. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *The journals of gerontology. Series A, Biological sciences and medical sciences.* Feb 2011;66(2):234-240.

113. Brauer SG, Morris ME. Can people with Parkinson's disease improve dual tasking when walking? *Gait & posture.* Feb 2010;31(2):229-233.

114. Yogev-Seligmann G, Giladi N, Brozgol M, Hausdorff JM. A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Archives of physical medicine and rehabilitation.* Jan 2012;93(1):176-181.

115. Strouwen C, Molenaar EA, Munks L, et al. Dual tasking in Parkinson's disease: should we train hazardous behavior? *Expert review of neurotherapeutics.* 2015;15(9):1031-1039.

116. Fok P, Farrell M, McMeeken J. Prioritizing gait in dual-task conditions in people with Parkinson's. *Human movement science.* Oct 2010;29(5):831-842.

117. Plummer P, Osborne MB. What Are We Attempting to Improve When We Train Dual-Task Performance? *Journal of neurologic physical therapy : JNPT.* Jul 2015;39(3):154-155.

118. Klamroth S, Steib S, Devan S, Pfeifer K. Effects of Exercise Therapy on Postural Instability in Parkinson Disease: A Meta-analysis. *Journal of neurologic physical therapy : JNPT.* Jan 2016;40(1):3-14.

119. Tomlinson CL, Herd CP, Clarke CE, et al. Physiotherapy for Parkinson's disease: a comparison of techniques. *The Cochrane database of systematic reviews.* 2014;6:CD002815.

120. Paterson K, Hill K, Lythgo N. Stride dynamics, gait variability and prospective falls risk in active community dwelling older women. *Gait & posture.* Feb 2011;33(2):251-255.

121. Delval A, Salleron J, Bourriez JL, et al. Kinematic angular parameters in PD: reliability of joint angle curves and comparison with healthy subjects. *Gait & posture.* Oct 2008;28(3):495-501.

122. Soangra R, Lockhart TE. Comparison of intra individual physiological sway complexity from force plate and inertial measurement unit - biomed 2013. *Biomedical sciences instrumentation.* 2013;49:180-186.

123. Mancini M, Horak FB. The relevance of clinical balance assessment tools to differentiate balance deficits. *European journal of physical and rehabilitation medicine.* Jun 2010;46(2):239-248.

124. de Vet HC, Terwee CB, Knol DL, Bouter LM. When to use agreement versus reliability measures. *Journal of clinical epidemiology.* Oct 2006;59(10):1033-1039.

125. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *Journal of strength and conditioning research / National Strength & Conditioning Association.* Feb 2005;19(1):231-240.

126. Steffen T, Seney M. Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-item short-form health survey, and the unified Parkinson disease rating scale in people with parkinsonism. *Physical therapy.* Jun 2008;88(6):733-746.

127. Tsang CS, Liao LR, Chung RC, Pang MY. Psychometric properties of the Mini-Balance Evaluation Systems Test (Mini-BESTest) in community-dwelling individuals with chronic stroke. *Physical therapy.* Aug 2013;93(8):1102-1115.

128. Godi M, Franchignoni F, Caligari M, Giordano A, Turcato AM, Nardone A. Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders. *Physical therapy.* Feb 2013;93(2):158-167.

129. Smania N, Corato E, Tinazzi M, et al. Effect of balance training on postural instability in patients with idiopathic Parkinson's disease. *Neurorehabilitation and neural repair.* Nov-Dec 2010;24(9):826-834.

130. Tarakci E, Yeldan I, Huseyinsinoglu BE, Zenginler Y, Eraksoy M. Group exercise training for balance, functional status, spasticity, fatigue and quality of life in multiple sclerosis: a randomized controlled trial. *Clinical rehabilitation.* Sep 2013;27(9):813-822.

131. Harro CC, Shoemaker MJ, Frey O, et al. The effects of speed-dependent treadmill training and rhythmic auditory-cued overground walking on balance function, fall incidence, and quality of life in individuals with idiopathic Parkinson's disease: a randomized controlled trial. *NeuroRehabilitation.* 2014;34(3):541-556.

132. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *Journal of rehabilitation medicine.* Apr 2010;42(4):323-331.

133. Padgett PK, Jacobs JV, Kasser SL. Is the BESTest at its best? A suggested brief version based on interrater reliability, validity, internal consistency, and theoretical construct. *Physical therapy.* Sep 2012;92(9):1197-1207.

134. King L, Horak F. On the mini-BESTest: scoring and the reporting of total scores. *Physical therapy.* Apr 2013;93(4):571-575.

135. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *Journal of clinical epidemiology.* Jul 2010;63(7):737-745.

136. Stratford P. Reliability: consistency or differentiating among subjects? *Physical therapy.* Apr 1989;69(4):299-300.

137. Looney MA. When Is the Intraclass Correlation Coefficient Misleading? *Measurement in Physical Education and Exercise Science.* 2000;4(2):73-78.

138. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. *Journal of chronic diseases.* 1987;40(2):171-178.

139. Beckerman H, Roebroeck ME, Lankhorst GJ, Becher JG, Bezemer PD, Verbeek AL. Smallest real difference, a link between reproducibility and responsiveness. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2001;10(7):571-578.

140. Terwee CB, Bot SDM, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of clinical epidemiology.* 2007;60(1):34-42.

141. Borsboom D, Mellenbergh G, van Heerden J. The concept of validity. *Psychological Review.* 2004;111(4):1061-1071.

142. Cronbach LJ, Meehl PE. Construct validity in psychological tests. *Psychological bulletin.* Jul 1955;52(4):281-302.

143. Allen NE, Sherrington C, Paul SS, Canning CG. Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. *Movement disorders : official journal of the Movement Disorder Society.* Aug 1 2011;26(9):1605-1615.

144. Conradsson D, Lofgren N, Stahle A, Franzen E. Is highly challenging and progressive balance training feasible in older adults with Parkinson's disease? *Archives of physical medicine and rehabilitation.* May 2014;95(5):1000-1003.

145. Jacobs JV, Horak FB, Tran VK, Nutt JG. Multiple balance tests improve the assessment of postural stability in subjects with Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry.* Mar 2006;77(3):322-326.

146. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of neurology, neurosurgery, and psychiatry.* Mar 1992;55(3):181-184.

147. Leddy AL, Crowner BE, Earhart GM. Utility of the Mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *Journal of neurologic physical therapy : JNPT.* Jun 2011;35(2):90-97.

148. Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* May 2012;21(4):651-657.

149. Duncan RP, Earhart GM. Randomized controlled trial of community-based dancing to modify disease progression in Parkinson disease. *Neurorehabilitation and neural repair.* Feb 2012;26(2):132-143.

150. Poewe W, Rascol O, Sampaio C, Stebbins G. The Unified Parkinson’s Disease Rating Scale (UPDRS): Status and Recommendations. *Movement Disorders.* 2003;18(7):738-750.

151. Nonnekes J, Goselink R, Weerdesteyn V, Bloem BR. The retropulsion test: a good evaluation of postural instability in Parkinson's disease? *Journal of Parkinson's disease.* 2015;5(1):43-47.

152. Fahn S, Elton R. *Unified Parkinson's disease rating scale.* London: Macmillan; 1987.

153. Richards M, Marder K, Cote L, Mayeux R. Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination. *Movement disorders : official journal of the Movement Disorder Society.* Jan 1994;9(1):89-91.

154. Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. *Movement disorders : official journal of the Movement Disorder Society.* Jan 1994;9(1):76-83.

155. Louis ED, Lynch T, Marder K, Fahn S. Reliability of patient completion of the historical section of the Unified Parkinson's Disease Rating Scale. *Movement disorders : official journal of the Movement Disorder Society.* Mar 1996;11(2):185-192.

156. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research.* Nov 1975;12(3):189-198.

157. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Movement disorders : official journal of the Movement Disorder Society.* Dec 2007;22(16):2314-2324.

158. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society.* Feb 1991;39(2):142-148.

159. Verheyden G, Kampshoff CS, Burnett ME, et al. Psychometric properties of 3 functional mobility tests for people with Parkinson disease. *Physical therapy.* Feb 2014;94(2):230-239.

160. Nelson AJ, Zwick D, Brody S, et al. The validity of the GaitRite and the Functional Ambulation Performance scoring system in the analysis of Parkinson gait. *NeuroRehabilitation.* 2002;17(3):255-262.

161. Galna B, Lord S, Rochester L. Is gait variability reliable in older adults and Parkinson's disease? Towards an optimal testing protocol. *Gait & posture.* Apr 2013;37(4):580-585.

162. Lindemann U, Najafi B, Zijlstra W, et al. Distance to achieve steady state walking speed in frail elderly persons. *Gait & posture.* Jan 2008;27(1):91-96.

163. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. *Lancet.* Mar 1 1997;349(9052):617.

164. Brandler TC, Oh-Park M, Wang C, Holtzer R, Verghese J. Walking while talking: investigation of alternate forms. *Gait & posture*. Jan 2012;35(1):164-166.

165. Verghese J, Buschke H, Viola L, et al. Validity of divided attention tasks in predicting falls in older individuals: a preliminary study. *Journal of the American Geriatrics Society.* Sep 2002;50(9):1572-1576.

166. Yardley L, Beyer N, Hauer K, Kempen G, Piot-Ziegler C, Todd C. Development and initial validation of the Falls Efficacy Scale-International (FES-I). *Age and ageing.* Nov 2005;34(6):614-619.

167. Jonasson SB, Nilsson MH, Lexell J. Psychometric properties of four fear of falling rating scales in people with Parkinson's disease. *BMC geriatrics.* 2014;14:66.

168. Kelly LA, McMillan DG, Anderson A, Fippinger M, Fillerup G, Rider J. Validity of actigraphs uniaxial and triaxial accelerometers for assessment of physical activity in adults in laboratory conditions. *BMC medical physics.* 2013;13(1):5.

169. Altman DG. *Practical statistics for medical research.* London: Chapman & Hall/

CRC; 1991.

170. Hedges L. Distribution Theory for Glass's Estimator of Effect Size and Related Estimators *Journal of Educational Statistics.* 1981;6(2):107-128.

171. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* . Hillsadale: Lawrence Erbaum 1988.

172. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* Mar 1977;33(1):159-174.

173. Steiger JH. Tests for Comparing Elements of a Correlation Matrix. *Psychological bulletin.* 1980;87(2):245-251.

174. Zimmerman DW WR. Properties of the Spearman Correction for attenuation for normal and realistic non-normal distributions. *Applied Psychological Measurement.* 1997;21(3):253-270.

175. Spearman C. The proof and measurement of association between two things. *International journal of epidemiology.* Oct 2010;39(5):1137-1150.

176. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. *Journal of experimental psychology. General.* Feb 2012;141(1):2-18.

177. Li SC, Huxhold O, Schmiedek F. Aging and attenuated processing robustness. Evidence from cognitive and sensorimotor functioning. *Gerontology.* Jan-Feb 2004;50(1):28-34.

178. Burton CL, Strauss E, Hultsch DF, Moll A, Hunter MA. Intraindividual variability as a marker of neurological dysfunction: a comparison of Alzheimer's disease and Parkinson's disease. *Journal of clinical and experimental neuropsychology.* Jan 2006;28(1):67-83.

179. Gera G, Freeman DL, Blackinton MT, Horak FB, King L. Identification of Balance Deficits in People with Parkinson Disease; is the Sensory Organization Test Enough? *International journal of physical medicine & rehabilitation.* Feb 2016;4(1).

180. Mak MK, Auyeung MM. The mini-BESTest can predict parkinsonian recurrent fallers: a 6-month prospective study. *Journal of rehabilitation medicine.* Jun 2013;45(6):565-571.

181. Berg K, Wood-Dauphinée S, Williams J, Gayton D. Measuring balance in the elderly: preliminary development of an instrument. *Physiotherapy Canada.* 1989;41(6):304-311.

182. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *Journal of the American Geriatrics Society.* Feb 1986;34(2):119-126.

183. Muir SW, Berg K, Chesworth B, Klar N, Speechley M. Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis. *Journal of clinical epidemiology.* Apr 2010;63(4):389-406.

184. Ambrose AF, Cruz L, Paul G. Falls and Fractures: A systematic approach to screening and prevention. *Maturitas.* Sep 2015;82(1):85-93.

185. Shumway-Cook A, Horak FB. Assessing the influence of sensory interaction of balance. Suggestion from the field. *Physical therapy.* Oct 1986;66(10):1548-1550.

186. King LA, Priest KC, Salarian A, Pierce D, Horak FB. Comparing the Mini-BESTest with the Berg Balance Scale to Evaluate Balance Disorders in Parkinson's Disease. *Parkinson's disease.* 2012;2012:375419.

187. Wong-Yu IS, Mak MK. Multi-dimensional balance training programme improves balance and gait performance in people with Parkinson's disease: A pragmatic randomized controlled trial with 12-month follow-up. *Parkinsonism & related disorders.* Jun 2015;21(6):615-621.

188. Wulf G, Lewthwaite R. Optimizing performance through intrinsic motivation and attention for learning: The OPTIMAL theory of motor learning. *Psychonomic bulletin & review.* Jan 29 2016.

189. Strouwen C, Molenaar EA, Keus SH, et al. Protocol for a randomized comparison of integrated versus consecutive dual task practice in Parkinson's disease: the DUALITY trial. *BMC neurology.* 2014;14:61.

190. Strouwen C, Molenaar EA, Keus SH, et al. Are factors related to dual-task performance in people with Parkinson's disease dependent on the type of dual task? *Parkinsonism & related disorders.* Feb 2016;23:23-30.

191. O'Hoski S, Winship B, Herridge L, et al. Increasing the clinical utility of the BESTest, mini-BESTest, and brief-BESTest: normative values in Canadian adults who are healthy and aged 50 years or older. *Physical therapy.* Mar 2014;94(3):334-342.

192. Seidler RD, Bo J, Anguera JA. Neurocognitive contributions to motor skill learning: the role of working memory. *Journal of motor behavior.* 2012;44(6):445-453.

193. King LA, Peterson DS, Mancini M, et al. Do cognitive measures and brain circuitry predict outcomes of exercise in Parkinson Disease: a randomized clinical trial. *BMC neurology.* 2015;15:218.

194. Suresh K. An overview of randomization techniques: An unbiased assessment of outcome in clinical research. *Journal of human reproductive sciences.* Jan 2011;4(1):8-11.

195. Efird J. Blocked randomization with randomly selected block sizes. *International journal of environmental research and public health.* Jan 2011;8(1):15-20.

196. Slack MK, Draugalis JR. Establishing the internal and external validity of experimental studies. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists.* Nov 15 2001;58(22):2173-2181; quiz 2182-2173.

197. Aarsland D, Bronnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry.* Aug 2009;80(8):928-930.

198. den Brok MG, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RM, Richard E. Apathy in Parkinson's disease: A systematic review and meta-analysis. *Movement disorders : official journal of the Movement Disorder Society.* May 2015;30(6):759-769.

199. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* Jan 30 2008;23(2):183-189; quiz 313.

200. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G, Norwegian ParkWest Study G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology.* Mar 31 2009;72(13):1121-1126.

201. Franchignoni F, Godi M, Guglielmetti S, Nardone A, Giordano A. Enhancing the usefulness of the Mini-BESTest for measuring dynamic balance: a Rasch validation study. *European journal of physical and rehabilitation medicine.* Aug 2015;51(4):429-437.

202. Mehndiratta M, Garg RK, Pandey S. Nonmotor symptom complex of Parkinson's disease--an under-recognized entity. *The Journal of the Association of Physicians of India.* May 2011;59:302-308, 313.

203. Vervoort G, Alaerts K, Bengevoord A, et al. Functional connectivity alterations in the motor and fronto-parietal network relate to behavioral heterogeneity in Parkinson's disease. *Parkinsonism & related disorders.* Mar 2016;24:48-55.

204. Conradsson D. *Balance control in older adults with Parkinson's disease- effects of medication and exercise*, Karolinska Institutet; 2016.

205. Vidak S, Foisner R. Molecular insights into the premature aging disease progeria. *Histochemistry and cell biology.* Apr 2016;145(4):401-417.