The Contribution of Each Leg to Bipedal Balance Control

– it takes two –

Tjitske Boonstra

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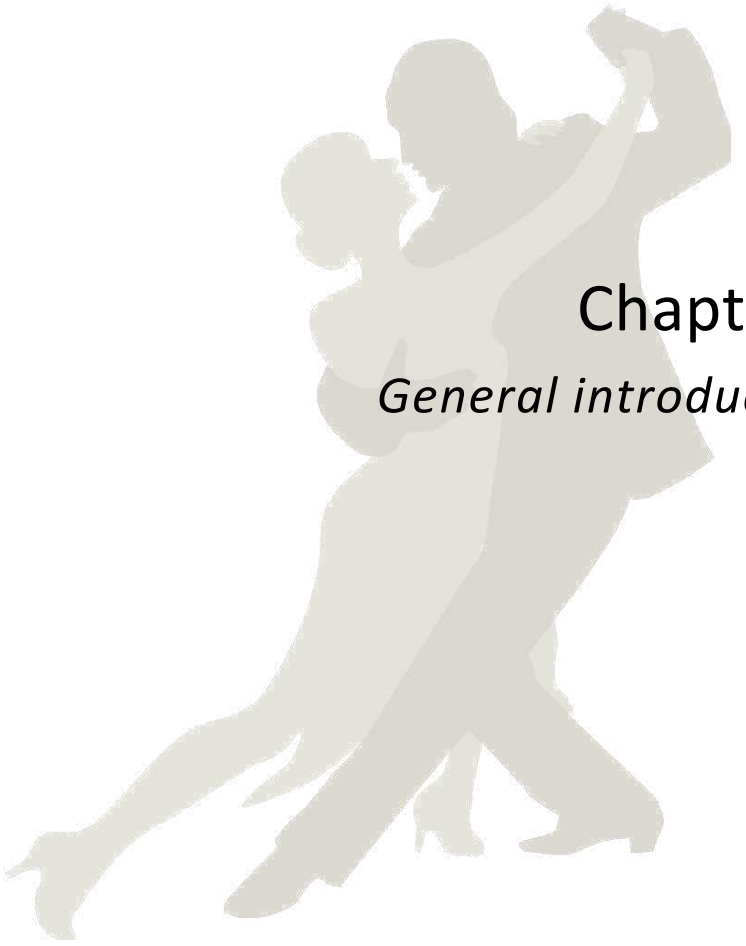

Chapter 1

General introduction

Introduction

Every day we move. We move our bodies to get out of bed, get dressed, eat breakfast, get on our bikes or get into the car to be on our way. Crucial for all these activities is that we keep our body upright and not fall over. Maintaining an upright posture seems effortless for healthy adults, but in fact it is a very complex task involving many brain structures, muscles and joints (Figure 1.1). This complexity become apparent when people age or when a neurological disorder develops, such as a stroke or Parkinson's disease (see Box 1). These are just examples of neurological conditions that are associated with balance impairments and an increased risk of falls (Hely *et al.*, 2008; Pickering *et al.*, 2007; Stolze *et al.*, 2004).

Falling and fall related injuries place a large burden on the healthcare system; in the Netherlands, yearly about 72.000 elderly people in the Netherlands visit the emergency room and about 40% is subsequently admitted to the hospital due to a fall. The annual costs associated with falls are estimated to be €650 million (Hartholt *et al.*, 2012). In addition, falls and fear of falling decrease a person's mobility and negatively influence the quality of life (Hartholt *et al.*, 2011).

Box 1: Parkinson's disease

Parkinson's disease (PD) is a progressive and complex neurodegenerative disorder, affecting about 5 million people worldwide and about 40.000 people in the Netherlands; this number is expected to increase in the coming years because of the ageing population (de Lau *et al.*, 2004). PD is most commonly known for the classical resting tremor of arms, hands or legs, but the symptoms and signs of PD encompass a much broader spectrum. Non-motor symptoms include olfactory loss, mood disorders, autonomic dysfunction and cognitive decline. The cardinal motor symptoms of PD can be separated into appendicular and axial symptoms. Appendicular symptoms include resting tremor, bradykinesia (i.e., slowness of movement) and rigidity. Axial symptoms include gait disorders and balance impairments, such as the characteristic stooped posture.

The progressive decrease in motor function is ascribed largely to a loss of dopaminergic neurons in the substantia nigra in the basal ganglia. The cause of PD remains unknown and there is currently no cure. PD symptoms can be treated by (a combination of) dopaminergic medication, deep brain stimulation and allied health interventions (e.g. physiotherapy). However, the axial symptoms are especially difficult to treat, certainly when the disease progresses. Therefore, PD patients are at great risk of falling, and this negatively affects their quality of life (Hely *et al.*, 2008; Pickering *et al.*, 2007; Stolze *et al.*, 2004).

The presumed causes of falls in PD patients are multifactorial; they can be due to mental deficits, such as a decreased cognitive functioning, motor deficits such as decreased muscle strength, or sensory deficits such as a decreased sensory integration.

Despite the large body of research on bipedal upright stance, many questions about the (patho)physiology of balance control remain currently unanswered. For example, what physiological correlate is minimized during upright stance? Some researchers claim it is stability (Kiemel *et al.*, 2011), others claim it is energy expenditure (van der Kooij *et al.*, 2011). How is sensory information integrated and how can a deteriorated sensory modality be compensated for (Dozza *et al.*, 2011; Dozza *et al.*, 2007; Nanhoe-Mahabier *et al.*, 2012)? Is the passive ankle stiffness sufficient to counteract the destabilizing effect of gravity (Loram *et al.*, 2002a)? Further research is needed to investigate the working mechanisms of upright stance and to identify risk factors for falling. In this thesis, new methods to investigate and quantify balance control are presented and evaluated. Subsequently, the methods are applied in a group of Parkinson's disease (PD) patients and healthy controls. This introductory chapter describes some background knowledge, basic concepts, the problem statement and the research questions of this thesis.

Balance control

Human upright stance is inherently unstable; a perturbation that causes the body to move from its equilibrium position will become exaggerated by gravity (Peterka, 2003). To maintain an upright posture, sensory information is sent to the central nervous system (CNS).

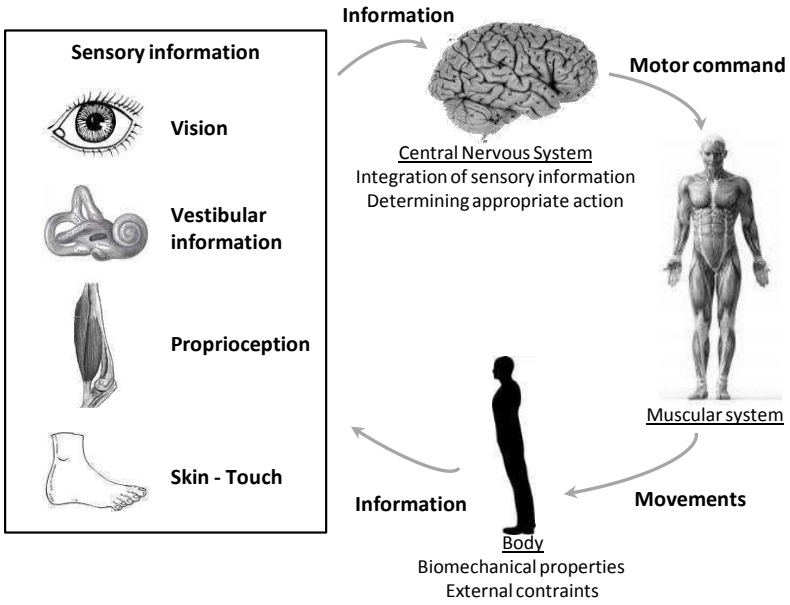

Figure 1.1: The general working of the balance control system.

Sensory information is coming from the vestibular organ (which measures the rotation and acceleration of the head with respect to the gravitational field; graviception), eyes (which measure the position of the head with respect to the surroundings; vision) and

muscle spindles (measuring the length and contraction velocity of muscles; proprioception). Further information is provided by tactile sensors in the soles of the feet and the Golgi tendon organs providing feedback of the pressure on the foot and of the tendon force, respectively. Based on this information an estimation of the body position is made, appropriate actions are determined and subsequently the CNS sends signals to the muscles, which causes corrective torques around the joints (Figure 1.1).

The way humans correct a balance disturbance can be separated into three categories of responses:

1) Feet-in-place (FIP) responses; the feet remain on the floor and torques around the ankle, hip and knee pull the body back to the upright position and prevent the body from falling over. It has been shown that the ankle mostly corrects perturbations that are small in amplitude and slow and that the hip corrects perturbations that are large and fast (Creath et al., 2005; Horak et al., 1986).
2) Making a protective step; when balance is truly jeopardized and the CoM is moved outside the base of support, one or more corrective steps can be made to help maintain balance (Carty et al., 2012; McIlroy et al., 1996).
3) Protective arm movements, by stretching out arms; when the perturbing forces increase, moving the arms can decrease the momentum on the center of mass, thereby decreasing the perturbing influence (Maki et al., 2006; Pijnappels et al., 2010; van Asseldonk et al., 2007). These protective arm movements can be seen in combination with both feet-in-place reactions and with corrective stepping (Maki et al., 1997).

Although the general working mechanisms of the balance control system are known, it is not yet fully understood how the different parts of the system work together and what happens in (neurological) patients. Moreover, the proverbial 'proof of the pudding' would be to be able to detect individuals that are at an increased risk of falling. Unfortunately, at the moment the best predictor whether people will fall in the future is the occurrence of previous falls (Hely *et al.*, 2008), and current posturography techniques have not been proven to be superior to this clinical wisdom.

Assessment of balance control

Balance ability can be investigated with questionnaires, clinical balance tests (alone, or bundled into rating scales) and posturography. Furthermore, models of the balance control system have been used to create insight into the biomechanics and motor control of upright stance.

At the end of the 19th century, Karl Vierordt (Vierordt, 1877) for the first time recorded body movements during quiet standing. His equipment consisted of a feather attached to a helmet that made traces on a glass plate covered with a powder attached to the ceiling (see Figure 1.2).

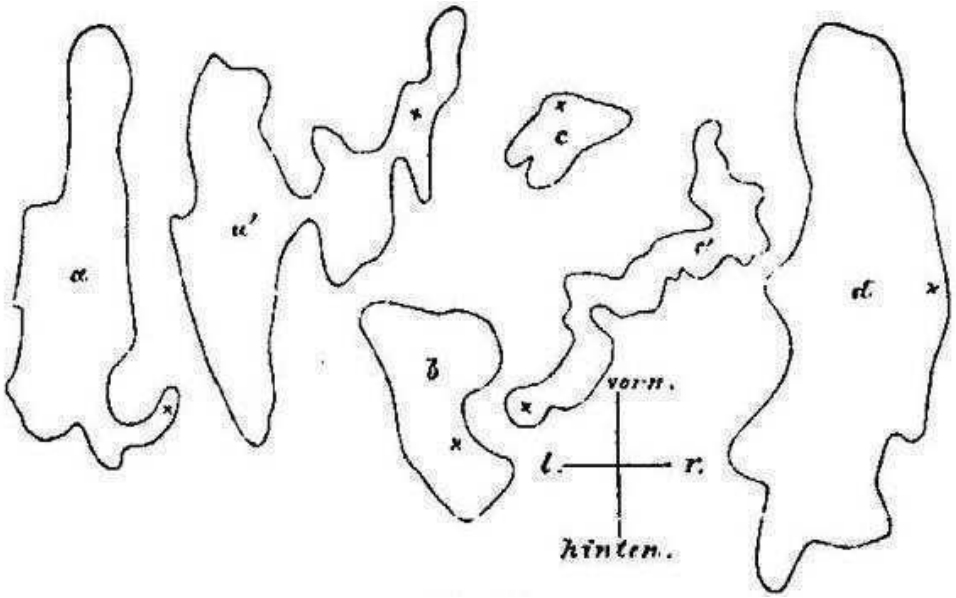

Figure 1.2: Recorded traces of body sway of Vierordt's experiment. a: military posture; a': the same but with eyes closed; b: standing at ease (the right leg being the support leg); c: sat; c': sat with eyes closed; d: standing on only one foot (the right foot here). The asterisk (*) indicates the starting position of the paintbrush. Recording duration was 3 minutes.

Fortunately, techniques and assessment methods have progressed since Vierordt's experiment. Current assessment methods of balance control can be separated in two categories: qualitative and quantitative.

Qualitative assessment of balance

To assess balance in individual patients, physicians and physiotherapists often use a combination of history taking and physical examination (Visser *et al.*, 2008).

Questionnaires

Several questionnaires have been developed to determine fall risk and fear of falling (Hill *et al.*, 1996; Peretz *et al.*, 2006). An example is the Activity specific Balance Confidence (ABC) scale that asks about balance confidence during specific activities such as stair climbing. However, the diagnostic and predictive value of questionnaires is limited. This is due to the subjective nature of the tests; for example patients tend to forget if and when and where they have fallen (Cummings *et al.*, 1988).

Physical examination

An example of physical examination is the so-called retropulsion test: the examiner pulls at the shoulders of the patient. Other tests entice patients performing a series of tasks

(i.e., Berg Balance Scale; BBS) or standing up from a chair, walk, turn and sit down again (Timed-Up-and-Go test; TUG).

Physical tests such as the retropulsion test have a subjective scoring system and the pull force exerted by the examiner is not standardized, creating inconsistencies across different raters (Jacobs *et al.*, 2006; Munhoz *et al.*, 2004). Furthermore, clinical testing has no predictive value for identifying people at risk of falling (Bloem *et al.*, 2001). As such, clinical examination of balance control only gives a rough and subjective estimation of potential balance deficits nor does it not create insight in the underlying causes (Visser *et al.*, 2008).

Quantitative assessment of balance

As an alternative to the subjective clinical tests, posturography can be used to study balance reactions in a standardized setting, using standardized balance perturbations and objective electrophysiological outcomes.

Posturography

Posturography is the measurement of body movements, reactive forces and muscle activity during a balance task of individual subjects. Movements can be recorded by a motion analysis camera system or potentiometers. Subsequently, the recorded movements are used to reconstruct the movement of the center of mass (CoM) of the whole body or of separate body segments. In this way the sway angle (the angle to body makes with the vertical) or joint angles can be determined. Furthermore, with a 6 DoF forceplate the position of the resultant force beneath the feet (center- of- pressure; CoP) or (in combination with inverse dynamics) joint torques can be calculated.

Posturography can be applied during 'static' tasks, where the subject is instructed to stand as still as possible or during dynamic situations, where the subjects' balance is perturbed with standardized well-characterized perturbations. When using continuous periodic perturbations, non-parametric closed-loop system identification methods can be applied to analyze the responses (Box 2). These methods are able to disentangle the dynamics of the (musculo)skeletal system from the dynamics of the stabilizing mechanisms (Figure 1.3).

Box 2: System identification for balance control

The balance control system can be regarded as a closed loop system (Fitzpatrick et al., 1996; Horak et al., 1996), that is, the CNS sends input to the periphery and receives sensory information from the different feedback pathways (see Figure 1.3). Therefore, it is impossible to determine causality; does the input (i.e., joint torque) influence the output (i.e., joint angles) or vice versa? In order to 'open' the loop and to determine the dynamics of the separate components, such as the body (Figure 1.3), perturbations should be

applied (Pintelon et al., 2001; van der Kooij et al., 2005). By externally exciting the system a unique input is provided that is not related to the internal signals of the system, creating a clear causal relation between perturbation and output signals (van der Kooij et al., 2005).

System identification entails dedicated experiments (by applying the proper perturbations), thereby efficiently generating informative data of dynamical systems. Subsequently, the appropriate analysis are performed to obtain an estimate of the dynamics of the studied system, for example the mechanisms that stabilize upright stance. Furthermore, a mathematical model of the system can be fitted to the acquired data, to determine system parameters such as stiffness, damping and noise levels (van der Kooij *et al.*, 2011). Describing the dynamical system in the frequency domain without model fitting is called non-parametric identification, versus parametric system identification with model fitting.

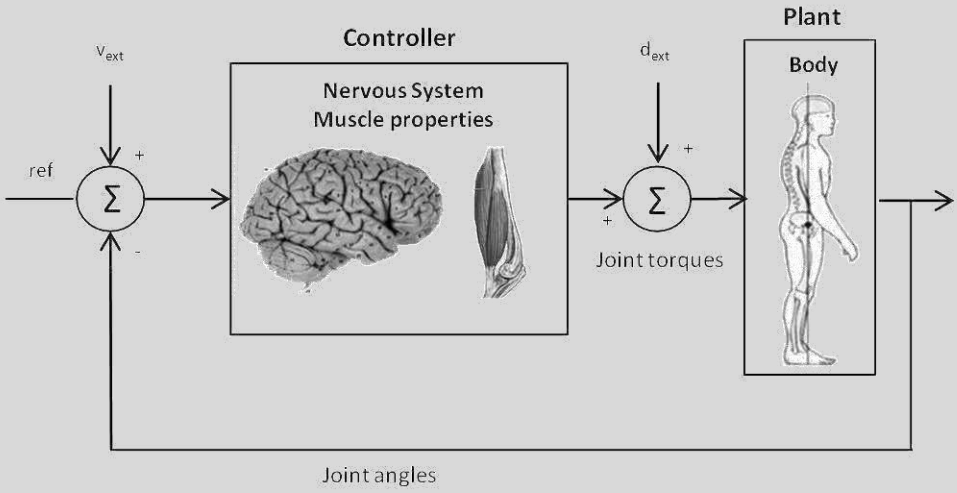

Figure 1.3: Closed-loop system of balance control. The plant represents the body with its mechanical and inertial properties. The controller consists of the passive and active muscle properties, the parts of the CNS that process sensory signals, determine the appropriate response and send efferent signals to the muscles. d_{ext} are mechanical perturbations (i.e., platform accelerations, forces or torques), v_{ext} are sensory perturbations, e.g. support surface rotations.

Perturbation signals

As mentioned above, perturbations are necessary to reliably estimate the dynamics of the studied system. In this thesis (**Chapters 3, 5 and 6)** I have used periodic perturbations that consist of many summed sinusoids with different amplitudes, phases and frequencies (i.e., mulitsines). In **Chapter 7** I used pseudorandom ternary sequences (PRTS; Davies, 1970). Applying periodic multisine or PRTS perturbations have the advantage that a) the signal is unpredictable for participants, b) decrease the measurement time, because they have power at specific frequencies c) they increase the participants' response and can therefore be used to obtain a reliable individual response.

Frequency response functions

By transforming the measured signals (i.e., joint torques and joint angles) to the frequency domain by Fourier transformation, the system can be described by Frequency Response Functions (FRFs).

A FRF has two components: the gain and the phase and these two capture the amount and timing of the response of the participant. As such, the gain of the FRF of the stabilizing mechanisms represents how much torque is exerted in response to body sway. The phase gives information about the timing of the response, if there is a phase lead the response of the joint torque advances the body movement and a phase lag implies that joint torque lags body sway.

Constraints

Currently, the available system identification methods for balance control are linear, time-invariant techniques. In order to apply linear techniques to a very nonlinear system (such as balance control), the movements should not be too large. Hence, perturbations that evoke large sway angles or push the participants to their limits of stability violate the assumption of linearity. Furthermore, during the course of the experiment, participants should not adjust their balance control strategy (i.e., switching between stiff and compliant control). Acquired data should therefore always be interpreted with caution. In addition, the reliability of the calculated estimate of the system's dynamics should be determined by examining for example, the ratio between the periodic (due to the perturbation) and non-periodic (due to nonlinearities, noise and time variant behavior) response.

Models of balance control

An elegant way to study and describe a system is to make a model of it. A good model simplifies a complex system, while still mimicking the main characteristics. Indeed, many models of balance control have been proposed, used and described (Kiemel *et al.*, 2011; Kuo *et al.*, 1993; Park *et al.*, 2004; Peterka, 2002; van der Kooij *et al.*, 1999; van der Kooij *et al.*, 2001).

One of the most commonly used models is the inverted pendulum model; the body is assumed to move as a rigid bar with a mass on top, pivoting at the ankles (Loram *et al.*, 2002b; Winter *et al.*, 2001). Not all muscles around the ankle joint are modeled independently, but the control actions are summed leading to a corrective torque. This system is unstable, but it can be controlled with a 'controller' that has proportional and derivative components. When fitting the model to the data, parameters such as stiffness, damping and the loop gain of the system can be determined. In this way it has been shown that postural tremor loop in combination with increased sensory-motor noise in PD patients is caused by abnormally high gains in the feedback loop (Maurer *et al.*, 2004). In

combination with a model of sensory channels, Peterka (Peterka, 2002) showed that healthy controls are able to suppress erroneous sensory information when exposed to platform or visual surround tilts.

The inverted pendulum model can be extended to a two or three degree system by adding joints such as the hip and the knee. However, the control becomes much more complicated due to the mechanical coupling between the segments (Nott *et al.*, 2010; Zajac *et al.*, 2002).

Bipedal balance control

The above described approaches, both the qualitative and quantitative assessments of balance and most models of balance control, do not distinguish between the separate balance contributions of each leg. However, humans have two legs and both legs are involved in maintaining an upright posture. Healthy controls use both legs to exert an equal amount of control to maintain an upright posture, in other words their balance is controlled symmetrically (Anker *et al.*, 2008; Maki *et al.*, 1993; van Asseldonk *et al.*, 2006), while asymmetric balance control is considered pathological. Asymmetries can be present in weight bearing (when one leg 'carries' more body weight than the other leg) or in balance control (when one leg produces more corrective force than the other leg). Asymmetries have been detected in stroke patients (Geurts *et al.*, 2005) and in people with Parkinson's disease (Rocchi *et al.*, 2002) and have been associated with impaired postural instability (Sackley, 1991). Therefore, one of the main goals of stroke rehabilitation is to reduce weight bearing asymmetries. Restoring symmetrical weight bearing in stroke has been associated with better motor performance and greater ADL independence (Geurts *et al.*, 2005). However, a weight bearing asymmetry is not necessarily accompanied by a control asymmetry in stroke patients, whereas in healthy controls a tight coupling was found (van Asseldonk *et al.*, 2006).

PD is a progressive neurological disorder that can cause severe gait and balance problems. In fact, of all neurological diseases, PD is associated with the highest risk of falling (Hely *et al.*, 2008; Pickering *et al.*, 2007; Stolze *et al.*, 2004). Interestingly, PD is an asymmetrical disease; motor symptoms start on one side of the body and this side remains the most prominently affected during the course of the disease (Djaldetti *et al.*, 2006).

It is generally assumed that asymmetries in balance control are a sign of impaired motor function, but in order to take a step, asymmetries are essential (Maki *et al.*, 1993). That is, the stepping leg needs to be unloaded (i.e., the stance leg needs to bear the full body weight) in order to swing freely forward and this requires a voluntary lateral weight shift. This raises the question whether an intrinsic balance asymmetry could hamper the necessary lateral weight shift for compensatory steps of gait initiation. Would it require more effort (muscular force, attention) to shift the weight to the least weight bearing,

least contributing leg? Could it be associated with gait impairments such as freezing of gait (Box 3), where patients seem to have lost the ability to shift their body weight to the stance leg (Jacobs *et al.*, 2009). In addition, investigating the responses of each leg separately has the advantage that one can look at compensation strategies between the legs. Theoretically, one leg could be used as a crutch, while the other leg takes over the control needed for upright stance. Can one leg work harder to compensate for the other leg and would there be differences in the balance contribution between the different joints involved in balance control (e.g., ankle versus hip)?

Furthermore, postural instability in PD has been assumed to be caused by disturbed postural corrections as generated by the basal ganglia ('efferent' deficit (Scholz *et al.*, 1987)). However, this view has been challenged by observations that some motor deficits in PD are (at least partially) due to defective afferent pathways (Carpenter *et al.*, 2011; Vaugoyeau *et al.*, 2007; Wright *et al.*, 2010). Currently, there is no knowledge about how the sensory information of each leg is integrated within the CNS and subsequently it has not been investigated whether there are differences in afferent deficits between the left and right side in PD. Developing and evaluating methods that manipulate sensory information of both legs separately would possibly create insight into the origin of motor asymmetries in PD patients. In addition, balance control asymmetries have seldom been studied in PD. The available studies investigated the presence of balance asymmetries in small samples (van der Kooij *et al.*, 2007), in severely affected patients and during quiet stance (Rocchi *et al.*, 2002) and did not relate the asymmetry to clinical signs. Therefore it is not clear whether asymmetries in balance control play a role in the postural problems of PD patients. Therefore, in this thesis I investigated the balance responses of each leg separately, by assessing balance control of PD patients (**Chapters 3-6**) and by applying a novel method that manipulates the sensory information of each leg individually in healthy young subjects (**Chapter 7**).

The following research questions were formulated:

1) Is balance control asymmetrically organized in Parkinson's disease patients?
2) Is asymmetrical balance control related to freezing in Parkinson's disease?
3) Can the most contributing leg compensate for the least contributing leg during balance control in Parkinson's disease and are there differences in compensation between the ankle and hip joint?
4) Can healthy controls suppress erroneous sensory information of each leg separately?

Box 3: Freezing of gait

Freezing of gait (FoG) is a disabling, episodic gait disorder whereby the patient has the subjective feeling that the feet are being 'glued' to the floor. This includes instances when the patient is not able to initiate gait ('start hesitation') or stops walking ('turn' and 'destination' hesitation), but also when patients are shuffling forward with small steps (millimeters to a couple of centimeters in length; (Nutt *et al.*, 2011). It occurs in about 50% of patients with PD (Peterson *et al.*, 2012). There are also other neurological disorders that show freezing (e.g. stroke (Bussin *et al.*, 1999). The pathophysiology of FoG is poorly understood, but it is associated with a) increased gait variability (spatial and temporal), b) increased gait asymmetry, c) disrupted automaticity of movements, d) an abnormal coupling of posture with gait, e) perceptual malfunction and f) executive dysfunction (Nutt *et al.*, 2011). FoG can be elicited by gait initiation or turning (Snijders *et al.*, 2012), by having the patient take small steps or by decreasing the step length during gait (Chee *et al.*, 2009). Because of the episodic nature of freezing, FoG is an important cause for falls and injuries (Snijders *et al.*, 2007), negatively influencing the quality of life (Moore *et al.*, 2007). Drug therapy, deep brain stimulation and rehabilitation therapy (e.g. cueing or treadmill training) can alleviate symptoms in some patients, but these treatments lack efficacy in patients with more advanced FoG. A better understanding of the phenomenon is needed to aid the development of effective therapeutic strategies.

Aim and outline of this thesis

The general goal of this thesis is to create further insight into the (patho)physiology of human balance control by specifically investigating the balance responses of each leg separately, in both healthy and people with PD.

Chapter 2 reviews the state of the art of gait and balance problem of patients with PD. It also examines whether asymmetries in gait and balance control are present in PD patients.

Chapter 3 introduces a new method to determine the contribution of the ankle and the hip joint to multi-segmental balance control. It uses closed-loop system identification methods (van Asseldonk *et al.*, 2006; van der Kooij *et al.*, 2005) that were extended to the Multiple-Input-Multiple-Output (MIMO) case. It was investigated whether the new method is able to reliably estimate the stabilizing mechanisms of a MIMO system, both with model simulations and a balance control experiment with healthy subjects and one PD patient.

Chapter 4 investigates whether balance responses during quiet stance of both separately legs can be different, i.e., asymmetric in PD patients, with current available methods (Anker *et al.*, 2008). As such, this study lays the foundation for **Chapters 5** and **6** where the implications for asymmetrical balance control in PD patients were studied in more detail, with the developed method as presented in **Chapter 3**.

Chapter 5 investigates the relationship between asymmetrical balance control and freezing of gait in a group of twenty PD patients. Within this group, nine freezers (patients who experienced freezing regularly) and 11 non-freezers were carefully matched. Patients were tested OFF medication. Closed-loop system identification techniques were applied, to separate weight bearing asymmetries from balance control asymmetries. Subsequently, the amount of balance asymmetry between freezers and non-freezers was compared and it was investigated whether the weightbearing-balance control relationship differed between freezers and non-freezers.

Chapter 6 addresses the question whether, and to what extent, the least affected leg can compensate for the most affected leg in PD. In addition, **Chapter 6** investigates whether the compensation differs at the ankle compared to the hip. The method as introduced in **Chapter 3** was applied in twenty PD patients and seven controls.

Chapter 7 applies a new method to investigate sensory reweighting of separate legs in healthy subjects, by rotating the support surfaces of each leg independently during upright stance. By increasing the perturbation amplitude of one foot while keeping the perturbation of the other leg constant, the sensory information of this leg became more unreliable compared to the other leg. Sensitivity functions of the ankle torques to the perturbation amplitudes, determined the sensitivity of the body's response to the perturbations. Furthermore, how much each leg contributes to stabilize stance (i.e. stabilizing mechanisms) was estimated (van Asseldonk *et al.*, 2006).

Chapter 8 summarizes and discusses the findings of this thesis. The applied methods and results are critically discussed and future directions are given.

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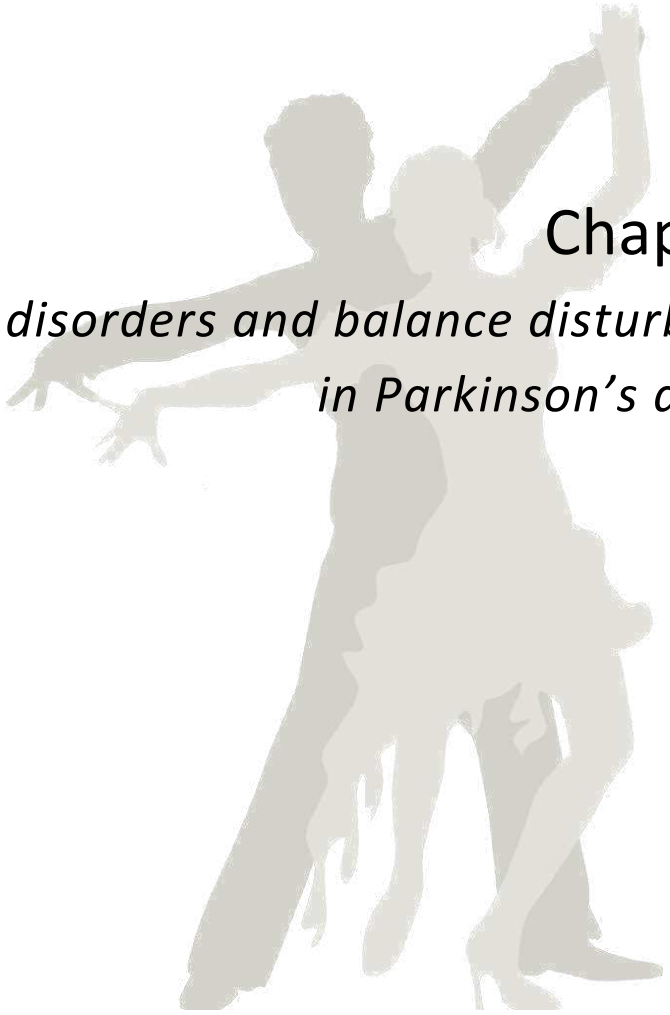

Chapter 2

Gait disorders and balance disturbances in Parkinson's disease

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Abstract

Gait disorders and balance impairments are one of the most incapacitating symptoms of Parkinson's disease (PD). Here, we discuss the latest findings regarding epidemiology, assessment, pathophysiology and treatment of gait and balance impairments in PD.

Recent studies have confirmed the high rate and high risk of falls of PD patients. Therefore, it is crucial to detect which patients are at risk of falling and how to prevent falls. Several studies have shown that multiple balance tests improve the prediction of falls in PD. Difficulty turning may be caused by axial rigidity, affected interlimb coordination and asymmetries. Turning difficulties are easily assessed by timed performance and number of steps during a turn. Impaired sensori-motor integration, inability of switching between sensory modalities and lack of compensatory stepping may all contribute to the high incidence of falls in PD patients. Similarly, various studies highlighted that pharmacotherapy, neurosurgery and physiotherapy may adversely affect balance and gait in PD.

Insights into the pathophysiology of PD continue to grow. At the same time, it is becoming clear that some patients may in fact deteriorate with treatment.

Future research should focus on the development and evaluation of multifactorial falls prevention strategies.

Introduction

Parkinson's disease (PD) is an incapacitating disease that negatively affects the quality of life for many reasons, not the least of which is the presence of axial disability (gait disorders, balance impairment, falls and fall-related injuries; Hely *et al.,* 2008; Pickering *et al.,* 2007). Here, we review recent clinical and fundamental studies dealing with gait, balance and falls in PD, covering approximately the period of January 2006 until February 2008. First, we provide an overview of the epidemiology and clinical significance, followed by recommendations on clinical assessment techniques. We subsequently discuss new pathophysiological insights, aiming specifically on turning strategies, the relevance of asymmetries in axial motor control and impaired sensorimotor integration. We also highlight developments in the field of neuroimaging. Treatment issues are covered next, focusing on drug treatment, deep brain stimulation (in particular pedunculopontine nucleus (PPN) stimulation) and physiotherapy. We conclude by providing recommendations for future research.

Epidemiology

Recent studies have confirmed the high rate of falls in PD. Additionally, risk factors and predictors for falls were identified.

Prevalence and clinical impact

Prior studies on falls in PD included relatively small patient groups. A recent meta-analysis addressed this by pooling the results of six independent prospective studies of falling in PD (Pickering *et al.,* 2007). The pooled sample size included 473 patients. The 3-month fall rate was 46% (95% confidence interval: 38 –54%). Interestingly, even among subjects without prior falls, this fall rate was substantial (21%, 12–35%). These results underscore that PD patients have a high risk of falling, even when they have not fallen previously. This high fall rate was also observed in the Sydney multicenter study, where 136 newly diagnosed PD patients were followed for 20 years (Hely *et al.,* 2008). Of the 36 survivors, 87% had experienced falls and 35% had sustained (multiple) fractures; Figure 2.1). These falls occurred despite maximal treatment with levodopa, confirming earlier impressions that axial disability in late-stage PD is largely dopa-resistant (likely due to extranigral and non-dopaminergic brain lesions). The high risk of fractures was also demonstrated in a large case-control study, which showed that patients with parkinsonism (not just PD) had a more than twofold increased risk of sustaining any fall-related fracture (Vestergaard *et al.,* 2007). Interestingly, levodopa was paradoxically associated with an *increased* overall risk of fractures, especially hip fractures. One possible explanation is that levodopa dose was merely a marker of disease severity, or that levodopa caused adverse effects that predisposed subjects to falls, e.g. violent dyskinesias or drug-induced orthostatic

hypotension (Vestergaard *et al.,* 2007). Another option is that patients on levodopa are simply more mobile and therefore more prone to fall. Indeed, fall rates tend to taper with disease progression, likely because patients become increasingly immobilized (Pickering *et al.,* 2007) and thereby "protect" themselves from further falls.

The negative impact of gait disorders on quality of life is widely appreciated, for example because of the resultant immobility (causing loss of independence) and the risk of falling. "Episodic" gait disorders – which are only intermittently present – are particularly incapacitating because patients cannot easily adjust their behaviour to these paroxysmal walking problems (Snijders *et al.,* 2007). A textbook example is freezing of gait (FOG), where parkinsonian patients experience debilitating episodes during which they are unable to start walking or – while walking – suddenly fail to continue moving forward. Because of this sudden and unpredictable nature, FOG is an important cause of falls and injuries. Perhaps not surprisingly, a recent study showed that FOG was independently associated with a decreased quality of life (Moore *et al.,* 2007a).

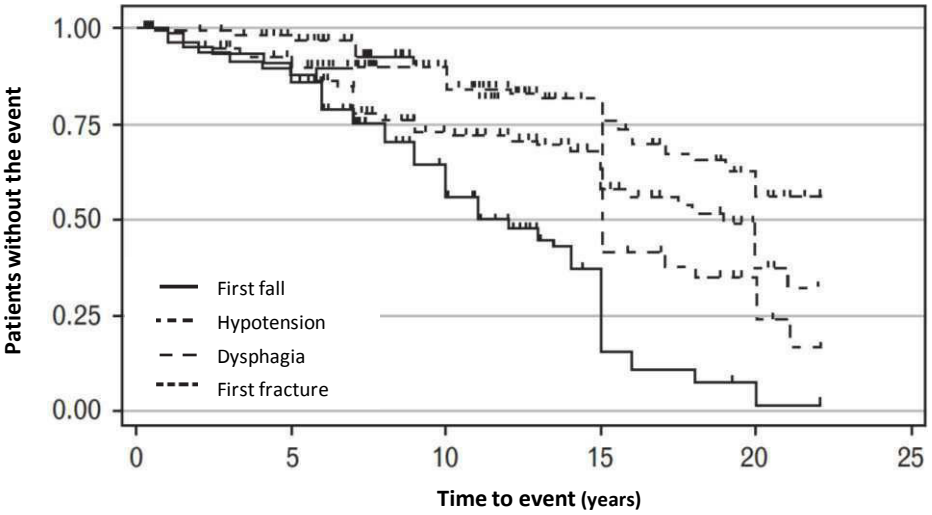

Figure 2.1: Kaplan–Meier plot of time to falls, dysphagia, symptomatic postural hypotension, and first fracture. Figure adopted from Hely et al., 2008 and reprinted with permission from John Wiley and sons.

Risk factors and predictors

It remains difficult to predict which patients (and in particular which prior non-fallers) are most likely to fall next, as these persons would be ideal candidates for an intensive falls prevention program. In the aforementioned meta-analysis (Pickering *et al.,* 2007), the best predictor of falling was two or more falls in the previous year (which is unsatisfactory as predictor because patients have already begun falling), and even this had a relatively modest predictive ability (sensitivity only 68%; specificity acceptable at 81%). Interestingly, among prior-non fallers, fear of falling had a moderate sensitivity in predicting falls, so

maybe people sense their own instability before doctors can detect this physically. Fear of falling can be evaluated using the ABC scale, which has been validated for use in PD and, more recently, also in abbreviated form (using only six of the original 16 questions) (Oude Nijhuis *et al.,* 2007; Peretz *et al.,* 2006). Fear of falling was also associated with prior falls in another study, although the strongest determinants of falls were impaired ambulation, impaired lower-limb motor planning and, interestingly, orthostasis (Dennison *et al.,* 2007). The relevance of orthostasis was also suggested by a retrospective case notes review (Williams *et al.,* 2006), exploring the relation between clinical features and falls and fractures in pathologically diagnosed cases. Among confirmed PD cases, autonomic instability was one of the few factors that independently predicted the time to the first fall. Falls due to syncope are thought to be uncommon in PD (Bloem *et al.,* 2004a), but these two studies suggest that clinicians may perhaps miss relevant orthostatic hypotension in some patients, either because it is simply not measured or because clinical ascertainment is not infallible (Bloem *et al.,* 2004b). Another potentially interesting predictor of falls is asking about prior near-falls as these may precede overt falls (Pickering *et al.,* 2007), but more work is needed to develop clear definitions and a reliable way of ascertaining near-falls.

Clinical and quantitative assessment of axial disability

Several researchers have developed methods to assess gait, FOG, postural instability and balance confidence (Table 2.1). Note that three studies focused on predicting falls in PD (Dibble *et al.,* 2008; Dibble *et al.,* 2006; Jacobs *et al.,* 2006b).

Pathophysiology

New insights were gained in the area of turning, axial asymmetry, sensorimotor integration impairments and neuroimaging.

Turning

PD patients often have difficulty turning around, not only while lying recumbent in bed, but also while standing upright. These turning problems have great clinical relevance because of the relation with FOG and hip fractures. It would be helpful to have simple tools to detect turning difficulties, to estimate the risk of falling, and to record the outcome of therapeutic interventions. Several recent studies have shown that simply a timed performance and counting the number of steps during a 180 degree axial turn may suffice, as PD patients require more steps and also turn slower than controls (Crenna *et al.,* 2007; Dibble *et al.,* 2008; Huxham *et al.,* 2006; Stack *et al.,* 2006; Willems *et al.,* 2007).

Table 2.1: Overview of new assessment techniques to measure axial disability (gait, balance, posture and falls) in Parkinson's disease.

Technique	Type	Main outcome	Remarks / critique
ABC-6 (shortened version of ABC-16, a questionnaire focused on fear of falling)[1, 2]	C	A shortened version of the ABC-16, featuring only 6 of the original 16 questions, is a valid tool to assess fear of falling	Minor variants may exist between different countries
Combination of multiple clinically based balance tests[*]	C	Improved prediction of falls in PD, compared to individual tests	Ideal combination remains unknown
"Push & release" test (variant to the commonly used pull test)[3]	C	Less inter-rater variability and better prediction of self-reported prior falls	Relation to prospectively documented falls unknown; some patients experience the test as threatening
Tinetti Mobility test (TMT)[4]	C	Interrater and intrarater reliability good to excellent; moderate relation to faller status	Generic scale which fails to accommodate PD-specific features, such as asymmetrically reduced arm swing or turning 'en bloc'; relation to historical falls only moderate, and relation to prospectively documented falls unknown
Quantitative kinematic gait analysis[5]	Q	At the group level, significant differences between patients and controls, and within patients before versus after rehabilitation	Utility at individual patient level not determined; feasibility for use in clinical practice remains unclear
Global Mobility Task (GMT): qualitative and quantitative assessment of ability to roll over on the floor and stand up in five steps[6]	Q	Good consistency and inter-rater reproducibility, closely related to clinical scales and able to changes after rehabilitation	Requires independent confirmation

Technique	Type	Main outcome	Remarks / critique
Phase coordination index (PCI)[7]	Q	PCI measures interlimb coordination during gait	Feasibility for use in clinical practice remains to be determined
Ambulatory gait assessment, using goniometers on the shank[8]	Q	Reliable detection of stride length and motor fluctuation due to Levodopa therapy in the home situation.	Other symptoms of PD, such as tremor and bradykinesia can not be detected with the stride monitor
Ambulatory freezing assessment using goniometers on the shank[9]	Q	89% sensitivity for the detection of freezing, with 10% false negatives, after individual calibration in a laboratory setting.	Individual calibration is needed. Discussion remains about the frequency of freezing. Feasibility for the home environment needs to be determined.
GAITRite system[10]	Q	The gaitrite system is an effective and efficient method to evaluate parkinsonian bradykinesia. Also, it is possible to use the system as a substitute for the traditional timed tests.	Requires a GAITRight system to assess quantitatively assess gait.

C; Clinical, Q: Quantitative *Functional reach test (FRT), Berg balance scale, dynamic gait index, (cognitive) timed up and go tests[11,12]. One-leg stance test, FRT, and the UPDRS-III. Fear of falling was assessed by the ABC scale and participants reported how often they fell during the previous year[13].

[1] Oude Nijhuis et al., 2007; [2] Peretz et al., 2006; [3] Jacobs et al., 2006c; [4] Kegelmeyer et al., 2007; [5] Peppe et al., 2007a; [6] Peppe et al., 2007b; [7] Plotnik et al., 2007; [8] Moore et al., 2007b; [9] Moore et al., 2008; [10] Chien et al., 2006; [11] Dibble et al., 2008; [12] Dibble et al., 2006; [13] Jacobs et al., 2006b

Quantitative measures may assist clinicians in evaluating these turning difficulties, and this would be particularly helpful for home-based assessments. Ambulatory monitors are used increasingly to better understand mobility deficits in PD (Moore *et al.,* 2008; Plotnik *et al.,* 2007; Salarian *et al.,* 2007). For example, it was shown that turn duration is longer in PD patients compared to controls, and peak yaw and peak roll angular velocity of the trunk were reduced in PD (Visser *et al.,* 2007). Future studies need to determine whether such ambulatory monitoring techniques might be used for clinical examination in single subjects, or as objective outcome measure of axial turning or FOG in a domestic setting, e.g. in intervention studies.

Turning problems may result from inability to adequately maintain an interlimb coordination (Baltadjieva *et al.,* 2006; Hausdorff *et al.,* 2003; Plotnik *et al.,* 2007). This is extra difficult during turning when – by necessity – the two legs have to move more "in phase", rather than "out of phase" as is usual during over ground walking. Another important factor is axial "stiffness" and loss of intersegmental flexibility. One study measured trunk resistance to passive axial rotations and found an increased axial rigidity in PD (Wright *et al.,* 2007). Importantly, levodopa gave no improvement, again suggesting that axial disability is largely dopa-resistant, unlike the "appendicular" movements (hand control) which appear to be controlled by separate dopaminergic neural systems. Two other studies showed a loss of intersegmental axial coordination in PD (Baltadjieva *et al.,* 2006; Crenna *et al.,* 2007) which corresponds to the well-known clinical phenomenon of "en bloc" turning in this disease.

Orthostatic myoclonus

A new factor that may contribute to postural instability was identified in 11 PD patients with unexplained unsteadiness. Polygraphic recordings, including surface EMG, showed an orthostatic tremor of varying frequency (ranging from 4 to 18 Hz) in eight patients and, interestingly, a hitherto undiscovered orthostatic myoclonus in the remaining three patients (Leu-Semenescu *et al.,* 2007). The findings also had treatment implications: patients with fast tremor improved on clonazepam, while patients with slow tremor or myoclonus improved on levodopa, and sometimes benefited further when clonazepam was added.

Asymmetries in gait and posture

By definition, PD is an asymmetrical disease. A unique study in 35 "de novo" PD patients who were not yet treated with any anti-parkinsonian medication showed that asymmetries in gait (detected with simple pressure-sensitive insoles) are also an inherent symptom of early stage PD, and not merely a side effect of medication or a late disease complication (Baltadjieva *et al.,* 2006). Interestingly, this asymmetry was present even though stride-to-stride variability (previously thought to be one of the most sensitive

measures of gait changes in PD) was normal in these early patients. Moreover, subtle asymmetries in balance control can be detected in PD by carefully analysing the independent contribution of both legs to stance control, even before these changes are detected with the naked clinical eye (van der Kooij *et al.,* 2007).

Cognitive influences on gait and balance

An important new insight is the recognition that walking and standing are not purely automatic tasks, regulated by subcortical control mechanisms and requiring little if any conscious attention. Instead, gait is now increasingly seen as a complex "higher-order" form of motor behaviour, with prominent and varied influences of mental processes (Yogev-Seligmann *et al.,* 2008). For example, this becomes evident under complex circumstances, where PD patients are unable to deal with multiple tasks simultaneously, either because the central processing abilities have become too limited, or because patients fail to properly prioritize their balance control over other, less important secondary tasks, placing patients at a higher risk of falling (Bloem *et al.,* 2006).

Sensorimotor integration

Most investigators would regard postural instability as being caused by disturbed motor programming of postural corrections within the basal ganglia ("efferent" deficit). However, this view has been challenged by observations that some motor deficits in PD are at least partially due to central proprioceptive disturbances ("afferent" deficit). Thus far, proprioceptive disturbances have mostly been demonstrated for arm movements, including e.g. defective kinaesthesia, defective joint position sense or disturbed tactile spatial acuity. Recent work suggests that afferent (mainly proprioceptive) disturbances could also play a role in the pathophysiology of postural deficits in PD. For example, one study perturbed standing PD patients using very slow horizontal sinusoidal oscillations of a supporting platform, delivered at an amplitude and frequency that was kept below the semicircular canal perception threshold (i.e. subjects were dependent on proprioceptive feedback to maintain balance) (Vaugoyeau *et al.,* 2007). Patients swayed abnormally under these circumstances, but were able to partially correct this using visual feedback. Interestingly, this switch from kinaesthetic-dependent to vision-dependent balance control is slower in PD patients compared to controls, suggesting a difficulty in changing between different sensory modalities – an ability that is much needed in everyday life with its constantly changing environment (Brown *et al.,* 2006; De Nunzio *et al.,* 2007). Another group showed that the response to tendon vibration – a way to deceive the muscle spindles and create a false sensation of muscle stretch – is exaggerated in patients with advanced PD and does not habituate well, resulting in changed patterns of body sway (Valkovic *et al.,* 2006a; Valkovic *et al.,* 2006b). Such somatosensory deficits may produce an abnormally constructed body scheme and explain e.g. the stooped posture of PD

patients, of which they are often subjectively unaware (Wijnberg *et al.,* 2001). This concept was confirmed by an interesting study where PD patients were asked to perform a Functional Reach task (extending the arm forward as far as possible, with both feet fixed at the floor) (Kamata *et al.,* 2007). PD patients tended to overestimate their limits of stability, and this may be related to their falling tendency in everyday life.

Compensatory stepping

When equilibrium is truly jeopardized, there are two crucial balance correcting strategies to prevent subjects from falling: stretching out the arms, and taking compensatory steps. Various studies addressed the nature of compensatory stepping and showed that PD patients have difficulties initiating a compensatory step (Jacobs *et al.,* 2006a; King *et al.,* 2008). A newly emerging concept is that failure to initiate compensatory stepping could be due to impairment of anticipatory postural adjustments (a lateral weight shift is normally required to allow for a contralateral limb swing) (King *et al.,* 2008). The fascinating inference is that a walking problem (gait akinesia) is in fact caused by a primary balance deficit, i.e. the inability to shift weight. A related and equally interesting finding showed that PD patients, when provided with an assistive (externally imposed) anticipatory postural adjustment, could step faster (Mille *et al.,* 2007). One report showed that visual inputs may also ameliorate compensatory stepping: PD patients took longer steps when a visual target was provided, but performance deteriorated when participants were unable to see their legs (Jacobs *et al.,* 2006a). These results underscore the importance of visual feedback to compensate for motor disabilities in PD (see section on physiotherapy).

Neuroimaging

Structural and functional neuroimaging are used increasingly to better understand the pathophysiology associated with gait and balance impairment in PD. An example of a structural imaging study – using magnetic resonance imaging (MRI) – showed that, in contrast to tremor, axial deficits were related to increases in ventricular volume in PD, but this association was accounted for by age (Acharya *et al.,* 2007).

Several groups have examined cerebral perfusion at rest to investigate the cerebral bases gait impairment in PD. This approach has the considerable advantage of perfectly matched “performance” across different subject groups (assuming that pathological alterations in brain activity are present not only during task performance but also during rest). One study used N-isopropyl-p[123I] iodoamphetamine SPECT to compare cerebral blood flow between patients with either the “tremor-dominant (TD)” subtype or the “postural instability and gait difficulty (PIGD)” subtype of PD (Mito *et al.,* 2006). The results showed hypoperfusion in the anterior cingulate cortex and primary visual cortex, but only in the PIGD group. The frontal reduction in perfusion is particularly interesting in light of the aforementioned relation with frontal executive deficits (Yogev-Seligmann *et al.,*

2008). A further study used PET, allowing for better spatial resolution than previous studies (Bartels *et al.,* 2006). Specifically, the relation between FOG and using 2-deoxy-2[18F]fluoro-D-glucose-PET (FDG-PET) – to measure striatal glucose uptake – and 18[F]-6-fluoro-levodopa (FDOPA)-PET – to measure striatal decarboxylase activity – was measured in PD patients with and without FOG. In patients with FOG, lower putaminal FDOPA uptake with increased FDG uptake was observed, whereas caudate uptake of both FDG and FDOPA was reduced. In addition, patients with FOG had a decreased FDG uptake in the parietal cortices. However, a general problem in interpreting such studies is the matching between subgroups. Ideally, the only difference between groups would be their gait problems, and this is difficult to achieve because gait is closely related to other relevant variables such as disease severity and disease duration. This is illustrated by the above cited papers, where subgroups were not matched for disease severity or disease duration (Acharya *et al.,* 2007; Mito *et al.,* 2006).

Motor imagery of gait is a new approach to partially circumvent the problems associated with functional imaging of gait, assuming that imagined walking shares at least some of the cerebral processes with gait, but without the need to engage in actual gait. Several groups have developed paradigms for this (Bakker *et al.,* 2007; Jahn *et al.,* 2008). In such studies, it is crucial to verify performance and ascertain that subjects are actually specifically engaged in motor imagery of gait, e.g. by testing whether imagined movement times increase as a function of distance that subjects are requested to travel. This approach has been used successfully in healthy subjects (Bakker *et al.,* 2008; Jahn *et al.,* 2008), and are now ready for application in PD.

Treatment

New insights were gained in the field of pharmacotherapy, deep brain stimulation and physiotherapy. A brief discussion of recruitment issues and guidelines for RCT's is given.

Pharmacotherapy

Gait and balance problems in PD tend to be perceived as being "untreatable", but there are various therapeutic options (Bloem *et al.,* 2008). For example, one report showed that, although the proportion of "midline" motor disability increases with time, these deficits do not become unresponsive to levodopa (Clissold *et al.,* 2006). Vital information also came from the seminal ELLDOPA study (a placebo-controlled trial comparing various doses of levodopa) which showed that FOG was most common in the placebo group and low-dose levodopa group, compared to groups taking higher levodopa dosages (Fahn *et al.,* 2004). However, levodopa may also adversely affect gait or balance control. For example, one study showed that timing of gait to an external stimulus was worse in medicated patients compared to patients who had withdrawn from medication, perhaps due to drug-induced dyskinesias (Almeida *et al.,* 2007). PD patients using neuroleptics have an

increased risk of sustaining any fall-related fracture (Vestergaard *et al.,* 2007), but causality is difficult to prove (patients requiring neuroleptics may simply have more advanced disease). A new approach is methylphenidate (traditionally used to combat attention-deficit-hyperactivity disorder). Methylphenidate can decrease fall risks in community dwelling older adults, conceivably by increasing availability of striatal dopamine or by improving attention (Ben-Itzhak *et al.,* 2008). Three further trials have now shown that methylphenidate also improves gait and FOG in PD (Auriel *et al.,* 2006; Devos *et al.,* 2007; Pollak *et al.,* 2007).

Stereotactic neurosurgery

Bilateral subthalamic nucleus (STN) stimulation is an effective treatment for PD, especially for appendicular symptoms that responded well to levodopa preoperatively. However, the effects of STN stimulation on axial motor signs remain debatable. It is impossible to draw overriding conclusions because of the differences in surgical techniques, candidates selected for surgery and outcome measures used. A few tendencies are worth reporting. First, it has been suggested that medication and deep brain surgery may affect axial mobility deficits by acting on different neural systems. Indeed, some studies reported improvement of postural deficits, beyond the effects afforded by medication alone (Gan *et al.,* 2007; Guehl *et al.,* 2006; Shivitz *et al.,* 2006). Specifically, at least some of the effect of STN stimulation may act via "downward" projections onto the PPN (Gan *et al.,* 2007).

Second, there are increasing concerns that deep brain stimulation may worsen axial mobility, sometimes as an immediate adverse effect of surgery, but also as a long-term complication. For example, one report showed that after a 3 year follow-up of 36 PD patients, STN stimulation had improved the UPDRS motor score by 54.2% and gait scores by 45.3%, but dopa-unresponsive axial signs had worsened in some patients (Gan *et al.,* 2007). Another study investigated gait changes after STN stimulation and found that gait had improved in half the patients, but had worsened in the others (Kelly *et al.,* 2006). This inconsistent response was also found in a dynamic posturography study that assessed postural control in PD patients exposed to a random mix of multidirectional tilts of a supporting forceplate (Visser *et al.,* 2008). Participants were tested with their STN stimulators switched on and off, 60-90 min after a suprathreshold dose of levodopa. Overall balance – defined as displacement of the center of mass following the postural perturbation – improved in nine patients but deteriorated for the remaining four patients. A particular worry is the development of new gait and balance deficits several years after surgery, even in the face of persistent beneficial effects on appendicular motor control. This was demonstrated in a study that used a standardized questionnaire to ask patients about both their global outcome and gait, at six months postoperatively and at the time of examination (about 2.7 years postoperatively; van Nuenen *et al.,* 2008). A striking 42% of patients experienced a worsening of gait in the medication OFF phase, and this appeared

to be fairly selective because global outcome scales continued to be improved. A major drawback of this study was the lack of control group, hence some postoperative gait problems could have been ascribed to natural disease progression.

An important target for future research is the development of reliable determinants for success or failure of deep brain surgery. It has been speculated that variability in electrode placement can explain the inconsistent effects on axial mobility across subjects. Specifically, it could be that misplaced electrodes project unintentionally to the PPN (Tommasi *et al.,* 2007) which, when stimulated at high frequencies, worsens gait and balance (Androulidakis *et al.,* 2008; Stefani *et al.,* 2007). This hypothesis was addressed in an interesting study of 13 PD patients with severe postoperative gait disorders whose typical stimulator settings (130 Hz) were changed a much lower frequency of 60 Hz, while keeping the total energy delivered constant (Moreau *et al.,* 2008). All outcome measures (including UPDRS, a timed walking task and FOG) clearly improved during the 60 Hz condition compared to the 130 Hz condition. The explanation put forward was that, because the PPN is just 5 mm away from the STN, high-frequency STN stimulation could negatively affect the PPN (and the opposite for low-frequency STN stimulation of course). Based on these findings, the authors proposed a two-staged STN frequency optimization: 130Hz during the initial years of STN stimulation; and 60 Hz (at a higher voltage) after gait disorders have become manifest.

Others examined the merits of direct PPN stimulation. Smaller previous studies had shown the technical feasibility of this approach, but interesting new insights came from a study of six PD patients whose gait and balance responded unsatisfactorily to drug treatment, and therefore underwent bilateral implantation of electrodes in both the STN and PPN (Stefani *et al.,* 2007). The most interesting results were seen during the medication ON phase, when an extra treatment push (i.e. over and above optimal drug therapy) is mostly needed. During this ON state, PPN stimulation alone had a positive effect on the UPDRS items for gait and balance, whereas STN stimulation did not. PPN stimulation improved axial symptoms directly postoperatively and this persisted for 6 months. However, an extended follow-up is needed to evaluate the long-term effects. An important critique was that the electrodes might have been misplaced, i.e. not in the PPN, but rather in the nucleus peripeduncularis (Yelnik, 2007). Therefore, the obtained results should be interpreted with care, and further research is needed to investigate the effects in more detail (e.g. using objective measures such as posturography), to study the effects of electrode (mis)placements and to evaluate long-term effects.

Physiotherapy

Cueing

It is widely appreciated from clinical experience and experimental, mainly lab-based studies that PD patients can improve their gait using external cues. In a seminal study for

the field of physiotherapy, this knowledge was taken to the test in a large, multicenter and single-blind crossover study (RESCUE trial) that examined the effect of a 3-week training program, featuring three rhythmic cueing modalities: visual, auditory, or tactile (Nieuwboer *et al.,* 2007). Immediately after the training period, small but significant improvements were found for clinical gait and balance scores, for FOG severity (among freezers), for gait speed and step length, and for timed balance tests. There was no control group, so it cannot be excluded that the effects were due to gait training per se, rather than specifically due to training of cueing.

Knowing whether beneficial effects persist after training has ended is crucially important if one wants to implement cueing as treatment into clinical practice. In a lab-based study, improvements in gait after rhythmic auditory stimulation persisted at 2 and 15 minutes after actual cueing, suggesting some degree of retention (Hausdorff *et al.,* 2007). However, in the RESCUE trial, the observed improvements were no longer present in the non-cued situation 6 weeks after training (Nieuwboer *et al.,* 2007).

Another relevant issue is a possible carry-over of specific training effects to other, non-trained tasks. Encouraging findings were reported in a study where participants completed a 4-week training program in which they practised gait and rhythmic tapping (del Olmo *et al.,* 2006). The tasks used as outcome measure did not match the practised tasks, but nevertheless showed significant improvements following this non-specific training. In contrast, the much larger RESCUE trial found no carry-over of gait cueing to other modalities, such as functional outcome measures or quality of life (Nieuwboer *et al.,* 2007).

A further issue – again with great clinical relevance – is the emerging insight that cueing can also have adverse effects. For example, one study showed that rhythmic auditory stimulation can differentially affect freezers and non-freezers (Willems *et al.,* 2006). Specifically, the results showed that rhythmic auditory stimulation (set at 110% of preferred walking speed) afforded increases in step length for non-freezers, but produced the opposite effect for freezers. Another study showed that visual cueing may also adversely affect gait, depending on disease severity (Arias *et al.,* 2008). Falls may paradoxically increase when patients receive cueing treatment, simply because mobility improves, and also because the cueing may distract patients from paying attention to environmental hazards. Fortunately, cueing was not associated with more falls in the RESCUE trial, although the study was not properly powered to address this issue (Nieuwboer *et al.,* 2007). The take home message is that cueing should not be prescribed as a “one size fits all” treatment, but should be carefully tailored to specific factors such as disease severity and individual symptomatology.

A final practical concern is whether cueing – even when effective in the lab under carefully controlled “single task” conditions – will also benefit patients in daily life with its complex situations, typically requiring subjects to deal with multiple tasks simultaneously. This was addressed in two studies that, somewhat surprisingly, showed that rhythmic

auditory cues improved gait better in a dual task situation (e.g. walking with filled cups on a tray) compared to a single task situation (normal walking; Baker *et al.,* 2007; Rochester *et al.,* 2007). Perhaps participants were challenged more during the dual task, with heightened levels of arousal, or patients relied more on external information during the complex tasks (Rochester *et al.,* 2007). External cues could theoretically reduce attentional loads by reducing the need to prepare and plan a movement, but this hypothesis requires further testing.

Exercise

There is increasing attention for the possible beneficial effects of physical exercise for PD (Goodwin *et al.,* 2008). Overall, physical functioning, balance, gait speed, strength and health-related quality of life improve for people with PD after a physical exercise intervention. Exercise therapy may also lead to a reduction in FOG (Brichetto *et al.,* 2006). Management guidelines of the American Academy for Neurology concluded that exercise may be helpful to improve motor function in people with PD (Suchowersky *et al.,* 2006). However, there is insufficient evidence to support (or refute) that physical exercise is beneficial for reducing falls or depression (Goodwin *et al.,* 2008). The lack of clear effect on falls was also shown in a randomised controlled trial which showed that a combination of exercise and movement strategies (i.e. prevention of falls and movement initiation) only tended to decrease the incidence of falls compared to controls receiving usual care (Ashburn *et al.,* 2007a). However, it was encouraging that recurrent near-falls were decreased in the intervention group, and either with longer follow-up, a more intensive intervention or prolonged treatment this may eventually translate into fewer actual falls and injuries, possibly even among prior non-fallers.

Treadmill training may be one way to safely exercise patients with PD, for example because supervision is present or because a safety harness can prevent actual falls. Several studies have shown that treadmill training can improve gait in PD (Cakit *et al.,* 2007; Herman *et al.,* 2007). In addition, the Berg Balance Test, the Dynamic Gait Index (a measure of gait adaptability) and Falls Efficacy Scale scores (a measure of balance confidence) improved after six weeks of intensive treadmill training (Cakit *et al.,* 2007). An alternative – and perhaps more enjoyable – way of exercise training is dancing. One single-blind, small sample RCT showed that tango dancing (20 sessions) benefits PD patients, with improvements in UPDRS, Berg Balance scale and a tendency for less FOG (Hackney *et al.,* 2007).

A novel approach in delivering exercise is using motor imagery, engaged previously to promote recovery of stroke patients (Zimmermann-Schlatter *et al.,* 2008). An innovative study compared a control group that was treated with physical exercise alone to an experimental group that was treated with a combination of actual physical exercise plus imagery of the very same exercises (Tamir *et al.,* 2007). The combined treatment group

showed the greatest improvement, but much work is needed to fully underpin the merits of motor imagery for rehabilitation in PD.

Recruitment problems

A coincidental finding in two physiotherapy trials was the problems encountered in finding and recruiting eligible patients. In one UK-based study, only 13% out of all patients listed in the clinical registers of PD specialists could be included in a falls prevention trial, eligibility being the main problem (Ashburn *et al.,* 2007b). Similarly, a pilot study based in the Netherlands was also troubled by recruitment problems, but now mainly because most patients in the Netherlands already receive physiotherapy, so many declined the risk of being randomly allocated to a "no physiotherapy" control group (Keus *et al.,* 2007b). These studies provide important lessons for future trials of physiotherapy in PD.

Guidelines

In 2007, evidence-based guidelines of physiotherapy for PD were published, including definitions of the core treatment goals for physiotherapy (transfers, posture, reaching and grasping, balance, gait, and physical capacity), as well as menus of treatment strategies tailored to each of these domains (Keus *et al.,* 2007a). Specific recommendations included: cueing strategies to improve gait; cognitive movement strategies to improve transfers; exercises to improve balance; and training of joint mobility and muscle power to improve physical capacity.

Conclusions and future recommendations

The field of axial mobility deficits in PD continues to advance at a rapid pace, with significant progress both at the fundamental level (improved insights into the complex, multifactorial etiology of falls, gait and balance impairment) and at the clinical level (with large scale trials now beginning to see the light). Having said that, further work remains necessary to design optimal treatment strategies and to adequately prevent falls in PD. Key targets for new research include development of reliable and sensitive outcome measures that are sufficiently feasible for widespread application, in trials as well as everyday clinical practice; the development of improved treatment strategies, including both pharmacotherapy (aimed at more than just dopaminergic motor circuitries), stereotactic surgery (optimising STN stimulation; and defining new targets such as the PPN) and physiotherapy. A particular challenge will be to combine these insights into a comprehensive multifactorial approach aimed to prevent falls, not only among those who have already presented with falls, but also among prior non-fallers.

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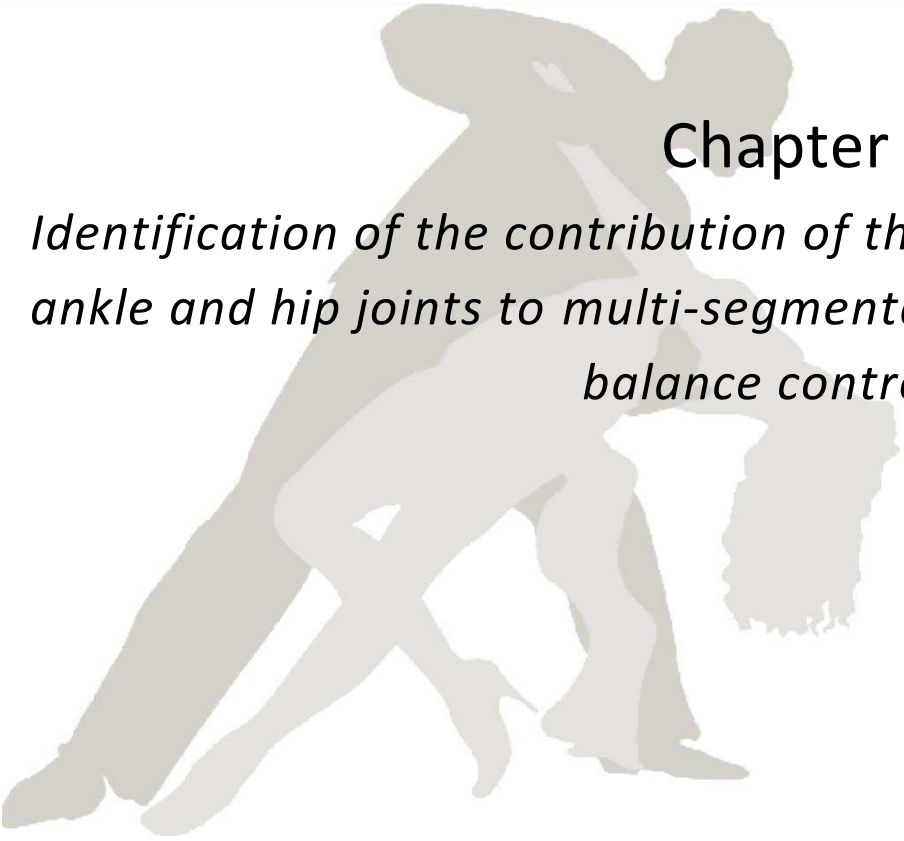

Chapter 3

Identification of the contribution of the ankle and hip joints to multi-segmental balance control

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Abstract

Human stance involves multiple segments, including the legs and trunk, and requires coordinated actions of both. A novel method was developed that reliably estimates the contribution of the left and right leg (i.e., the ankle and hip joints) to balance control of individual subjects.

The method was evaluated using simulations of a double-inverted pendulum model and the applicability was demonstrated with an experiment with seven healthy and one Parkinsonian participant. Model simulations indicated that two perturbations are required to reliably estimate the dynamics of a double-inverted pendulum. In the experiment, two multisine perturbation signals were applied simultaneously. The dynamic behaviour of the participants was estimated by Frequency Response Functions (FRFs), which relate ankle and hip joint angles to joint torques, using a multivariate closed-loop system identification technique.

In the model simulations, the FRFs were reliably estimated, also in the presence of realistic levels of noise. In the experiment, the participants responded consistently to the perturbations, indicated by low noise-to-signal ratios of the ankle angle (0.24), hip angle (0.28), ankle torque (0.07), and hip torque (0.33). The developed method could detect that the Parkinson patient controlled his balance asymmetrically, that is, the right ankle and hip joints produced more corrective torque.

The method allows for a reliable estimate of the multisegmental feedback mechanism that stabilizes stance, of individual participants and of separate legs.

Introduction

Maintaining an upright posture is a relatively easy task for healthy humans (Kiemel *et al.,* 2011a; Peterka, 2002). However, bipedal upright stance is inherently unstable, as small deviations from the upright posture result in disturbing torques due to gravity, which drives the system further away from upright posture (Peterka, 2003). To stay upright, the body generates corrective torques to counteract the effects of internal (e.g., motor and sensory noise) and external (e.g., uneven surfaces) perturbations.

When postural deviations are small, the body is often simplified as an inverted pendulum pivoting at the ankles, which describes the so-called ankle strategy (Peterka, 2003; van Asseldonk *et al.,* 2006; van Soest *et al.,* 2008). However, several studies demonstrated that human movement during stance is multi-segmental (Creath *et al.,* 2005; Horlings *et al.,* 2009; Pinter *et al.,* 2008) and for example, the hips substantially contribute to upright stance (i.e., the hip strategy; Horak *et al.,* 1986). Human balance control is a closed-loop multi-segmental process, i.e., sensory signals about the movement of the body are fed back to the central nervous system (CNS), and the CNS controls the muscles to generate adequate responses (Fitzpatrick *et al.*, 1996; Horak *et al.*, 1996). In a noisy closed-loop system, like human balance control, causality is difficult to determine and the dynamics of the different components (i.e., the body and the stabilizing mechanisms located in the CNS) affect both the input (joint angles) and output signals (joint torques). To "open" the loop and to separate the dynamics of the different components the balance, systems needs to be perturbed (Fitzpatrick *et al.*, 1996; van der Kooij *et al.*, 2005). Furthermore, when estimating the dynamics in a noisy multivariate system, multiple perturbations need to be applied (de Vlugt *et al.*, 2003; Pintelon *et al.*, 2001).

Most studies investigating the multivariate nature of balance control do not take the multivariate noisy closed-loop nature into account, by either not using perturbations (Alexandrov *et al.*, 2001; Kuo *et al.*, 1998; Speers *et al.*, 2002), or by using only one perturbation (Alexandrov *et al.*, 2005; Kim *et al.*, 2009; Park *et al.*, 2004). Only two studies investigate the multivariate nature of balance control by applying two perturbations (Fujisawa *et al.*, 2005; Kiemel *et al.*, 2011a).

Fujisawa and colleagues (Fujisawa *et al.,* 2005) investigated the role of the hip joint to upright stance by applying pseudorandom perturbations (bandwidth 0 - 0.83 Hz) while manipulating the support surface width. Subsequently, an ARMAX model (with joint angles as input and joint torques as outputs) was fitted to the data to obtain the Frequency Response Functions (FRFs) of a two-segment model of balance control. Results showed an increase of balance contribution of the hip joint, when the support surface became narrower.

Jeka and colleagues (Kiemel *et al.,* 2011a) identified neural feedback during upright stance in 18 subjects, while applying two mechanical perturbations (springs attached to a linear motor) and one sensory perturbation (visual scene rotations). By comparing the identified neural feedback (from joint angles to weighted electromyograms (EMGs) of the leg and trunk segments) with a large range of cost functions, it was concluded that the CNS stabilizes stance with near minimum muscle activation.

Ageing and many neurological diseases are associated with balance impairments and falls (Stolze *et al.,* 2004). Understanding the (patho)physiology of upright stance could aid to detect individuals with an increased risk of falls, help to design and evaluate intervention programs or monitor disease progression. Therefore, for clinical applications, it is very important to obtain a reliable individual estimate of balance control.

Of all neurological diseases, PD patients are at the highest risk of falling (Hely *et al.*, 2008; Pickering *et al.*, 2007; Stolze *et al.*, 2004), but the pathophysiology of balance impairments in PD remains unclear (Boonstra *et al.*, 2008; Grimbergen *et al.*, 2004). Recently, it was suggested that one of the factors contributing to decreased balance control in PD patients, is impaired trunk control (Carpenter *et al.*, 2004; Colnat-Coulbois *et al.*, 2011) or a decreased intersegmental coordination (Maurer *et al.*, 2003; Termoz *et al.*, 2008). Another factor could be asymmetrical balance control, that is, when one leg produces more force than the other leg to maintain an upright posture. Asymmetries in balance control have been rarely studied in PD, although it is an asymmetrical disease (Djaldetti *et al.,* 2006). One study (Geurts *et al.,* 2011) found balance control asymmetries in 24% of the PD participants, indicating that balance asymmetries are important in PD.

Currently, there is no method available that can identify a multisegmental stabilizing mechanism of balance control on an individual level, separating the contribution of the joints of the left and right body side. We developed and evaluated a non-parametric MIMO (Multiple-Input-Multiple-Output) identification method based on the previously used non-parametric system SISO (Single-Input-Single-Output) identification method (van Asseldonk *et al.,* 2006). To obtain a reliable individual response, periodic perturbations were applied, which have the advantage of having power at specific frequencies, decreasing the measurement time, and increasing the participants' response. In addition, the stabilizing mechanisms were estimated based on left and right joint torques (contrary to weighted EMGs; Kiemel *et al.,* 2011a), to be able to investigate balance control asymmetries.

In sum, our goal was to develop a method that can reliably estimate the stabilizing mechanisms of the closed-loop multivariate balance control system of *individual* participants, which makes a distinction between the contribution of the left and right leg to maintaining balance. The (clinical) applicability is demonstrated in an experiment that perturbed the balance of seven healthy participants and a PD patient with a novel device that can apply two independent mechanical perturbations.

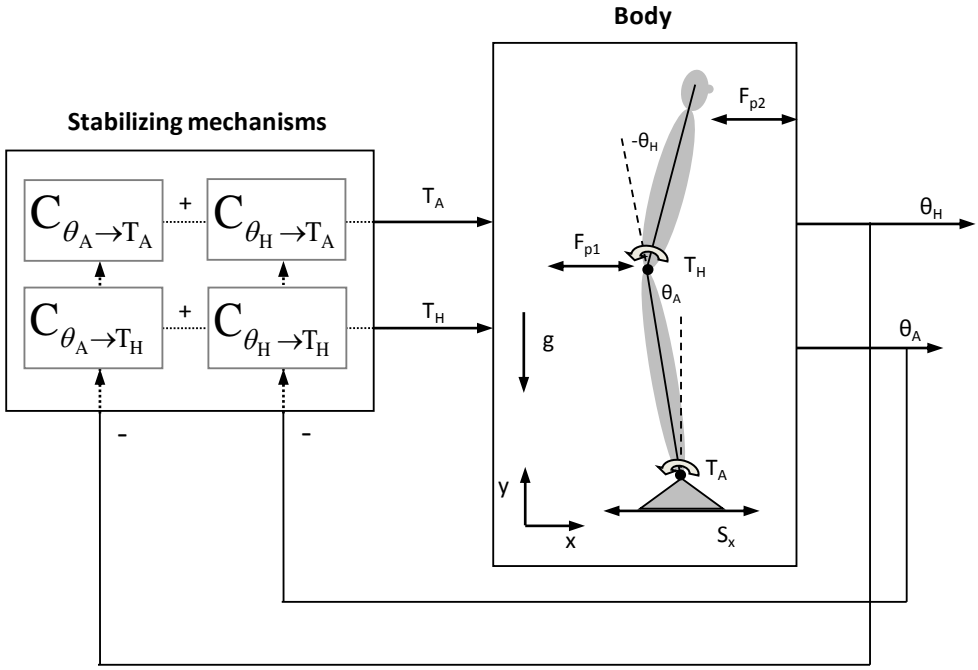

Figure 3.1: Multiple-Input-Multiple-Output closed-loop balance control system. The body mechanics represent the dynamics of a double-inverted pendulum with the corrective ankle and hip torques as inputs and the joint angles as outputs. The stabilizing mechanisms represents the dynamics of the combination of active and passive feedback pathways of the concerned body(part) and generates a torque to correct for the deviation of upright stance. The balance control model can be perturbed with support surface movements (S_x), perturbation forces at the hip (F_{p1}) or at the shoulder (F_{p2}). Positive torques and positive angles are defined as counterclockwise.

Methods

Model simulations

A two degree of freedom (DoF) balance control model (described extensively in Appendix A) was implemented in Matlab (The Mathworks, Natick, USA) and simulated with Simulink (equations were solved with a 5th order Dormand-Prince algorithm). The human balance model consisted of a two-segment human body with two actuators (ankle and hip), which were controlled using feedback of the joint angles (ankle and hip). In the model, no distinction between the left and right leg was made.

We perturbed the model with one and two perturbations. Two possible perturbation configurations of the two perturbations were evaluated: 1) external forces at the hip and shoulder (see Figure 3.1), similar to push-pull rods and 2) a combination of platform forward-backward platform translations and a perturbation torque around the ankle (see Figure 3.2). Also, simulations without and with pink sensor noise (van der Kooij *et al.,* 2011) and white (measurement) noise were evaluated:

i. two perturbation forces with noise (2F-N),
ii. two perturbation forces without noise (2F-Nn)
iii. platform perturbation and pusher torque with noise (PLT-N),
iv. platform perturbation and ankle torque without noise (PLT-Nn),
v. One perturbation and one perturbation round with noise (PL-N)
vi. One perturbation and one perturbation round without noise.

The characteristics of the perturbation signals are described in detail in the 'Disturbance signals' section and the amplitudes and power spectra are reported in Table 3.1. The input and output signals of the model were sampled at 120 Hz.

Experiment

Participants

Seven healthy participants (two female, mean age 65 yrs., std 5.7) and a PD patient (male, 57yrs) participated in the study. The participants gave written informed consent prior to participation. The protocol was approved by the local medical ethics committee and in accordance with the Declaration of Helsinki.

Apparatus and recording

Two independent perturbations were administered with a computer-controlled six DoF motion platform (Caren, Motek, Amsterdam, The Netherlands) and a custom-built actuated device able to apply perturbing forces in the anterior and posterior direction at the sacrum, called the pusher Figure 3.2. The pusher was attached to the platform and actuated using a series elastic actuator (Robinson et al., 1999) controlled with an electro motor (Maxon motor ag, Sachseln, Switzerland).

The pusher was force-controlled using a custom-built controller in xPC (The Mathworks, Natick, USA) and had a bandwidth of 10 Hz and a maximum torque of 50 Nm. The gravitational pull due to the weight of the pusher was compensated for, such that the participants did not experience additional forces other than the perturbation force and a small force due to the pusher's inertia. The interaction force in between the subject and the pusher was measured with a six DoF force transducer (ATI-Mini45-SI-580-20).

Body kinematics and the platform movements were measured using motion capture (Vicon Oxford Metrics, Oxford, UK) at a sample frequency of 120 Hz. Reflective spherical markers were attached to the following anatomical landmarks: the first metatarsal, calcaneus, medial malleolus, the sacrum, the manubrium and the last vertebrae of the cervical spine (C7). In addition, a cluster of three markers was attached to both anterior superior iliac spines on the pelvis. Furthermore, one additional marker was attached to the foot and two markers were attached to the lower leg (one on the tibia) to improve the estimation of the ankle joint rotational axis. Also, markers were attached to the knee (just

below the lateral epicondyle) and shoulder joints (just in front of the acromion). Three markers were attached to the platform. Reactive forces from both feet were measured with a dual forceplate (AMTI, Watertown, USA), embedded in the motion platform. The signals from the dual forceplate, the 6 DoF force transducer, and the perturbation of the pusher were sampled at 600 Hz and stored for further processing.

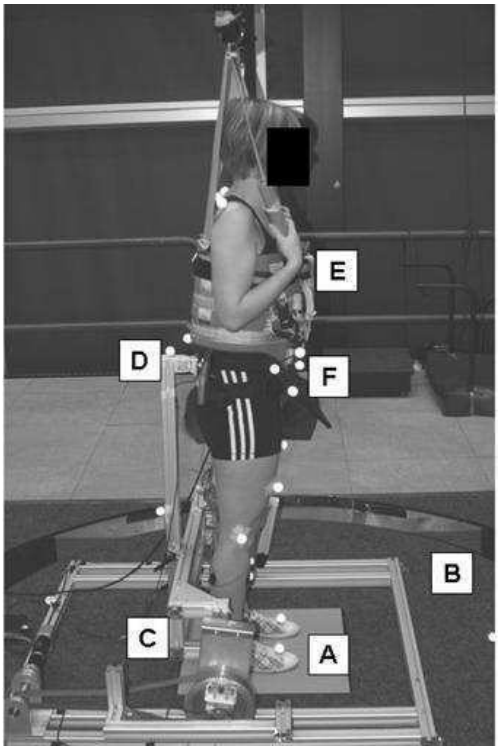

Figure 3.2: Experimental set-up. The participant stands on the dual forceplate (A) embedded in the movement platform (B). Two independent perturbations are applied with the movement platform (B) and the pusher (C) in the forward-backward direction. Interaction forces between the pusher (C) and the participant are measured with a force sensor (D). Actual falls are prevented by the safety harness (E). Reflective spherical markers (F) measure the movements of the participant.

Procedure

During the experiment, participants stood with their arms folded in front of their chest on the dual forceplate and strapped to the pusher, with a strap band that opened with a click buckle, with their eyes open. They were instructed to maintain their balance without moving their feet, while multisine platform movements and multisine force perturbations were applied simultaneously in the forward-backward direction; see 'Disturbance signals'. Participants wore a safety harness to prevent falling, but it did not constrain movements, provide support or orientation information in any way.

Before any data was recorded, the participants got acquainted to the perturbations. The experimenter determined the maximal amplitude the participant could withstand while keeping the feet flat on the floor, and assessed whether the participant could withstand this amplitude for the total of four trials. Four double perturbation trials of 180s were recorded: in the first two trials, the perturbations had the same sign. In the other two trials, the perturbations had opposite signs. If needed, the participants were allowed rest in between trials.

Disturbance signals

For both the model simulations and the experiment we used the same perturbation signal. During the model simulations the perturbation signal was used to either produce two perturbing forces, or a combination of a platform translation and a torque around the ankle (see 'Model simulations'). In the experiment the perturbations were applied with a movement platform and an actuated backboard (see 'Apparatus and recording').

The perturbation signal was a multisine with a period of 34.13 s (equal to 2^{12} = 4096 samples at a sample rate of 120 Hz; van Asseldonk *et al.*, 2006; van der Kooij *et al.*, 2007a). This signal contained power at 112 frequencies in the range of 0.06–4.25 Hz. To increase the power at the excited frequencies the signal was divided into five frequency bands: 0.06-2.37 Hz (80 frequencies), 2.63-2.84 Hz (8 frequencies), 3.11-3.31 Hz (8 frequencies), 3.57-3.78 Hz (8 frequencies), 4.04-4.25 Hz (8 frequencies). The frequency points outside these frequency bands were not excited. The signal is unpredictable for participants, because the signal consists of many sinusoids. The power of the signal was optimized by crest optimization (Pintelon *et al.,* 2001).

Data Analysis

The human body, i.e. the plant, is considered as a double-inverted pendulum, consisting of a leg and a Head-Arms-Trunk (HAT) segment. Stabilizing mechanisms generate ankle and hip torques based on sensory information of the joint angles (see Figure 3.1).

The stabilizing mechanisms have passive components such as muscle stiffness, generated by passive muscle properties and tonic activation. The active part incorporates the controller within the CNS (e.g. reflexive muscle activation), muscle activation dynamics, and time-delays, representing the neural signal conduction times.

Movements from the upper body segment will influence the movements of the lower body segment and vice versa due to mechanical coupling (Nott *et al.,* 2010; Zajac, 2002). The stabilizing mechanisms have to deal with this mechanical coupling, which is especially expressed in coupling terms between ankles and hips (i.e., $C_{\theta_A \to T_H}$ and $C_{\theta_H \to T_A}$). The direct terms ($C_{\theta_A \to T_A}$ and $C_{\theta_H \to T_H}$) represent the corrective actions of the ankle and hip joint, based on the ankle and hip joint angle. In other words, this system is a multiple input (two joint angles) multiple output (two joint torques) system.

When considering the corrective actions of both legs separately, two stabilizing mechanisms are defined; one for each leg (Pasma *et al.*, 2012; van Asseldonk *et al.*, 2006).

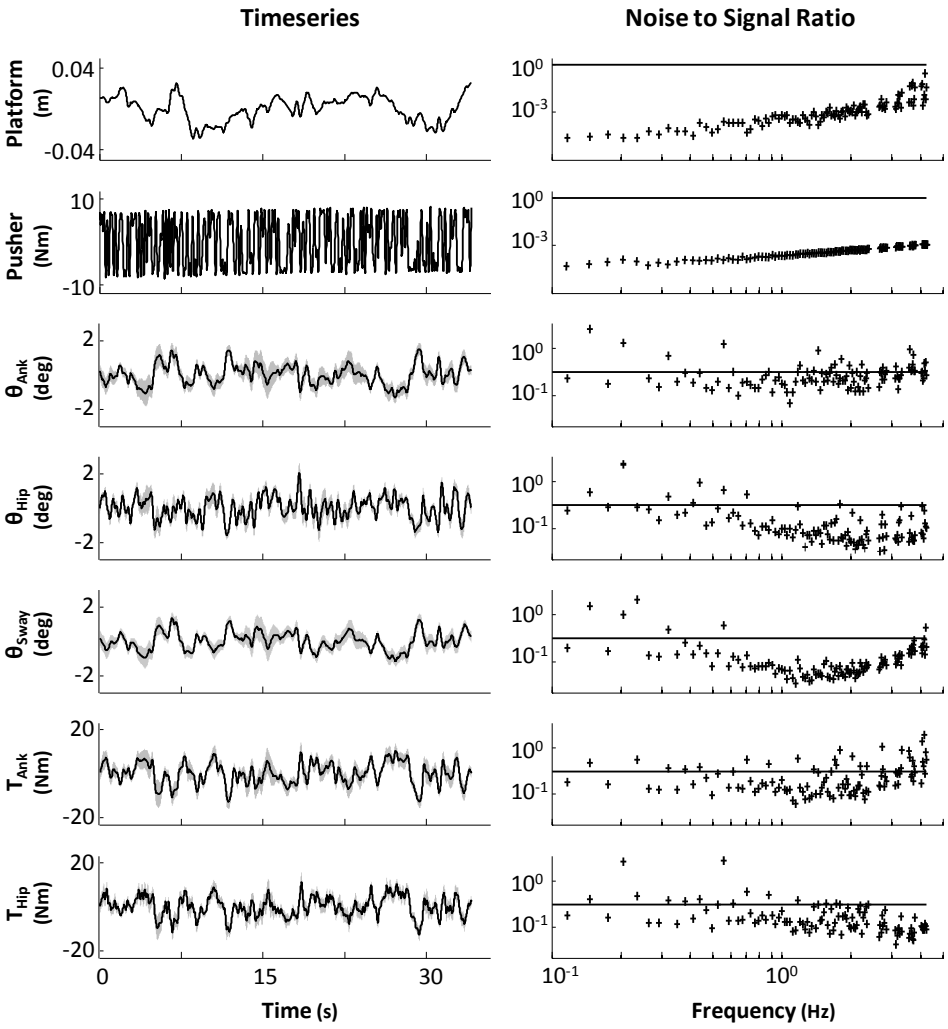

Figure 3.3: Timeseries (left panels) and NSRs (right panels) of the first perturbation round of one representative healthy participant. From top to bottom: platform perturbation, pusher perturbation, ankle angle, hip angle, sway angle, ankle torque, and hip, respectively. The angles are depicted in degrees, the torques in N/m. The mean is depicted by the solid line and the standard deviation over the eight cycles by the grey area. The black line in the right panels depicts NSR = 1. Ideally, the average NSR of the responses remains below one. The responses of the participant are consistent as evidenced by small standard deviations over the adjacent segments and low NSRs. This means that a large part of the data is captured by the time-invariant MIMO system identification technique.

For the model simulations, the perturbations, inputs (joint angles) and outputs (joint torques) of the model were determined for further processing. For the experiment these signals were calculated as described below.

From the recorded movement trajectories of the markers, the position of the center-of-mass (CoM) of the predefined segments and of the whole body and the position of the joints were estimated by custom written software (Koopman *et al.*, 1995; Koopman, 1989). In short, in each segment a local coordinate frame was determined on the basis of the position of anatomical landmarks, according to the method described by (Brand *et al.,* 1982). The mass, CoM position and the inertia tensor moment of the predefined segments (i.e., feet, legs and HAT) and the joint positions were determined with regression equations (Brand *et al.,* 1982; Chandler *et al.,* 1975). Subsequently, the CoMs were determined as the weighted sum of the separate segment CoM positions (Koopman *et al.,* 1995). From the static trial, the average distance in the sagittal plane from the ankle to the total body CoM (i.e., the length of the pendulum (l_{CoM}) was determined. The sway angle was calculated from l_{CoM} and the horizontal distance from the CoM to the mean position of the ankles. Forces and torques of the force plate and force sensor were filtered with a fourth-order low-pass Butterworth filter with a cut-off frequency of 8 Hz and subsequently resampled to 120 Hz. Forces and torques of the force plate were corrected for the inertia and mass of the top cover (Preuss *et al.,* 2004). On the basis of the corrected forces and torques and recorded body kinematics, ankle and hip joint torques were calculated with inverse dynamics (Koopman *et al.,* 1995). In addition, the applied platform perturbation was reconstructed from the platform markers.

Multiple Input Multiple Output Closed-Loop System Identification

To obtain a non-parametric spectral estimate of a two Degree-of-Freedom (DoF) multivariate closed-loop system we adopted a method described by Pintelon and colleagues stating that **two** different combinations of a periodic excitation signal, *D(k)*, in **two** separate experiments should be applied (Pintelon *et al.,* 2001). An optimal choice of *D(f)* (maximizing det (**P**(f)) using periodic excitation is given by:

$$\mathbf{P}(\mathrm{f}) = \begin{bmatrix} 1 & 1 \\ 1 & -1 \end{bmatrix} \mathrm{D}(\mathrm{f}) \tag{3.1}$$

With $D(f)$ the two perturbation signals. All calculations were performed in the frequency domain with f the frequency in Hz. This means that in the first round, both inputs were excited with the same periodic excitation, while in the second round the sign of the second perturbation was changed. These perturbations excited the system and the system responded with movements (joint angles) and torques (corrective joint torques) at the frequencies of the perturbation signal. Corrective torques are the torques that restore the body's equilibrium in response to motor and sensor noise and the perturbation signal.

Then, the estimate from the perturbation to inputs (joint angles) and outputs (corrective joint torques) was first obtained from:

$$\hat{G}_{py}(f) = Y(f)P^{-1}(f) \tag{3.2}$$

With Y(f), a two-by-two matrix with on the first column, the responses of the first perturbation round (i.e., ankle and hip joint angles or torques), and on the second column the responses of the second perturbation round. $\hat{G}_{py}(f)$ denotes the estimate of the cross spectral density (CSD) of the disturbance and the outputs (joint angles and joint torques). Subsequently, the stabilizing mechanisms were estimated using the joint input-output approach (van der Kooij *et al.*, 2005):

$$\hat{C}_{\theta T_c}(f) = \hat{G}_{pT_c}(f)\hat{G}_{p\theta}^{-1}(f) \tag{3.3}$$

With $\hat{G}_{pT_c}$ and $\hat{G}_{p\theta}^{-1}$ the estimated CSD from the perturbations to the corrective torques and from the perturbations to the joint angles. Note that C is a two-by-two matrix, see also Figure 3.1. p is a vector with the two disturbances, θ(f) is a vector with ankle and hip joint angles, and $T_c(f)$ is a vector with ankle and hip joint torques for each frequency *f*; all expressed as Fourier coefficients. The method assumes that the system does not change between the two separate perturbation rounds with the **two** different combinations of the periodic excitation signal (Eq. 3.1).

For both the model simulations and the experiment, data was obtained for eight response cycles of the perturbation signal for each perturbation round. Subsequently, the data were Fourier transformed and only the Fourier coefficients at the excited frequencies were used for further processing. These were averaged over the eight cycles, and the average Fourier coefficients were used to calculate the power- and cross spectral density (PSD and CSD, respectively). The PSDs and the CSDs were smoothed by averaging over four adjacent frequency points (Jenkins *et al.,* 1969). The FRFs were calculated according to Eq. 3.2-3.3 to obtain a non-parametric spectral estimate of the total stabilizing mechanism.

As the corrective torque which has to be delivered by the participants is dependent on gravity, all FRFs were normalized for the participants' mass and length, i.e. the gravitational stiffness (*mgl*), with *m* the total body mass, *l* the length of the pendulum (from the ankles to the Center of Mass (CoM), and *g* the gravitational constant. The average FRF over all participants was obtained by taking the mean over the individual normalized FRFs. Note that, as we used a dual forceplate in the experiment, the experimentally obtained Fourier coefficients of the left and right FRFs were added to obtain the total FRFs.

Reliability of the estimated MIMO frequency response functions

To determine whether the above-described MIMO closed-loop system identification technique gives reliable estimates of the stabilizing mechanisms, several indicators were calculated (described below).

Goodness of estimate

For the model simulations, the goodness of fit (GOF) was determined by the object function (van der Kooij *et al.,* 2011). This function compared the theoretical Transfer Function (TF) as incorporated in the model (appendix A) with the estimated FRF as obtained in the model simulations:

$$\mathrm{GOF} = \sum_{\mathrm{f}} \left(\frac{\left| \mathrm{H}_{\mathrm{theoretical}}(\mathrm{f}) - \mathrm{H}_{\mathrm{estimated}}(\mathrm{f}) \right|}{\left| \mathrm{H}_{\mathrm{theoretical}}(\mathrm{f}) \right|} \right)^2 \tag{3.4}$$

Where a perfect estimation of the transfer function will result in a GOF of zero, i.e., the lower the GOF the better the estimation.

Noise- to- Signal Ratio

As a result of a periodic perturbation to the balance control system, the system's response was periodic, while time-variant behavior and/or noise resulted in a stochastic, i.e. non-periodic response (van der Kooij *et al.*, 2007a). The ratio of the non-periodic (also called the remnant) and periodic response is expressed by the noise-to-signal ratio (NSR):

$$\mathrm{NSR}_{\mathrm{U}}(\mathrm{f}) = \frac{\sigma_{\mathrm{u}}^2(\mathrm{f})}{\left| \mathrm{U}_{\mathrm{p}}(\mathrm{f})^2 \right|} \tag{3.5}$$

Where $\mathrm{U}_{\mathrm{p}}(\mathrm{f})$ represents the periodic response and $\sigma_{\mathrm{u}}^2(\mathrm{f})$ the variance of the remnant. The NSR was calculated in the frequency domain with f frequency in Hz. When multiple realizations are simulated or recorded, the periodic response is obtained by calculating the average over the realizations; the remnant can be estimated by calculating the variance over the realizations. A small NSR indicates low variability of the system's response to the perturbation signal over the multiple periods. This indicates time invariant behavior and a low presence of noise (van der Kooij *et al.*, 2007a). As such, it gives insight into whether linear, time-invariant, system-identification methods can be used and it gives an estimate of how well the system is perturbed. More importantly, it quantifies how reliable the estimate of the stabilizing mechanism is. For example, a NSR of 1 indicates that the recorded data contains 50 percent response and 50 percent remnant. This means that describing the system as a deterministic linear time invariant (LTI) system (expressed by the estimated FRFs in this study) explains 50 percent of the recorded data.

Single Input Single Output Frequency Response Functions

To assess whether the two perturbation rounds in the experiment lead to a change in strategy of the participants (i.e., time-variant behavior), we estimated Single Input Single Output (SISO) FRFs from sway angle to ankle torque and from sway angle to hip torque with the joint-input-output-method (Eq. 3.3; van Asseldonk *et al.,* 2006).

Coherence

For the SISO FRFs the (magnitude-squared) coherence was calculated between the input signal (perturbations) and output signals (ankle torques, hip torques, and body sway).

$$\gamma^2_{p,y} = \left|\phi_{p,y}\right|^2 . \left[\phi_{p,p}(f).\phi_{y,y}(f)\right]^{-1} \tag{3.6}$$

In which p represents the platform disturbance and y an output signal. $\phi_{p,y}$, $\phi_{p,p}$ and $\phi_{y,y}$ are the CSDs and PSDS of the perturbation and output signals. By definition, coherence varies between 0 and 1, where coherence close to one indicates a low noise level and time-invariant behaviour.

Balance contribution of the left and right body side

For the experiment we determined the relative contribution of each ankle and hip joint to the total amount of generated corrective torque to resist the perturbations by calculating the contribution of the gain and phase of each leg to the gain and phase of the total body (van Asseldonk *et al.,* 2006):

$$\text{Contribution}_{l,r}(f) = \sum_{f\,min}^{f\,max} \left(\frac{\text{FRF}_{l,r}(f) \bullet \text{FRF}_t(f)}{\left\|\text{FRF}_t(f)\right\|^2} \right) \tag{3.7}$$

With $FRF_{l,r}$ the left or right FRF and FRF_t the total FRF. The $\bullet$ indicates the dot product of the FRFs. f_{min} and f_{max} denote the lowest and highest frequency in the perturbation signal. In this way the contribution of the left or right leg to the total balance control was expressed as a proportion For example a proportion of 0.8 for the left leg, means that the left leg contributed for 80% to the total body stabilization. This was done for each separate MIMO FRF (see Eq. 3.2-3.3).

Results

Model simulations

Table 3.1 shows the GOF values and NSRs of the different simulations. In case of no sensor and measurement noise, a platform acceleration in combination with a perturbation torque around the ankle (PLT-Nn) gave the same results as two perturbation forces (2F-Nn). In these conditions, the small GOF values indicated that the stabilizing mechanisms were well estimated. Adding sensor (pink) and measurement (white) noise to the

simulations resulted in slightly worse estimations; the GOF values increased. However, the stabilizing mechanisms were still correctly estimated (see Figure 3.4). Platform acceleration and a perturbation torque around the ankle (PLT-N) resulted in better estimations than two perturbation forces (2F-N).

Figure 3.4 shows the model transfer function and the estimated frequency response functions of the PLT-N and PL-N conditions. Clearly, applying two perturbations resulted in very good estimations (see also Table 3.1). However, applying only **one** perturbation to estimate the stabilizing mechanisms of a MIMO system resulted in incorrect estimates, although the responses were time-invariant as shown by the NSRs values. In other words, applying one perturbation resulted in biased estimates of the stabilizing mechanisms. Note that, the GOF values of the PL-Nn and PL-N simulations were of the same magnitude.

Experiment

Time series

Figure 3.3 shows the perturbations and the response of one representative healthy participant to the applied perturbations. For the healthy controls, the average peak-to-peak amplitudes were 0.068 m (*std*: 0.005) for the platform and 18.4 Nm (*std*: 1.05) for the pusher. For the PD patient the peak-to-peak amplitudes were 0.06 m and 20 Nm, see also Table 3.1. In general, the participant responded in a consistent fashion as indicated by the low standard deviation over the adjacent segments and corresponding low NSRs (Table 3.1). The average median NSRs (of both perturbation rounds) of all healthy participants were: 0.24 (ankle angle); 0.28 (hip angle); 0.15 (sway angle); 0.56 (ankle torque), and 0.35 (hip torque). Hence, on average, the healthy participants responded in a consistent fashion (see Figure 3.3). Note, however, that the response of the sway angle was even more consistent than the joint angles.

The PD patient was able to complete the balance control experiment without any problems. He could withstand the perturbations and the duration of the trials. The patient also responded in a time-invariant fashion. He had even slightly lower NSRs than the healthy controls.

Table 3.1: Perturbation amplitudes, scaling of the perturbation signal, Goodness of Fit (GOF) and Noise-to-Signal Ratios (NSR; averaged over the two perturbation rounds) of the model simulations and the balance control experiment. The GOF is reported for each estimate of the model transfer function ($C_{\theta_A \to T_A}$, $C_{\theta_A \to T_H}$, $C_{\theta_H \to T_A}$ and $C_{\theta_H \to T_H}$). The median NSR is reported for the input (joint torques) and output (joint angles) for the model simulations and the balance control experiment. Six perturbation conditions were simulated: a platform translation+ perturbation torque without and with noise (PLT-Nn and PLT-N), two perturbation forces with and without noise (2F-Nn and 2F-N) and a platform translation with and without noise (PL-N and PL-Nn). For the balance control experiment, the median NSRs of one representative healthy control (HC), the average of the healthy controls and of the PD patient are shown.

	Simulations						**Experiment**		
	PLT-Nn	**PLT-N**	**2F-Nn**	**2F-N**	**PL-Nn**	**PL-N**	**HC**	**HC mean**	**PD patient**
Signal									
Amplitude	PL: 0.06; T: 20 Nm	PL: 0.06m; T: 16 Nm	20 N	20 N	0.12 m	0.12 m	PL: 0.07 m; T: 18.4 Nm	PL: 0.06 m; T: 16 Nm	PL: 0.06 m; T: 20 Nm
Scaling	PL: 1/*f*	PL: 1/*f*	-	-	1/*f*	1/*f*	PL: 1/*f*	PL: 1/*f*	PL: 1/*f*
GOF ($1/Hz^2$)									
$C_{\theta_A \to T_A}$	1.11	11.64	1.11	23.64	26.44	29.83	-	-	-
$C_{\theta_A \to T_H}$	0.25	4.99	0.25	7.16	21.56	22.59	-	-	-
$C_{\theta_H \to T_A}$	0.79	7.30	0.79	14.42	28.18	36.09	-	-	-
$C_{\theta_H \to T_H}$	0.25	2.94	0.25	4.38	12.51	14.55	-	-	-
NSR									
T_A	0	0.54	0	0.43	0	1.17	0.55	0.24	0.11
T_H	0	0.39	0	0.10	0	0.59	0.08	0.28	0.06
θ_{sway}	-	-	-	-	-	-	0.10	0.15	0.08

GOF: Goodness of Fit. NSR: Noise-to-Signal Ratio.;PL: Platform; T: Torque. Amplitude values are given in peak-to-peak values. *f*: frequencies of the perturbation signals

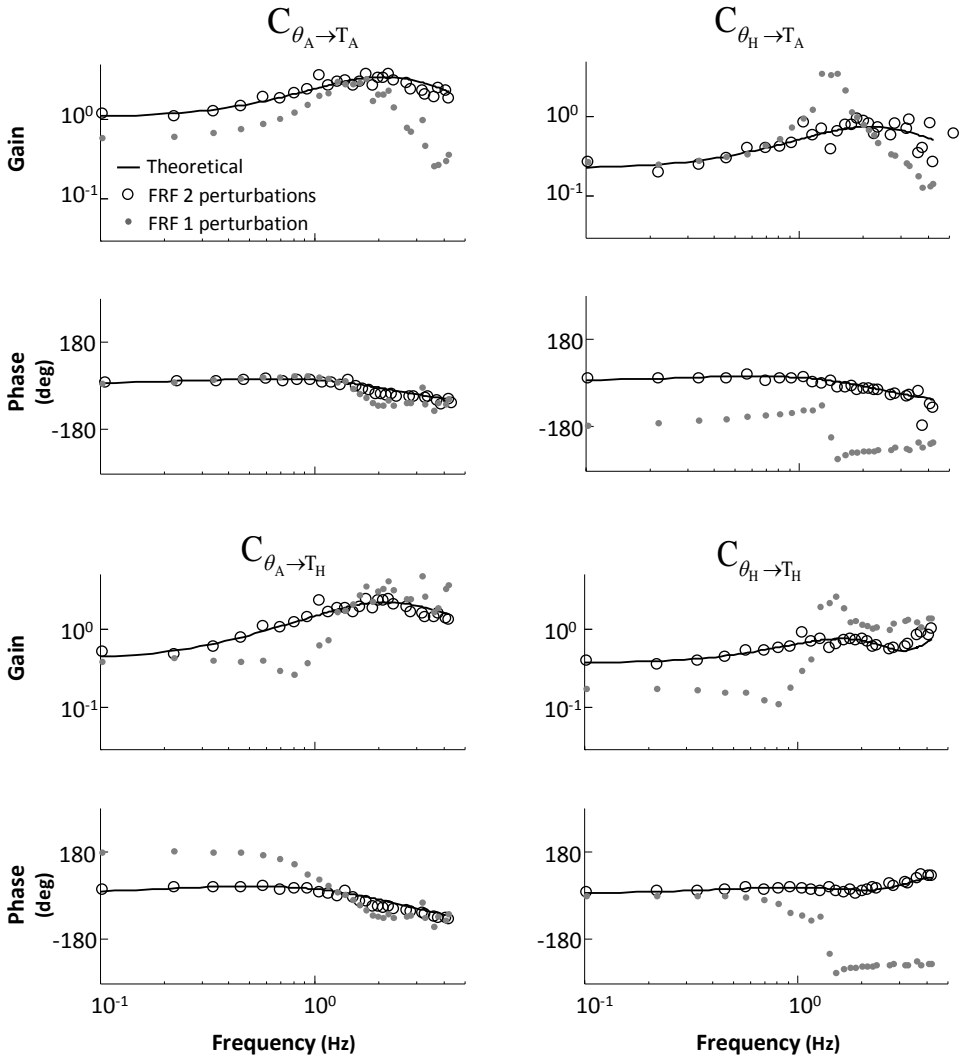

Figure 3.4: Theoretical transfer function and estimated frequency response functions ($C_{\theta_A \to T_A}$, $C_{\theta_A \to T_H}$, $C_{\theta_H \to T_A}$ and $C_{\theta_H \to T_H}$). Results of the model simulations in the presence of pink and white noise during the condition with a platform acceleration and perturbation torque around the ankle are depicted (PLT-N; open dots); and during the condition with one perturbation (PL-N; solid grey dots). The bold solid line represents the model transfer function of the stabilizing mechanism. Applying two independent perturbations in combination with a multivariate closed-loop system identification method resulted in a correct estimation of the stabilizing mechanisms (FRF 2 perturbations indicated with open dots), whereas one perturbation resulted in an erroneous estimate (FRF 1 perturbation indicated with solid grey dots).

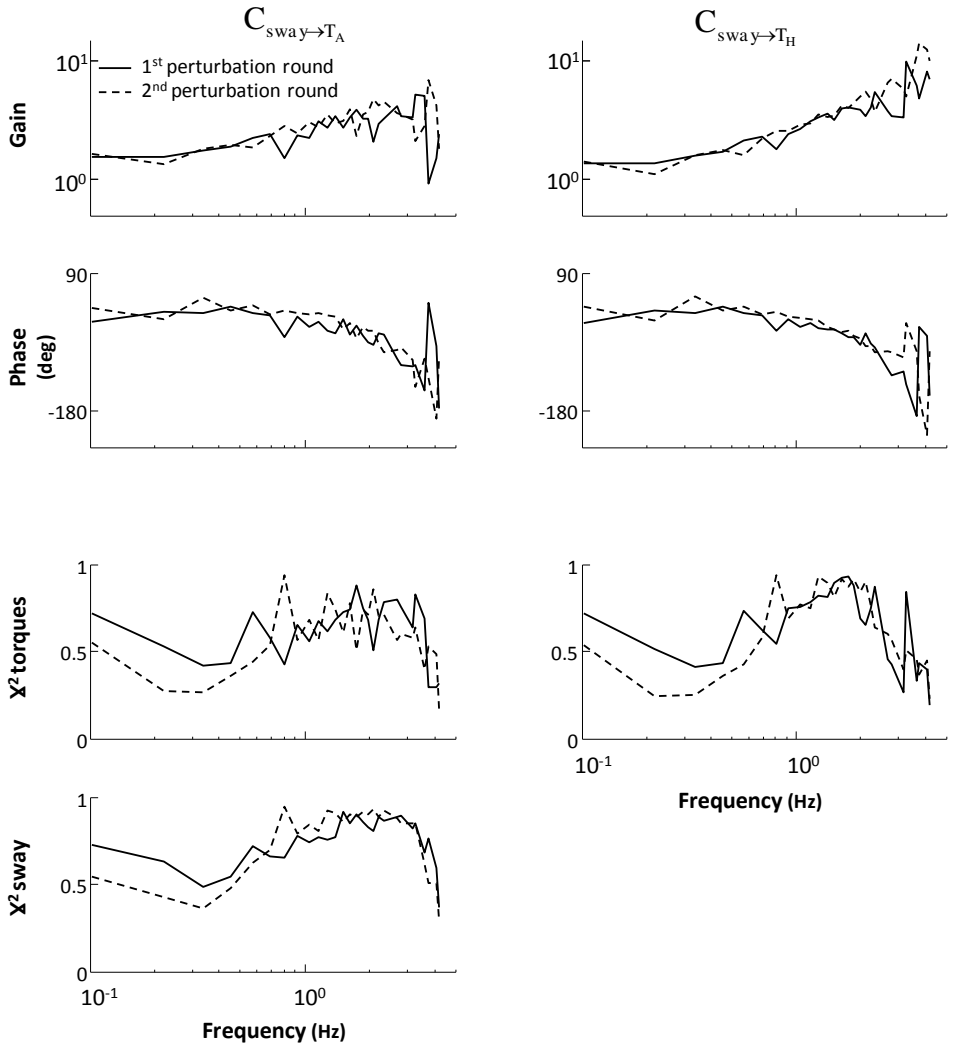

Figure 3.5: Single-Input-Single-Output frequency response functions and coherences of first and second perturbation round. The left panel depicts the FRF from the sway angle to the ankle joint torque; the right panel the FRF from the sway angle to the hip joint torque. The lower panels show the coherence between the perturbation, and the ankle joint torque, hip joint torque, and the sway angle, respectively. Similar gains and phases of the frequency response functions of the first and second perturbation round indicate that participants did not change their balance control strategy.

SISO frequency response functions

Figure 3.5 shows the SISO FRFs from sway angle to ankle torque and hip torque of each perturbation round of the healthy controls. Gain and phase of the FRFs and coherence of the joint torques were similar for both perturbation rounds. There was a small discrepancy between the gain of the FRFs at the lower and higher frequencies, but this can be

attributed to a less periodic response at these frequencies (indicated by a decreased coherence), and hence the reliability of the FRFs decreased. In addition, the coherence of the sway angle was lower in the second perturbation round, especially at frequencies below 0.7 Hz. This resulted in a slightly worse estimate of the FRFs, compared to the first perturbation round. Similar results were found for the PD patient (data not shown).

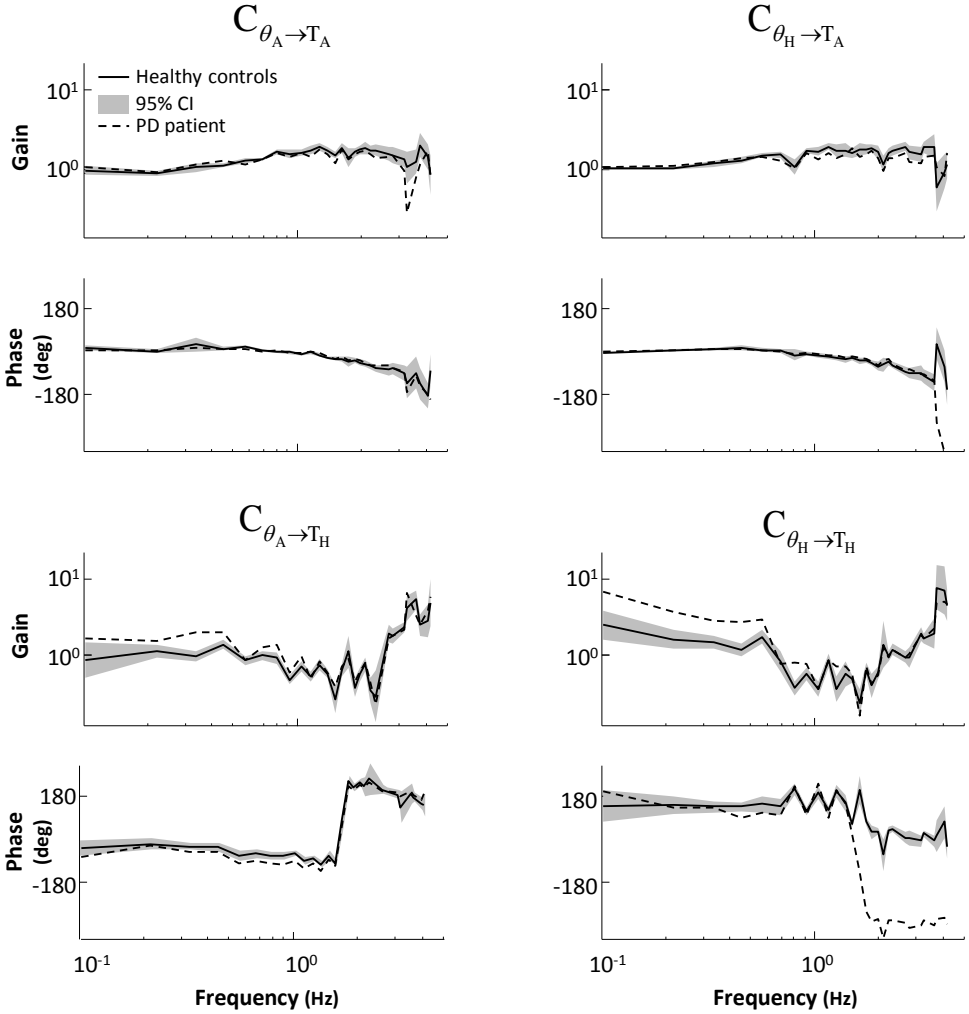

Figure 3.6: Multiple-Input-Multiple-Output frequency response functions of the stabilizing mechanisms. The solid line represents the average of the healthy participants, with the shaded area indicating the 95% confidence interval and the dotted line the Parkinson patient.

MIMO frequency response functions

The MIMO FRFs of the stabilizing mechanisms of healthy controls and the PD patient are shown in Figure 3.6. The total of four FRFs are shown: from ankle angle to ankle torque ($C_{\theta_A \to T_A}$), from ankle angle to hip torque ($C_{\theta_A \to T_H}$), from hip angle to ankle torque ($C_{\theta_H \to T_A}$) and from hip angle to hip torque ($C_{\theta_H \to T_H}$) representing the multivariate stabilizing mechanisms of the participants.

In general, for the healthy controls, the relationship between the ankle joint angle and the ankle joint torque remained roughly constant over the whole frequency range, whereas the hip joint gain was high at the low frequencies (< 0.7 Hz), low at the mid frequencies (0.7-2 Hz) and increased at higher frequencies (> 2 Hz). The coupling between the ankle joint angle to hip torque increased with frequency, whereas the $C_{\theta_H \to T_A}$ FRF remained roughly constant over the frequency range. The PD patient showed similar gain patterns for the $C_{\theta_A \to T_A}$ and $C_{\theta_H \to T_A}$ FRFs, but for the $C_{\theta_A \to T_H}$ and $C_{\theta_H \to T_H}$ FRFs the gains at the lower frequencies were much higher than those of the healthy controls indicating an increased postural stiffness in the PD patient.

The phase of the $C_{\theta_A \to T_A}$ and $C_{\theta_H \to T_A}$ FRFs of both the HC and the PD patient decreased with increasing frequency (i.e. a phase lag), indicating a neural time delay. The phase of the $C_{\theta_A \to T_H}$ showed a phase shift of about +360° around 1. 5 Hz. For the phase the largest difference between the HC and PD patients is found in the $C_{\theta_A \to T_H}$ FRF. Both groups showed a negative phase shift around 2 Hz, but this shift was larger in the PD patient.

Balance contribution of the left and right body side

In healthy controls both legs contributed equally to the body stabilization; the proportion for each FRF was 0.5. However, for the patient, the right leg contributed more to the balance control than the left leg, and this was the case for both the ankle and the hip joint. Note that the patient is clearly outside the 95% confidence interval (CI) of healthy controls (see Figure 3.7). It can be seen that for the FRFs $C_{\theta_A \to T_A}$ and $C_{\theta_H \to T_A}$ the proportion between both legs was similar over the whole frequency range, whereas for the FRFs $C_{\theta_A \to T_H}$ and $C_{\theta_H \to T_H}$ the asymmetry decreased with increasing frequency and eventually disappeared above 1 Hz.

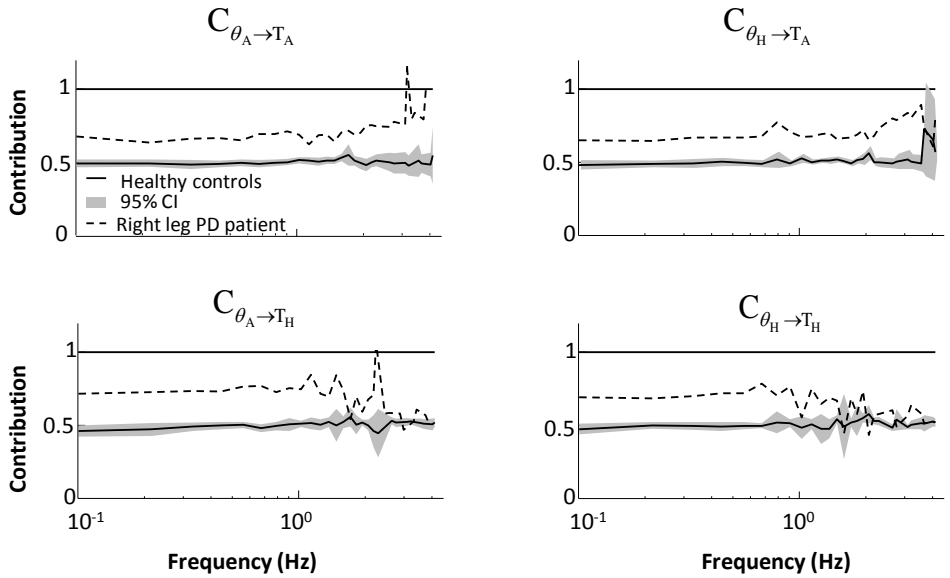

Figure 3.7: The average contribution of the right leg of the healthy controls and of the PD patient to each Multiple-Input-Multiple-Output frequency response function. The average contribution of the right leg for the healthy controls (HC) is shown by the solid line (mean) and the grey area (95% confidence interval). The patient (dashed line) clearly controlled his balance asymmetrically, with the right leg producing more corrective torque than the left leg to resist the perturbations.

Discussion

Bipedal upright stance is multisegmental and requires the coordinated activity of multiple joints, including the ankles and hips. We developed a system identification method to investigate the balance control contribution of the ankles and hips of the left and right leg separately of individual subjects. To investigate both DoF and their interactions in a feedback loop, two perturbations are required. Therefore, in our lab we developed an actuated pusher placed on a motion platform to provide these independent perturbations. Using model simulations, it was demonstrated that these perturbations can identify the system reliably. The (clinical) applicability of the method was demonstrated in seven healthy controls and a PD patient.

Evaluation of Multiple-Input-Multiple-Output identification method

Model

The model simulations indicated that two independent perturbations are necessary to identify the stabilizing mechanisms of a two DoF MIMO system. Applying only one perturbation to the model resulted in biased and estimates of the stabilizing mechanisms. This bias was not influenced by noise level. Two configurations with two independent perturbations were evaluated, that is, a combination of a platform acceleration and a

disturbance torque around the ankle and two perturbation forces in the forward-backward direction. The stabilizing mechanisms were estimated very well with both configurations, and the differences between the two approaches were small. After adding sensor and measurement noise to the simulation, the stabilizing mechanisms were still estimated well with both configurations, with a slightly worse result when perturbing with two forces. In short, the model simulations showed that the implemented MIMO identification method correctly identified the stabilizing mechanisms indicated by small differences between the theoretical transfer function of the model and the estimated frequency response functions, even in the presence of realistic levels of noise.

Experiment

In the experiment with human participants, the perturbations were applied with a motion platform and a custom-made actuated backboard (i.e., the first configuration of the model simulations, which gave slightly better results). The amplitudes of the applied perturbations were easy to withstand, both for the healthy participant as for the PD patient, making the method suitable for use in a large range of participants.

To be clinically relevant, the MIMO identification method should be able to reliably estimate the different segmental contributions to the total balance control of a single participant. First, the quality of our estimation was expressed in the NSR. A low NSR indicates that a large percentage of the data is captured by the estimated stabilizing mechanisms. The NSR gives the ratio between the (periodic) response to the perturbations and the remnant. As the method assumes a LTI system, remnants can be due to a) nonlinearities of the perturbed system, b) time-variant system behavior, c) unmeasured system noise, and d) measurement noise (van der Kooij *et al.*, 2007a). Note that a low NSR does not necessarily mean that the system is linear.

The average NSRs of the healthy controls of the ankle and hip joint angle and of the ankle and hip torque were 0.24 and 0.28, 0.56 and 0.35, respectively. This results in an average NSR of 0.36, meaning that about 74 percent (i.e., 1/(1+0.36)) of the response is captured by the estimated stabilizing feedback mechanisms. The PD patient had lower NSRs than the average healthy subject, indicating less variability over the repetitions of the perturbation signal. Unfortunately, it is impossible to compare our results with respect to reliability of the estimates with other studies using two perturbations as these studies did not report any parameters quantifying reliability and only report averages over participants.

Secondly, the used MIMO identification scheme consists of two perturbation rounds: in one round, the perturbations have the same sign, while in the other round, the perturbations have opposite signs. To determine whether participants did not change their balance control behaviour in both perturbation rounds, SISO FRFs for the ankle and hip joints were determined. Gain, phase, and joint torque coherence were comparable for

both perturbation rounds; hence the participants did not change their balance control strategies. Note that the sway angle and ankle and hip coherence was lower in the second perturbation round at the lower frequencies (<0.7 Hz), indicating less time invariant behavior (possibly due to fatigue) and/or a higher noise level. This could be due to not randomizing the perturbation rounds. However, this did not result into quantitatively different behavior, as the SISO FRFs were similar for both perturbation rounds.

The last requirement of the method is that it is able to distinguish between the balance contributions of the separate legs to investigate balance asymmetry. By using a dual forceplate and calculating the FRFs for each leg separately, balance control asymmetries were detected in a PD patient.

Perturbing with a different set-up (for example two push-pull rods), at different locations or by using different signals could have elicited different responses. This is not an artifact of the method, but reflects the adaptability of the nervous system (Kim *et al.,* 2012).

In sum, two unique features of the presented method are the applicability on the individual level and separation of balance contribution of each body side. The first was accomplished by applying multisine perturbation signals, which have the advantage of improving the estimation of FRFs because they concentrate signal power in a limited set of frequencies and are periodic. This results in reliable *individual* results and shorter measurement times (de Vlugt *et al.*, 2006; van der Kooij *et al.*, 2007a). Secondly, by measuring the reaction forces of each foot with a dual forceplate balance control, asymmetries can be detected.

Comparison with other multivariate methods

Most published studies investigating the multivariate nature of balance control do not use perturbations, or use only one perturbation (Alexandrov *et al.*, 2005; Kim *et al.*, 2009; Kuo *et al.*, 1998; Park *et al.*, 2004; Speers *et al.*, 2002). However, the model simulations indicated that two independent perturbations are required to estimate the stabilizing mechanisms of a multivariate balance control system. Using only one perturbation in the model simulations gave biased and erroneous results.

The other two available methods (Fujisawa *et al.*, 2005; Kiemel *et al.*, 2011a) differ from the presented method in this paper. Our method is non-parametric, where Fujisawa (2005) used a parametric method (ARMAX model structure). A parametric method has the advantage that it, theoretically, can better separate the measurement noise from the actual signals. However, knowledge about the structure of the system is required. A non-parametric method has the advantage that no prior knowledge of the system is needed (de Vlugt *et al.,* 2003). Despite the differences between the applied methods in (Fujisawa *et al.,* 2005) and in this manuscript the obtained FRFs are in the same range for the low frequencies. That is the $C_{\theta_A \to T_A}$ FRF starts at unity gain which slightly increases with

frequency, whereas the $C_{\theta_A \to T_H}$, $C_{\theta_H \to T_A}$ and $C_{\theta_H \to T_H}$ have lower gains at the lower frequencies (Gain:~0.05) but also increase with frequency. Note that we can compare the FRFs only in the low frequency range, as Fujisawa *et al.,* 2005 used a perturbation signal with frequencies up to 0.83 Hz.

Recently, Jeka and colleagues (Kiemel *et al.*, 2008; Kiemel *et al.*, 2011a) used an approach to investigate task goals for upright stance, similar to the one presented here. There are, however, a few fundamental differences. First of all, Kiemel et al. (Kiemel *et al.,* 2011a) used filtered white noise as a perturbation signal, whereas we used multisines, which have the advantage of improving the individual estimate of the stabilizing mechanisms. Also, they define the input of the stabilizing mechanisms as weighted EMG signals of the anterior and posterior body sides, whereas we have used joint torques. Therefore, the method presented by Jeka and colleagues (Kiemel *et al.*, 2008; Kiemel *et al.*, 2011a) focused on separating the reflexive from the total contribution of the stabilizing mechanisms by measuring EMG signals. This measurement and analysis of EMG signals can easily be added to our method. In order to detect balance control asymmetries, joint torques (which we have used in this study) are more suitable than EMG signals. Differences in EMG amplitude can, for example be due to different electrode placement on contra- lateral legs, different skin conductivity or due to different background activity, making these signals more prone to measurement artifacts. In addition, joint torques are more suitable for investigating joint stiffness.

Applications

Multisegmental balance control

With a MIMO method and by applying multiple perturbations, multisegmental balance control strategies and the interplay between the joints can be investigated. This approach can be used to test hypotheses about the role of the different joints, and also of sensory information (Kiemel *et al.,* 2011b).

Clinical applications

It has been suggested that PD patients have a decreased intersegmental coordination (Maurer *et al.*, 2003; Termoz *et al.*, 2008) or an increased hip stiffness (Carpenter *et al.*, 2004; Grimbergen *et al.*, 2004). In this study, the most pronounced difference between the healthy controls and the PD patients was found in the $C_{\theta_H \to T_H}$ FRF, that is, the PD patient had a higher gain at the lower frequencies, indicating an increased hip stiffness. With our method we can now distinguish between coordination between the upper and lower body and of coordination of the upper/lower body separately. Further investigation of intersegmental coordination could lead to a better understanding of the

pathophysiology of balance impairments in PD and possibly improve intervention programs.

The PD patient asymmetrically controlled his balance with both the ankle and the hip joint. This means that one leg contributed more to body stability than the other leg. Balance control asymmetries have been shown before in PD patients, both during quiet stance (Geurts *et al.*, 2011; Rocchi *et al.*, 2002) and with a single degree-of-freedom approach (van der Kooij *et al.*, 2007b), but not taking into account the contribution of the hip joint. The balance asymmetry was also present in the intersegmental coordination, i.e. in the FRFs from ankle angle to hip torque and from hip angle to ankle torque. Hence, our new method has the advantage of assessing balance control asymmetries during perturbations, considering the role of the hip joint and the interplay between joints. This creates the possibility of assessing differences in balance control contribution between distal and proximal joints and, it can be investigated whether balance asymmetries influence intersegmental coordination. Further necessary research in a large group of PD patients and healthy matched controls should demonstrate the (potential) clinical value of the new method.

Balance control can also be asymmetrical in stroke patients (Roerdink *et al.*, 2009; van Asseldonk *et al.*, 2006). During the recovering process, restoration of the paretic body side and/or compensation in the non-paretic body side may contribute to improved balance maintenance. Investigating balance control asymmetries provides the possibility of investigating different recovery and compensation strategies during the rehabilitation process.

Conclusions

Here, we presented a new method to identify the multisegmental stabilizing mechanisms in human stance control using non-parametric system identification techniques and evaluated its performance. Model simulations showed that the newly presented method correctly and reliably estimate the balance control contribution of the ankle and hip joints and interactions between the segments. A balance control experiment showed the application in both healthy and pathological participants. Furthermore, the method can distinguish between the balance control contribution of each ankle and hip joint separately. Taken together, this can be used to create insights into the pathophysiology of postural instability and asymmetry in patients and possibly aid to develop and evaluate treatments.

Appendix A

Human balance control model

To test the feasibility of the MIMO identification method, model simulations were performed. A two-DoF mechanical model with a stabilizing mechanism was derived, Figure A1 shows the general model; the derivation of the subsystems is described below.

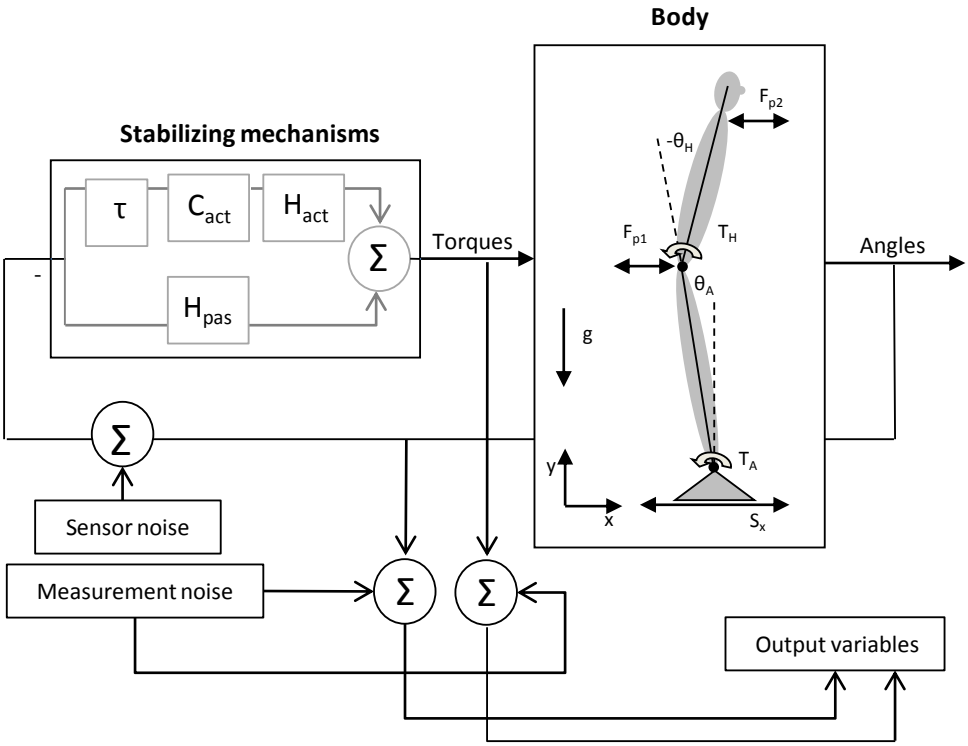

Figure A1: Model of human balance control. The model consists of body mechanics and a controller with intrinsic stiffness and damping (C_{pas}), an active PD controller (C_{act}), timedelays (τ), muscle activation dynamics (H_{act}), sensor and measurement noise. T_{ank} and T_{hip} denote the respective joint torques, θ_1 and θ_2 the joint angles. S_x and F_{pert} are the force and platform perturbations, respectively. g is the gravitational acceleration.

Derivation of the equations of motion

Kane's method (TMT method) was used to derive the equations of motions. In this method, the principles of virtual power are used to rewrite the Newton-Euler equations.

The first step is to define the degrees of freedom (generalized coordinates, q_t) of the model, which are in this case the support surface (S_x) and segment angles: θ_1 and θ_2.

Secondly, a transformation matrix T_j, which describes the Cartesian coordinates of the center of mass of the segments (x,y coordinates)in the degrees of freedom of the system (i.e., the generalized coordinates S_x, θ_1 and θ_2) is defined:

$$T_j = \begin{bmatrix} S_x \\ S_x + d_1 * \cos(\theta_1) \\ d_1 * \sin(\theta_1) \\ \theta_1 \\ S_x + l_1 * \cos(\theta_1) + d_2 * \cos(\theta_2) \\ l_1 * \sin(\theta_1) + d_2 * \sin(\theta_2) \\ \theta_2 \end{bmatrix} \quad \text{(A3.1)}$$

With d_1 and d_2 the distance to the segment's center of gravity from the distal point, l_1 denotes the length of the leg segment. This matrix can be differentiated to the generalized coordinates to obtain the first ($T_{j,t}$) and second derivative ($T_{j,tl}$) of the transformation matrix.

The mass matrix is also defined:

$$M = \mathrm{diag}(m_f, m_1, m_1, I_1, m_2, m_2, I_2) \quad \text{(A3.2)}$$

With m_f, m_1, m_2, I_1 and I_2, the mass of the foot, the segments masses and inertia's respectively.

And we also define the external forces and moments (f): this is the sum of the gravitational forces $F_{grav,i}$, the external forces $F_{ext,i}$, and the joint torques ($\tau_{joint,i}$):

$$\begin{matrix} f \\ \\ \\ \\ \\ \\ \\ \\ \end{matrix} = \begin{matrix} F_{grav,i} \\ \\ \\ \\ \\ \\ \\ \\ \end{matrix} + \begin{matrix} F_{ext,i} \\ \\ \\ \\ \\ \\ \\ \\ \end{matrix} + \begin{matrix} \tau_{joint,i} \\ \\ \\ \\ \\ \\ \\ \\ \end{matrix}$$

$$\begin{bmatrix} F_{sx} \\ 0 \\ -m_1 * g \\ (\tau_{ank} - \tau_{hip}) + \tau_{p1} \\ 0 \\ -m_2 * g \\ \tau_{hip} \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ -m_1 * g \\ 0 \\ 0 \\ -m_2 * g \\ 0 \end{bmatrix} + \begin{bmatrix} F_{sx} \\ 0 \\ 0 \\ -F_{p1} * p_1 * \sin(\theta_1) \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ (\tau_{ank} - \tau_{hip}) \\ 0 \\ 0 \\ \tau_{hip} \end{bmatrix} \quad \text{(A3.3)}$$

With g the gravitational acceleration (9.81), $\tau_{p1} = -F_{p1} * p_1 * \sin(\theta_1)$, the perturbation torques due to the external perturbation force. Note that joint moments (τ_{ank} and τ_{hip}) are the inputs of the model (forward simulation). Note, that the internal forces are not incorporated in the force matrix; these are implicitly incorporated in the $T_{j,t}$ and $T_{j,tl}$ matrices.

The movement equations with the TMT method lead to the following expression:

$$\overline{M}_{red1}\ddot{q} = \bar{f}_{red1} \tag{A3.4}$$

With $\overline{M}_{red1} = T^T M T$ and T = ($T_{i,t}$), is the first derivative of the transformation matrix. And

$$\bar{f}_{red1} = T^T\left[\sum f - Mg\right] \tag{A3.5}$$

With f the external forces, M the mass matrix and $g = T_{j,tm}\dot{q}_t\dot{q}_m$; this term corresponds to the centripetal term of the movement equations. In the case of forward simulation, we want to know the accelerations and the torques that are the inputs of the model:

$$\ddot{q} = \overline{M}^{-1}\bar{f} \tag{A3.6}$$

It can be deduced from Eq A3.4 and A3.5 that the equations of motion can be rewritten as:

$$M_{ij}(T_{j,t}\ddot{q} + T_{j,tm}\dot{q}_t\dot{q}_m) = F_{grav,i} + F_{ext,i} + \tau_{joint,i} \tag{A3.7}$$

For which we have used the index notation.

Drivers

In the case of a platform disturbance and a perturbation force, one of the generalized coordinates is specified, namely the platform movement (note that platform accelerations generate the perturbation). Therefore, the platform movement (S_x) can be considered as a known degree of freedom, while the remaining degrees of freedom are unknown:

$$q_t = \begin{bmatrix} q_u \\ q_k \end{bmatrix} \tag{A3.8}$$

This results in a split up of the $T_{j,t}$ matrix in a part for the known ($T_{j,k}$) and unknown degrees of freedom ($T_{j,u}$) and differentiation of these matrices results in $g = T_{j,kp}\dot{q}_k\dot{q}_p$ and $g = T_{j,un}\dot{q}_u\dot{q}_n$, respectively. Note that the subscripts u and k denote the unknown and known coordinates, respectively.

By substitution of these matrices in equation 7, we get:

$$M_{ij}(T_{j,k}\ddot{q}_k + T_{j,u}\ddot{q}_u + T_{j,un}\dot{q}_u\dot{q}_n + T_{j,kp}\dot{q}_k\dot{q}_p) = F_{grav,i} + F_{exter,i} + \tau_{joint,j} \tag{A3.9.1}$$

$$\begin{aligned} &T_{j,u}^T M_{ij} T_{j,u}\ddot{q}_u = \\ &T_{j,u}^T(F_{grav,i} + F_{ext,i} + \tau_{joint,j} - M_{ij}T_{j,k}\ddot{q}_k - M_{ij}T_{j,un}\dot{q}_u\dot{q}_n - M_{ij}T_{j,kp}\dot{q}_k\dot{q}_p \end{aligned} \tag{A3.10.2}$$

$$\begin{aligned} &\ddot{q}_u = M_{red1}^{-1}F_{red1} \\ &M_{red1} = T_{j,u}^T M_{ij} T_{j,u} \\ &F_{red1} = T_{j,u}^T(F_{grav,i} + F_{ext,i} + \tau_{joint,j} - M_{ij}T_{j,k}\ddot{q}_k - M_{ij}T_{j,un}\dot{q}_u\dot{q}_n - M_{ij}T_{j,kp}\dot{q}_k\dot{q}_p) \end{aligned} \tag{A3.11.3}$$

Linearization and state space notation

Subsequently, the equations of motion are linearized by differentiating the equations of motion to the states of the system ($\theta_1^0, \dot{\theta}_1^0, \theta_2^0, \dot{\theta}_2^0$; the joint angles and joint angle velocity) and to the system inputs and external disturbances ($\tau_{\mathrm{ank}}, \tau_{\mathrm{hip}}, \mathrm{S_x}$) with a first order Taylor approximation:

$$\mathrm{F_{lin}} = \mathrm{f(a)} + \mathrm{f'(a)} * (\mathrm{x} - \mathrm{a}) \tag{A3.12}$$

Where a is the equilibrium point and x the deviation from the operating point. In our case, the equilibrium position is straight stance (segment angles are 90°, angular velocities, external perturbations, and joint torques are zero). Note that the centripetal term of the movement equations disappears with linearization.

Finally, the equations are rewritten in a state-space notation:

$$\begin{aligned} \dot{\mathrm{x}} &= \mathrm{A_{ss}x} + \mathrm{B_{ss}u} \\ \mathrm{y} &= \mathrm{C_{ss}x} + \mathrm{D_{ss}u} \end{aligned} \tag{A3.13}$$

With $\dot{\mathrm{x}} = \dot{\theta}_1^0, \ddot{\theta}_1^0, \dot{\theta}_2^0, \ddot{\theta}_2^0$ (thus the derivative of the systems states) and x the states. U are the inputs of the system and represent the joint torques, perturbation force, and the platform perturbation.

Stabilizing mechanism

Passive muscle stiffness and damping were added to each joint; hence, only mono-articular muscles are added. The built-up of muscle force is described by the muscle activation dynamics and these were modeled as a second-order dynamical system:

$$\mathrm{H_{act}}(\omega) = \frac{1}{\frac{1}{{\omega_\mathrm{n}}^2}\mathrm{s}^2 + \frac{2\beta}{\omega_\mathrm{n}}\mathrm{s} + 1} \tag{A3.14}$$

With s = jω, the natural frequency (ω_n) was set at 13.8 rad/s (≈2.2 Hz) and the relative damping (β) was 0.7. As the sensory signals do not reach the CNS instantaneously (because of neural conduction times) a time delay is also modeled as a pure transport delay, see also Figure A1. Parameter values were taken from the literature (Kiemel *et al.*, 2008; Winter, 1990), see Table A3.2.

Based on the A and B matrices of the state space equations and intrinsic joint stiffness and damping, the steady-state linear quadratic regulator (LQR), was used to uniquely determine the components of the optimal state feedback matrix C_{act} (see Figure A1). For the optimization, activation dynamics and timedelays are not included in the feedback pathway. The feedback parameters are obtained by minimizing the cost function *J* of the form:

$$J = \int (x'Qx + u'Ru)dt \quad \text{(A3.15)}$$

With x the system's states and u the system's input. Q and R are diagonal matrices; the elements in Q are set to 1 and in R set to 10^6.

As the sensory signals do not reach the CNS instantaneously (because of neural conduction times) a time delay is included as a pure transport delay, see Figure A1. Parameter values were taken from the literature (Kiemel *et al.,* 2008), see Table A3.2.

Table A3.2: Human balance control model parameters

Anthropomorphic		**Controller properties**	
Parameter	**Value**	**Parameter**	**Value**
mass	70 kg	Ankle stiffness	293 Nm/rad
m_1	22.54 kg	Ankle damping	2.2 Nm·s/rad
m_2	47.46 kg	Hip stiffness	95 Nm/rad
length	1.70 m	Hip damping	27.4 Nm·s/rad
l_1	1 m	Time delay ankle	60 ms
l_2	0.7 m	Time delay hip	40 ms
d_1	0.57 m		
d_2	0.26 m		
l_1	0.65 m	Muscle dynamics	
l_2	0.44 m	Eigen frequency (ω_n)	4.4π rad/s
g	9.81 m/s^2	Damping (β)	0.7 -

Anthropomorphic data is taken from (Winter, 1990). The controller properties values are taken from (Kiemel et al.*, 2008)*

Pink sensor noise was created off line, by scaling the power spectrum of a random timeseries by 1.2 such that at 1 Hz, the power of the signal was $1.5 \cdot 10^{-7}$. Subsequently, this signal was added to the joint angles in the model simulations; this lead to a spontaneous sway of around 0.6° (peak-to-peak amplitude; comparable with human quiet stance data). Measurement noise was modeled as white noise (zero mean and 0.0001 variance) and added to the joint angles and joint torques.

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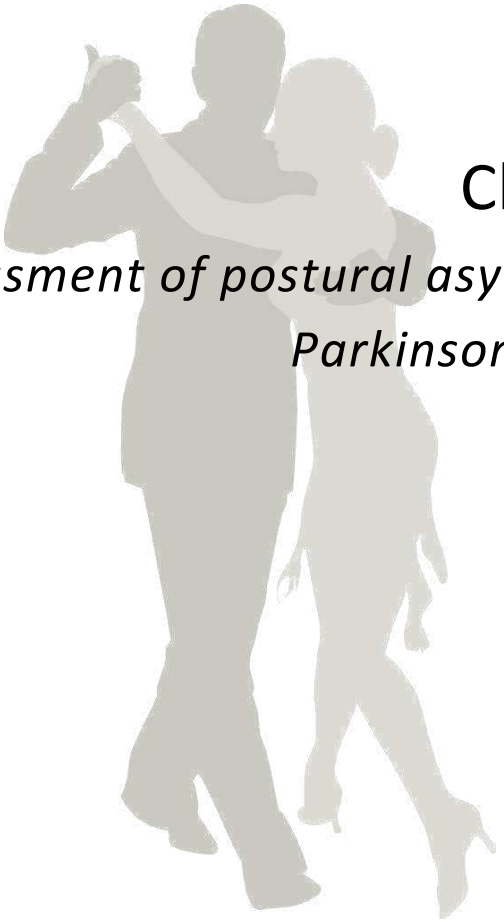

Chapter 4

Assessment of postural asymmetry in Parkinson's disease

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Assessment of postural asymmetry in mild to moderate Parkinson's disease
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Abstract

Asymmetry of symptoms of Parkinson's disease is clinically most evident for appendicular impairments. For axial impairments such as freezing of gait, asymmetry is less obvious. To date, asymmetries in balance control in PD patients have seldom been studied. Therefore, in this study we investigated whether postural control can be asymmetrically affected in mild to moderate PD patients.

Seventeen PD patients were instructed to stand as still and symmetrically as possible on a dual force-plate during two trials. Dynamic postural asymmetry was assessed by comparing the centre-of-pressure velocities between both legs.

Results showed that four patients (24%) had dynamic postural asymmetry, even after correcting for weight-bearing asymmetry. Hence, this study suggests that postural control can be asymmetrical in early PD. However, future studies should investigate the prevalence of dynamic postural asymmetry, in a larger group of PD patients. It should also be further investigated whether this approach can be used as a tool to support the initial diagnosis or monitor disease progression, or as an outcome measure for interventions aimed at improving balance in PD.

Introduction

Motor symptoms in Parkinson's disease (PD) are typically asymmetrical (Djaldetti *et al.,* 2006). This is clinically most evident for the appendicular impairments (e.g., upper and lower limb rigidity, bradykinesia and tremor). It is clinically less obvious whether axial impairments (i.e., stooped posture, shuffling gait, postural imbalance and freezing) are also asymmetric.

Recent studies showed that asymmetries of gait can be found in "de novo" PD patients who have never been treated with anti-parkinsonian medication (Baltadjieva *et al.,* 2006), and linked asymmetries in bilateral leg coordination to freezing of gait (Plotnik *et al.,* 2005).

Asymmetries in posture have thus far rarely been studied. Indeed, clinical scales used to assess disease severity (e.g., the Unified Parkinson's Disease Rating Scale, the UPDRS) do not explicitly evaluate asymmetries in axial impairments. One study using posturography showed a significant asymmetry in the Center-of-Pressure (COP) velocity and frequency characteristics in PD patients compared to healthy controls (Rocchi *et al.,* 2002) . While important as "proof of principle", this study was not conclusive as the normal distribution of dynamic postural asymmetry in healthy subjects was not taken into account as a reference for assessing patients, nor was the possible influence of static (weight-bearing) asymmetry on the dynamic COP characteristics of each leg accommodated. Also, this study included relatively severely affected PD patients and did not relate the direction of the dynamic postural asymmetry to the clinical asymmetry.

It has not yet been investigated whether postural control is asymmetrical in a larger sample of relatively mildly affected and unselected PD patients (van der Kooij et al, 2007 only tested two patients). In addition, postural asymmetry as assessed with dual force plates has not been related to clinical asymmetry (i.e., appendicular symptoms). Therefore, in this study we investigated whether postural control can be asymmetrically affected in mild to moderate PD patients and whether postural asymmetry is associated with appendicular asymmetry.

Methods

Participants and task

Seventeen PD patients participated (Table 4.1). Inclusion criteria were: idiopathic PD according to established criteria (Pickering *et al.,* 2007), Hoehn & Yahr score ≤2 and ability to stand independently for at least one minute. Exclusion criteria: (i) other, concomitant diseases impairing balance or posture (Kelly *et al.,* 2006); (ii) psychiatric disorders; (iii) use of medication known to impair balance; and (iv) dyskinesias that could affect postural sway.

Motor UPDRS items 20-26 assessed appendicular asymmetry; this was defined as a difference between the right and left body side for at least one of these items. A postural instability–gait difficulty (PIGD) score was calculated for each patient (sum UPDRS items 27-30). The local medical ethical committee approved the study protocol; all subjects gave written informed consent.

Subjects stood barefoot on a force-plate against a fixed foot frame, which positioned the medial sides of their heels 8.4 cm apart and the toes outward at a 9° angle from the sagittal midline. They were instructed to stand as still and symmetrically as possible, for two 30 s, eyes open, quiet-standing trials. Subjects were tested during their subjectively best ON phase (Bloem *et al.,* 1996)

Apparatus

Two separate aluminium plates were each placed on three force transducers, connected to a personal computer. Signals were sampled at 500 Hz, amplified, and led through a first-order low-pass filter (cut-off frequency 30 Hz). The coordinates of the COP were filtered with an additional off-line low-pass Fourier filter using a cut-off frequency of 3 Hz, because three patients showed small rhythmic (6 Hz) oscillations in their COP (most likely related to Parkinsonian leg tremor and not to postural regulation).

The COP of the resultant of the ground reaction forces was determined in a 2-dimensional transverse plane by means of digital moment-of-force calculations for each set of force samples.

Data analysis

Postural asymmetry was calculated based on the differences in anterior-posterior COP velocities ($V_{COP,}$ in mm/s) between both feet, averaged for both trials. These differences were expressed in a symmetry index (Anker *et al.,* 2008):

$$SI = \frac{2*(Vcop_{Left} - Vcop_{Right})}{Vcop_{Left} + Vcop_{Right}} * 100\% \quad (4.1)$$

An absolute SI > 66 indicates asymmetrical balance control (based on the findings in Anker, et al., 2008). Static weight bearing asymmetry was determined as the difference between the vertical reaction forces on each force plate normalized to the total vertical force. Consistency between trials was calculated with the intraclass correlation coefficient (ICC).

Table 4.1: Clinical characteristics of the Parkinson's Disease patients. The right column shows the symmetry index (SI) of the RMS COP velocity (V_{COP}) in the AP direction for individual patients. The bold values are outside the normal distribution of the reference values obtained from healthy controls.

Patient	Gender	Age (yr)	Hoehn & Yahr stage (0-5)	UPDRS Motor score (0-56)	PIGD score (0-16)	Clinically most affected side	MMSE (0-30)	Goetz dyskinesia rating scale (0-16)	SI V_{COP}
1	F	42	1	12	0	Right	30	0	**67.3**
2	F	53	1.5	9	0	Right	29	0	-43.6
3	F	55	2	8	0	Right	29	0	**82.2**
4	F	62	2	14	4	Right	29	0	-2.0
5	F	65	2	15	1	Left	28	0	19.7
6	F	73	3	23	5	Left	30	0	-17.1
7	F	74	2.5	16	0	Left	27	1	44.1
8	M	43	1.5	7	1	Right	29	0	2.3
9	M	44	2.5	14	0	Left	27	0	33.8
10	M	49	2.5	20	0	Right	28	0	11.5
11	M	51	3	20	3	Indifferent	29	0	-64.5
12	M	57	2.5	14	1	Left	27	0	-22.8
13	M	63	2	7	0	Left	28	0	**-101.1**
14	M	67	3	9	1	Left	28	0	**-72.4**
15	M	67	1.5	9	1	Left	30	0	-23.9
16	M	71	3	14	2	Left	28	0	42.3
17	M	74	3	16	4	Right	29	1	-32.0
Mean		**59**	**2.4**	**13**	**1.4**		**29**	**0**	

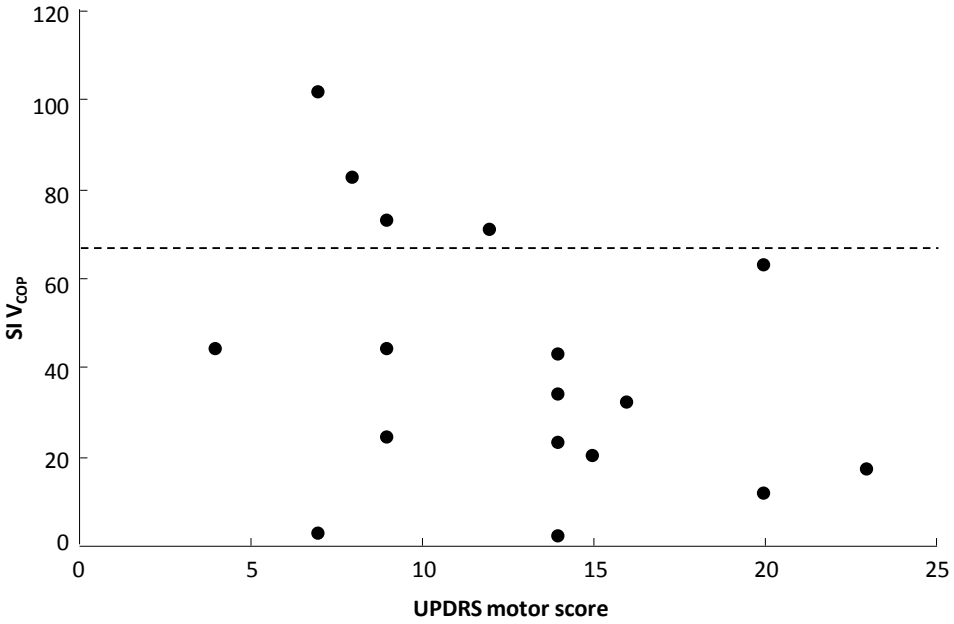

Figure 4.1: Individual absolute symmetry indices (absolute SIs) derived from the V_{COP} values in the AP direction versus UPDRS motor scores. The horizontal dashed line indicates the 95% upper limit of the normal reference values (absolute SI = 66).

Results

Postural asymmetry

Table 4.1 shows the SIs of individual patients. Figure 4.1 depicts the individual absolute SIs versus the individual UPDRS motor scores. Four of the seventeen PD patients had an absolute SI >66, indicating an abnormal level of postural asymmetry. Two of these patients also showed a significant degree of static (weight-bearing) asymmetry (10 and 12%). The SIs of these patients remained above the 95% upper limits of the control data after correction for their weight-bearing asymmetry (cf: Anker *et al.,* 2008). Consistency between trials was high ($ICC_{(case=2)}$ = 0.911, p = 0.000). Figure 4.2 shows the SIs compared to the clinically most affected side. In all patients, the postural asymmetry corresponded to the most affected side as assessed with the UPDRS.

Discussion

This study investigated the presence of dynamic postural asymmetry in a group of unselected mild to moderate PD patients using relatively simple dual-plate posturography. Four out of seventeen patients (24%) showed clear signs of dynamic postural asymmetry, even after correcting for weight-bearing asymmetry. This suggests that postural asymmetry can be present in early PD, although it is not apparent in all patients. These

results extend earlier reports of asymmetries in parkinsonian gait (Baltadjieva *et al.,* 2006; Plotnik *et al.,* 2005) and postural control (Rocchi *et al.*, 2002; van der Kooij *et al.*, 2007). Note that age did not influence the normal limits of postural asymmetry in a previous study of healthy young and elderly (Anker *et al.,* 2008). Thus, the dynamic postural asymmetry of PD patients in the present study appears to be attributable to the disease itself and not to ageing (Anker *et al.,* 2008).

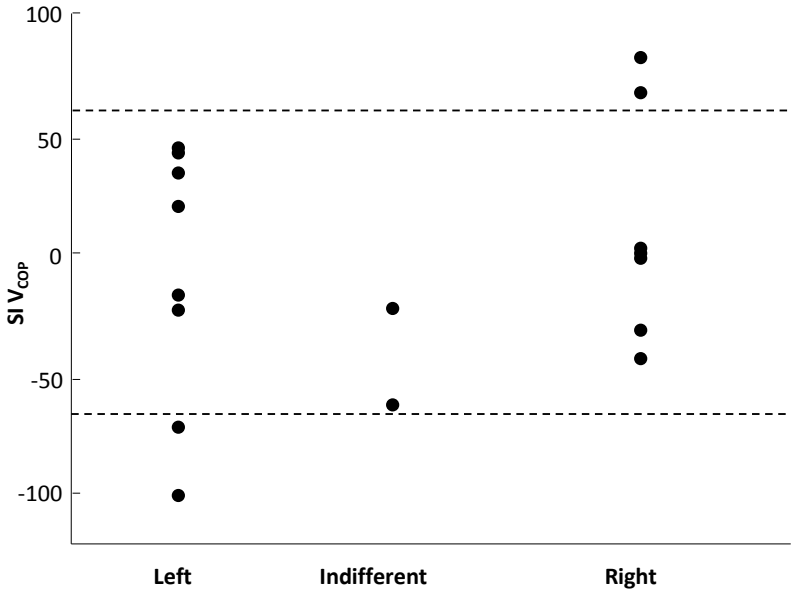

Figure 4.2: Individual symmetry indices (SIs) derived from the V_{COP} values in the AP direction versus clinically most affected body side (appendicular asymmetry). The horizontal dashed lines indicate the 95% limits of the normal reference values (SI = –66 and 66).

The observed dynamic postural asymmetry always corresponded with the individually identified appendicular asymmetry. Hence, simple dual-plate posturography can be used to identify an asymmetric contribution of the legs to postural control in PD patients. As such, it provides a first indication that this method may possibly support a diagnosis of PD (Hughes, 2002). Moreover, assessment of postural asymmetry – rather than "overall" postural control – might prove useful for monitoring disease progression, or as an outcome measure for interventions aimed at improving balance in PD. A recent discussion (Chastan *et al.,* 2008; Valkovic *et al.,* 2009) about postural imbalance in early PD highlighted the need for clearly defined outcome measures to determine balance abnormalities in patients. We suggest that for PD patients both static and dynamic aspects of postural asymmetry should be taken into account when investigating balance abnormalities.

Our study investigated a limited sample of PD patients. Therefore, we do not intend to report prevalence rates of postural asymmetry, but rather to provide an indication that balance control can be asymmetrical in early PD. Future studies should investigate the prevalence of postural asymmetry in a larger sample of patients, its relation with disease severity and progression, and its value for initial diagnosis and therapy evaluation.

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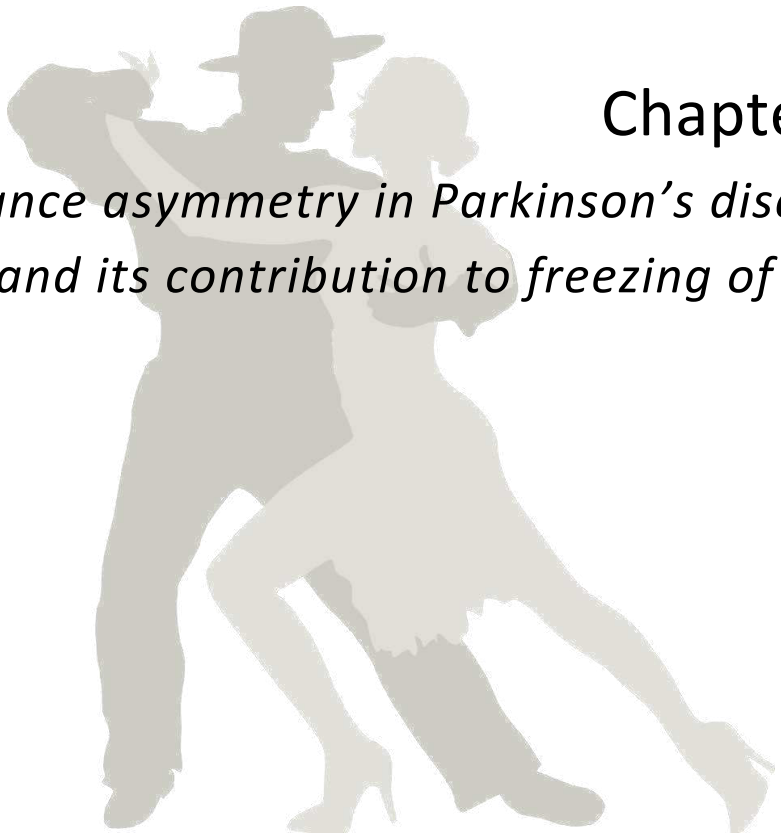

Chapter 5

Balance asymmetry in Parkinson's disease and its contribution to freezing of gait

T. A. Boonstra, J.P.P. van Vugt, H van der Kooij and B. R. Bloem
Balance asymmetry in Parkinson's disease and its contribution to freezing of gait
Under review

Abstract

Balance control is asymmetrical in a proportion of patients with Parkinson's disease and gait asymmetries have been linked to the pathophysiology of freezing of gait. We speculate that asymmetries in balance could contribute to freezing, by hampering the unloading of the stepping leg. To investigate this, we examined the relationship between balance control and weight bearing asymmetries and freezing.

We included 20 patients with Parkinson (tested OFF medication; nine freezers) and nine healthy controls. Balance was perturbed in the sagittal plane, using continuous multi-sine perturbations. Applying closed-loop system identification techniques, relating the body sway angle to the joint torques of each leg separately, determined the relative contribution of each ankle and hip joint to the total amount of joint torque. We also calculated weight bearing asymmetries.

We determined the 99% confidence interval of weight bearing and balance control asymmetry using the responses of the healthy controls. Freezers did not have larger asymmetries in weight bearing (p = 0.85) nor more asymmetrical balance control compared to non-freezers (p = 0.25). The healthy linear one-to-one coupling between weight bearing and balance control was significantly different for freezers and non-freezers (p = 0.01). Specifically, non-freezers had a significant coupling between weight bearing and balance control (p = 0.02), whereas this relation was not significant for freezers (p = 0.15).

Balance control is asymmetrical in most patients with Parkinson's disease, but this asymmetry is not related to freezing. However, the coupling between weight bearing and balance control is absent in freezers while present in healthy controls and non-freezers.

Introduction

Parkinson's disease (PD) is typically an asymmetrical disease. The motor symptoms usually affect one side of the body first, and even though the contralateral side becomes involved later on, the initially affected side remains most prominently affected throughout the course of the disease in about 80% of patients (Djaldetti *et al.,* 2006; Uitti *et al.,* 2005). Asymmetries in balance control (i.e. when one leg is producing more force than the other leg in order to keep the body upright) have rarely been investigated. Pilot studies using posturography have shown that balance control – which is intuitively a very symmetrical task – can also be asymmetrically affected in PD (Rocchi *et al.*, 2002; van der Kooij *et al.*, 2007b). A study of balance control asymmetries in 17 PD patients (tested ON medication) showed that 24% of patients had a postural asymmetry (Geurts *et al.,* 2011). This suggests that balance control can be asymmetrical in PD, but not in all individual patients.

Gait is also typically asymmetrically affected in PD (Baltadjieva *et al.*, 2006; Frazzitta *et al.*, 2012; Lewek *et al.*, 2010). Asymmetries in leg coordination have been linked to the pathophysiology of freezing of gait (FoG; Plotnik *et al.,* 2005; Plotnik *et al.,* 2008). Specifically, PD patients with FoG ('freezers') had more asymmetric leg swing times compared to PD patients who never experienced FoG ('non-freezers'). FoG is an episodic, disabling gait disorder during which the feet appear to be 'glued to the floor' (Nutt *et al.,* 2011). About 50% of patients with PD experience FoG, hence like balance asymmetry, this is not a consistent sign across all patients (Peterson *et al.,* 2012). Interestingly, FoG most frequently occurs during tasks that require asymmetric motor control, such as turning while walking or when patients start walking (Schaafsma *et al.,* 2003). Gait initiation again involves motor asymmetry, because the step leg must be unloaded, thereby introducing an asymmetric medio-lateral weight distribution.

Based on these observations, we speculated that asymmetries in balance control could prevent subjects from making an adequate weight shift that is needed to unload the stepping leg, and thus produce FoG. Such a possible relationship between asymmetric balance control and FoG has never been investigated.

We hypothesized that patients with FoG would have larger asymmetries in balance control compared to non-freezers. To investigate this, we assessed balance responses to perturbations in the anterior-posterior direction using system identification techniques, within a large group of PD patients (tested OFF medication), including both freezers and matched non-freezers, as well as healthy controls. We determined weight bearing and balance control asymmetries and related these to FoG, disease severity, walking difficulties and history of falls.

Methods

Participants

We included 20 patients with PD (nine with FoG, matched for disease severity with the 11 non-freezers) and nine matched healthy controls (Table 5.1 and Table 5.2). Patients were assessed in a practically defined OFF state, at least 12 hours after intake of their last dose of dopaminergic medication. Disease severity was determined using the Hoehn and Yahr stages and the motor part of the Unified Parkinson's Disease Rating Scale (Goetz *et al.,* 2008). Freezing of gait was quantified using the new freezing of gait questionnaire (Nieuwboer *et al.*, 2009). Patients were classified as freezers when they reported unequivocal subjective episodes of FOG (i.e. frequently experiencing the typical feeling of the feet being glued to the floor) during an interview with an experienced assessor. Non-freezers reported never to have experienced freezing episodes. Furthermore, we provoked FoG by having the patients make fast and slow 360° turns towards the left and right body side (Snijders *et al.,* 2012). Of the nine freezers, three of them showed freezing, while the non-freezers showed no freezing episodes during this test. Items 3.9- 3.13 of the UPDRS were used to determine the Postural Instability and Gait Difficulty score. Clinical asymmetry was defined as a difference between the summed UPDRS scores of the left and right extremities (items 3.3-3.8 and 3.15-3.17). We asked about prior (near-) falls and about fear of falling. Fear of falling was also individually determined with the modified Falls Efficacy Scale (Hill *et al.,* 1996). In addition, the 10-meter walk test and the Timed-Up-and-Go-Test were administered to quantify gait and balance impairment. Lastly, we determined the dominant leg by assessing which leg was used when forced to take a step. We repeated this test three times and the dominant leg was the leg that was used the most for stepping.

We excluded patients with marked cognitive dysfunction (Mini Mental State Examination <24 or Frontal Assessment Battery <13 (Cohen *et al.*, 2012; Crum *et al.*, 1993; Royall, 2001), or with visual, vestibular, orthopaedic, psychiatric or other neurological diseases. In addition, participants with a history of joint injuries were excluded. All participants gave prior written informed consent. The protocol was approved by the local medical ethics committee, in accordance with the Declaration of Helsinki.

Apparatus and recording

We applied methods described in detail elsewhere (Boonstra *et al.*, 2013; van Asseldonk *et al.*, 2006). In short, two independent perturbations were administered with a computer-controlled six degrees-of-freedom motion platform (Caren, Motek, Amsterdam, The Netherlands) and a custom-built actuated device that was able to apply perturbing forces at the sacrum, called the pusher (Figure 5.1). The data presented here are part of a larger dataset that also enables the investigation of multi-segmental balance control, i.e.

the interactions between the ankle and hip joints and therefore two perturbations were applied (Boonstra *et al.*, 2013; Pintelon *et al.*, 2001). Body kinematics and platform movements were measured using motion capture (Vicon Oxford Metrics, Oxford, UK) at a sample frequency of 120 Hz. Reflective spherical markers were attached to the first metatarsal, calcaneus, medial malleolus, the sacrum, the manubrium and the last vertebrae of the cervical spine (C7). A cluster of three markers was attached to the anterior superior iliac spines on the pelvis. One additional marker was attached to the foot and two markers were attached to the lower leg (one on the tibia) to improve the estimation of the rotational axis of the ankle joint. Also, markers were attached on the knee (just below the lateral epicondyle) and shoulder joints (just in front of the acromion). Furthermore, three markers were attached to the platform. Reactive forces from both feet were measured with a dual forceplate (AMTI, Watertown, USA), embedded in the motion platform. The signals from the dual forceplate, the six degrees-of-freedom force transducer, and the perturbation by the pusher were sampled at 600 Hz and stored for further processing.

Disturbance signals

The perturbation signal was a multisine with a period of 34.13 s (van Asseldonk *et al.,* 2006; van der Kooij *et al.,* 2007a; van der Kooij *et al.,* 2007b). A multisine has the advantage that it is unpredictable for participants, because the signal consists of many sinusoids (de Vlugt *et al.,* 2003). The signal contained power at 112 frequencies in the range of 0.06–4.25 Hz. To increase the power at the excited frequencies the signal was divided in five frequency bands: 0.06-2.37 Hz, 2.63-2.84 Hz, 3.11-3.31 Hz, 3.57-3.78 Hz and 4.04-4.25 Hz. Frequency points outside these frequency bands were not excited. The perturbation signal was used for both the platform (scaled by the inverse of the frequency) and the pusher (not scaled).

Procedure

During the experiment, participants stood with their eyes open and with their arms folded in front of their chest (to prevent time varying responses) on the dual forceplate while being attached with a band strap that opened with a click buckle to the pusher. Heel-to-heel distance was fixed at 14 cm and the feet contours were taped to ensure the same foot position across trials. They were instructed to maintain their balance without moving their feet, while continuous, pseudorandom platform movement and continuous, pseudorandom force perturbations were applied simultaneously in the forward-backward direction (see 'Disturbance' signals and supplementary materials).

Table 5.1: Patient characteristics and clinical scores

Patient	Age (yrs)	Gender	Disease duration (yrs)	H&Y	FOG	UPDRS III	PIGD	Clinical asymmetry	Fall risk	mFES	TUG (s)	TMW (m/s)
1	47	F	3	2	0	24	3	Left	1	8	9,5	1,23
2	54	F	3	2	0	11	0	Right	0	1	12,5	1,32
3	58	M	2,5	1	0	14	1	Left	0	2	9,4	1,38
4	67	M	7,0	2	0	34	2	Left	1	4	7,9	1,36
5	73	M	3,0	2	0	26	1	Right	0	6	10,9	1,25
6	79	F	4,5	2	0	36	4	Left	0	6	7,8	1,06
7	55	F	3,5	2	0	23	5	Left	0	5	10,4	1,10
8	77	F	4,0	2	0	30	4	Left	1	1	11	1,10
9	73	M	8	2	0	30	2	Left	1	3	7,9	1,38
10	61	M	1,5	1	0	15	1	Left	0	0	12,9	1,41
11	66	M	4,5	2	0	26	4	Left	0	2	9,5	1,05
12	67	M	7	3	1	57	6	Left	1	7	19	0,77
13	58	M	6	3	1	17	5	Right	1	2	11,7	1,18
14	64	F	15	2	1	35	8	Right	0	14	10,7	0,94

Patient	Age (yrs)	Gender	Disease duration (yrs)	H&Y	FOG	UPDRS III	PIGD	Clinical asymmetry	Fall risk	mFES	TUG (s)	TMW (m/s)
15	69	M	9,0	2	1	24	1	Right	0	8	10,4	1,20
16	57	M	3,0	2	1	39	1	Left	0	0	6,9	1,33
17	62	M	4,0	1	1	20	1	Right	0	0	8,2	1,39
18	59	M	7,0	2	1	32	3	Left	1	3	9,9	1,65
19	58	M	6	2	1	33	5	Right	0	2	11,3	1,25
20	54	M	4,5	2	1	25	2	Left	1	14	13,8	1,32
Mean	**63,3**		**5,21**	**1,95**		**27,55**	**2,95**			**4**	**11**	**1,23**

M: Male; F: Female; H&Y: Hoehn & Yahr; FOG: 1) freezer; 0) non freezer; UPDRS: Unified Parkinson‘s Disease Rating Scale; PIGD: Postural Instability and Gait Difficulty; Fall risk: 1) yes, 0) no; mFES: Modified Falls Efficacy Scale; TUG; Timed-Up-and-go-Test; TMT: Ten Meter Walk test

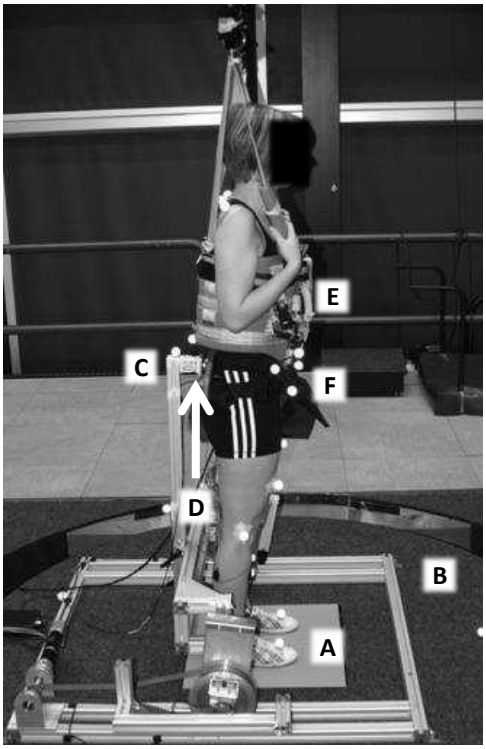

Figure 5.1: Experimental set-up. Participants stood on the dual forceplate (A) embedded in the movable platform (B). Two independent perturbations in the forward-backward direction were applied simultaneously using both the movable platform (B) and the pusher (C). Interaction forces between the pusher (C) and the participant were measured with a force sensor (D). Actual falls were prevented by the safety harness (E). Reflective spherical markers (F) measured movements of the participant.

Participants wore a safety harness to prevent falling, but it did not constrain movements, provide support or orientation information in any way. Before any data were recorded, the participants were familiarized with the perturbations. The experimenter determined the maximal amplitude that each participant could withstand while keeping their feet flat on the floor, and assessed whether the participant could withstand this amplitude for the total number of trials. Four perturbation trials of 180s each were recorded. If needed, the participants were allowed to rest in between trials.

Data analysis

Data obtained during the first two trials were analyzed. From the recorded movement trajectories of the markers, the position of the center-of-mass of the predefined segments (i.e., feet, legs, and the HAT) and of the whole body (CoM) were estimated by first calculating the separate positions and rotations of the body segments (Koopman *et al.*, 1995; Koopman, 1989). Subsequently, the CoM was determined as the weighted sum of

the separate segment positions (Koopman *et al.,* 1995). From the static trial, the average distance in the sagittal plane from the ankle to the total body CoM (i.e., the length of the pendulum (l_{CoM}) was determined. The sway angle was calculated from l_{CoM} and the horizontal distance from the CoM to the mean position of the ankles. Forces and torques of the force plate and force sensor were filtered with a fourth-order low-pass Butterworth filter with a cut-off frequency of 8 Hz and subsequently resampled to 120 Hz. Forces and torques of the force plate were corrected for the inertia and mass of the top cover (Preuss *et al.,* 2004). On the basis of the corrected forces and torques and recorded body kinematics, ankle and hip joint torques were calculated with inverse dynamics (Koopman *et al.,* 1995). In addition, the applied platform perturbation was reconstructed from the platform markers.

Frequency response functions

The time series of the perturbations, sway angle, joint angles and joint torques were separated into eight data blocks of 34.14 s (i.e., the length of the perturbation signal). Data blocks with missing markers or with unwanted movements such as a step or weight shifting were excluded from further analysis. In this way it was ensured no actual freezing episodes were recorded during the balance task. To avoid any transient effects, the first perturbation cycle of each trial was discarded. This resulted in eight whole perturbation cycles for the balance control asymmetry estimation. Subsequently, the responses were Fourier transformed at the 112 frequencies of the perturbation signal using the fast Fourier transform in Matlab. These were averaged over the eight cycles to obtain the average individual response, and the average Fourier coefficients were used to calculate the power- and cross spectral density (PSD and CSD, respectively). The PSDs and the CSDs were smoothed by averaging over four adjacent frequency points (Jenkins *et al.,* 1969). Lastly, the Frequency Response Function (FRF) of the stabilizing mechanism was estimated with a SISO joint-input-joint-output system identification technique (van Asseldonk *et al.,* 2006; van der Kooij *et al.,* 2005a). A FRF captures the amount and timing of the response of the participant. As such, the gain of the FRF of the stabilizing mechanisms represents how much torque is exerted in response to body sway. The phase gives information about the timing of the response, if there is a phase lead the response of the joint advances the body movement and an increasing phase lag for example indicates a neural timedelay (Peterka, 2002).

The FRFs were calculated from sway angle to left and right ankle and hip torques separately. Furthermore, the FRFs were normalized by the mass and length of the participants to compensate for differences in the subjects' mass and pendulum length, which influence the FRF (Peterka, 2002).

Balance asymmetries

We calculated three balance proportions of both legs; of the weight bearing and the balance control contribution of both the ankle and the hip joint separately. As these indices are obtained during perturbed upright stance, we added the adjective dynamic.

The dynamic weight bearing proportion (DWB) was calculated by calculating the relative weight bearing on the left and right leg:

$$\mathrm{DWB}_{l,r} = \sum_{t_0}^{t_{end}} \frac{\mathrm{WB}_{l,r}}{\mathrm{WB}_l + \mathrm{WB}_r} \tag{5.1}$$

With t_0 and t_{end} the first and last sample of the trial.

To determine the relative contribution of each ankle and hip joint to the total amount of generated corrective torque to resist the perturbations, the contribution of the gain and phase of the FRFs of each leg to the gain of the total body was calculated (van Asseldonk *et al.,* 2006). Subsequently, the contributions were averaged over the frequencies of the perturbation signal to obtain one the dynamic balance contribution (DBC) for each leg:

$$\mathrm{DBC}_{l,r}(f) = \sum_{f\,min}^{f\,max} \left(\frac{\mathrm{FRF}_{l,r}(f) \bullet \mathrm{FRF}_t(f)}{\left\| \mathrm{FRF}_t(f) \right\|^2} \right) \tag{5.2}$$

With $\mathrm{FRF}_{l,r}$ the left or right FRF and FRF_t the total FRF. The $\bullet$ indicates the dot product of the FRFs. In this way the contribution of the left or right leg to the total balance control was expressed as a proportion.

For example, a DBC of 0.8 means that one leg contributed for 80% to upright stance, while the other contributed for 20%. In order to compare the amount of asymmetry between the non-freezers and freezers, the absolute amount of asymmetry was determined by: |DBC - 0.5|. Note that we separated *weight bearing* asymmetries from *control* asymmetries during upright perturbed stance in this study.

Statistical analysis

Based on the weight bearing and balance control contribution values of the healthy controls the 99% confidence interval (CI) for the weight bearing (DWB), for the ankle (DBC_{Ank}) and the hip joint (DBC_{Hip}) were determined. Patients whose balance contributions were outside this confidence interval were classified as having asymmetrical balance control.

The patients with asymmetrical balance control (PDASYM) were compared to their symmetrical counterparts (PDSYM). This comparison was made for age, UPDRS and PIGD score, fear of falling, 10m walk and TUG test, using independent t-tests.

In case of non-normal distribution of the data, Mann-Whitney U tests were applied. Gender, H&Y, occurrence of FoG and prior falls were compared with a χ^2 test. These comparisons were made separately for WB, DBC_{Ank} and DBC_{Hip}. In addition, the absolute amount of balance control asymmetry was compared with independent t-tests, between freezers and non-freezers.

Furthermore, we performed an ANCOVA to evaluate the effect of group (i.e., freezer or non-freezer) on the relationship between balance control and weight bearing. Subsequently, we calculated this regression for freezers and non-freezers separately. Alpha was set at 0.05 and to correct for multiple comparisons, the confidence level was adjusted with Bonferroni correction.

Results

Both patients and controls were able to maintain their balance in the face of the two applied perturbations in the anterior-posterior direction. The average amplitudes for the platform were similar for controls (0.028 m, std: 0.002) and patients (0.028 m, std: 0.004; $t_{(25)} = 0.6$, $p = 0.68$). The average amplitudes of the pusher were slightly higher for healthy controls (9 Nm, std: 1) compared to the patients (7.8 Nm, std: 1.56; $t_{(25)} = 2.4$, $p = 0.04$; see also Figure 5.2. Controls and patients swayed just as much (mean RMS PD: 0.71; HC: 0.74; $t_{(177)} = 2.98$, $p = 0.13$) in response to the perturbations.

Asymmetries in weight bearing and balance control

Figure 5.3 shows the weight bearing proportion and balance control contributions (DBC_{Ank} and DBC_{Hip}) of the left and right leg of the PD patients. Individual PD patients showed highly asymmetric weight bearing and balance control, whereas healthy controls distributed their weight evenly and exerted equal corrective torques with both legs ($mean_{WB}$: 0.49, std_{WB}: 0.056; $mean_{Ank}$: 0.48, std_{Ank}: 0.044; $mean_{Hip}$: 0.49, std_{Hip}; 0.04; 99% Confidence Intervals (CI) shown in Figure 5.3). For example, for PD patient six the left ankle contributed by 13%, whereas the right ankle contributed by 87% to upright stance.

However, there were also PD patients who controlled their balance symmetrically, for example patient two. Although there were balance control asymmetries at both joints, Figure 2 shows that these were less pronounced at the hip joint. Furthermore, a weight bearing asymmetry was not always accompanied by a balance control asymmetry (e.g., pt 5) or vice versa (e.g., pt 13). Also, the amount of weight bearing asymmetry was not always the same as the of balance control asymmetry. For example, in patients six and 11, the weight bearing asymmetry was smaller than the balance control asymmetry of the ankle joint. Most patients used their right leg more than their left leg to maintain upright balance. Except for patient two, all patients showed balance asymmetries; either in unevenly distributed weight or in different balance control contributions of the left and right leg at the ankle or hip joint.

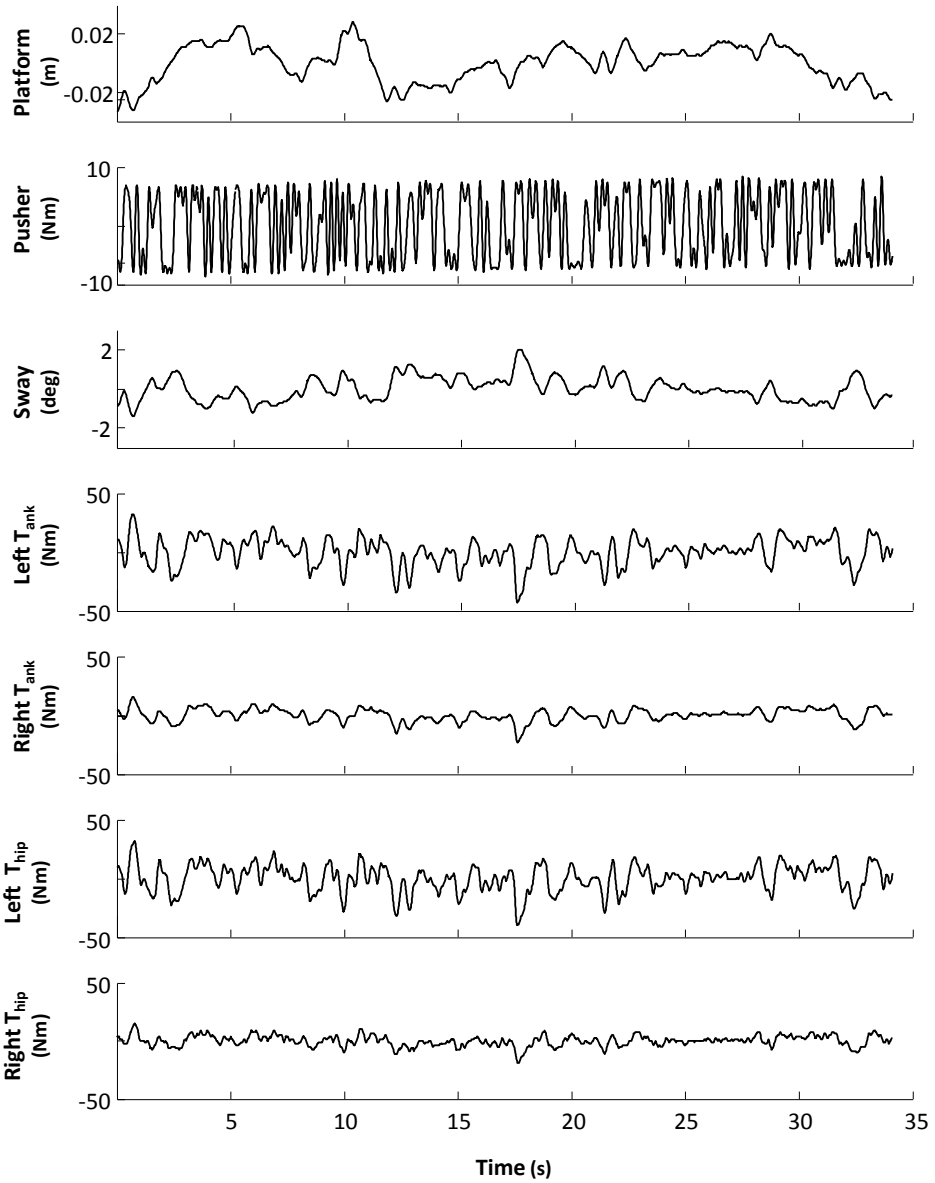

Figure 5.2: Timeseries of a representative Parkinson patient of one perturbation cycle. The upper two panels represent the platform and pusher perturbations. The lower four panels show the participants' response. Note that there are clear asymmetries in the joint torque responses

Table 5.2: Participant characteristics. Patients were assessed during the OFF state. There were no significant differences between patients and controls, or between freezers and non-freezers.

	Patients	**Freezers**	**Non-freezers**	**Controls**	**Group differences**
N	20	9	11	9	-
Age	63.3 (8.35)	61.27 (4.84)	64.97 (10.34)	64.67 (5.24)	0.33
Women (%)	30	11	46	22	0.69
Disease duration (years)	5.21 (3.11)	6.81 (3.77)	4.05 (2)	-	0.18
H&Y stage (1 |2|3)	3 | 15 | 3	1 | 6 | 3	2 | 9 | 0	-	0.27
UPDRS III	27.55 (10.44)	31.33 (12.05)	24.45 (8.20)	-	0.65[†]
Left clinical asymmetry (%)	65	44	82	-	0.08
Clinical asymmetry score	6.3 (3.9)	7.4 (4.4)	5.7 (3.5)	-	0.35
FAB	16 (2.46)	15.44 (2.07)	15.64 (2.84)	-	0.99
NFoG-Q (max 24)	-	12.78 (3.99)	0 (0)	-	<0.0001

Data reflect means (standard deviation between brackets). N; number of subjects, NS; not significant, UPDRS; Unified Parkinson 's Disease Rating Scale, L: Left side most affected H&Y; Hoehn & Yahr, FAB; Frontal Assessment Battery. NFoG-Q; new freezing of gait questionnaire.

[†]Mann-Whitney U test

Table 5.3: Comparison of clinical outcome measures between patients with (ASYM) and without (SYM) asymmetrical weight bearing or asymmetric balance control, based on the 99% CI of weight bearing, the ankle joint or the hip joint contributions of the healthy controls. There were no significant differences in clinical outcome measures between patients with and without asymmetrical weight bearing or balance control.

	Weight bearing			**Ankle joint**			**Hip joint**		
	ASYMWB	**SYMWB**	***p***	**ASYMAnk**	**SYMAnk**	***p***	**ASYMHip**	**SYMHip**	***p***
N	14	6		15	5		16	4	
Age (yrs)	63.79 (8.98)	62.5 (6.97)	0.74	63.9 (8)	61.8 (9.9)	0.36	63.63 (8.9)	62.5 (5.8)	0.84
Women (%)	36	17	0.38~	20	60	0.09~	33	50	0.33~
Dominant leg (% left)	50	33	0.27~	47	40	0.78~	50	25	0.11~
Disease duration (yrs)	5.29 (3.45)	4.17 (2.8)	0.26	5.2 (2.5)	5.8 (5.2)	0.83	4.25 (2.2)	7.75 (5.5)	0.25
Freezers (%)	50	33	0.49~	47	40	0.79~	38	75	0.18~
H&Y (1 | 2 | 3)	2 | 11 | 1	1 | 4 | 1	0.43~	2 | 11 | 2	1 | 4 | 0	0.67~	2 | 12 | 2	1 | 3 | 0	0.54~
MDS-UPDRS III	31.71 (9.14)	17.83 (5.91)	0.004	29 (10.4)	23 (10.3)	0.36	28.81 (10.5)	22.5 (9.95)	0.27
PIGD	3.57 (1.99)	1.5 (1.76)	0.02	2.93 (1.8)	3 (3.2)	0.72	3.06 (1.69)	2.5 (3.7)	0.25
Prior falls (% with falls)	50	20	0.16~	40	20	0.69~	50	0	0.07~
Fear of falling	4.93 (4.55)	3.17 (3.13)	0.43	3.73 (2.82)	6.4 (6.9)	0.79	4.06 (3.6)	5.75 (6.55)	0.89
TMT (m/s)	1.21 (0.22)	1.29 (0.94)	0.32	1.24 (0.2)	1.22 (0.18)	0.82	1.23 (0.2)	1.21 (0.2)	0.93
TUG (s)	11.15 (2.83)	9.25 (1.93)	0.21	11.05 (2.85)	9.19 (1.65)	0.19	11.07 (2.73)	8.67 (1.57)	0.05

Data reflect means with the standard deviation (between brackets). N, number of subjects, UPDRS Unified Parkinson 's Disease Rating Scale; H&Y; Hoehn & Yahr; PIGD; Postural Instability and Gait Difficulty; TMT; Ten Meter walk Test, TUG; Timed-Up-and-go-Test; ASYM = asymmetrical patients. SYM = symmetrical patients. Due the small sample we used non-parametric tests (Mann Whitney U test) or $\chi 2$ tests indicated with (~).The significance level reduced 0.005 due to Bonferoni correction.

Furthermore, in most cases the most affected side as determined clinically (the difference between left and right UPDRS scores) coincided with the balance control asymmetry as determined with our balance experiment and analysis methods (see Figure 5.3). However, there were no significant correlations between clinical asymmetry and balance asymmetry (WB, $R^2 = 0.24$, $p = 0.32$; DBC_{Ank}: $R^2 = 0.21$, $p = 0.37$ and DBC_{Hip}: $R^2 = 0.08$, p = 0.75).

Clinical comparison between PDSYM and PDASYM

When considering weight bearing, 14 of the 20 patients were outside the normative values. This number increased to 15 when assessing balance control asymmetries at the ankle and to 16 at the hip joint. Subsequently, the clinical characteristics of the symmetrical patients (PDSYM) were compared to the asymmetrical patients (PDASYM) patients based on the normative values of the weight bearing, and the balance control contribution of the ankle and hip joint (Table 5.3). In general, patients in the PDASYM group were slightly older and were more likely to be men (except for WB). UPDRS scores, prior falls, fear of falling, walking speed and turn speed did not significantly differ between both groups. Also, the proportion of freezers was comparable in the PDASYM and PDSYM groups.

Comparison of balance asymmetries between freezers and non-freezers

We also compared absolute weight bearing and balance control asymmetries between freezers and non-freezers. Freezers did not have a more asymmetric weight distribution (mean: 0.07, std: 0.04) compared to non-freezers (mean: 0.07, std: 0.05; $t_{(18)} = -0.20$, $p = 0.85$). The mean absolute joint asymmetry was slightly smaller for freezers (DBC_{Ank}: 0.12, std: 0.09; DBC_{Hip}: 0.09, std: 0.07) than for non-freezers (DBC_{Ank}: 0.09, std: 0.07; DBC_{Hip}: 0.13, std: 0.06). However, freezers did not control their balance more or less asymmetrically than non-freezers (DBC_{Ank}; $t_{(18)} = -1.18$, $p = 0.25$, DBC_{Hip}; $t_{(18)} = -1.51$, $p = 0.15$).

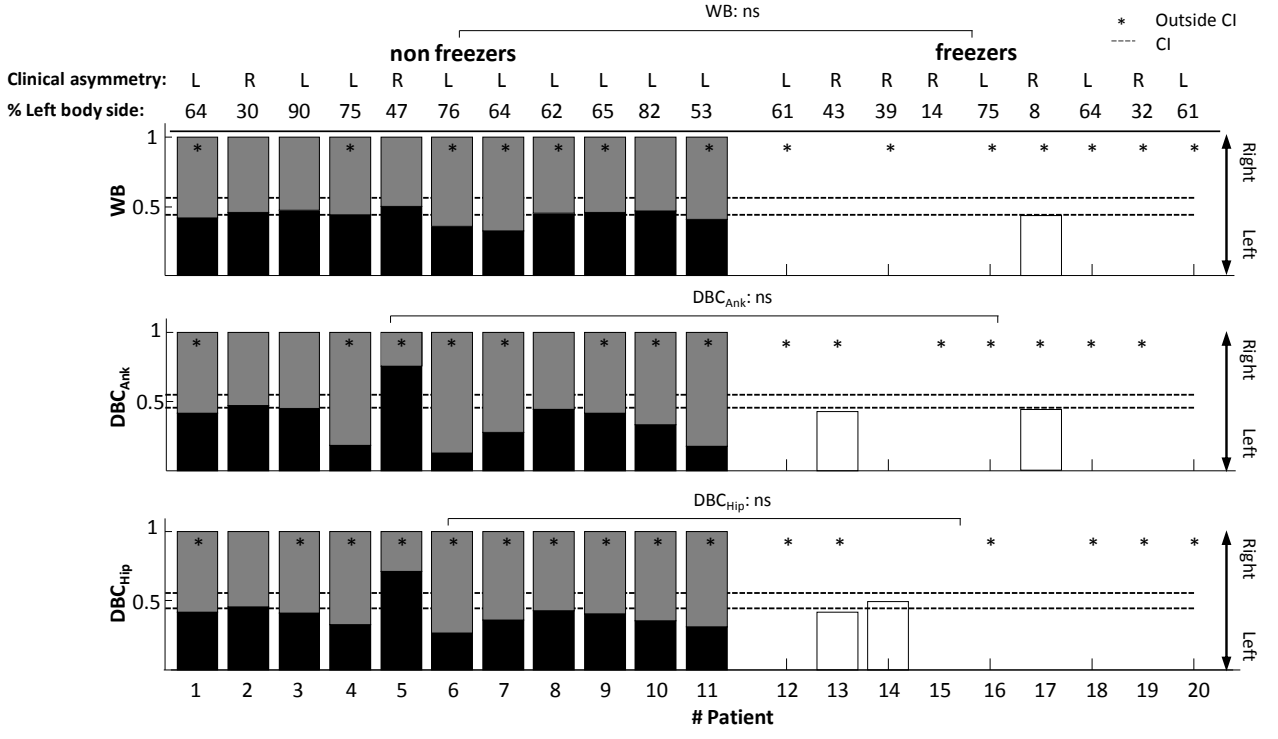

Figure 5.3: Clinical asymmetry, weight bearing and balance control contribution of the left (lower bar) and right leg (upper bar) of the individual PD patients. The absolute value and the most affected side of the clinical asymmetry is shown above the bar graphs. The upper panel indicate the dynamical weight bearing (DWB), the middle panel the dynamic balance contribution of the ankle joint (DBC_{Ank}) and the lower panel is of the hip joint (DBC_{Hip}). The group is separated in non-freezers (the first 11 patients, indicated by the solid bars) and freezers (patient 12 through 20, indicated by the dashed bars). There were no significant differences in asymmetry of WB, DBC_{Ank} nor DBC_{Hip} between non-freezers and freezers. The dashed line indicate the 99% confidence intervals of the healthy controls for the WB , DBC_{Ank} and DBC_{Hip}. The asterisk (*) denotes balance contributions outside the respective confidence intervals. For WB, 14 patients were outside the 99% CI, this number increased to 15 considering DBC_{Ank} and to 16 for DBC_{Hip}. ns = not significant. The clinically most affected side coincided in most cases with weight bearing and balance control asymmetry. However, there were no significant correlations between clinical asymmetry and balance asymmetry (WB, p = 0.32; DBC_{Ank}, p = 0.37 and DBC_{Hip}, p = 0.75).

Relationship between weight bearing and balance control

In healthy controls, there is a linear relationship between weight bearing and balance control. In other words, when healthy controls put more weight on one leg, they also use that leg more to produce corrective torques, i.e., they control their balance more with that leg (van Asseldonk *et al.,* 2006). This is reflected by a one-to-one relationship between weight bearing and balance control in healthy controls.

We investigated this relationship by determining the linear regression between DBC_{Ank} and WB of the left leg for PD patients, and separately for freezers and non-freezers (Figure 5.4). We found a significant linear regression in all PD patients (R^2 =0.41; p =0.002). Freezers had a different relationship between weight bearing and balance control compared to non-freezers ($F_{(2,16)}$ = 5.96, p = 0.01). Specifically, in non-freezers this relationship was significant (R^2 = 0.48; p = 0.02), contrary to the freezers where it was not significant (R^2 = 0.28; p = 0.15). Similar results were obtained when calculating linear regression between DBC_{Hip} and WB. This means that the (healthy) coupling between weight bearing and balance control is less pronounced in freezers.

One could argue that the difference in the coupling between weight bearing and balance control between freezers and non-freezers is due to the fact that freezers were more severely affected and had a larger variability (see Table 5.1). Further inspection of the data showed that one of the freezers had a high UPDRS score (in fact this patients' UPDRS score can be considered an outlier) which increased the variability of the freezers UPDRS scores. Excluding this patient from the analysis resulted in different UPDRS scores for the freezers (mean: 28.13; SD: 7.8), but did not alter the main findings of this paper. That is, without this patient there were still no significant differences between freezers and non-freezers for clinical scores. Also, freezers did not have larger asymmetries in balance control compared to non-freezers. The coupling between weight bearing and balance control remained non-significant in freezers (R^2 = 0.3, p = 0.16) and the regression lines of freezers and non-freezers were still significantly different from each other (p = 0.02). Note that the differences and variance between freezers and non-freezers are comparable to other studies that used a similar experimental design (Nanhoe-Mahabier *et al.*, 2011; Snijders *et al.*, 2011).

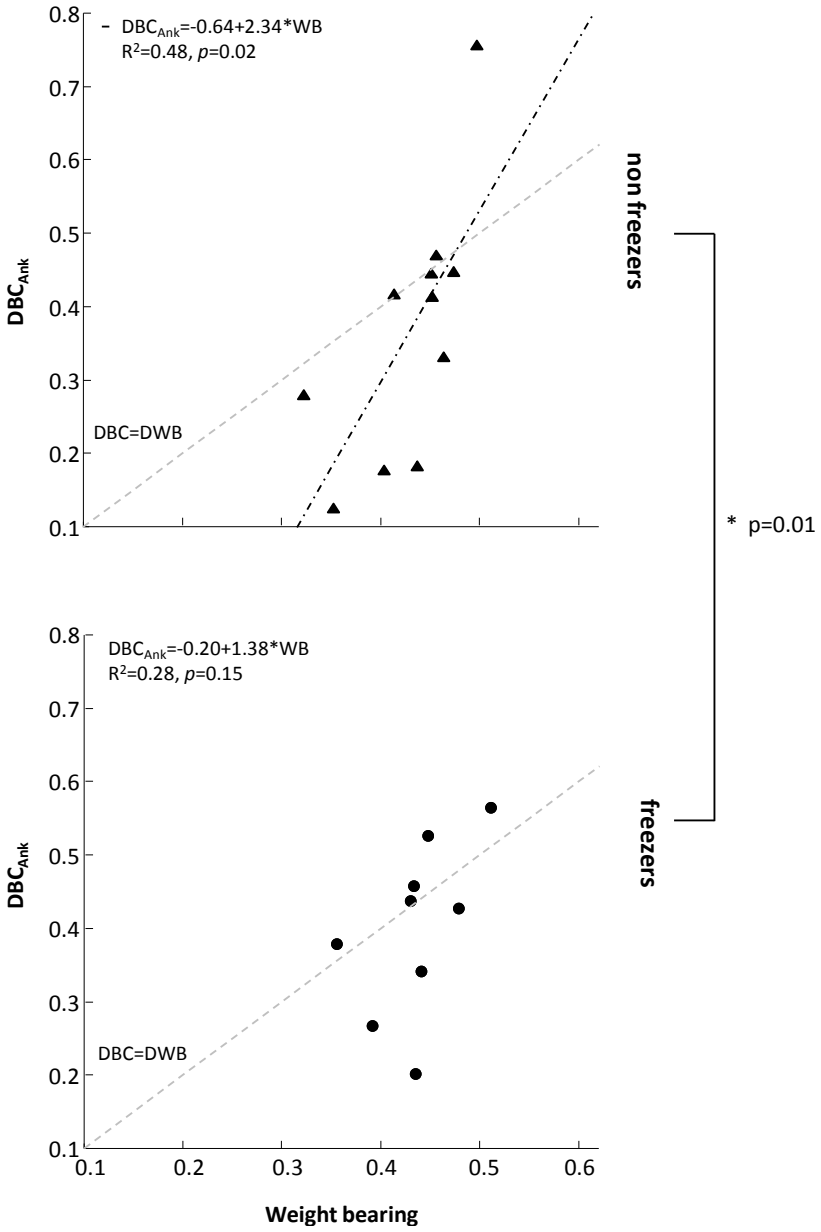

*Figure 5.4: Dynamic balance contribution of the ankle (DBC_{Ank}) versus weight bearing of PD patients, shown separately for non-freezers (left panel; triangles) and freezers (right panel; circles). The healthy one-to-one coupling (DBC = DBW) is indicated by the grey dashed line in both panels. The linear regression line between weight bearing and balance control for the non-freezers is indicated by dotted line. There was a significant difference between regression lines of freezers and non-freezers (p = 0.01). Freezers showed a non-significant relationship between weight bearing and balance control (R^2 = 0.28, p = 0.15), whereas non-freezers showed a significant relationship (R^2 = 0.48, p = 0.02). The * indicates a significant difference between the regression lines of the non-freezers and freezers.*

Discussion

The main findings of this study were that most PD patients in our sample showed asymmetries in either weight bearing or in balance control. These balance asymmetries were not related to FoG or other clinical outcomes. However, the normal coupling between weight bearing and balance control was not significant in freezers, but preserved in non-freezers.

Balance control is asymmetrical in patients with Parkinson's disease

PD patients used one leg more than the other leg to control their balance. When considering the ankle joint, 15 of the 20 PD patients were outside the normative values. This proportion of patients with asymmetrical balance increased to 16 when separately considering the hip joint. Balance asymmetries in PD patients have been shown before (Geurts *et al.*, 2011; Rocchi *et al.*, 2002; van der Kooij *et al.*, 2007b), but the present study is the first to investigate balance control asymmetries in a large group of patients, tested OFF medication, and by applying continuous perturbations in combination with a well-defined model of balance control (Fitzpatrick *et al.*, 1996; Peterka, 2003; van Asseldonk *et al.*, 2006). As balance control is a closed-loop system, perturbations are necessary to disentangle the control actions from the body mechanics (van der Kooij *et al.,* 2005b), in this way balance control and weight bearing asymmetries can be separated.

One prior study reported that four out of 17 PD patients (24%) showed asymmetrical postural control during quiet stance (Geurts *et al.,* 2011). In the present study about 75% of patients showed asymmetrical balance control. There are various explanations for this difference in proportion of asymmetrical balance. First, patients in the study of Geurts and colleagues were assessed during quiet unperturbed stance, whereas we perturbed the patients' balance. The perturbations could have stimulated the use of anticipatory strategies, such as unloading of the stepping leg to facilitate a compensatory step. However, we did control for this by assessing the balance asymmetries of patients during quiet stance (data not shown), and this analysis yielded similar results compared to the dynamic condition reported here. Second, patients were tested ON medication in the study by Geurts and colleagues, whereas we assessed patients OFF medication. The effect of dopaminergic medication on postural control is difficult to predict, as some elements may improve, while others are resistant to medication or even worsen in the ON state (Beckley *et al.*, 1995; Bloem *et al.*, 2008; Burleigh-Jacobs *et al.*, 1997). Indeed, one other study reported that levodopa increased balance asymmetry (Rocchi *et al.,* 2002), perhaps because of dyskinesia's in two of the six patients during the ON phase. None of the patients in our study showed any discernible dyskinesia's and the CoP traces did not show any random weight shifting. Taken together, the present results and those of Geurts et al. (2011) suggest that depletion of levodopa increases postural asymmetry in patients with PD.

Balance control asymmetries are not related to freezing of gait

Our study confirms that asymmetries in weight bearing or balance control are not necessarily present in each individual patient with PD (Geurts *et al.,* 2011). Our primary interest was to examine whether the presence or severity of balance asymmetries might relate to FoG. This question was driven by the notion that for gait, asymmetries are related to FoG in PD (Danoudis *et al.*, 2012; Fasano *et al.*, 2011; Plotnik *et al.*, 2005; Plotnik *et al.*, 2008). However, our hypothesis was not confirmed: (a) freezers did not have greater asymmetries in balance control than non-freezers; and (b) freezers were not overrepresented in the group of patients with balance asymmetries. This suggests that motor asymmetries, and specifically corrective balance control asymmetries in the sagittal plane, are not related to FoG.

Recent work is actually in accordance with our findings. That is, two recent studies found no differences in asymmetries during gait between freezers and non-freezers (Frazzitta *et al.,* 2012; Nanhoe-Mahabier *et al.,* 2011). Also, when systematically controlling for step length, no differences in gait asymmetry were found between freezers and non-freezers during the condition were most freezing episodes occurred (Danoudis *et al.,* 2012). In addition, freezing episodes were equally common during turning towards either the most or least affected leg (Spildooren *et al.,* 2012), again suggesting that motor asymmetry does not play a major role for FoG. Taken together, we feel that other pathophysiological explanations seem more likely, in particular the hypothesis that FoG results from an abnormal *coupling* of balance with gait (Nutt *et al.,* 2011), rather than absolute asymmetries in postural control that were addressed here.

Coupling between weight bearing and balance control is disturbed in freezers

Our results indicate that a coupling between weight bearing and balance control is preserved in PD patients who are non-freezers, although not in a one-to-one fashion as is normally seen in healthy controls (van Asseldonk *et al.,* 2006). In contrast, this coupling was even less robust in freezers, and in fact significantly less than in non-freezers. We want to stress that we have only investigated the relationship on a group level and future experiments should further investigate this notion in individual patients (see also 'Future studies').

There are no other studies that explicitly investigated this relationship. However, one study found that freezers require *multiple* medio-lateral weight shifts (i.e., anticipatory postural adjustments; APAs) towards the stance leg) before taking a step (Jacobs *et al.,* 2009). In contrast, healthy subjects and non-freezers generate only a *single* lateral weight shift. The authors suggested that these multiple APAs in freezers reflected an inability to couple a normal APA to the stepping motor pattern. Our results seem to extend these findings, suggesting that it is not merely the coupling between weight bearing and the

stepping motor pattern that is abnormal, but rather that weight bearing and balance control in general are not normally coupled in freezers, also during feet-in-place responses. This abnormal coupling between weight bearing and balance control could cause FoG episodes: the patient wants to lift the foot, but is unable to automatically shift the body weight towards the stance leg, or conversely the patient can shift the weight, but the balance control is not following, causing the characteristic feeling of being 'glued' to the floor.

Limitations

We determined the normative values based on the results of only nine healthy controls, which is a relatively small group. However, the postural responses of this control group were very homogeneous, as reflected by the small standard deviations and they regulated their balance very symmetrically. Therefore, even small balance asymmetries in patients placed them outside the normative values. Consequently, both PD patients with a relatively mild asymmetry and patients with severe asymmetry were classified as being abnormal. In addition, based on prior work (Geurts *et al.,* 2011), we expected to find 50% patients with asymmetrical balance control, but instead we found that was balance was asymmetric in 75% of our sample; this decreased the statistical power for the comparisons between the symmetrical patients and asymmetrical patients.

We included nine freezers (defined as patients who reported the characteristic FOG episodes), but only three of these freezers experienced a FOG episode during the neurological assessments. However, we are confident that the other patients were correctly classified as freezers, as they all reported the typical FoG events during history taking and the scores on the NFOG-Q (including a video with FoG) were high in these patients. FoG is difficult to elicit in an experimental setting, so asking about FoG and using validated questionnaires is often a better indicator for the presence and severity of this phenomenon (Nutt *et al.,* 2011). Furthermore, the results of the relationship between weight bearing and balance control need to be interpreted with care, as we compared relatively small groups and the differences were not that large.

Future perspectives

Future studies should focus on investigating the underlying pathophysiology of balance control asymmetries and the coupling between weight bearing and balance control. What causes balance control asymmetries? Are these due to asymmetries in rigidity, or is it perhaps a lateralized proprioceptive problem which has been suggested to play a role in Pisa syndrome, another example of a postural asymmetry (Doherty *et al.,* 2011)? In addition, it has been shown that PD patients have asymmetries in axial kinesthesia (Wright *et al.,* 2010) and that levodopa – surprisingly- worsens this. The role of proprioceptive information could be investigated by assessing muscle properties and sensory reweighting

capacities of each leg separately (Pasma *et al.,* 2012). Also, the effect of levodopa on sensory integration and balance control asymmetries in general could be tested by assessing patients ON and OFF medication. Furthermore, to study the relationship between weight bearing and balance control in both freezers and non-freezers, patients should be instructed to put a predefined amount of weight on one leg (e.g., 30, 40 and 50% of body weight) and subsequently the amount of control exerted with (Anker *et al.,* 2008) or the quality of a protective step of that leg should be assessed. Moreover, group sizes should be increased to show the robustness of our findings.

In addition, this study suggest that the coupling between weight bearing and balance control is disturbed in freezers, which could possibly hamper APAs to unload the stepping leg. This weight shift is mainly caused by movements in the medio-lateral plane and therefore it would interesting to perturb patients' balance in the frontal plane. These types of experiments should further clarify the pathophysiology and clinical relevance of postural asymmetries in PD.

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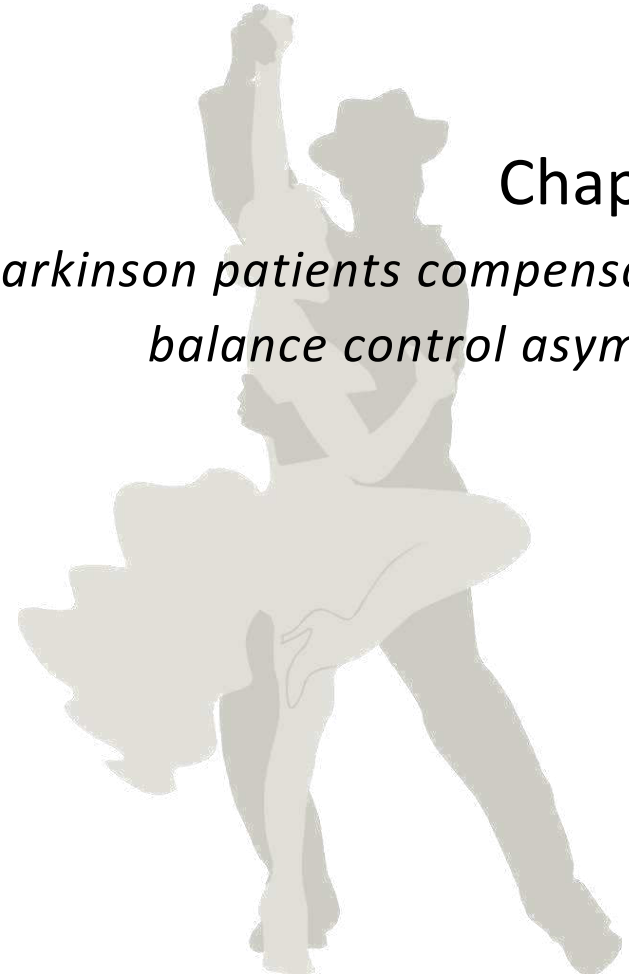

Chapter 6

Parkinson patients compensate for balance control asymmetry

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Parkinson patients compensate for balance control asymmetry
Submitted

Abstract

Parkinson's disease (PD) patients have an increased risk of falling, especially in later disease stages. However, subtle balance impairments can be detected in newly diagnosed patients. One feature of impaired balance control in PD patients is asymmetry: one leg produces more corrective force than the other. We hypothesize that in mild to moderately affected PD patients, the least impaired leg can compensate for the more impaired leg.

20 PD patients (six women; Hoehn and Yahr range: 1-3) and seven healthy matched controls (two women) participated. Clinical asymmetry was determined by the difference between the left and right body side scores on the Unified Parkinson's Disease Rating Scale. Balance was perturbed using two independent continuous multi-sine perturbations in the forward-backward direction. Subsequently, we applied dedicated multivariate closed-loop system identification, that determined the spectral estimate of the stabilizing mechanisms; one for each leg separately.

The total balance control behaviour was similar in PD patients and healthy controls at the ankle. However, stiffness at the hip was increased in PD patients. Healthy subjects controlled their balance symmetrically, but in PD patients the balance control contribution of the least affected leg was higher, whereas the most affected leg contributed less than the matched leg of healthy controls.

Our results suggest that PD patients compensate for balance control asymmetries by increasing the control of their least affected leg. This compensation is successful at the ankle, but is accompanied by an increased stiffness at the hip and it could paradoxically increase postural instability in PD patients..

Introduction

Patients with Parkinson's disease (PD) have an increased risk of falling, especially in later disease stages (Pickering *et al.,* 2007; Stolze *et al.,* 2004). However, subtle balance impairments, such as an increased body sway, have been detected in 'de novo' PD patients (Chastan *et al.,* 2008; Mancini *et al.,* 2011). In these earlier disease stages, actual falls are perhaps prevented because PD patients can compensate for such mild balance impairments. Indeed, functional imaging studies in PD patients during a hand task have suggested that preserved brain areas can take over the role of other brain areas that are affected by the disease process. Hence, helping to maintain normal performance on a motor task (van Nuenen *et al.,* 2012; van Nuenen *et al.,* 2009). Whether such compensation mechanisms are also at play during a postural task has not yet been investigated.

A possibility to assess postural compensation is to investigate the balance responses of each leg separately. PD is a neurodegenerative disorder that typically presents with asymmetrical motor symptoms and recent work suggests that balance control is no exception (Geurts *et al.*, 2011; Rocchi *et al.*, 2002; van der Kooij *et al.*, 2007b). Specifically, one leg produced more force than the other leg in order to help maintain balance. Patients might compensate for such asymmetries by augmenting the relative contribution of the least affected leg, as a way to compensate for e.g. increased stiffness in the most affected leg. This approach is fruitfully applied in stroke patients, who compensate for the paretic leg by increasing muscle activation in the non-paretic leg (de Haart *et al.,* 2004; Garland *et al.,* 2003; Kirker *et al.,* 2000). In stroke patients, there is ususally only one body side that is affected, wheras the other side is still intact. In contrast, in PD one side of the body is affected first, and this asymmetry is preserved throughout the disease, even when the contralateral side becomes involved later on (Djaldetti *et al.,* 2006). It is not clear whether this least affected side could compensate for the most affected side and to what extent (partially or fully). Also, it is not clear whether postural compensation might differ between the ankle and the hip joints. However, PD patients have increased postural stiffness (Grimbergen *et al.*, 2004; Kim *et al.*, 2009; Termoz *et al.*, 2008), especially at the hip (Carpenter *et al.*, 2004; Colnat-Coulbois *et al.*, 2011; Maurer *et al.*, 2003) and this might hamper compensation strategies

Based on these findings, we hypothesized that PD patients with mild to moderate impairment are able to compensate for their balance control asymmetries by increasing the balance control contribution of their least affected leg. In order to investigate how and to what extent (i.e., fully or partially) PD patients can compensate for their balance control asymmetries, and to search for differences between the ankle and hip joints, we applied multivariate closed-loop system identification techniques that separate the balance control contribution of the left and right ankle and hip joint (Boonstra *et al.,* 2013).

Methods

The methods are described in detail elsewhere (Boonstra *et al.*, 2013; Kuo *et al.*, 1998), but are shortly described below.

Participants

20 PD patients and seven healthy matched controls were included (Table 6.1). Patients were assessed in the morning, at least 12 hours after intake of their last dose of dopaminergic medication (practically defined OFF state). Disease severity was determined using the Hoehn and Yahr stages and the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz *et al.,* 2008). Clinical asymmetry was defined as a difference between the summed UPDRS scores of the left and right body side (items 3.3-3.8 and 3.15-3.17). The most affected body side was defined as the side with the highest UPDRS score. Participants were excluded with visual, vestibular, orthopaedic, psychiatric or other neurological diseases or with marked cognitive dysfunction (Mini Mental State Examination <24 or Frontal Assessment Battery <13;Cohen *et al.*, 2012; Crum *et al.*, 1993; Royall, 2001). All participants gave written informed consent prior to the experiment, which was approved by the local medical ethics committee and in accordance with the Declaration of Helsinki.

Table 6.1: Participant characteristics. Patients were tested OFF medication.

	Patients (n = 20)	**Controls (n = 7)**	**Group differences**
Age (yrs)	63.3 (8.35)	63.8 (7.97)	NS
Women (%)	30	29	NS
Disease duration (yrs)	5.21 (3.11)	-	
H&Y (1 | 2 |3)	3 | 15 | 3	-	
Total UPDRS III	27.55 (10.44)	-	
Left UPDRS III	10.95 (6.53)		
Right UPDRS III	8.45 (3.84)		

Data reflect means (standard deviation between brackets). n; number of subjects, NS; not significant, UPDRS; Unified Parkinson's Disease Rating Scale, H&Y; Hoehn & Yahr, 1: Unilateral signs, 2: Bilateral signs without balance impairments, 3: Mild to moderate involvement, physically independent, but needs assistance to recover from pull test.

Apparatus and recording

Perturbations in the forward-backward direction were applied using a computer-controlled six DoF motion platform (Caren, Motek, Amsterdam, The Netherlands) and a custom-built actuated device (called the Pusher) attached to the platform (see Figure 6.1). Body kinematics and the platform movements were measured using motion capture (Vicon Oxford Metrics, Oxford, UK) at a sample frequency of 120 Hz.

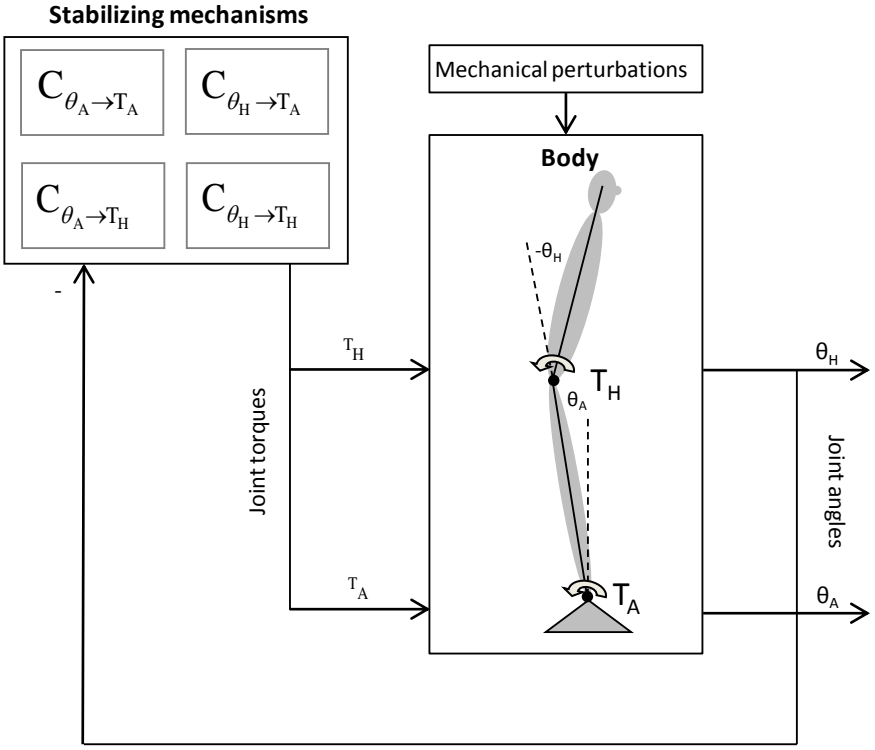

Figure 6.1: Approach to determine the stabilizing mechanisms of a Multiple-Input-Multiple-Output closed-loop balance control system. The stabilizing mechanisms represent the dynamics of the combination of active and passive feedback pathways and generate joint torques to correct for the deviation of upright stance. The direct terms ($C_{\theta_A \to T_A}$ and $C_{\theta_H \to T_H}$) represent the corrective torques of the ankle (T_A) and the hip (T_H), based on the ankle (θ_A) and hip joint (θ_H) angle. Note that movements from the lower segments will influence the movements of the upper segments due to the mechanical coupling, therefore the stabilizing mechanisms have to compensate for the mechanical coupling, which is expressed in coupling terms between ankles and hips (i.e., $C_{\theta_A \to T_H}$ and $C_{\theta_H \to T_A}$).

Reflective spherical markers were attached to the first metatarsal, calcaneus, medial malleolus, the sacrum, the manubrium and the last vertebrae of the cervical spine (C7). In addition, a cluster of three markers was attached to both anterior superior iliac spines on the pelvis. Also, markers were attached just below the lateral epicondyle and in front of

the acromion and an additional marker were attached to each foot and lower leg. Three markers were attached to the platform. Reactive forces and torques from both feet were measured with a dual forceplate (AMTI, Watertown, USA), and were sampled at 600 Hz together with the perturbation of the pusher.

Procedure

Participants were instructed to maintain their balance without moving their feet, while independent multisine platform movements and multisine force perturbations were applied simultaneously in the forward-backward direction. The perturbation signal was a multisine with a period of 34.13 s and contained power at 112 frequencies in the range of 0.06–4.25 Hz (Boonstra *et al.*, 2013; van Asseldonk *et al.*, 2006; van der Kooij *et al.*, 2007a). The average platform amplitude was 0.03 m for the healthy controls and PD patients ($t_{(25)}$ = 0.60; p = 0.53), the pusher's amplitude was 9.3 Nm for the healthy controls and 7.8 Nm for the PD patients ($t_{(25)}$ = 2.39; p = 0.02). Participants stood with eyes open and arms folded in front of their chest on the dual forceplate, strapped to the pusher and wore a safety harness to prevent falling. The harness did not constrain movements, provide support or orientation information in any way. Four trials of 180 s were recorded and if needed, the participants were allowed rest in between trials.

Data Analysis

Here we approached upright stance as a two Degree-of-Freedom (DoF) multivariate system. The human body is modeled as a double-inverted pendulum, consisting of two legs and a Head-Arms-Trunk (HAT) segment.

Joint angles and joint torques

From the recorded movement trajectories of the markers, the position of the center-of-mass (CoM) and the joint angles (i.e. ankle and hip) were estimated by custom written software (Koopman *et al.*, 1995; Koopman, 1989). From a static trial, the average distance in the sagittal plane from the ankle to the total body CoM (i.e., the length of the pendulum (l_{CoM}) was determined. Subsequently, the sway angle was calculated from l_{CoM} and the horizontal distance from the CoM to the mean position of the ankles. The applied platform perturbation was calculated based on the platform markers movement.

The kinematic and kinetic data were filtered with a Butterworth filter (4^{th} order low-pass; cut-off 8 Hz) and subsequently resampled to 120 Hz. The recorded forces and torques were corrected for the inertia and mass of the top cover of the forceplate (Preuss *et al.,* 2004). On the basis of the corrected forces and torques and the recorded body kinematics, ankle and hip joint torques of the left and right leg were calculated with inverse dynamics (Koopman *et al.,* 1995).

Covariance descriptor of multi-segmental kinematics

The kinematic coupling between the upper and lower body can be described by the four-by-four covariance matrix of the leg and hip angle (Kuo *et al.,* 1998):

$$\mathrm{Q} = \mathrm{cov}(\theta) = \frac{1}{\mathrm{n}-1}\sum_{\mathrm{i}=1}^{\mathrm{n}}(\theta_{\mathrm{i}} - \bar{\theta})(\theta_{\mathrm{i}} - \bar{\theta})^{\mathrm{T}} \tag{6.1}$$

Where θ_{i} is the i^{th} sample out of a vector containing the leg and hip angles. Q is a matrix with diagonal entries (Q_{11} and Q_{22}) equal to the individual joint variances. The off-diagonal terms (Q_{12} and Q_{21}) are related to the intersegmental kinematic coupling (i.e., covariance between joints). We calculated the average covariance matrix by first calculating the matrix per cycle (i.e., 4096 samples) for each participant and subsequently we averaged over these cycles.

Frequency response functions

To reliably identify the stabilizing mechanisms that generate ankle and hip torques based on sensory information of the joint angles, (see Figure 6.1) we applied multiple-input-multiple-output (MIMO) system identification techniques (Boonstra *et al.*, 2013; Pintelon *et al.*, 2001).

The data of each of the four trials was segmented in response periods of the perturbation signal, yielding five periods of 34.13 s per trial, resulting in a total of 16 perturbation cycles for the estimation of the stabilizing mechanisms (the first cycle was discarded). The data was Fourier transformed, averaged over the periods and the power- and cross spectral densities (PSD and CSD, respectively) were calculated. The PSDs and the CSDs were smoothed by averaging over four adjacent frequency points (Jenkins *et al.,* 1969). The stabilizing mechanisms were estimated using the joint input-joint output approach (van der Kooij *et al.*, 2005):

$$\hat{\mathrm{C}}_{\theta\mathrm{Tc}}(\mathrm{f}) = -\hat{\mathrm{G}}_{\mathrm{pTc}}(\mathrm{f})\hat{\mathrm{G}}_{\mathrm{p}\theta}^{-1}(\mathrm{f}) \tag{6.2}$$

With $\hat{\mathrm{G}}_{\mathrm{pTc}}(\mathrm{f})$ and $\hat{\mathrm{G}}_{\mathrm{p}\theta}^{-1}(\mathrm{f})$ the estimated CSD from the perturbations to the corrective torques and from the perturbations to the joint angles of one body side. Note that C is a two-by-two matrix, see also Figure 1, p is a vector with the two disturbances, $\theta_{(f)}$ is a vector with ankle and hip joint angles, and $T_c(f)$ is a vector with ankle and hip joint torques for each frequency *f*, expressed as Fourier coefficients.

The FRFs were normalized for the gravitational stiffness (*mgl; m:* total body mass, *l*: CoM height and *g:* gravitational constant), because the exerted corrective torque depends on gravity. The average FRF over all participants was obtained by taking the mean over the individual normalized FRFs. Note that, as we used a dual forceplate, the obtained Fourier coefficients of the left and right FRFs were added to obtain the total FRFs.

Table 6.2: Average root mean square (RMS) values of joint angles and joint torque responses of healthy controls and Parkinson's disease patients.

	Healthy controls		PD patients		Group difference
	mean	**std**	**mean**	**std**	**p**
Ankle angle (deg)	0.829	0.365	0.692	0.004	<0.001*
Hip angle (deg)	1.042	0.689	0.695	0.006	<0.001*
Sway angle (deg)	0.816	0.341	0.713	0.129	<0.001*
Ankle torque (total; Nm)	15.850	6.974	10.721	2.682	<0.001*
Ankle torque (left; Nm)	7.925	3.487	5.361	1.881	<0.001*
Ankle torque (right; Nm)	8.066	4.650	7.528	1.796	0.092
Hip torque (total; Nm)	13.785	4.912	9.748	2.508	<0.001*
Hip torque (left; Nm)	6.892	2.456	4.874	1.950	<0.001*
Hip torque (right; Nm)	7.216	3.903	7.230	1.791	0.960

*Significant difference

Balance contribution of the left and right body side

The relative contribution of the left and right leg to the total amount of generated corrective torque to resist the perturbations was determined, by calculating the contribution of the gain and phase of each MIMO FRF to the gain and phase of the total MIMO FRF per frequency (Boonstra *et al.*, 2013; van Asseldonk *et al.*, 2006). The most contributing leg was defined as the leg with the highest balance control contribution.

Statistics

For statistical analysis the gain of each MIMO FRF was log transformed to make the data normally distributed. Subsequently, the gains were averaged within three frequency bands (<1 Hz, 1-2.5 Hz and 2.6-4.2 Hz) and compared with either a paired t-test (within groups) for each frequency band or a one-way ANOVA (between groups) with group (i.e., healthy control or PD patient) as a factor.

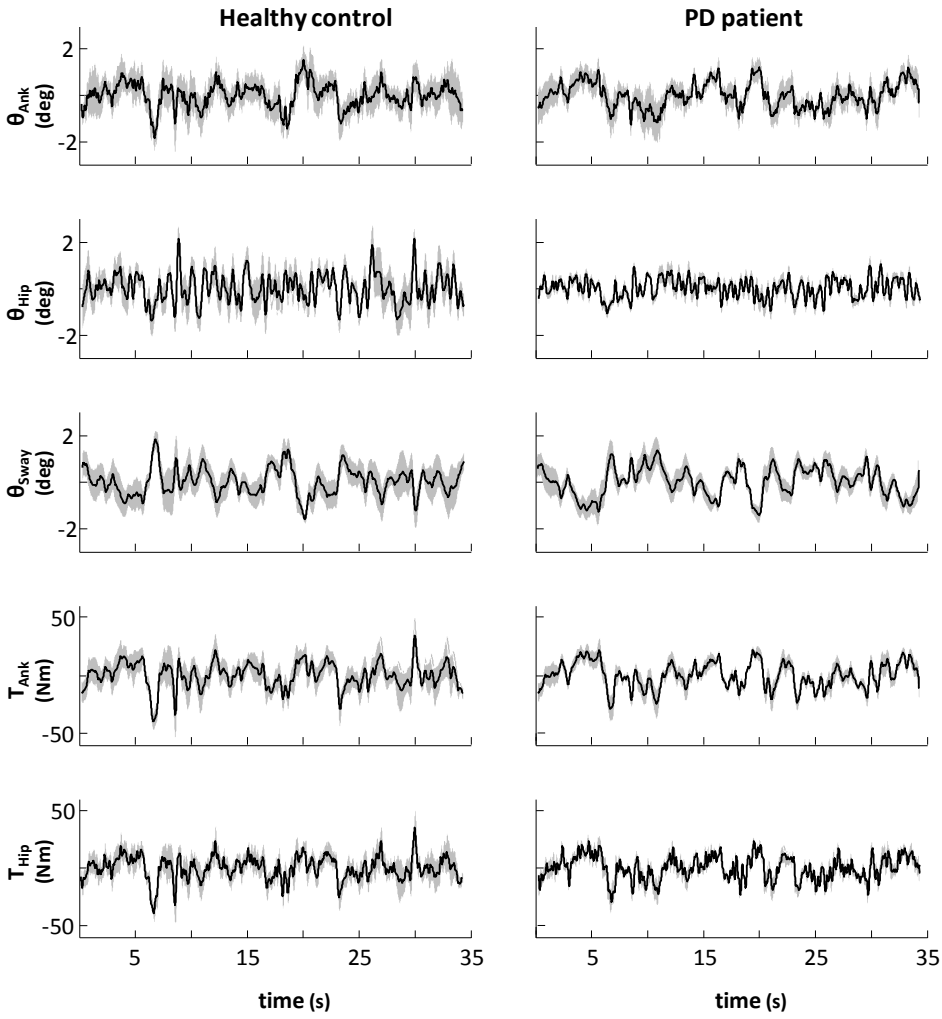

Figure 6.2: Joint angles, sway angle and joint torques in response to the applied perturbations of a representative healthy control (left) and PD patient (right). The average over the eight perturbation cycles is indicated with the black line; the grey area depicts the SD. Perturbation amplitudes and phase of the perturbation cycle were the same for the healthy control and the PD patient.

Results

Both patients and controls were able to maintain their balance in the face of the applied perturbations. Furthermore, the response could be treated as linear and time-invariant, as indicated by low noise-to-signal ratio's (data not reported, see Boonstra *et al.,* 2013), justifying the application of linear time-invariant closed-loop system identification techniques (Boonstra *et al.*, 2013; van der Kooij *et al.*, 2007a).

Time series

Figure 6.2 shows the joint angles and torques of a representative healthy control and PD patient in response to the perturbations. In general, the PD patients swayed about 1% less than healthy controls ($t_{(177)}$ =2.98; p< 0.01, see Table 6.2) and this was accompanied by a smaller exerted total ankle and hip joint torque. Note that the PD patients were also perturbed with a 1% smaller amplitude compared to the healthy controls (see 'Methods'). Compared to healthy controls PD patients, on average, had smaller joint torques at the left body side compared to the right side, while healthy controls were symmetric.

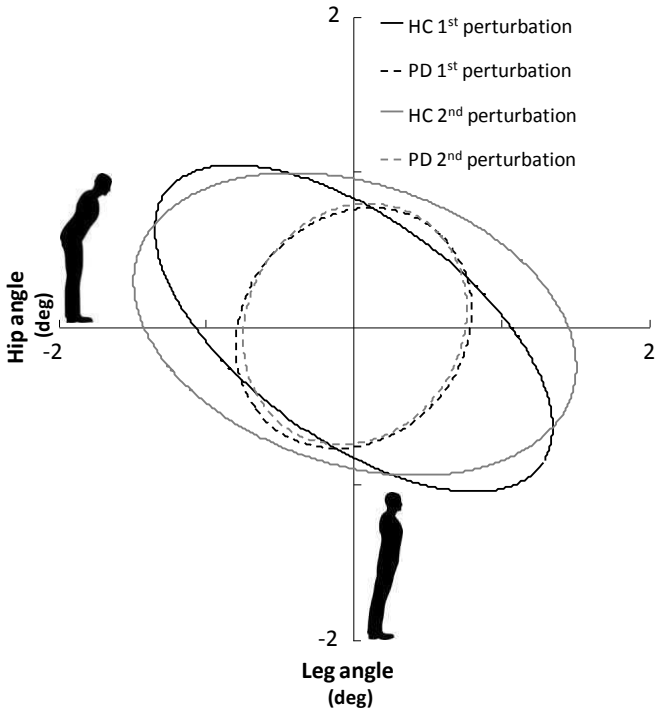

Figure 6.3 Graphical depiction of covariance descriptor values of the healthy controls (solid line) and PD patients (dashed line) between the leg and hip angle of the first and second perturbation round. The covariance matrix can be graphically represented by three measures: 1) the length of the ellipse major semi-axis is given by the square root of the first eigenvalue of Q, 2) the length of the minor semi-axis is given by the second eigenvalue and 3) the major axis orientation is given by the eigenvector associated with the largest eigenvalue and is used to calculate the orientation angle α. Hence, a negative angle indicates that a positive leg angle is accompanied by a negative hip angle and therefore it quantifies the direction of the relationship between the segment angles.
The angle of the ellipse-like shape represents how the hip and leg angle are coupled; for the healthy controls a positive leg angle is accompanied by a negative hip angle. The length and width of the ellipse represent the strength of this kinematic coupling (Kuo et al., 1998). For PD patients the kinematic coupling was weaker than for healthy controls.

Kinematic coupling of the upper and lower body

The kinematic coupling of the upper and lower body parts was calculating by the covariance between the leg and hip angle, see
Figure 6.3. In healthy controls there was a negative coupling between the leg angle and hip joint angle; a positive leg angle is accompanied by a negative hip angle, i.e. sway is kinematically minimized. In PD patients this coupling was much weaker ($t_{(410)} = -6.33$; $p < 0.001$) and both groups did not change their kinematic coupling significantly over the perturbation rounds (HC: $t_{(299)} = -0.67$; $p = 0.5$; PD: $t_{(523)} = -1.7$; $p = 0.09$).

Multiple input multiple output frequency response functions

Figure 6.4 shows the MIMO FRFs of stabilizing mechanisms of the healthy controls and PD patients, averaged over the populations. In general, the gain of the stabilizing mechanism of the ankle increased with frequency until 2 Hz; above 2 Hz the gain decreased. The gain of the hip stabilizing mechanism was flat until 0.7 Hz, decreased until 2 Hz, and subsequently increased. The stabilizing mechanism from hip to ankle remained roughly constant over the frequency range, whereas the stabilizing mechanism from ankle to hip increased above 2 Hz. The phase of all the stabilizing mechanisms decreased with frequency (i.e. a phase lag), indicating the presence of a neural time delay.

There were no significant differences in FRF gain between healthy controls and PD patients at the ankle joint, or at the cross-coupling from hip joint angle to ankle torque. However, in the cross-coupling from ankle angle to hip torque, there was a trend ($F_{(26)} = 3.85$; $p = 0.06$) toward a higher gain at the lower frequencies for the PD patients. Furthermore, the FRF gain of the hip below 1 Hz was significantly higher in PD patients compared to healthy controls ($F_{(26)} = 8.15$; $p = 0.009$), indicating a higher hip stiffness in PD patients.

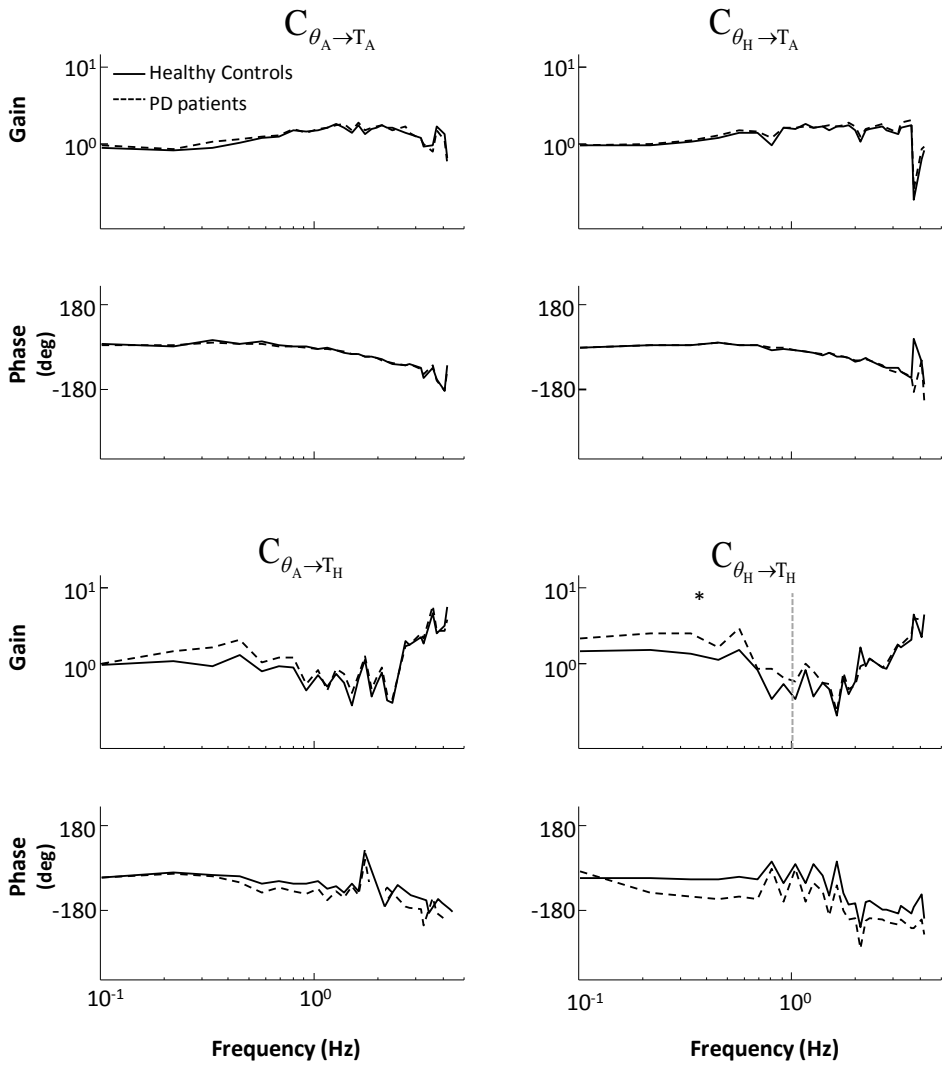

Figure 6.4: Multi segmental frequency response functions of the stabilizing mechanisms. There were no differences between the healthy controls and the PD patients for the $C_{\theta_A \to T_A}$, $C_{\theta_H \to T_A}$ *and* $C_{\theta_A \to T_H}$ *FRFs. For the* $C_{\theta_H \to T_H}$ *FRF there was a significant difference of the gain in the lower frequency band, indicating a higher hip stiffness in PD patients. The healthy controls are depicted with the solid line, the PD patients with the dashed line. The * indicates a significant difference.*

Balance control contribution of the most and least contributing leg

PD patients exerted different amounts of torque with the left and right leg, i.e., there were asymmetries in balance, see Table 6.2. Figure 6.5 indicates the balance control contribution of the right leg of the PD patients, calculated on the basis of the MIMO FRFs. Most patients controlled their balance asymmetrically, hence, one leg was contributing

more (i.e., the most contributing leg) to upright stabilization than the other leg ($t_{(19)}$<-2.19; p< 0.01; in all frequency bands). The asymmetries were evident at both the ankle and the hip joint and in the joint interaction terms. In contrast, healthy controls controlled their balance symmetrically with no differences between the left and right leg ($t_{(6)}$<0.71; p > 0.21).

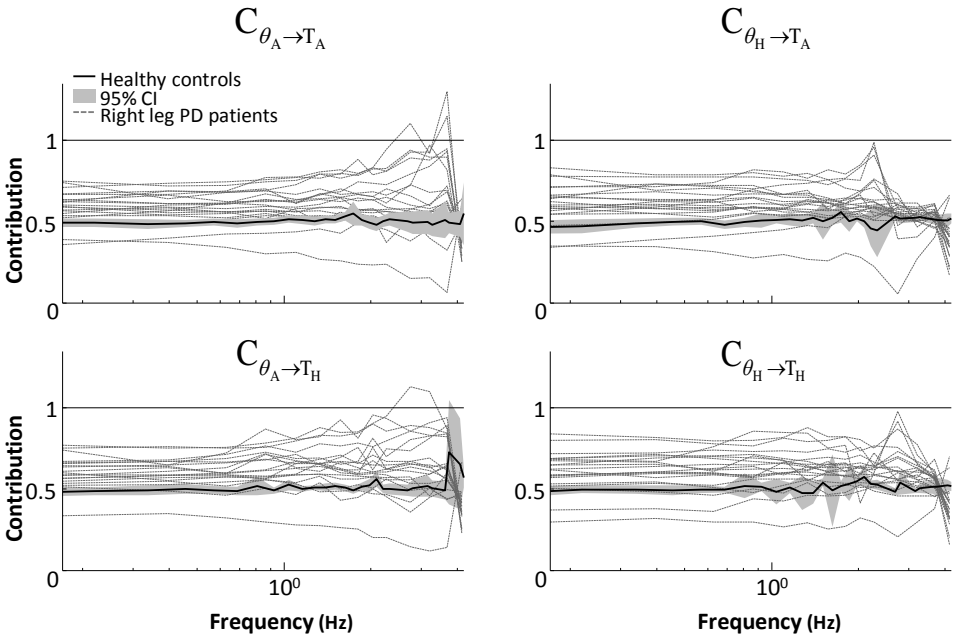

Figure 6.5: Balance control contribution of the right leg of the healthy controls (average depicted by the solid black line with in grey the 95% confidence interval) and of the individual PD patients (indicated by the dashed grey lines). Healthy controls controlled their balance symmetrically, whereas in PD patients one leg contributed more to upright stabilization than the other leg.

Figure 6.6 depicts the average FRFs of the most and least contributing leg of the PD patients together with the right leg of the healthy controls. At the ankle, the least contributing leg had a similar gain ($F_{(26)}$> 0.04; p-values > 0.20), whereas the most contributing leg had a higher gain than the right leg of the healthy controls, in the low ($F_{(26)}$> 3.16; p-values < 0.05) frequency bins. In the mid frequency bins there was a trend towards a higher gain ($F_{(26)}$ = 3.20; p-values < 0.09). At the hip joint, the least affected leg of the PD patients had a similar gain as the right leg of the healthy controls at the ($F_{(26)}$; p > 0.14). However, the most contributing leg had a higher gain than the right leg of the healthy controls and this difference was most pronounced at the lower ($F_{(26)}$ > 6.98; p < 0.01) and mid ($F_{(26)}$ > 6.64; p < 0.02) frequencies. The most contributing leg had a lower total UPDRS score (total: 7.25) compared to the least contributing leg (11.05; $t_{(19)}$= 2.54, p = 0.02), indicating that the larger gain coincided with the least affected body side. The most contributing leg also had a lower UPDRS leg score (1.85), compared to the least

contributing leg (2.55), but this difference was not significant ($t_{(19)}$= 1.61, p = 0.13). Interestingly, bear in mind that the results in Figure 6.4 depicted that the total gains of the ankle FRFs over the whole frequency were similar for PD patients and healthy controls for the all MIMO FRFs, except the FRF that related the hip angle to the hip torque.

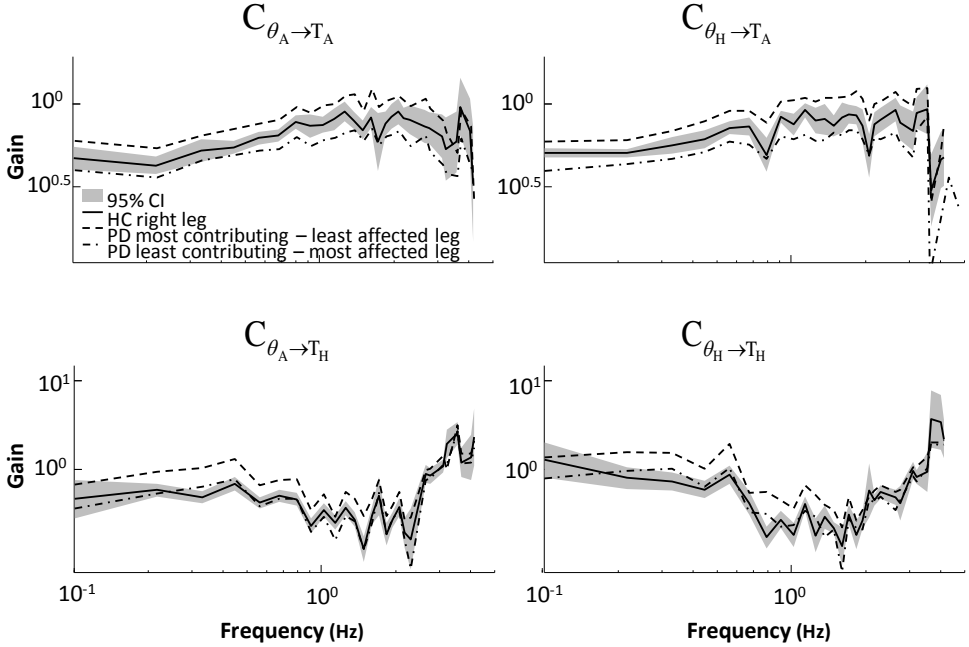

Figure 6.6: Gains of the Multiple Input Multiple Output Frequency Response Functions of the right leg of the healthy controls (average indicated by the solid black line, with 95% confidence interval in grey) and of the most (..) and least (-.) contributing leg of the PD patients. For all FRFs the most contributing leg of the PD patients had a higher gain than the least contributing leg (p< 0.001). In healthy controls there were no differences between the left and the right leg for all FRFs. For the $C_{\theta_A \to T_A}$ *and the* $C_{\theta_H \to T_A}$ *FRFs the least contributed had a smaller gain than the right leg of the healthy controls, whereas at the hip (*$C_{\theta_A \to T_H}$ *and* $C_{\theta_H \to T_H}$ *) the least contributing leg had a similar gains compared to the healthy controls. Note that the scale of the vertical axis of the upper panels is different that the lower panels.*

Discussion

In this study we determined the balance control responses of PD patients and controls of each leg separately, by applying mechanical perturbations in the sagittal plane. Our results demonstrate that the clinically least affected leg can compensate for balance impairments in the more affected leg. Specifically, PD patients had marked asymmetries in their balance control; the better leg contributed more to upright stabilization (even compared to controls), but the worse leg of PD patients contributed less to balance control. This compensation helped to preserve a normal motor output at the ankle; the total contribution (summed for the left and right ankle) equaled the total balance response of

controls. However, at the hip, the same compensation strategy was associated with an overall increased stiffness.

PD patients can compensate for balance control asymmetry at the ankle, but not at the hip

PD manifests itself clinically after loss of 60-80% of dopaminergic neurons (Lloyd, 1977). This latency is explained by compensatory mechanisms in the brain (Bezard *et al.*, 2003; van Nuenen *et al.*, 2009) which remain active when the disease symptoms are manifested (Helmich *et al.,* 2007). Behavioral compensatory strategies help to improve performance in the symptomatic phase of PD, as is illustrated by the well-known effects of cueing on the hypokinetic gait (Nieuwboer, 2008; Nieuwboer *et al.*, 2007; van Wegen *et al.*, 2006). Whether compensatory mechanisms are also at play to improve balance control in PD has thus far received very little attention.

In this paper we investigated one specific form of postural compensation, namely whether one leg can compensate for impaired balance control of the other leg, by determining the balance control actions of each leg separately. Our results showed that most patients controlled their balance asymmetrically, as previously reported (Boonstra *et al.*, submitted; Geurts *et al.*, 2011; van der Kooij *et al.*, 2007b) and that these asymmetries were also evident in multisegmental balance control. At the ankle, the gain of the most affected leg was lower (but not significantly) than the gain of the right leg of healthy controls over the whole frequency range, whereas the gain of the least affected leg was significantly higher than that of healthy controls. Added together, the dynamics of the most and least affected leg were similar to that of healthy controls, suggesting a good compensation for the balance control asymmetry at the ankle. Contrary to this, the gain of the most affected leg at the hip was similar to that of healthy controls, whereas the gain of the least affected leg was higher, especially at the low frequencies, resulting in an increased total hip stiffness. The UPDRS scores of the most contributing leg (i.e., with the highest gain) were lower than of the least contributing leg, suggesting that the least impaired body side compensated for the most impaired side by increasing the exerted torque.

The ability to compensate for an impaired body side has been shown previously in stroke survivors (Garland *et al.,* 2003; Kirker *et al.,* 2000); these patients increased their muscle activity at the non-paretic side. Stroke patients generally have only one body side that is impaired, whereas in PD patients both body sides become involved, although the initial side typically remains the most affected (Djaldetti *et al.,* 2006; Hughes *et al.,* 1992). Our results suggest that the least impaired side in PD patients is able to partly compensate for balance impairments of the most impaired side. This could possibly explain why we did not find any differences in previous self-reported falls between patients with and without asymmetrical balance control (unpublished results).

We can only speculate why the compensation strategy was different at the ankle and the hip. It could be that the common neural input to the least impaired side was upregulated to compensate for at the ankle. Because of the already increased hip balance contribution, this resulted in increased overall hip joint stiffness.

Increasing the corrective forces at one body side effectively aggravates balance asymmetries and therefore the observed asymmetries are most likely due to the balance impairment (asymmetry) plus the compensation strategy. From this perspective, asymmetric balance control might paradoxically be a good phenomenon in certain stages of the disease, possibly preventing falls. Results of another recent study actually point in this direction: in primates asymmetry between brain hemispheres improved clinical signs (Blesa *et al.,* 2011).

Balance control is disturbed in PD patients due to increased hip stiffness

Our results indicated that the total gain at the lower frequencies for the hip angle to hip torque was significantly higher in PD patients, compared to healthy controls. In this paper we applied system identification techniques and performed the analysis in the frequency domain, which has the advantage that it can assess the dynamics over a broad frequency range where the low frequencies (<1 Hz) are dominated by stiffness. Hence, it can be concluded that the PD patients in our study had an increased total hip stiffness.

Increased hip stiffness in PD patients has been reported before in mild to moderately affected patients (Carpenter *et al.*, 2004; Kim *et al.*, 2009; Termoz *et al.*, 2008). Our results confirm these findings and this shows that this finding is robust across applied methodologies. For example, (Carpenter *et al.,* 2004) used platform rotations, whereas (Kim *et al.,* 2009) used platform translations. Increased ankle stiffness in PD has also been proposed (Carpenter *et al.,* 2004; Lauk *et al.,* 1999), but there also have been reports of decreased ankle stiffness (Colnat-Coulbois *et al.*, 2011; Kim *et al.*, 2009). Our results showed that the total ankle stiffness in PD patients was similar to healthy controls. We found no evidence for an altered or increased intersegmental coordination. That is, the cross terms of the FRFs were not significantly different from controls in PD patients. In contrast, an increased intersegmental coupling has been proposed by Maurer and colleagues (Maurer *et al.,* 2003), but they studied a much smaller group of only eight patients that differed markedly from the patients in our sample: their patients were more severely affected and had been treated with STN-DBS.

Previous mentioned studies used either no external balance perturbations (Termoz *et al.,* 2008), or only one perturbation (Carpenter *et al.*, 2004; Colnat-Coulbois *et al.*, 2011; Kim *et al.*, 2009; Maurer *et al.*, 2003). However, to determine multisegmental balance control mechanisms, it may be better to use two perturbations (Boonstra *et al.,* 2013). This is the first study to apply such combined perturbations, coupled with system identification methods, to investigate joint stiffness and intersegmental coupling during

upright stance. This new and possibly better suited methodological approach, instead of differences in patient characteristics, could also explain why results differed from previous work, as outlined above.

Limitations

We determined the average healthy control FRFs on the postural responses of only seven healthy controls, which is a small group. However, the FRFs of this control group had a small variation, as reflected by the tight standard deviations. Furthermore, the perturbation amplitudes of PD patients were slightly smaller than of the healthy controls and this was accompanied by significantly smaller sway amplitude in PD patients. However, we assessed carefully whether the participants were able to withstand the perturbations, while keeping the feet flat on the floor, for the total of four trials. Therefore, we are confident that we perturbed each participant within the same range of their limits of stability. Finally, in order to investigate multisegmental balance control with our applied method, the patient must be able to withstand postural perturbations. This could be a potential problem in patients who have marked balance control instability, making the method less suitable for more severely impaired patients.

Future perspectives

Our results indicate that multisegmental balance control is altered in PD patients, due to an increased hip stiffness, and suggest that PD patients can partly compensate for their balance control asymmetries with their least affected leg, by increasing the exerted force. Future studies should follow PD patients over the course of their disease to monitor the progression of asymmetrical balance control. Does the least affected leg compensate for the most affected leg already from symptom onset? When is the least affected leg no longer able to compensate, and does this correlate with a worsening of clinical signs (greater postural instability) and onset of falls? What is the effect of levodopa on the overall balance control and on the balance control asymmetries? In healthy controls postural compensation could be tested by manipulating the balance control ability of one leg, with e.g. a cuff or tendon vibration. With this knowledge, interventions to stimulate postural compensation can be designed and evaluated.

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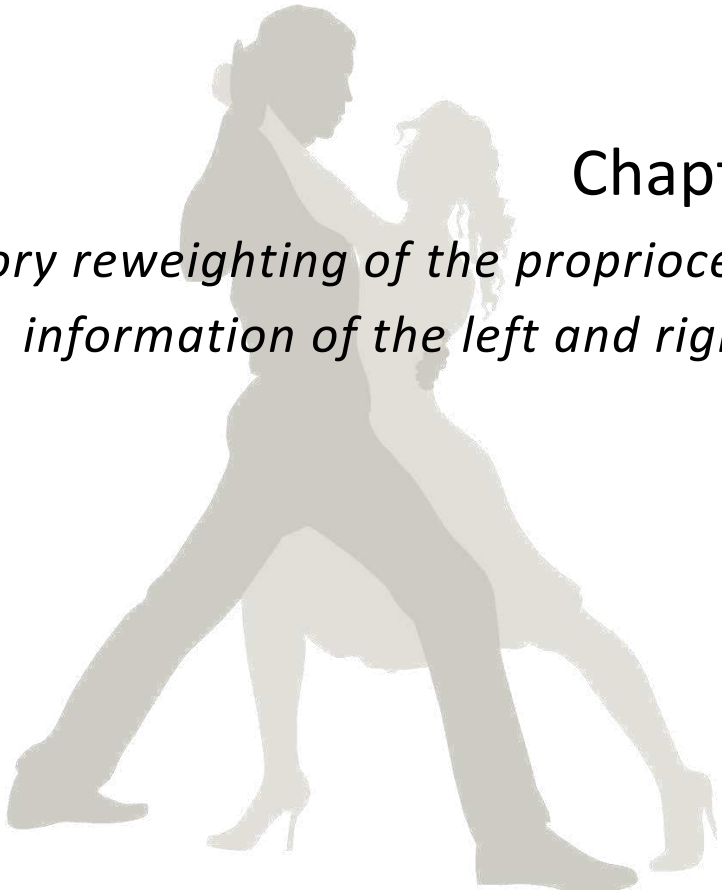

Chapter 7

Sensory reweighting of the proprioceptive information of the left and right leg

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Abstract

To keep balance, information from different sensory systems is integrated to generate corrective torques. Current literature suggests that this information is combined according to the sensory reweighting hypothesis, i.e. more reliable information is weighted stronger than less reliable information. In this approach no distinction has been made between the contributions of both legs. Here, we investigated how proprioceptive information from both legs is combined to maintain upright stance.

Healthy subjects maintained balance with closed eyes while proprioceptive information of each leg was perturbed independently by continuous rotations of the support surfaces (SS) and the human body by platform translation. Two conditions were tested: perturbation amplitude of one SS was increased over trials, while the other SS 1) did not move or 2) was perturbed with constant amplitude. Using system identification techniques, the response of the ankle torques to the perturbation amplitudes (i.e. the torque sensitivity functions) was determined and how much each leg contributes to stabilize stance (i.e. stabilizing mechanisms) was estimated.

Increased amplitude of one SS resulted in a decreased torque sensitivity. The torque sensitivity to the constant perturbed SS showed no significant differences. The properties of the stabilizing mechanisms remained constant during perturbations of each SS.

This study demonstrates that proprioceptive information from each leg is weighted independently and the weight decreases with perturbation amplitude. Weighting of proprioceptive information of one leg has no influence on the weight of the proprioceptive information of the other leg. According to the sensory reweighting hypothesis vestibular information must be up weighted, as closing the eyes eliminated visual information.

Introduction

Balance is described as the ability to maintain upright posture in a gravitational field (Niam *et al.,* 1999) and is involved in many daily life activities, like bipedal stance, walking and cycling. For small deviations the gravitational pull effectively is a negative stiffness; a deviation from a perfect upright position results in a torque that accelerates the body further away from this position. External mechanical disturbances, like a misstep or a slip, and conflicting information of the sensory systems can disturb the equilibrium of the balance system. The central nervous system (CNS) has to cope with these disturbances to maintain the body in upright position.

The CNS receives feedback about the body orientation from three main sensory systems: the visual, proprioceptive and vestibular system. The CNS integrates this sensory feedback and subsequently generates a corrective, stabilizing torque by selectively activating muscles (Peterka, 2002).

Nowadays, it is still not fully understood how sensory feedback of the different sensory systems is integrated by the CNS to generate corrective torques (Peterka, 2002).

The integration of the signals from the different sensory systems seems to be dynamically regulated to adapt to changes in the environment and the available sensory information, i.e. sensory reweighting (Cenciarini *et al.*, 2006; Kiemel *et al.*, 2002; Mahboobin *et al.*, 2009; Mahboobin *et al.*, 2005; Maurer *et al.*, 2006; Peterka, 2002; Peterka *et al.*, 2004; van der Kooij *et al.*, 2001). The hypothesis of Peterka (2002) states that the CNS adapts to different circumstances by adjusting the relative weight of the different sensory sources that control stance. When one sensory modality becomes less reliable, for example the proprioception by rotation of the support surface, the CNS reduces the relative weight of this sensory system and has to rely more on the other sensory systems (Mergner, 2010; Peterka, 2002).

The sensory reweighting hypothesis has been confirmed by experiments in which a sensory system was perturbed with increasing perturbation amplitude. With increasing perturbation amplitude the body sway saturated; i.e. a nonlinear relationship between the perturbation amplitude and the response amplitude was found. The relative response to larger amplitude perturbations decreased in accordance with the sensory reweighting hypothesis (Cenciarini *et al.*, 2006; Peterka, 2002). Peterka (2002) showed with model fits that the decrease in response of the body sway to the perturbation by increasing perturbation amplitude was due to a decrease in the weight of the perturbed sensory system (Peterka, 2002). Vestibular loss patients with closed eyes did not show sensory reweighting, i.e. they present a linear relationship between the perturbation amplitude and the response amplitude. Due to the loss of vestibular information and elimination of visual information by closing the eyes, only proprioceptive information was available to keep balance and reweighting between sensory channels was not possible.

To date, no distinction is made between the proprioceptive contribution of each leg, as the support surfaces of both feet were perturbed simultaneously (Peterka, 2002). Consequently, it is unknown whether the CNS uses the proprioceptive information of both legs independently to maintain balance, if so, how this information is integrated and if this influences how the legs contribute to stabilize stance (i.e. the stabilizing mechanisms).

By perturbing proprioceptive information of both legs independently, multiple ways of integrating sensory information are plausible. In a situation where visual information is eliminated by closing the eyes and the proprioceptive information of one leg is perturbed, there are the following theoretical possibilities: The first possibility is, a down weighting of proprioceptive information of both legs accompanied by an up weighting of vestibular information. The second possibility could be that proprioceptive information of only the perturbed leg is down weighted and the vestibular information is up weighted for this leg only. The third possibility is a down weighting of the proprioceptive information of the perturbed leg with an up weighting of the proprioceptive information of the opposite (unperturbed) leg, which would implicate asymmetry between the stabilizing mechanisms of the legs.

Here, we investigated the sensory reweighting of proprioceptive information of both legs independently in healthy subjects. In our approach, we consider two sensory sources (i.e., proprioception of the right and left leg) and two actuators (i.e., the musculature of both ankles). We identified whether separate perturbations of the proprioceptive information of the left and right leg, caused by rotation of the support surfaces, will result in sensory reweighting of the proprioceptive information of each leg independently. Concurrently, we investigated the influence of the separate sensory perturbations on the stabilizing mechanisms using constant platform accelerations in posterior-anterior direction.

We hypothesized that when applying different proprioceptive perturbations to each leg, sensory reweighting mechanisms would account for the sensory integration of the separate proprioceptive information from both legs. The CNS will down weight the less reliable information of one leg and up weight the more reliable information from other sensory systems. In other words, we hypothesized that in bipeds proprioceptive information of both legs is weighted separately and combined in balance control (Day *et al.,* 2010; Deliagina *et al.,* 2008).

Materials and methods

Subjects

Ten healthy subjects (six women, age 25.8 $\pm$ S.D. 2.4 years, weight 75.8 $\pm$ S.D. 10.9 kg) with no history of balance disorders, no injuries of the legs and no use of medication, which affects balance, participated. This study was performed according to the principles

of the Declaration of Helsinki and all subjects gave written informed consent to participate in this study.

Apparatus

In this study a bilateral ankle perturbator (BAP) was used to perturb the proprioceptive information of both legs independently by applying support surfaces rotations of both feet separately around the ankle axis, see Figure 7.1 (Schouten *et al.*, 2011). Each support surface consists of a custom-made 6 DoF force plate (Forcelink B.V., Culemborg, The Netherlands) connected to a servomotor via a lever arm. The actual angles of rotation (i.e. motor angles) and the applied torques to both support surfaces (i.e. motor torques) are available for measurement.

The BAP was placed on a 6 DoF motion platform (Motek Medical B.V., Amsterdam, The Netherlands) to apply support surface translations in the anterior-posterior direction to the BAP with the subject on top. The platform translation (s_{ext}) accelerates the base of support which is equivalent to a virtual torque applied at the ankles. The magnitude of the perturbation depends on the mass of the subjects and the center of mass location (Eq. (7.1; van der Kooij *et al.*, 2005).

$$d_{ext} = \frac{d^2 s_{ext}}{dt^2} \cdot m \cdot l_{com} \qquad (7.1)$$

Procedure

Before the trials, data was recorded for ten seconds while the subjects stood still on the BAP. This trial was used to calculate the height of the centre of mass (l_{CoM}) (Winter, 1990). Furthermore the maximum amplitude of the platform perturbations a subject could withstand without falling or stepping during rotation of the support surfaces, was determined by the experimenter (on average 3.1 cm).

In the main experiment the subjects were instructed to close their eyes and the subjects wore a backboard (mass 1.2 kg, moment of inertia 0.134 kgm^2 around the axis through the center located at the subjects' center of mass; l_{CoM}) minimize the use of the hip joint (Creath *et al.,* 2005) and stood with their arms crossed over their chest. The subjects were repeatedly instructed to distribute their body weight equally over both legs during the trials to eliminate the influence of weight bearing asymmetry (van Asseldonk *et al.,* 2006).

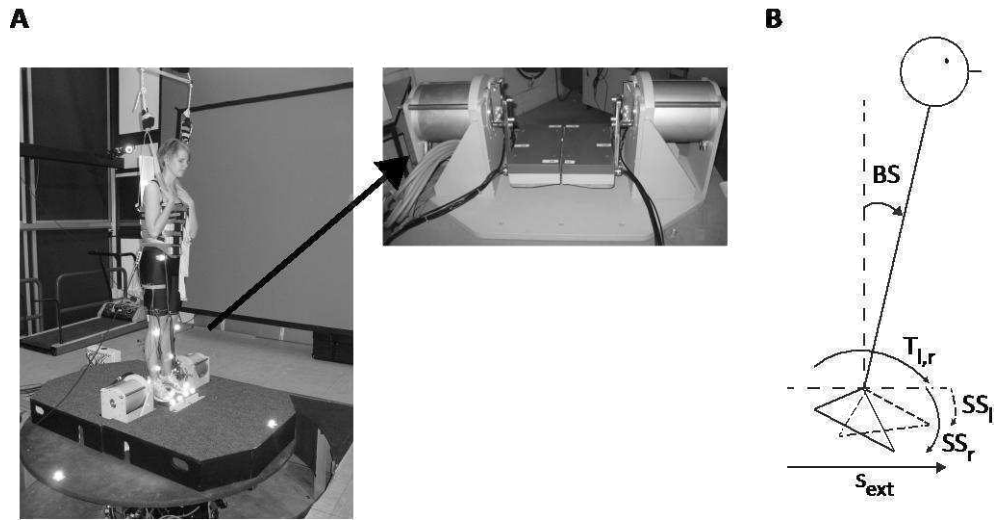

Figure 7.1: A) Experimental set-up with a subject standing on the bilateral ankle perturbator (BAP) on top of the motion platform. The hip was fixed using a backboard and the subject wore a safety harness to prevent a fall. The inset on the right displays the BAP with the support surfaces (i.e. 6 DoF force plates) and the servomotors. B) Schematic figure of the experimental set-up with s_{ext} the platform movement in anterior-posterior direction and $SS_{l,r}$ the platform rotations around the ankle axis applied separately to each leg. The ankle torques ($T_{l,r}$) and the body sway (BS) are the outcome measures.

The experiments consisted of two conditions: 1) the left support surface rotated with different amplitudes, while the right support surface did not rotate; 2) the right support surface rotated with different amplitudes, while the left support surface rotated with constant amplitude. In addition, the motion platform with the BAP was translated in anterior-posterior direction (see Table 7.1).

Each condition was presented twice in random order and each trial lasted 180 seconds. Before each trial the subjects were given about 30 seconds to get accustomed to the perturbations, to close their eyes and to reach a steady state. Between trials subjects were given sufficient time to rest.

Perturbation signals

Three different pseudo-random unpredictable perturbation signals were used in this study, namely for the left and right support surface rotation (SS rotation) and for the anterior-posterior platform translation (Pintelon, 2001). To be able to disentangle the effects of the different perturbations, the signals were designed to have separate frequency contents, see Figure 7.2.

Table 7.1: Overview of the different conditions.

Condition	Platform (d_{ext})	Left support surface (SS_l) (rad)	Right support surface (SS_r) (rad)
		One-leg perturbation	
L1R0	√	0.01	-
L3R0	√	0.03	-
L8R0	√	0.08	-
		Two-leg perturbation	
L3R1	√	0.03	0.01
L3R3	√	0.03	0.03
L3R8	√	0.03	0.08

The amplitude of the rotations of the support surfaces is given in radians. The platform perturbation amplitude (on average 3.1 cm) was set by the experimenter for each subject individually to the maximal value a subject could withstand without falling or stepping.

Pseudorandom ternary sequences (PRTS) of numbers were designed (Davies, 1970) as support surface angular velocity. Integration of these velocity signals provided the reference SS rotations. The method described in Peterka (2002) was used (Peterka, 2002) to generate two different perturbation signals for the left and right support surface with a time increment of $\Delta t = 0.16$ s and $\Delta t = 0.08$ s, respectively. In this case the period of each signal was 29.04 s and 14.52 s, respectively.

The platform perturbation was a multisine signal consisting of 30 frequencies between 0.0517 and 4.0461 Hz having a flat velocity spectrum resulting in a declining position spectrum (Pintelon, 2001; see Figure 7.2). All excited frequencies were multiples of 0.0172 Hz, resulting into a period of 58.08 s. Crest optimization was applied to minimize the root mean square of both the position and the acceleration of the multisine to guarantee a good signal to noise ratio (Pintelon, 2001).

The perturbation signals of the left and right support surface each fit exactly 2 and 4 times in the platform perturbation signal, respectively. This resulted into a total length of the perturbation signals of 58.08 s per cycle. Each trial consisted of three whole cycles of the perturbation signals.

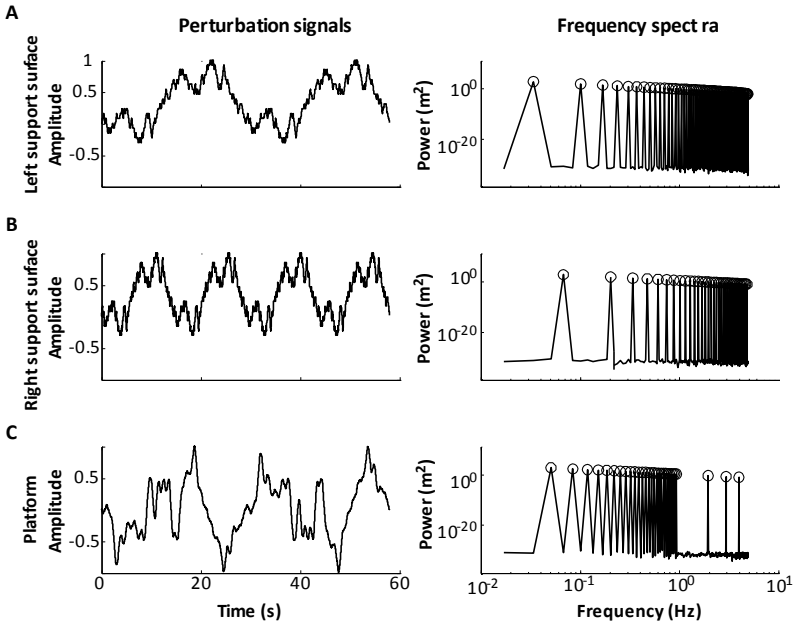

Figure 7.2: Time signals (left column), presented with normalized amplitude, and the corresponding power spectra (right column) of the perturbation of the left (A) and right support surface (B) of the bilateral ankle perturbator (BAP) and the perturbation of the motion platform (C).

Data recording and processing

Kinematic data were collected using a 6 camera motion capture system (Vicon Motion Systems Ltd., Oxford, UK), at a sample frequency of 120 Hz. Reflective spherical markers were attached bilaterally to the subject on the toe, lateral malleolus, heel, tibialis, knee, anterior superior iliac spine and shoulder to measure the movement of the body segments. Furthermore, three markers were attached to the platform. The motor angles, motor torques, and the signals of the force plates were recorded using the Vicon Workstation with a sample frequency of 2520 Hz. Data analysis was performed with Matlab (The MathWorks, Natick, MA).

The anterior-posterior platform movement (s_{ext}) was determined by averaging the three markers on the platform. From the markers on the body the location of the Centre of Mass (CoM) was determined according to Winter et al. (1990). The body sway angle (BS) was calculated from the anterior-posterior movement of the CoM and the distance between the lateral malleolus and the CoM, i.e. the length of the pendulum (l_{CoM}). The data of the force plates, motor angles (SS) and motor torques were resampled from 2520 Hz to 120 Hz. The data were filtered with a second order low pass digital Butterworth filter with cut-off frequency of 10 Hz. The ankle torques (T_l, T_r) were obtained by subtracting the contribution of the mass and inertia of the support surfaces from the recorded motor torques. The data of the 6 DoF force plates were corrected for the influence of the inertia

and mass of the top layer according to the procedure of Preuss and Fung (Preuss *et al.*, 2004). Weight bearing of the subject was calculated by dividing the mean vertical force below the left foot by the mean of the summed vertical forces below both feet.

The time series were split into three data blocks of 58.08 seconds (i.e. the length of the perturbation signal). Data blocks with missing markers were excluded from further analysis. The two trials of each condition resulted in six data blocks (2 trials of 3 data blocks).

Data analysis

Movement of one support surface influences the movement of the whole body and as such influences both ankle torques. Due to this biomechanical coupling between the legs it is difficult to indicate the effects of the right and left support surface perturbations on both ankle torques in time domain. Therefore, Frequency Response Functions (FRFs) were estimated based on a two-leg approach of postural control. In this approach the human body is assumed to move as an inverted pendulum, which is stabilized by the sum of the two corrective ankle torques generated by two stabilizing mechanisms, see Figure 7.3 (van Asseldonk *et al.,* 2006). The stabilizing mechanisms comprise of passive and active components of the CNS. However, the passive stabilizing mechanisms alone are not sufficient enough to keep balance (Loram *et al.*, 2002). The active stabilizing mechanisms are formed by the parts of the CNS that processes sensory signals, send efferent signals to the muscles and the muscles themselves. Stabilizing mechanisms of both legs incorporate vestibular and left and right proprioceptive information.

According to the sensory reweighting hypothesis each sensory system is presented by a sensory channel consisting of a weighting factor, which represents the relative weight of the sensory information (Peterka, 2003). The sum of all weighting factors equals one (Peterka, 2003). Therefore, a decrease in the weighting factor of one sensory channel must always be accompanied by an increase in the weighting factor of another sensory channel. This approach allows for asymmetry between the stabilizing mechanisms, i.e. the sum of weights used by the left stabilizing mechanism can be different from the sum of weights used by the right stabilizing mechanism ($\sum W_l \neq \sum W_r$).

To be able to detect sensory reweighting of the separate legs, the stabilizing mechanisms should only be influenced by the sensory weights. Two other factors could also contribute to asymmetry between the stabilizing mechanisms: 1) asymmetry in weight bearing (van Asseldonk *et al.,* 2006) and 2) asymmetry of left and right muscle properties and neural feedback loops. Therefore, subjects were instructed to distribute their weight equally over both legs, so it was reasonable to assume that the muscle and neural (passive) feedback properties were similar for both legs.

Sensory perturbations of proprioceptive information by rotation of the left and right support surfaces affect the output of the stabilizing mechanisms, which are represented

by the ankle torques of the left and right leg. To assess sensory reweighting and the properties of the stabilizing mechanisms, the closed loop balance control system will be disturbed by sensory perturbations (i.e. support surface rotations) and external perturbations (i.e. platform translation in anterior-posterior direction; Peterka, 2002).

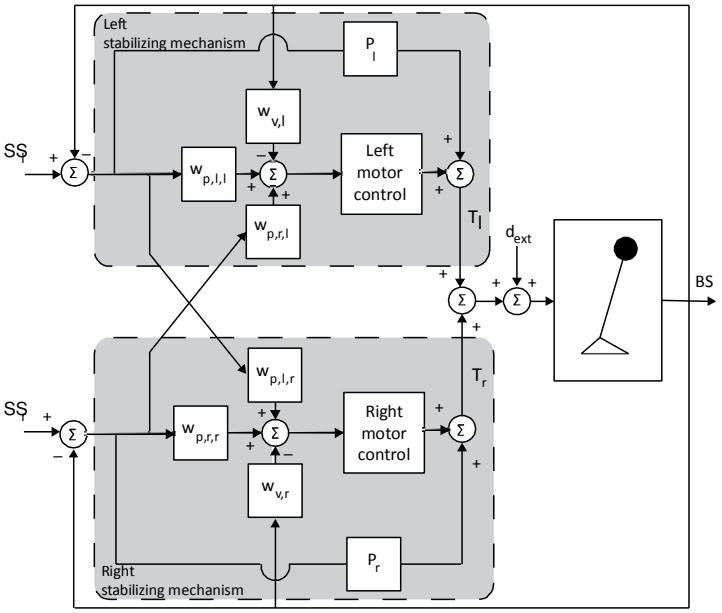

Figure 7.3: The two-leg approach of the balance control system. The body is represented as an inverted pendulum. Each leg has a stabilizing mechanism consisting of the passive feedback mechanism ($P_{l,r}$), weighting factors of the vestibular system (W_v), left ($W_{p,l}$) and right ($W_{p,r}$) proprioception and a (motor) controller. The torques (T_l, T_r) generated by each stabilizing mechanism affect the body sway (BS) angle. The control loop can be disturbed by sensory perturbations of the proprioceptive information of both legs (SS_l, SS_r) and by external perturbations (d_{ext}).

Frequency Response Functions

The data was transformed to the frequency domain. The periodic part of the frequency coefficients was determined by averaging over the data blocks (van der Kooij *et al.*, 2007a). The Power Spectral Densities (PSD) and Cross Spectral Densities (CSD) were computed to calculate the FRFs according to Pintelon and Schoukens (Pintelon, 2001; van der Kooij *et al.*, 2005). Only the excited frequencies were analyzed (see 'Perturbation Signals').

The stabilizing mechanisms were estimated using the joint input-output approach (equation 7.2; van der Kooij *et al.*, 2005).

$$\begin{bmatrix} C_{AP,r}(f) \\ C_{AP,l}(f) \end{bmatrix} = \begin{bmatrix} \Phi_{dext,T_r}(f) \\ \Phi_{dext,T_l}(f) \end{bmatrix} \cdot \left[\Phi_{dext,BS}(f)\right]^{-1} \qquad (7.2)$$

In which $\Phi_{dext,T}$ is the CSD of the platform perturbation (d_{ext}) and the left and right ankle torque (T_l and T_r) and $\Phi_{dext,BS}$ the CSD of d_{ext} and the body sway (BS).

Sensory reweighting is illustrated by the sensitivity functions. First, the body sway sensitivity function describes the relationship between the sensory perturbations and the body sway per frequency (Peterka, 2002). Secondly, the total torque sensitivity function describes the relationship between the sensory perturbations and the torque exerted by both ankles. To identify the influence of the perturbations on each leg separately, the torque sensitivity functions of each leg were estimated. Hence, a total of eight different sensitivity functions were estimated. The sensitivity functions are estimated by calculating the Frequency Response Functions (FRFs) from support surface rotation to ankle torque. The effect of increased support surface rotation amplitude could be indicated (Peterka, 2002) on the perturbed and on the contralateral leg. Therefore, four sensitivity functions were estimated; from the left and right ankle torque to the left support surface rotation ($^{SSl}S_{Tl}$ and $^{SSl}S_{Tr}$) and from the left and right ankle torque to the right support surface rotation ($^{SSr}S_{Tr}$ and $^{SSr}S_{Tl}$). The sensitivity functions were estimated using the indirect approach (equation 3; van der Kooij et al., 2005).

$$^{SS}S_T(f) = \Phi_{SS,T}(f) \cdot \left[\Phi_{SS,SS}(f)\right]^{-1} \quad (7.3)$$

In which $\Phi_{SS,T}$ is the CSD of the left and right support surface rotation (SS_l and SS_r) and the left and right ankle torque (T_l and T_r) and $\Phi_{SS,SS}$ the PSD of the left and right support surface rotation (SS_l and SS_r). As the corrective torque which has to be delivered by the subject is dependent ongravity, athe FRFs were normalized for the subject's mass and length, i.e. the gravitational stiffness (mgl_{CoM}).

Coherence

The (magnitude-squared) coherence was calculated between the perturbations and ankle torques or body sway using equation 3.

$$\gamma^2_{x,y}(f) = \left|\Phi_{x,y}(f)\right|^2 \cdot \left[\Phi_{x,x}(f) \cdot \Phi_{y,y}(f)\right]^{-1} \quad (7.4)$$

In which *x* represents a perturbation signal (SS_l, SS_r or d_{ext}) and *y* an output signal (T_l, T_r or BS). By definition coherence varies between 0 and 1, where coherence close to one indicates a good signal to noise ratio and linear behavior.

Statistical analysis

For statistical analysis the PSDs and CSDs were averaged within seven frequency bands (0.03-0.1 Hz, 0.1-0.3 Hz, 0.3-0.7 Hz, 0.7-1.4 Hz, 1.4-2.2 Hz, 2.2-3.1 Hz and 3.1-4.1 Hz) before calculating the FRFs according to the method of Peterka (2002) in which the number of points over which is averaged increases with frequency (Peterka, 2002). Subsequently, the gain of each FRF was log transformed to make the data normally distributed.

The one-leg and two-leg conditions were analyzed separately. First it was tested whether the weight bearing differed across conditions with a one-way repeated measures (RM) analysis of variance (ANOVA). In addition, to test for changes in strategy, a two-way RM ANOVA was performed to evaluate the effect of the perturbation amplitude (condition) across the different frequency bands and their interaction (condition x frequency band) on the averaged gain of the left and right stabilizing mechanisms. Within conditions, it was tested whether there were balance control asymmetries by comparing the left and right stabilizing mechanisms (covariate body side). Finally, to test for sensory reweighting a two-way RM ANOVA was performed to evaluate the effect of the perturbation amplitude (condition) across the frequency bands and their interaction (condition x frequency bands) on the gains of the sensitivity functions. The gains of the sensitivity functions ${}^{SSI}S_{Tl}$ and ${}^{SSI}S_{Tr}$ of the two-leg conditions were also compared with condition L3R0. During those conditions the perturbation of the left leg was constant.

For all tests significance (α) was set at 0.05. Sphericity was tested with the Mauchly's test. In case of lack of sphericity a Huynh-Feldt correction was applied. When a significant difference was found, a post-hoc test was performed using pair wise comparison with Bonferroni correction. All analyses were performed with SPSS version 16.0 (SPSS, Chicago, IL).

Table 7.2: Weight bearing during each condition.

Condition	Weight (%)
One-leg perturbation	
L1R0	49.7 ± 5.5
L3R0	49.5 ± 5.3
L8R0	49.4 ± 6.1
Two-leg perturbation	
L3R1	50.1 ± 5.9
L3R3	50.8 ± 7.4
L3R8	52.1 ± 6.9*

The mean ± SD over all subjects is shown for the weight bearing on the left leg. * indicates p value < 0.05.

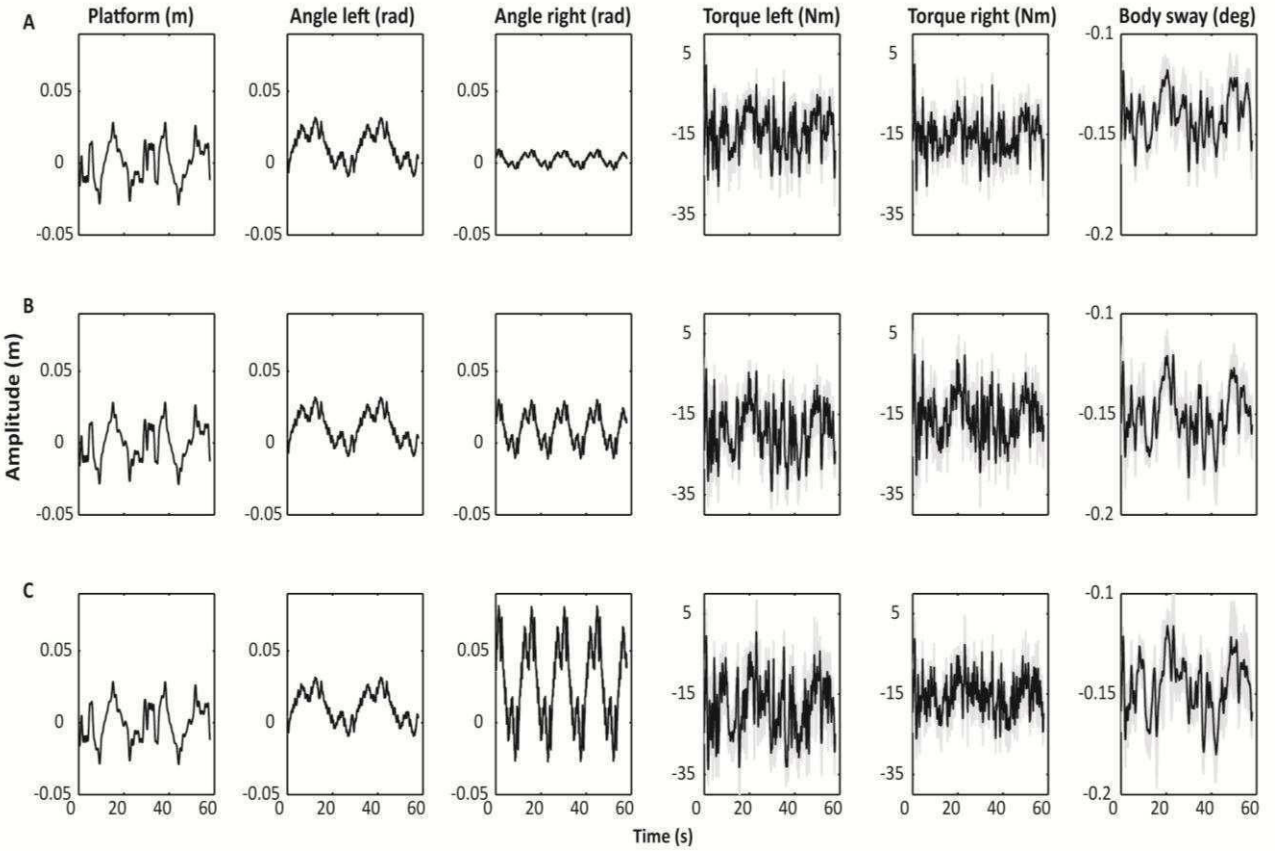

Figure 7.4: Time series of the condition with translation of the platform and rotations of both support surfaces, with constant amplitude of the left support surface and increasing amplitude of the right support surface (condition L3R1 (A), L3R3 (B) and L3R8 (C)). Data are for a typical subject per condition with the mean (solid line) and standard deviation over the six cycles (grey area).

Results

Table 7.2 gives an overview of the average weight bearing (percentage of weight on left leg) during all conditions. It was tested whether weight bearing differed between conditions, as this can cause an asymmetry in the stabilizing mechanisms (van Asseldonk *et al.,* 2006). Weight bearing was not significantly different for the one-leg perturbation conditions (p = 0.87). However, there was a significant difference between the two-leg perturbation conditions (p = 0.024). This was due to a difference between the L3R8 condition and the L3R1 condition (p = 0.06), showing that subjects tended to distribute their weight asymmetrically in L3R8 condition. Note that due to the Bonferroni correction the significant difference reduced to a trend towards asymmetrical weight bearing.

Time series

Figure 7.4 shows the time series of the support surface rotations, the platform disturbance, the ankle torques and the body sway of a typical subject for the two-leg perturbation conditions (i.e. L3R1, L3R3 and L3R8). A nonlinear relationship between the perturbation amplitude and the ankle torques is indicated by the saturation of the torque of the most perturbed leg during the L3R8 condition. Note that the body sway also saturated across conditions. The same phenomenon was found for the one-leg perturbation condition (not shown).

Frequency Response Functions

Stabilizing mechanisms

Figure 7.5 shows an example of the mean stabilizing mechanisms from one test condition to illustrate the variability between subjects. Figure 6 shows the left and right stabilizing mechanisms for all conditions. The perturbation amplitude of the support surface rotations had no significant influence on the stabilizing mechanisms during the one-leg perturbation conditions (p = 0.39) and during the two-leg perturbation conditions (p = 0.59).

There was no significant main difference between the left and right stabilizing mechanisms during the one-leg (p = 0.77) and two-leg (p = 0.17) perturbation conditions, However, during the two-leg perturbation conditions an interaction effect was found between body side (i.e. left and right stabilizing mechanism) and perturbation amplitude (p = 0.002). Post-hoc analysis showed that the gain of the left stabilizing mechanism was significantly higher than the gain of the right stabilizing mechanism in condition L3R8 (p = 0.017) between frequency 0.03 and 1.4 Hz (p = 0.001, p < 0.001, p = 0.007 and p = 0.004 respectively; see Figure 7.5). This means that there was an asymmetry between the left and right stabilizing mechanisms in the L3R8 condition, i.e. the left leg contributed more

to total body stability. Note that subjects also tended to put more weight on the left leg during this condition.

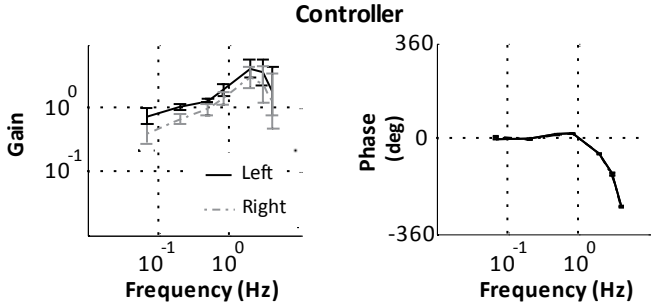

Figure 7.5: Example of the estimated left (black) and right (gray) stabilizing mechanisms averaged over all subjects for condition L3R8. The gain and phase are shown as average over the frequency bands with standard deviation.

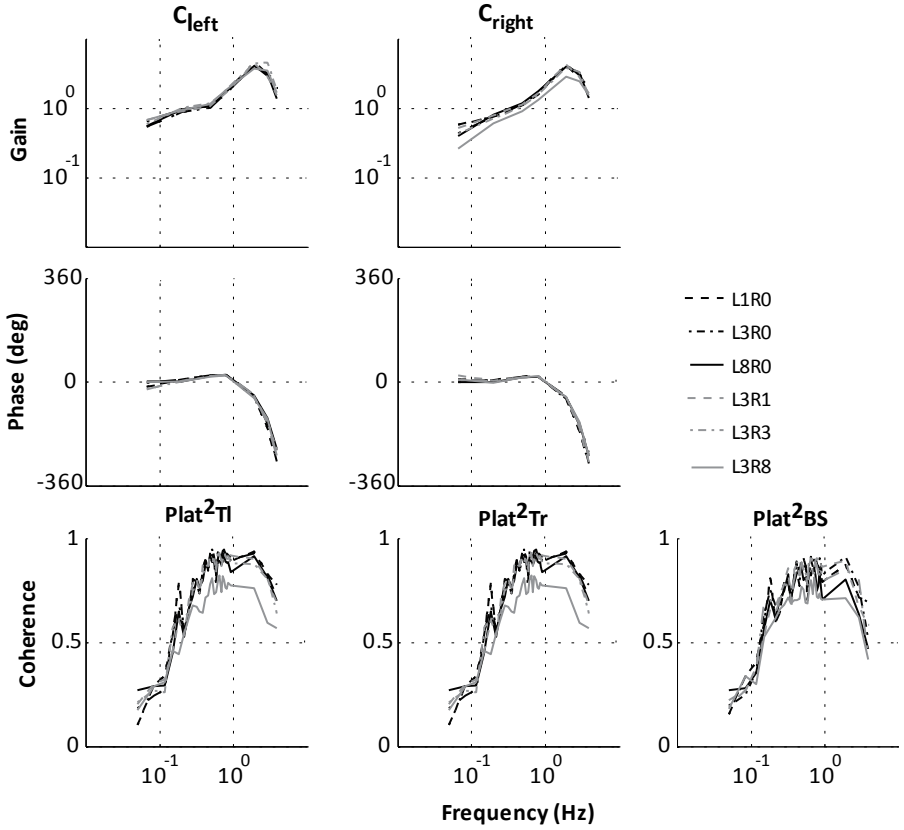

Figure 7.6: Estimated left and right stabilizing mechanisms (C_{left} and C_{right}) averaged over all subjects for all conditions. The gain and phase are shown for the excited frequencies. The coherence is shown between the platform perturbation and the left and right ankle torque ($Plat^2Tl$ and $Plat^2Tr$) and between the platform perturbation and the body sway ($Plat^2BS$).

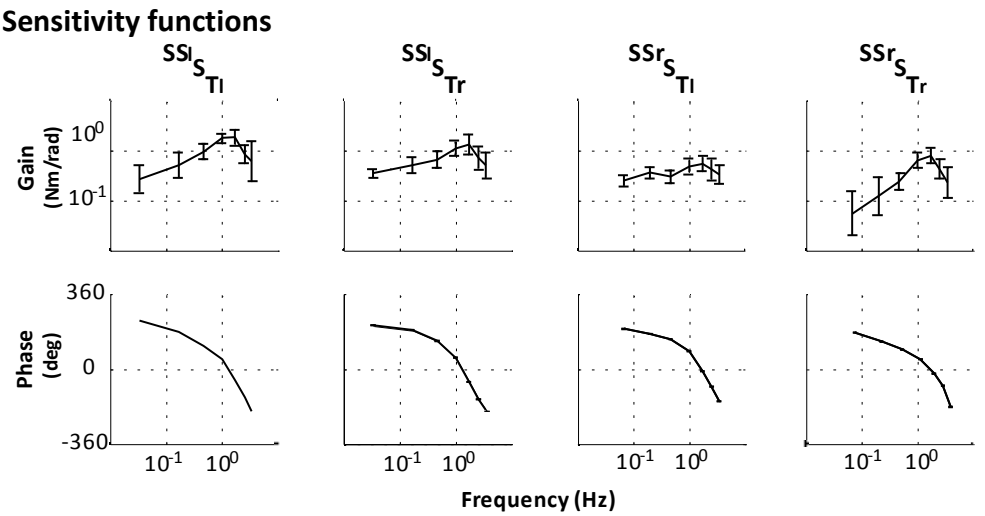

Figure 7.7: Example of the mean sensitivity functions over the subjects for the condition L3R8. The sensitivity functions of the left torque and of the right torque to the rotation of the left support surface ($^{SSl}S_{Tl}$ and $^{SSl}S_{Tr}$) and the sensitivity functions of the left torque and of the right torque to the rotation of the right support surface ($^{SSr}S_{Tl}$ and $^{SSr}S_{Tr}$) are shown as average over the frequency bands with standard deviation.

One-leg perturbation

Figure 7.7 shows an example of the mean torque sensitivity functions of one condition to illustrate the variability across the subjects. Figure 7.8 presents the body sway and total torque sensitivity functions to the perturbations. These sensitivity functions both decreased with increasing perturbation amplitude.

In Figure 7.9 the torque sensitivity functions are displayed for the conditions with rotation of one support surface (condition L1R0, L3R0 and L8R0). The gains of $^{SSl}S_{Tl}$ and $^{SSl}S_{Tr}$ decreased both for higher amplitudes (both $p< 0.001$), indicating a saturation of the ankle torques with increasing support surface rotation amplitude. Hence, the perturbation of the left leg was suppressed more when the perturbation stimulus amplitude increased.

In addition, an interaction effect between perturbation amplitude and frequency band was found for $^{SSl}S_{Tl}$ ($p< 0.001$) indicating that sensory reweighting is frequency dependent. No interaction effect was found for $^{SSl}S_{Tr}$ ($p = 0.36$). Both torque sensitivity functions, $^{SSl}S_{Tl}$ and $^{SSl}S_{Tr}$, showed a significant difference between the three conditions in all frequency bands, except between 2.2 and 3.1 Hz for the $^{SSl}S_{Tl}$ and between 0.3 and 0.7 and between 3.1 and 4.1 Hz for $^{SSl}S_{Tr}$.

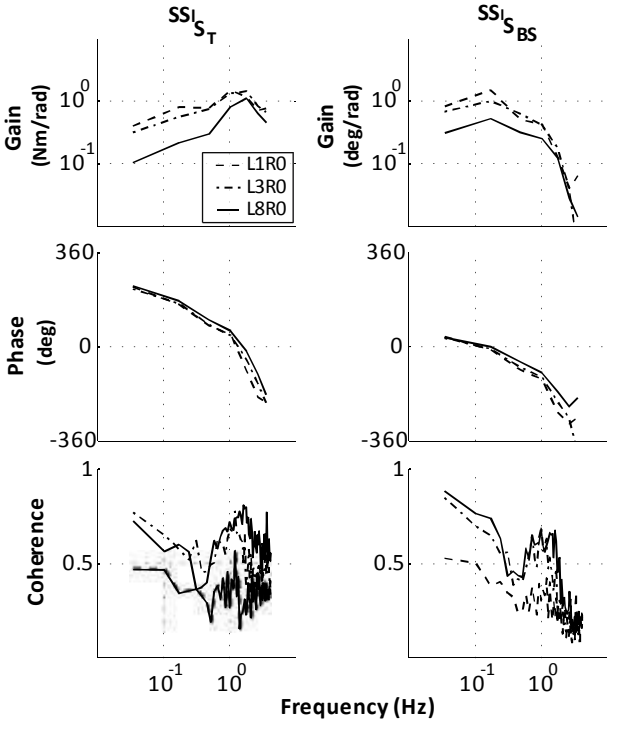

Figure 7.8: Total torque and body sway sensitivity functions (mean over subjects) of the three conditions with perturbation of only the left support surface (condition L1R0, L3R0 and L8R0). The gain and phase of the sensitivities of the total torque to the rotation of the left support surface (${}^{SSI}S_T$) and of the body sway to the left support surface (${}^{SSI}S_{BS}$) are shown. The coherence is shown between the perturbation and the total ankle torque and the perturbation and the body sway.

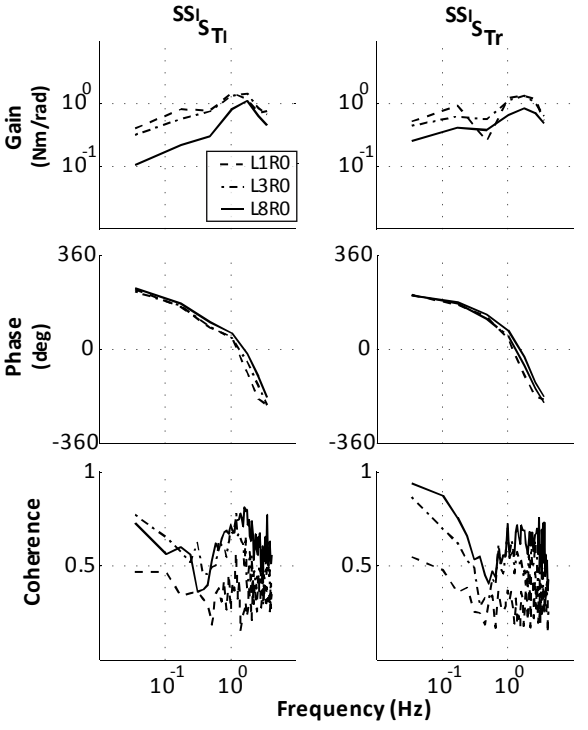

Figure 7.9: Mean torque sensitivity functions over the subjects of the three conditions with only perturbation of the left support surface (condition L1R0, L3R0 and L8R0). The gain and phase of the sensitivities of the left torque to the rotation of the left support surface (${}^{SSI}S_{Tl}$) and of the right torque to the rotation of the left support surface (${}^{SSI}S_{Tr}$) are shown. The coherence is shown between the perturbation and the left and right ankle torque.

Two-leg perturbation

The estimated torque sensitivity functions of the conditions with rotation of two support surfaces (condition L3R1, L3R3 and L3R8) are presented in Figure 7.10. The gains of ${}^{SSr}S_{Tr}$ and ${}^{SSr}S_{Tl}$ significantly decreased with increasing perturbation amplitude (both $p< 0.001$), which indicates a saturation of the ankle torques. An interaction effect between perturbation amplitude and frequency band was found for ${}^{SSr}S_{Tr}$ ($p< 0.001$), indicating a frequency dependent effect of perturbation amplitude. No interaction effect was found for ${}^{SSr}S_{Tl}$ ($p = 0.08$). Post-hoc analysis showed that both torque sensitivity functions were significantly different in all frequency bands across all three conditions.

The gains of the torque sensitivity functions to the constantly rotating left support surface (${}^{SSl}S_{Tl}$ and ${}^{SSl}S_{Tr}$) did not change over conditions ($p = 0.26$ and $p = 0.32$, respectively). This indicates that increasing the amplitude of the right support surface does not affect the sensitivity on the left support surface perturbation. Condition L3R8 differed from the L3R1 and L3R3 conditions with respect to weight bearing and the stabilizing mechanisms. Changes between the stabilizing mechanisms across conditions could result in changes of the sensitivity functions. In this case it would be impossible to draw conclusions about sensory reweighting. Therefore, the statistical analysis was also performed without the L3R8 condition. These comparisons still showed a significant decrease of the gains of the ${}^{SSr}S_{Tr}$ and ${}^{SSr}S_{Tl}$ sensitivity functions ($p < 0.001$ and $p = 0.001$, respectively) and no significant difference in the gains of ${}^{SSl}S_{Tl}$ and ${}^{SSl}S_{Tr}$ ($p= 0.15$ and $p= 0.49$, respectively).

Coherence

The coherence between the platform translation and the torques or body sway increased with higher frequencies (Figure 7.6). Coherence between the support surface rotations and the torques was high for low frequencies and frequencies higher than 0.5 Hz (Figure 7.9 and Figure 7.10).

With higher amplitudes the coherence increased, likely due to the increased signal to noise ratio with higher perturbation amplitudes, i.e. more signal power.

Discussion

Balance control involves the stabilization of the body in response to perturbations, i.e. ankle torques are generated to control body sway. Body sway is sensed by different sensory systems (vision, proprioception, vestibular system) and used by the (motor) controller. The (motor) controller, muscles and sensory systems together form a stabilizing mechanism. Here, we applied platform perturbations to investigate this stabilizing mechanism in combination with support surface rotations to investigate the relative weights of the different sensory systems, i.e. sensory reweighting. The support surface rotations affect both the active and passive feedback mechanisms.

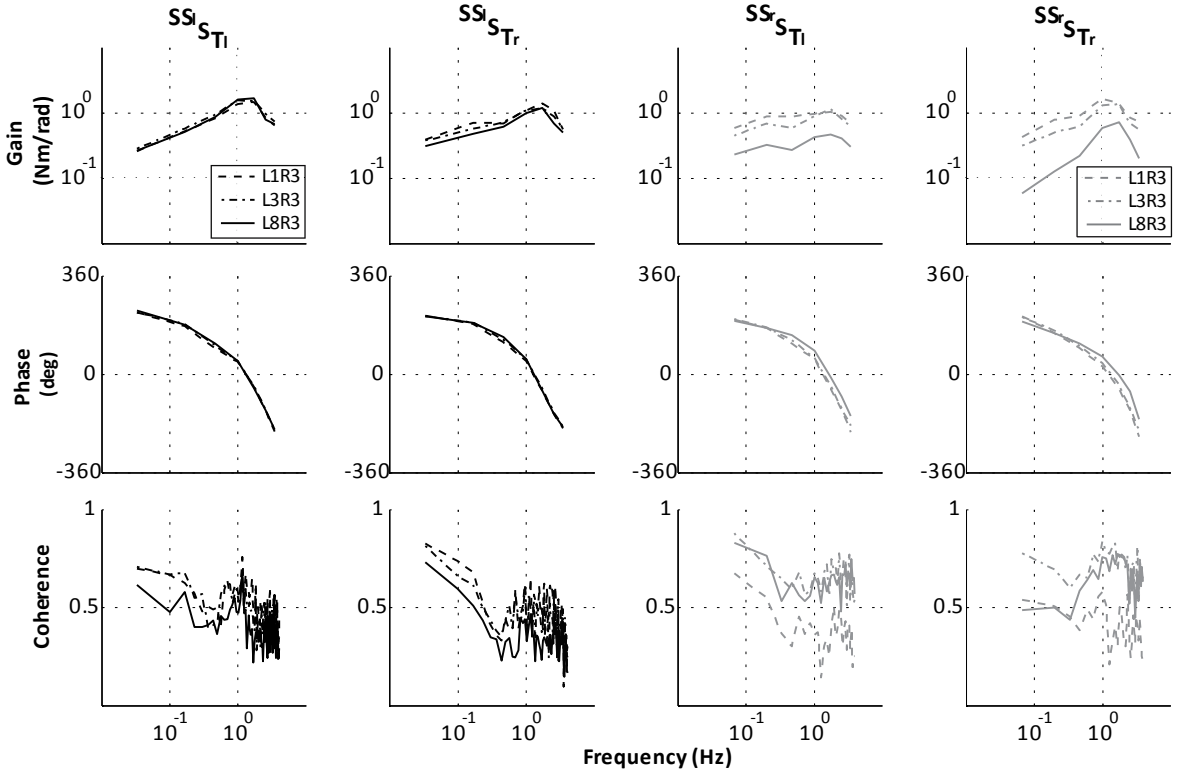

Figure 7.10: Mean sensitivity functions of the conditions with perturbation of both support surfaces (condition L3R1, L3R3 and L3R8). The sensitivity functions of the left torque and of the right torque to the rotation of the left support surface ($^{SSl}S_{Tl}$ and $^{SSl}S_{Tr}$) and the sensitivity functions of the left torque and of the right torque to the rotation of the right support surface ($^{SSr}S_{Tl}$ and $^{SSr}S_{Tr}$) are shown for the three conditions. Both phase and gain are displayed. The coherence is shown between each perturbation and the left and right ankle torque.

Methodological issues

When considering small deviations around an operating point, a nonlinear system, like balance control, can be linearized. In this experiment linear models were used to identify nonlinear characteristics over the different operating points (i.e. the different conditions). By applying support surface rotations, the variables that cause the nonlinearity (i.e. sensory weights) are controlled experimentally. The coherence indicates that the system can be considered linear in the operation points. By changing the stimulus amplitude the nonlinearities become apparent demonstrated by the variation between the conditions (as expressed by the sensitivity functions).

Stabilizing mechanisms

Theoretically, asymmetry between the stabilizing mechanisms can be due to a) asymmetry between the sums of weights of each stabilizing mechanism, b) asymmetry in weight bearing (van Asseldonk *et al.,* 2006) or c) asymmetry in controller properties (i.e. muscle properties and neural pathways). Previous studies (Peterka, 2002) showed differences in controller properties (stiffness, damping and time delay) between conditions, indicating that the CNS used also other adaptive strategies besides sensory reweighting. As our goal was to investigate whether sensory reweighting between legs is possible, it was important that the stabilizing mechanisms of each leg were only influenced by the sensory weights. To check whether this was the case, both the weight bearing and the stabilizing mechanisms of each leg were calculated.

The stabilizing mechanisms of both legs were constant and symmetrical during all conditions, except for the L3R8 condition. Although significant, the resulted differences between the left and right stabilizing mechanism during this condition were very small. Note that the asymmetry in the L3R8 condition was accompanied by a trend towards asymmetrical weight bearing. This indicates that the found balance control asymmetry is most likely due to a weight bearing asymmetry.

Using model simulations (van der Kooij *et al.,* 2011) it was shown that the dynamics of the stabilizing mechanism do not need to change during increasing amplitude sensory perturbations. Here, we confirmed these findings in human subjects using non-parametric system identification techniques. Also, similar to previous findings, the stabilizing mechanisms and weight bearing were coupled in this study (van Asseldonk *et al.,* 2006). These results showed that the sums of weights of *each* stabilizing mechanism remained constant and symmetrical between stabilizing mechanisms throughout the experiment.

Sensory reweighting between legs

Sensory reweighting is the ability of the human body to suppress erroneous sensory information, while becoming more sensitive to the other available sensory information. To date, studies investigating balance control have considered the proprioceptive

information of both legs as one sensory source (Maurer *et al.*, 2006; Peterka, 2002; Peterka *et al.*, 2004; van der Kooij *et al.*, 2001), which is a simplification as humans have two legs. These studies found that the proprioceptive weight decreased with support surface rotation amplitude.

In this study we applied support surface rotations to each leg individually; either only the left support surface rotated with different amplitudes or the right support surface rotated with different amplitudes while the left support surface rotated with constant amplitude.

One-leg perturbations

During one-leg perturbation the gain of the torque sensitivity functions to support surface perturbation ($^{SSl}S_{Tl}$ and $^{SSl}S_{Tr}$) decreased significantly with increasing support surface rotation amplitude. These results are comparable with the results found in previous studies where both legs were perturbed simultaneously (Maurer *et al.*, 2006; Peterka, 2003; van der Kooij *et al.*, 2001). The decrease in gain implies a relative reduction in responsiveness to the proprioceptive perturbations (the input), i.e. a decrease in the proprioceptive weighting factor. The CNS used a different combination of sensory channel weights, such that the proprioceptive weight decreased and the other weights increased.

The sensory reweighting differs on specific frequency ranges. At low frequencies, the sensory reweighting was most pronounced. This was expected as the proprioceptive sensory system is especially sensitive to slow movements (Peterka, 2002). At higher frequencies, the body sway response became increasingly dominated by inertial torques and sensory reweighting had no effect (Peterka, 2002).

Two-leg perturbations

During two-leg perturbation the gain of the torque sensitivity functions to the right support surface perturbation ($^{SSr}S_{Tl}$ and $^{SSr}S_{Tr}$) decreased significantly with increasing amplitude of the right support surface. These results are similar to the condition with one-leg perturbation and to previous studies where both legs were perturbed simultaneously.

In the two-leg perturbation conditions, the torque sensitivity functions to the left (constant) support surface perturbation ($^{SSl}S_{Tl}$ and $^{SSl}S_{Tr}$) could also be estimated. Results showed that they were not influenced by increasing the amplitude of the right support surface, indicating that the sensory weights of the left proprioceptive information did not change. Hence, when perturbing two legs, the weight of the proprioceptive information of the least perturbed leg was not influenced by the decreased weight of the proprioceptive information of the most perturbed leg.

Sensory reweighting within legs

Down weighting of the proprioceptive information of one leg has to be accompanied by up weighting of another sensory system (Peterka, 2002). In this case, the vestibular information should be up weighted, as the visual system is eliminated and the weight of proprioceptive information of the other leg remained constant. More specifically, the weight of the ipsilateral vestibular information was increased, because the stabilizing mechanisms remained constant and symmetrical across conditions. This is in accordance with a study of Day et al. (2010) who showed that vestibular information of both labyrinths (i.e., also coming from two sensors), provided independent estimates of head motion (Day *et al.*). Our results also confirm the findings by Van der Kooij et al. (2001) in another experimental setting. Because both legs are perturbed, proprioceptive information from both legs is less reliable and a conflict appears between the proprioceptive information of both legs and the other sensory systems. Van der Kooij et al. (2001; 2011) showed that vestibular information is necessary to solve sensory conflicts (van der Kooij *et al.*, 2001; van der Kooij *et al.*, 2011). In conclusion, our results indicate that sensory reweighting of both legs is independent.

Conclusions

In sum, this study demonstrates that proprioceptive information of the left and right leg is weighted independently during balance control. Sensory information of a perturbed leg (by support surface rotations) is down weighted with perturbation amplitude, irrespective whether the contralateral leg is perturbed or not. The down weighting of proprioceptive information of one leg is compensated by up weighting of the vestibular information and not by up weighting of the proprioceptive information of the contralateral leg.

Implications

To our knowledge this is the first study which demonstrates that proprioceptive information of both legs is weighted independently during balance control. Surprisingly, down weighting the proprioceptive information of one leg was accompanied by up weighting of the vestibular information and not by up weighting of the proprioceptive information of the contralateral leg. The question arises why people do not up weigh the proprioceptive information of the contralateral leg. Whether people are able to up weigh proprioceptive information of the contralateral leg, could be tested in vestibular loss patients, who have no vestibular contribution at all.

Distinguishing between the balance contribution of both legs and sensory reweighting of individual limbs may also have clinical applications for certain neurological disorders, such as Parkinson's disease (PD; Geurts *et al.*, 2011; van der Kooij *et al.*, 2007b) and stroke (Geurts *et al.,* 2005), possibly aiding in the development and evaluation of treatments. In both disorders it has been shown that asymmetry in balance control is an issue. This

asymmetry cannot be attributed solely to weight bearing asymmetries (Genthon *et al.*, 2008; van Asseldonk *et al.*, 2006; van der Kooij *et al.*, 2007b). Therefore, it has been hypothesized that the lower limb proprioception and regulation of sensory weights has been affected (Boonstra *et al.*, 2008; Geurts *et al.*, 2005; Marigold *et al.*, 2006; Vaugoyeau *et al.*, 2007). With our new approach we are able to test this, creating new unique insights into the pathophysiology of Parkinson's disease and stroke.

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Chapter 8

Discussion

Introduction

Most studies investigating human balance control assume that both legs contribute equally to upright stabilization, i.e., they lump the control actions of both legs together. This may be a valid simplification in healthy subjects, but in neurological patients there can be differences in the amount of force exerted by each foot. Furthermore, humans have two legs and two feet and both legs are involved in maintaining balance.

This thesis aimed to investigate how each leg contributes to human bipedal upright stance in both healthy subjects and in people with Parkinson's disease. A review (**Chapter 2**) and five studies were described in this thesis. In **Chapter 3** and **7** two newly developed techniques were described that are suited to investigate bipedal balance control. Furthermore, four separate research questions were addressed, with respect to asymmetrical balance control (**Chapter 4**), its relation with FoG in PD patients (**Chapter 5**), postural compensation mechanisms (**Chapter 6**; PD patients) and the interplay between sensory information between the independent legs (**Chapter 7**; healthy subjects).

In this discussion I will briefly summarize and critically discuss the applied methods and findings. Furthermore, I will discuss implications and directions for future research. I will conclude with some remarks about the long term perspective of balance control research and its clinical application.

Summary, results and conclusions

Methodologies for investigating bipedal balance control

In this thesis two new methods to investigate bipedal balance control are presented and successfully applied in healthy controls and PD patients. The first method (**Chapter 3**) dealt with determining the balance control contribution of the ankle and hip joints with closed-loop multivariate system identification techniques. The other method (**Chapter 7**) investigated whether erroneous sensory information of one leg can be suppressed, both when the sensory information of the other leg was and was not perturbed. Both methods and the obtained results are described briefly in the following paragraphs.

Two perturbations are necessary to investigate multi-segmental balance control

Human upright stance involves the stabilization of multiple joints, such as the ankles, knees and hips. Extending the commonly used inverted pendulum balance control model, to a double inverted pendulum makes the mechanics more complex, as movements from the upper segment will influence the movements of the lower segment and vice versa (Nott *et al.*, 2010; Zajac *et al.*, 2002). To reliably identify the stabilizing mechanisms of a double inverted pendulum, we developed a novel closed-loop multivariate system identification technique. We tested the method with model simulations and a balance control experiment with seven healthy participants and one PD patient.

The model simulations unequivocally showed that two independent perturbations are necessary to reliably identify the balance control contribution of the ankle and the hip joint. By applying multisine perturbations, reliable estimates of the stabilizing mechanisms of individual participants were obtained. Moreover, by measuring the reactive forces of each leg separately, balance control asymmetries were detected in the PD patient. Existing multivariate methods are not capable of determining individual estimates of the stabilizing mechanisms, nor can they determine balance control asymmetries (Fujisawa *et al.*, 2005; Kiemel *et al.*, 2011). The thrust of the developed method lies in applying periodic perturbations, contrary to the existing methods who applied pseudorandom maximum-length binary signal (Fujisawa *et al.,* 2005) or filtered white noise (Kiemel *et al.*, 2011). Periodic perturbations have the advantage of having power at specific frequencies, thereby increasing the participants' response and decreasing the measurement time. Therefore, the newly developed method is unique and suitable for clinical applications. The method presented in this chapter was further applied in a larger group of PD patients to assess multisegmental balance control (**Chapter 6**).

Two independent support surface rotations create the possibility to investigate sensory reweighting between legs

During upright stance, information from different sensory modalities (e.g., vision, proprioception and vestibular organ) is combined in the CNS to determine the position of the body in space. Research has shown that when one of the sensory modalities becomes less reliable, humans are able to suppress this information (Cenciarini *et al.*, 2006; Mahboobin *et al.*, 2009; Peterka, 2002), which is called sensory reweighting.

A possible way to make sensory information less reliable in an experimental setting, is by rotating the support surface through the ankle axis of a participant while standing. In this way, the usual coupling between the ankle joint angle and body lean is perturbed, and therefore the proprioceptive information becomes less reliable. To date, researchers perturbed the proprioceptive information of both legs simultaneously. In **Chapter 7**, the ankle proprioception of both legs was perturbed independently, by applying two independent support surface rotations; one for each foot, while participants maintained their balance with eyes closed. The results showed that healthy young subjects are capable of suppressing proprioceptive information of each ankle independently. To accommodate this change, the use of vestibular information was increased.

Besides fundamental insights into balance control mechanisms, this method may have applications in pathologies such as stroke and Parkinson's disease, both afflictions that can cause asymmetries in balance control (Rocchi *et al.*, 2002; Roerdink *et al.*, 2009; van Asseldonk *et al.*, 2006; van der Kooij *et al.*, 2007). With the developed methodology, it could be investigated whether the most affected side has a decreased or increased

capacity of suppressing erroneous proprioceptive information. In this way, proprioceptive deficits in both legs can be detected.

Bipedal balance control in Parkinson's disease

PD is an asymmetrical disease (Djaldetti *et al.,* 2006), but motor asymmetries are most evident in appendicular symptoms (e.g., tremor, bradykinesia). In **Chapters 5-7** we focused on balance control asymmetries in PD patients, by separately investigating the responses of each foot and leg with the method as presented in **Chapter 4** and as described in (van Asseldonk *et al.,* 2006).

Freezing of gait is not related to asymmetrical balance control

In **Chapter 4** and **5** it was established that PD patients can have asymmetrical balance control. This finding rose the question whether certain phenotypes of PD (such as freezing) may have a relationship with asymmetrical balance control. Freezing episodes occur most frequently during asymmetrical motor tasks such as turning and step initiation (Schaafsma *et al.,* 2003). In addition, asymmetrical gait patterns have been associated with freezing (Fasano *et al.*, 2011; Hausdorff *et al.*, 2003; Plotnik *et al.*, 2005; Plotnik *et al.*, 2008). Furthermore, freezing often occurs during step initiation and we hypothesized that that balance asymmetries could hamper the lateral weight shift that is necessary to unload the leg that will make the next step.

Our results showed no relationship between the amount of balance control asymmetry and freezing. However, we did find that the one-to-one coupling between weight bearing and balance control found in healthy controls was not significant in freezers compared to non freezers.

No other studies explicitly investigated the relationship between the amount of weight put on one leg and the amount of control exerted with that leg in PD. However, one other study suggested that freezers have an inability to couple a normal lateral weight shift to the stepping motor pattern, by investigating lateral weight shifts during step initiation (Jacobs *et al.,* 2009). Furthermore, anecdotal evidence suggests that freezing episodes reduce when PD patients consciously move their upper body while walking, where the movement of the upper body may help to make an adequate weight shift. It can be hypothesized that an abnormal coupling between weight-bearing and balance control may cause FoG. That is, in healthy subjects during walking the body weight is shifted between the contralateral stance legs. During the swing phase, the whole body weight is supported with one leg and therefore the body's balance must also be controlled with that leg. It has been shown, that in healthy control the amount of balance control scales with the amount of weight bearing and it can be assumed that this is a very automatic coupling. But what happens when this coupling becomes weaker? Specifically, what happens when the amount of balance control lags behind the amount of weight

bearing, as observed in most of the cases in **Chapter 5**? This weaker coupling between weight bearing and balance control could very well cause FoG episodes: the patient shifts his weight toward the stance leg, but is not yet controlling his balance with that leg, hence he is not yet ready to step, doesn't step, thereby causing the characteristic feeling of being 'glued' to the floor. Also, this weaker coupling could cause instabilities, because the stance leg is not producing adequate amounts of corrective torque. Interestingly, freezing is one of the leading causes for falls in patients with a Parkinsonism (Kerr *et al.,* 2010; Latt *et al.,* 2009) and perhaps the abnormal coupling between weight bearing and balance control contributes to this increased fall risk.

Balance control asymmetries are compensated for by the least affected leg in Parkinson's disease

In **Chapter 6** we investigated 'the other side of the coin' of asymmetries in balance control, namely whether PD patients can compensate for their most impaired leg. Despite marked asymmetries, the summed balance control behavior of both legs was similar to healthy controls at the ankle. Here, the least affected leg (as determined with the UPDRS) compensated fully for the most affected leg, by having a larger contribution than the most affected leg and one of the legs of the healthy controls. A different pattern was found at the hip; the least affected leg had a larger contribution, whereas the most affected leg had a similar contribution compared to the healthy controls. This resulted in an overall increased stabilization at the lower frequencies, indicative of increased postural hip stiffness in PD patients. We hypothesized that postural compensation could possibly explain why we did not find any differences in self-reported falls between patients with and without asymmetrical balance control (**Chapter 5**).

It was speculated about why the compensation strategy had a different result at the ankle compared to the hip. It could be that the common neural input to the least impaired side was up regulated to compensate for the asymmetry at the ankle. Because of the already increased hip balance contribution of the most affected leg, probably due to a stiffening response (Grimbergen *et al.,* 2004), this resulted in an increased overall hip joint stiffness.

Bipedal balance control - Two legs make a pair

This thesis investigated how each leg contributes to the stabilization of upright stance. In healthy adults, balance control is symmetrical: both feet bear the same amount of weight and both ankles exert the same amount of torque (Anker *et al.,* 2008). Also, in healthy there is a very strong one-to-one coupling between weight bearing and balance control (van Asseldonk *et al.,* 2006). This thesis confirmed these findings, but also expanded the knowledge of bipedal balance control.

It showed that the legs are communicating vessels; both take the balance control response of the contra-lateral leg into account. This was especially shown in **Chapter 6**, were PD patients compensated for the impaired balance response of the most affected leg, by increasing the control actions of the least affected leg to stabilize stance. **Chapter 7** confirmed these findings, as participants decreased the balance control contribution of one leg, while increasing the contribution of the other leg, during the condition where both feet were perturbed. **Chapter 7** also showed that the relative weight of the proprioceptive information is not necessary coupled. Here, an increasing proprioceptive perturbation of one leg, did not result in the upregulation of the use of proprioceptive information of the contra-lateral leg, but rather of the vestibular information. Future studies should investigate whether it is possible to upregulate the sensory information of the contra-lateral, least perturbed leg, instead of the vestibular information.

Furthermore, investigating bipedal balance control creates the possibility to explore the ultimate boundary between posture and gait: gait initiation. This thesis suggested that when the normal coupling within the leg, expressed by the balance control – weight bearing relationship, is decreased, gait initiation problems could arise.

Future scientific perspectives and recommendations

System identification techniques for the assessment of balance control impairments

The system identification methods used in this thesis (**Chapters 3** and **5-7**) assume that the investigated system is linear (or can be linearized) and that it does not change its properties over time, i.e., the system is considered as linear and time-invariant. However, the dynamics of the skeletal system are non-linear and the central nervous system is highly versatile, challenging the assumptions of linearity and time invariance. Therefore, only the steady state behavior of the system in one operation point can be determined and investigated with the applied methods, which limits the generalizability of the experimental results across different patient populations and conditions. For example, PD patients especially experience difficulties when switching between tasks (Chong *et al.*, 2000; Chong *et al.*, 1999) or between sensory information (De Nunzio *et al.,* 2007) and do not habituate their balance responses (Valkovic *et al.*, 2006). This was also nicely demonstrated by (Nanhoe-Mahabier *et al.*, 2012; Visser *et al.*, 2010), who showed that the largest differences between PD patients and healthy controls were observed in the first unpracticed response to a balance perturbation.

Practically, this means that the next generation closed-loop system identification methods have to be able to detect adaptive behavior, i.e., they must be able to handle time-variant behavior. Currently, there are some groups developing such methods (Guarin *et al.*, 2012; Ludvig *et al.*, 2011a; Ludvig *et al.*, 2011b), but these are only suited for a

single joint and applied when subjects are laying supine. Importantly, the above mentioned methods can only be applied to open-loop systems, while balance control is a closed-loop system.

Furthermore, falls do not occur very often when standing still, but while moving about in the environment. Hence, system identification techniques that can be applied during walking need to be developed. This is a big challenge, because walking is highly nonlinear and the available methods are not suited to deal with large nonlinearities.

It can be expected that it will still take a considerable amount of time before time-variant closed-loop system identification techniques can be applied to human balance control system. In the meantime, researchers should always check whether the assumption of linearity and time-invariance is justified. Linearity and time-invariance can be enhanced with clever experimental design, such as standardized instructions and small perturbation amplitudes, and can be quantified with measures such as coherence and noise-to-signal ratios.

Balance asymmetries in Parkinson's disease

This thesis showed and confirmed the presence of balance control asymmetries in Parkinson's disease (**Chapters 4** and **5**). This finding has practical implications for future research of balance control in PD patients, since it cannot be assumed that both legs contribute the same to upright stance. Hence, future studies should take this in account and always register the corrective actions of each leg separately. The necessity of this was nicely shown in **Chapter 6**, where overall differences between healthy controls and PD patients were only detected in the hip joint, although there were large asymmetries at the ankle. In other words, investigating the balance responses of each leg separately uncovers compensation strategies. It should be determined whether assessing the corrective actions of both legs separately, i.e., uncovering compensation strategies, might increase the (pre)clinical utility of balance control tests in PD patients.

Pathophysiology

Although this thesis showed large balance control asymmetries in PD patients, it did not investigate the underlying pathophysiology. Balance control asymmetry can have different origins such as decreased muscle force, an increased stiffness, a decreased quality of the efferent and/or afferent signals. Recently, it was shown that PD patients have difficulties integrating sensory information (Vaugoyeau *et al.*, 2011; Vaugoyeau *et al.*, 2007), especially proprioceptive information (Wright *et al.,* 2010), for a review see (Carpenter *et al.,* 2011). The methods presented in **Chapter 7** could very well be applied to PD patients, to determine the relative weight of proprioceptive information in PD patients compared to controls, whether PD patients are less effective in suppressing erroneous proprioceptive information and whether there are differences in sensory reweighting

capabilities between the legs. This would create further insights into the pathophysiology of balance control asymmetries in PD.

Freezing of gait and the coupling between balance control and weight shifting

Freezing of gait is a mysterious gait disorder, which causes sudden and unexpected motor blocks of the legs during gait (Nutt *et al.,* 2011). The pathophysiology of FoG is not well understood. Current hypothesis include a) an abnormal gait pattern generation, b) a problem with central drive and automaticity of movement, c) a perceptual malfunction, d) frontal executive dysfunction and e) an abnormal coupling of posture with gait (Nutt *et al.,* 2011). The results presented in **Chapter 5** suggest that balance control and weight bearing are not as tightly coupled in freezers compared to non freezers, which under scribes the hypothesis of an abnormal coupling between posture and gait. Future studies should further investigate this notion by designing experimental interventions that explicitly determine the relationship between weight bearing/shifting and balance control in individual patients. To investigate this, patients should be instructed to put a predefined amount of weight on one leg (e.g., 30, 40 and 50%) and subsequently the amount of control exerted with that leg should be assessed. In this way, the strength of the balance control- weight bearing coupling in individual patients can be determined. Subsequently, it can be assessed whether this relationship differs in freezers compared to non-freezers.

Taking it a step further, this relationship could also be explored during step initiation or during gait. Specifically, to test the hypothesis that a deteriorated coupling between weight bearing and balance control causes freezing, the coupling could be artificially altered. One option would be to decrease the support surface of one foot, by having participants stand with one foot on a small wooden block and instructing them to have a normal weight distribution (unpublished results). Another possibility could be to assist or perturb the medio-lateral movements during gait (initiation), to improve gait or provoke freezing episodes (King *et al.*, 2010; Mille *et al.*, 2007). However, it must be noted that FoG cannot solely be attributed to an impaired coupling between posture and gait, as some PD patients also experience freezing in hand movements (Nieuwboer *et al.*, 2009; Vercruysse *et al.*, 2012) and speech (Moreau *et al.,* 2007), both tasks were weight shifting does not play a role. Therefore, it is more likely that the proposed hypothesis are not mutually exclusive.

Investigating and stimulating compensatory mechanisms

Chapter 6 showed that PD patients can compensate for the impaired balance control ability of the most effected leg, most likely by increasing the corrective actions of the least affected leg. Investigating both legs separately creates the opportunity to investigate postural compensation mechanisms between the legs. Compensational strategies have been shown before in PD patients, where cueing (providing a visual or rhythmic stimulus)

is the most successful one (Nieuwboer *et al.*, 2006; Nieuwboer *et al.*, 2007). Future studies could follow PD patients over the course of the disease, to investigate whether postural compensation is already at play at the beginning of the disease or whether it starts at a later stage. Also, it should be investigated whether the amount of postural compensation correlates with a worsening of clinical signs (greater postural instability) and onset of falls. Furthermore, it could be assessed whether it is a successful compensation strategy. If so, would it be possible to enhance this postural compensation? Non-invasive brain stimulation may be a good intervention to enhance postural compensation. For example (Jayaram *et al.,* 2011) showed that motor adaptation can be enhanced with tDCS of the cerebellum. If postural compensation between legs is a successful strategy, it can be investigated whether PD patients can learn this strategy. If so, it might be a good candidate for physiotherapy programs.

On the horizon

Besides scientific merit, this thesis deals with the societal problem of balance and gait impairments and associated falls. Only in the Netherlands, the annual costs of falls and fall related injuries, such as fractures, are estimated to be M€675 and these costs are expected to increase dramatically because of the ageing population (Hartholt *et al.,* 2012).

Currently, the holy grail is to be able to detect the people who are at an increased risk of falling. Unfortunately, at the moment the best predictor of future falls are previous falls (Ganz *et al.*, 2007; Pickering *et al.*, 2007). Subsequently, in an ideal world, individuals with an increased risk of falling should follow an intervention program that takes away the deficit, learns successful compensation strategies and thus prevents falls. However, current intervention programs are only moderately effective (Allen *et al.*, 2010; Gillespie *et al.*, 2009; Tomlinson *et al.*, 2012; Weerdesteyn *et al.*, 2006).

This reflects how little we actually know about the (patho)physiology of balance control and it shows that there is still a long way towards practical applications, such as diagnostic tools for physicians and successful intervention programs. To get there, entails excellent hypothesis driven fundamental research with large sample sizes, in combination with the proper engineering tools, ingenious experimental design and intensive collaborations with physicians and patient groups. In conclusion, there is still an abundance of fundamental and clinical research that needs to be done to fully understand the complexities of maintaining balance, but bright minds and many hands will make light work.

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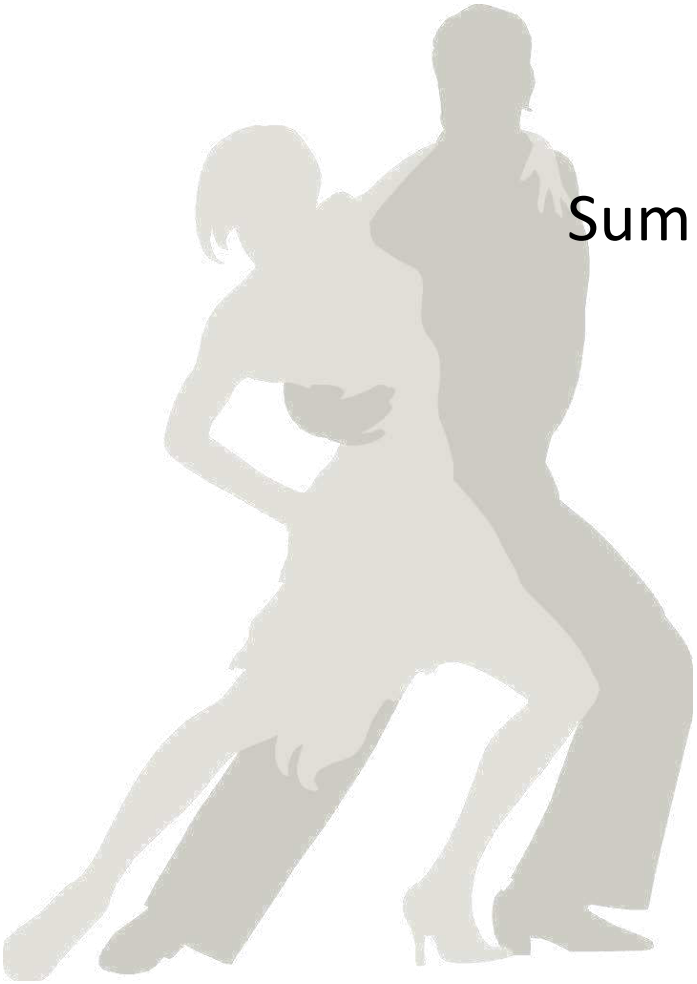


Summary

Standing upright on two feet is something humans do throughout the day. But it is a fragile balance and there is always a possibility of losing balance due to the inherent unstable musculoskeletal system.

The complexity of maintaining balance becomes apparent when people age or when a neurological disorder develops, such as Parkinson's disease. In this thesis, new methods to investigate and quantify balance control are presented and evaluated.

The general goal of this thesis is to create further insight into the (patho)physiology of human balance control, by specifically investigating the balance responses of each leg separately, in both healthy and people with Parkinson's disease.

Gait and balance are impaired in people with Parkinson's disease

Gait disorders and balance impairments are one of the most incapacitating symptoms of Parkinson's disease (PD). In **Chapter 2** the latest findings regarding epidemiology, assessment, pathophysiology and treatment of gait and balance impairments in PD were discussed.

It was confirmed that PD patients have a high rate and high risk of falling. Several studies have shown that multiple balance tests improve the prediction of falls in PD. Difficulty turning may be caused by axial rigidity, affected interlimb coordination and asymmetries. Impaired sensori-motor integration, inability of switching between sensory modalities and lack of compensatory stepping may all contribute to the high incidence of falls in PD patients. Similarly, various studies highlighted that pharmacotherapy, neurosurgery and physiotherapy may adversely affect balance and gait in PD.

Two perturbations, in combination with multivariate system identification, are necessary to unravel multi-segmental balance control

Human stance requires coordinated action of multiple segments, including the legs and trunk. In **Chapter 3** a novel method was presented that reliably estimates the contribution of the left and right ankle and hip joints to balance control, of individual subjects.

The method was evaluated using simulations of a double-inverted pendulum model and the applicability was demonstrated with an experiment with seven healthy participants and one PD patient. Model simulations indicated that two perturbations are required to reliably estimate the dynamics of a double-inverted pendulum balance control system. In the experiment, two multisine perturbation signals were applied simultaneously. The dynamic behavior of the participants was estimated by Frequency Response Functions (FRFs), which relate ankle and hip joint angles to joint torques, using a multivariate closed-loop system identification technique.

In the model simulations, the FRFs were reliably estimated, also in the presence of realistic levels of noise. In the experiment, the participants responded consistently to the perturbations, indicated by low noise-to-signal ratios of the ankle angle (0.24), hip angle

(0.28), ankle torque (0.07), and hip torque (0.33). The developed method could detect that the Parkinson patient controlled his balance asymmetrically, that is, the right ankle and hip joints produced more corrective torque.

The method allows for a reliable estimate of the multisegmental feedback mechanism that stabilizes stance, of individual participants and of separate legs.

Balance control can be asymmetrical in Parkinson's disease

Asymmetry of symptoms of Parkinson's disease is clinically most evident for appendicular impairments. For axial impairments such as a stooped posture, asymmetry is less obvious. To date, asymmetries in balance control in PD patients have seldom been studied. Therefore, in **Chapter 4** we investigated whether postural control can be asymmetrically affected in mild to moderate PD patients.

Seventeen PD patients were instructed to stand as still and symmetrically as possible on a dual force-plate during two trials. Dynamic postural asymmetry was assessed by comparing the centre-of-pressure velocities between both legs. Results showed that four patients (24%) had dynamic postural asymmetry, even after correcting for weight-bearing asymmetry. Hence, this study suggests that postural control can be asymmetrical in early PD.

Asymmetrical balance control is not related to freezing of gait in Parkinson's disease

Balance control is asymmetrical in a proportion of patients with Parkinson's disease (see **Chapter 4**) and gait asymmetries have been linked to the pathophysiology of freezing of gait. We speculate that asymmetries in balance could contribute to freezing, by hampering the unloading of the stepping leg. To investigate this, we examined the relationship between balance control and weight bearing asymmetries and freezing.

We included 20 patients with Parkinson (tested OFF medication; nine freezers) and nine healthy controls. Balance was perturbed in the sagittal plane, using continuous multi-sine perturbations (see **Chapter 3**). Applying closed-loop system identification techniques, relating the body sway angle to the joint torques of each leg separately, determined the relative contribution of each ankle and hip joint to the total amount of joint torque. We also calculated weight bearing asymmetries.

Freezers did not have larger asymmetries in weight bearing (p = 0.85) nor more asymmetrical balance control compared to non-freezers (p = 0.25). The healthy linear one-to-one coupling between weight bearing and balance control was significantly different for freezers and non-freezers (p = 0.01). Specifically, non-freezers had a significant coupling between weight bearing and balance control (p = 0.02), whereas this relation was not significant for freezers (p = 0.15).

The least affected leg can compensate for the balance control impairments of the most affected leg in Parkinson's disease

Parkinson's disease (PD) patients have an increased risk of falling, especially in later disease stages. However, more subtle balance impairments can be detected even in newly diagnosed patients. One feature of impaired balance control in PD patients is asymmetry, reflected by one leg producing more corrective force than the other leg (see **Chapter 4** and **5**). It was hypothesized that in mild to moderately affected PD patients, the least impaired leg can compensate for the more impaired leg, by increasing its relative contribution to upright balance control.

We tested 20 PD patients (six women; Hoehn and Yahr range: 1-3) and seven healthy controls (two women; matched for age). Clinical asymmetry was determined by the difference between the left and right body side scores on the UPDRS. Balance was perturbed using two independent continuous multi-sine perturbations in the forward-backward direction, to disentangle the relative balance contribution of the ankle and hip joint. Subsequently, the responses of the participants were assessed with the method presented in **Chapter 3**.

Overall balance control behaviour (i.e., the control actions of both legs added together) was similar in PD patients and healthy controls at the ankle. However, stiffness at the hip was increased in PD patients. Furthermore, at the ankle, the balance control contribution of the least affected leg (i.e., with the lowest UPDRS score) of patients was higher than the matched leg of healthy controls, whereas the most affected leg contributed less. A similar pattern was found at the hip, but here this resulted in a total higher stiffness.

These results suggest that PD patients can compensate for balance control asymmetries by increasing the control actions of their least affected leg. This compensation is successful at the ankle, but is accompanied by an increased joint stiffness at the hip. This compensation strategy could paradoxically increase postural instability in PD patients.

Healthy subjects can suppress sensory information of independent legs

To keep balance, information from different sensory systems is integrated to generate corrective torques. Current literature suggests that this information is combined according to the sensory reweighting hypothesis, i.e. more reliable information is weighted stronger than less reliable information. In this approach no distinction has been made between the contributions of each leg. In **Chapter 7**, it was investigated how proprioceptive information from both legs is combined to maintain upright stance.

Healthy subjects maintained balance with closed eyes, while proprioceptive information of each leg was perturbed independently by continuous rotations of the support surfaces (SS) and the human body by platform translation. Two conditions were

tested: perturbation amplitude of one SS was increased over trials, while the other SS 1) did not move or 2) was perturbed with constant amplitude. Using system identification techniques, the response of the ankle torques to the perturbation amplitudes (i.e. the torque sensitivity functions) was determined. Also, how much each leg contributed to stabilize stance (i.e. stabilizing mechanisms) was estimated.

Increasing the amplitude of one SS resulted in a decreased torque sensitivity. The torque sensitivity to the constant perturbed SS showed no significant differences. The properties of the stabilizing mechanisms remained constant during perturbations of each SS.

This study demonstrates that proprioceptive information from each leg is weighted independently and the weight decreases with perturbation amplitude. Weighting of proprioceptive information of one leg has no influence on the weight of the proprioceptive information of the other leg. According to the sensory reweighting hypothesis vestibular information must be up weighted, as closing the eyes eliminated visual information.

Bipedal balance control

This thesis investigated how each leg contributes to the stabilization of upright stance. This thesis showed that the legs are communicating vessels; both take the balance control response of the contralateral leg into account. This was especially shown in **Chapter 6**, were PD patients compensated for the impaired balance response of the most affected leg, by increasing the control actions of the least affected leg to stabilize stance. **Chapter 7** confirmed these findings, as participants decreased the balance control contribution of one leg, while increasing the contribution of the other leg, during the condition where both feet were perturbed, with the largest amplitude.

Investigating bipedal balance control creates the possibility to explore the ultimate boundary between posture and gait: gait initiation. This thesis (**Chapter 5**) suggested that when the normal coupling within the leg, expressed by the balance control – weight bearing relationship, is decreased, gait initiation problems could arise.

Samenvatting

Op twee benen staan is iets wat mensen elke dag zonder veel moeite doen. Maar een ongeluk zit in een klein hoekje en er is altijd een kans op een val, omdat rechtop staan een onstabiel systeem is. De complexiteit van het balans systeem en de balans houden wordt duidelijk als mensen ouder worden, of als ze de ziekte van Parkinson krijgen, aangezien beide geassocieerd zijn met een verhoogde kans op vallen. In dit proefschrift werden nieuwe methodes beschreven en getest om balans controle te kunnen kwantificeren.
Het algemene doel was om nieuwe inzichten op het gebied van de (patho)fysiologie te generen, specifiek door de balansbijdrage van elk been apart te bepalen, zowel in gezonde mensen als mensen met de ziekte van Parkinson.

Het lopen en de balans zijn aangedaan bij mensen met de ziekte van Parkinson

Loop- en balansstoornissen behoren bij de meest invaliderende symptomen van de ziekte van Parkinson (ZvP). In **Hoofdstuk 2** worden de laatste bevindingen op het gebied van epidemiologie, diagnostiek, pathofysiologie en behandeling van loop- en balansstoornissen besproken.

De hoge prevalentie en kans op vallen bij mensen van de ZvP werd bevestigd. Meerdere studies lieten zien dat een combinatie van balanstesten, beter het valrisico kon voorspellen bij Parkinson dan één enkele test. Moeite met (om)draaien zou veroorzaakt kunnen worden door axiale stijfheid, een verstoorde coördinatie tussen ledematen en asymmetrie (het ene been werkt harder dan het andere been). Een verstoorde integratie van sensorische en motorische signalen, een onvermogen om te kunnen switchen tussen sensorische modaliteiten én de afwezigheid van compensatoire stap strategieën zouden allen kunnen bijdragen aan de hoge incidentie van vallen bij Parkinson patiënten. Ook toonden verschillende studies aan dat farmacotherapie, hersenoperaties en fysiotherapie balans en lopen soms juist negatief beïnvloeden.

Twee verstoringen, in combinatie met multivariate systeem identificatie, zijn nodig om multi- segmentale balans te kunnen doorgronden

Rechtop blijven staan vereist de gecoördineerde bewegingen van meerdere lichaamssegmenten, zoals de benen en de romp. In **Hoofdstuk 3** wordt een nieuwe methode gepresenteerd die in staat is om de balansbijdrage van de linker- en rechter enkel en heup, van individuele proefpersonen, betrouwbaar te bepalen.

De methode werd eerst getest met model simulaties van een dubbele omgekeerde slinger en de toepasbaarheid werd vervolgens gedemonstreerd met een balans experiment bij zeven gezonde controles en één Parkinson patiënt.

De model simulaties bevestigden de theorie dat twee verstoringen nodig zijn om de dynamica van een dubbele omgekeerde slinger balans systeem betrouwbaar te schatten. In het experiment werden twee multisinus verstoringen tegelijkertijd aangebracht. Het dynamische gedrag van de proefpersonen werd geschat met Frequentie Responsie

Functies (FRFs), die de gewrichtshoeken aan de gewrichtsmomenten relateren, door gebruik te maken van een multivariate gesloten- lus systeem identificatie techniek.
In de model simulaties, konden de FRFs betrouwbaar worden bepaald, ook bij realistische systeem- en meetruis niveaus. Tijdens het experiment reageerden de proefpersonen op een consistente manier, wat resulteerde in lage ruis-signaal ratio's van de enkel en heup hoek (0.24 en 0.28) en enkel en heup moment (0.28 en 0.07). De ontwikkelde methode liet ook zien dat de Parkinson patiënt zijn balans asymmetrisch controleerde; de rechter enkel en heup gewrichten produceerden meer stabiliserend moment dan het linker been.

De ontwikkelde methode is in staat om een betrouwbare schatting van een multisegmentaal feedback balance controle systeem te maken, zowel van individuele proefpersonen als van beide benen apart.

Balans controle kan asymmetrisch zijn bij mensen met de ziekte van Parkinson

Asymmetrie van symptomen bij de ZvP zijn klinisch het meest evident bij de appendiculaire (bijv. tremor en stijfheid) symptomen. Voor axiale symptomen, zoals de karakteristieke voorover gebogen houding, is asymmetrie veel minder duidelijk. Tot op heden waren asymmetrieën in balans controle bij mensen met de ZvP amper onderzocht. Daarom onderzochten we in **Hoofdstuk 4** of balans asymmetrisch aangedaan kan zijn bij mensen met Parkinson.

Zeventien patiënten werden geïnstrueerd om zo stil en symmetrisch mogelijk stil te staan op een duale krachtplaat. Dynamische posturele asymmetrie werd bepaald door het verschil van de snelheid van de aangrijpingspunt van de kracht op beide voeten. De resultaten lieten zien dat vier patiënten (24%) een balans asymmetrie hadden, zelfs als er werd gecorrigeerd voor asymmetrieën in gewichtsverdeling. Kortom, deze studie liet zien dat balans controle asymmetrisch kan zijn bij mensen met Parkinson, zelfs al in het begin van de ziekte.

Asymmetrische balans controle is niet gerelateerd aan het bevriezen van de benen tijdens het lopen bij Parkinson patiënten.

Balans controle kan asymmetrisch zijn bij mensen met Parkinson (zie **Hoofdstuk 4**). Asymmetriëen tijdens het lopen zijn gerelateerd aan het bevriezen van het de benen tijdens het lopen ('freezing'). In **Hoofstuk 5** werd de hypothese getest dat balans asymmetrieën kunnen bijdragen aan freezing. Om deze hypothese te testen werd de relatie tussen asymmetrische balans controle en gewichtsverdeling en freezing getest.

Twintig Parkinson patiënten (Off medicatie; negen freezers) en negen gezonde controles werden getest. Hun balans werd verstoord in de voorwaarts-achterwaartse richting (zie **Hoofdstuk 3**) met continue multisinus verstoringen. Met gesloten-lus systeem identificatie technieken, die de lichaamshoek relateren aan de gewrichtsmomenten van

elk been apart, werd de relatieve balansbijdrage van de enkel en de heup van elk been bepaald. Ook werden asymmetrieën in gewichtsverdeling bepaald.
Freezers hadden geen grotere gewichtsverdeling asymmetrieën (p = 0.85) of grotere balanscontrole asymmetrieën (p = 0.25). De gezonde lineaire één-op-één koppeling tussen balanscontrole en gewichtsverdeling was significant verschillend tussen freezers en niet-freezers (p=0.01); niet-freezers vertoonden wel een significante koppeling (p = 0.02), terwijl de freezers dit niet lieten zien (p = 0.15).

Parkinson patiënten kunnen compenseren voor hun asymmetrieën in balans controle

Parkinson patiënten hebben een groter risico op vallen (zie ook **Hoofdstuk 2**), zeker in de latere stadia van de ziekte. Toch kunnen er al subtiele symptomen van balansstoornissen waargenomen worden bij patiënten die net gediagnosticeerd zijn. Eén van die symptomen zijn asymmetrieën; wanneer één been een grotere balansbijdrage heeft dan het andere been (zie **Hoofdstuk 4 en 5**). In **Hoofdstuk 6** werd de hypothese getest dat Parkinson patiënten met hun minst aangedane been kunnen compenseren voor de verminderde balansbijdrage van het meest aangedane been.

Hetzelfde cohort patiënten als in **Hoofdstuk 5** werd met methode, zoals beschreven in **Hoofdstuk 3**, getest. Klinische asymmetrie werd gedefinieerd door het verschil scores tussen beide lichaamskanten, zoals bepaald met de UPDRS (Unified Parkinson's Disease Rating Scale).

De totale balanshandhaving (de corrigerende acties van beide benen bij elkaar) was het zelfde voor ZvP patiënten en gezonde controles bij de enkel. Bij de heup was de stijfheid van de Parkinson patiënten verhoogd. De balansbijdrage van het minst aangedane been (met de laagste UPDRS score) was hoger dan de bijdrage van het been van de gezonde controles, terwijl het meest aangedane been een lagere balansbijdrage had. Dit patroon werd ook geobserveerd bij de heup, maar hier leidde dit tot een hogere stijfheid.

De resultaten van **Hoofdstuk 6** suggereren dat Parkinson patiënten kunnen compenseren voor hun balans asymmetrieën door de balansbijdrage van het minst aangedane been te verhogen. Deze compensatie strategie is succesvol bij de enkel maar leidt tot een hogere stijfheid bij de heup. Ook zou deze compensatie strategie paradoxaal de lichaamsstabiliteit kunnen verminderen.

Gezonde proefpersonen kunnen de sensorische informatie van elk been apart onderdrukken

Om je lichaam in balans te kunnen houden, wordt informatie van verschillende sensorische systemen geïntegreerd om een schatting van de lichaamshouding te maken. De huidige literatuur suggereert dat betrouwbare informatie zwaarder wordt gewogen

dan minder betrouwbare informatie, dit noemen we de sensorische herweging hypothese. Tot nu toe maakte deze theorie geen onderscheid tussen sensorische informatie van het linker of rechterbeen. In **Hoofdstuk 7** werd onderzocht hoe proprioceptieve informatie van elk been apart wordt gecombineerd.

Gezonde proefpersonen moesten hun balans houden, met ogen gesloten, terwijl de proprioceptieve informatie van elk been apart werd verstoord, door continue rotatie van de ondergrond. Ook werd hun balans verstoord door translaties van het bewegingsplatform. Twee keer 3 condities werden uitgevoerd: de verstoringsamplitude van de ondergrond van één voet werd steeds groter (in 6 aparte trials), terwijl de andere voet 1) stilstond of 2) met een constante amplitude verstoord werd. Met systeem identificatie technieken werd vervolgens de responsie van de enkel momenten op de verstoringen bepaald, de zogenoemde gewrichtsmoment sensitiviteit functies. Ook werd de balansbijdrage (het stabiliserende mechanisme) van elk been apart geschat.

Het vergroten van de proprioceptieve verstoring van één been resulteerde in een verminderde gevoeligheid van het enkelmoment van dat been. Het andere moment (van het niet of constant verstoorde been) liet geen verandering in gevoeligheid zien.

De studie toonde aan dat sensorische informatie van elk been apart gewogen wordt en dat de weging afneemt, als de verstoringsamplitude vergroot wordt. Het herwegen van de proprioceptieve informatie van het ene been had geen invloed op de weging van de proprioceptieve informatie van het andere been. Volgens de sensorische herweging hypothese betekent dit dat de vestibulaire informatie moet worden opgehoogd, de ogen waren immers gesloten.

Balans houden met twee benen

Dit proefschrift onderzocht hoe elk been bijdraagt aan de stabilisatie van rechtop staan. Er werd aangetoond dat de benen werken als communicerende vaten; elk been houdt rekening met de balansbijdrage van het andere been. Dit werd voornamelijk aangetoond in **Hoofdstuk 6**, waar Parkinson patiënten compenseerden voor hun balans asymmetrie door de balansbijdrage van het minst aangedane been te verhogen. **Hoofdstuk 7** bevestigde deze resultaten, aangezien de proefpersonen hun balansbijdrage van het ene been verminderden, terwijl de balansbijdrage van het andere been verhoogd werd, in de conditie met de hoogste verstoor amplitude.

Door naar beide benen te kijken tijdens de balanshandhaving kunnen we de ultieme grens tussen balans en lopen onderzoeken, namelijk het beginnen met lopen. **Hoofdstuk 5** suggereerde dat wanneer de gezonde koppeling tussen gewichtsverdeling en balansbijdrage verstoord is, er problemen kunnen optreden bij loop initiatie.

Dankwoord

I get by with a little help from…

Geen proefschrift is compleet zonder dankwoord. Op deze pagina's wil ik graag de mensen bedanken die het afronden van mijn proefschrift mede mogelijk hebben gemaakt, of die de weg daar naar toe heel veel leuker hebben gemaakt.

I want to push you around

Allereerst wil ik alle proefpersonen bedanken. Zonder hun vrijwillige inzet was dit proefschrift er niet gekomen. Er zijn veel collega's, studenten en familieleden geweest die (pré-) proefpersoon wilden zijn toen ik de methodes aan het optimaliseren en testen was. In het bijzonder wil ik alle Parkinson patiënten bedanken die onbaatzuchtig, vaak zonder medicatie naar het lab kwamen om hun balans te laten verstoren.

Only the young

Prof. dr. ir. H. van der Kooij, beste Herman. Jij hebt me altijd met veel geduld begeleid bij het technische gedeelte van mijn promotie. Je hebt een groot oog voor detail en dat was zeer waardevol en leerzaam tijdens dit project. Door je kritische houding heb ik geleerd om zelfstandig mijn eigen werk op waarde te schatten en te verdedigen. Ook was je altijd te porren voor een (1 april) grapje, een biertje of een zeskamp. Kortom: "I am proud to be a Hermanoid"!

Seems like such a long time ago

Prof. dr. B.R. Bloem, professor Zonnebloem, beste Bas, hey B. Naast je rol als neurologisch geweten van mijn promotie, heb je ook een grote rol gespeeld in het bewaken van de hoofdlijnen en de planning. Ook ik heb mogen leren en profiteren van je alom geroemde positieve blik en je oplossingsgerichtheid; je ziet altijd overal kansen en dat pakte op bijna alle vlakken goed uit. Daarnaast heb je een goed gevoel voor humor en een uitstekende (muzikale) smaak. Hartelijk dank voor de bijzondere samenwerking de afgelopen jaren.

Paperback writer

dr.ir. A.C. Schouten, beste Alfred. Gedurende het voortschrijden van mijn promotietraject werd jij steeds meer ook een mentor. Je kennis en kunde op het gebied van apparatuur, begeleiden van studenten en de wetenschap in het algemeen was onontbeerlijk. Wat fijn dat je de tijd neemt om ergens samen voor te gaan zitten! Mede daardoor was het een feestje om samen artikelen te schrijven. Dat je uiteindelijk mede auteur bent op 4 artikelen doet onze samenwerking eer aan. Mijn dank hiervoor.

Ook al doet het niet echt pijn

Een vereiste van dit onderzoeksproject was dat ik ook met artsen moest samenwerken, gelukkig maakten de meeste artsen dit niet moeilijk. Een goed voorbeeld is dr. J.P.P. van Vugt, beste Jeroen; bedankt voor de prettige samenwerking, het rekruteren van patiënten en onze gezamenlijke inspanningen voor het TG onderwijs. Janneke Dielemans wil ik bedanken voor de hulp bij het rekruteren van patiënten en de metingen. Ook wil ik de

artsen op de UT bedanken die achterwacht wilden zijn tijdens mijn experiment. Gelukkig heb ik jullie niet nodig gehad ☺.

Monday, Monday

Na 6 jaar in Amsterdam gewoond te hebben was Enschede wel even wennen. Gelukkig was daar het warme bad van Biomedische werktuigbouwkunde. We zijn echt een leuke groep! Ik kan hier lang niet iedereen bij naam noemen, maar laat ik beginnen bij de mensen die me direct met mijn werk geholpen hebben. Geert voor alle hulp in het lab, Nikolai voor het helpen met de PC's in het lab, Ard voor je hulp met de pusher, Bart Koopman voor de hulp bij de analyse van meetgegevens en de inverse dynamica. Edwin, het was niet makkelijk om jouw 'opvolger' te zijn, maar gelukkig was je altijd bereid tips te geven, bedankt! Lianne uiteraard bedankt voor je organisatietalent, maar ook voor het vakgroep mamma zijn: je bent lief en adequaat! Denise en Jantsje dank voor de hulp bij de data verzameling.

Dan de mensen die er (ook) waren voor de persoonlijke noot. Jan V., ik weet niet wat het is: je Friese tongval, je ervaring als Hermanoid, of gewoon je humor, maar je hebt me meteen thuis laten voelen bij de vakgroep. Leuk dat er altijd tijd is voor een biertje of lunch als je weer in den lande bent.

Uiteraard de mensen uit de 'gezellige kamer': Ard, Alexander en Floor. We hebben lief, leed en frustraties gedeeld, maar bovenal was het gezellig ☺! Jullie zijn snel aan de beurt! Floor verdient wel een aparte vermelding (sorry heren): van student tot paranimf; je bent er het hele traject bij geweest. Dank voor al je steun, de samenwerking, de chocolademelk na submissie van papers, het contact houden tijdens mijn zwangerschapsverlof en de gesprekken over van alles en nog wat. Ik ga je missen! Gerdine, wat hebben we eigenlijk niet samen gedaan? We hebben gesport, gewinkeld, gekletst, gekookt, gezorgd, gezopen en we zijn elkaars paranimf. Je laat me thuis voelen in Twente. Tenslotte alle andere nog niet genoemde collega's (ook bij BSS en MIRA): dank voor alle koffiepauzes, discussies, adviezen, triathlons, girls night outs, zwembadlunches, zeskampen, biertjes, barbecues, uitjes en etentjes in de stad. I had a blast!

Let him come into the city

Mijn onderzoeksproject in het kader van het Braingain consortium zorgde ervoor dat ik ook veel met collega's buiten de UT te maken had. Hierbij wil ik mijn mede Braingain promovendi bedanken voor de steun, samenwerking en de gezelligheid. Mijn Delftse collega's (in het bijzonder Winfred en Frans) stonden altijd garant voor een gezellige avond en/of nieuwe waardevolle inzichten. Ook wil ik Noortje en Thea van het Radboud en de dames op het secretariaat van de neurologie op het MST bedanken voor de ondersteuning.

I am not the doctor

Dank aan de studenten die ik heb mogen begeleiden tijdens mijn promotietraject: Bianca, Hermen, Saskia, Geert, Daniel, Sjoerd, Floor, Jantsje, Robert-Jan en Mark. Ik heb ook veel van jullie geleerd.

It's a small crime and I got no excuse

Muziek is een vereiste in mijn leven, luisterend (met o.a. Aldo, Edwin, Tom, Carel, Bart, Erika, Paula en Wouter) op bijvoorbeeld Lowlands, dan wel erop dansend (o.a. met Sjoerd en Georg), maar het liefste eigenlijk zelf makend. Dank aan de mensen die dit afgelopen jaren mogelijk maakten: Popkoor Speechless, de Sad Scientists (Johan, Daniël, Joeke en Charlotte) en Meyke. Rock on!!

I do not feel ashamed

Lieve Erika, Paula en Marjolein. Jullie zorgden voor de broodnodige afleiding en afwisseling boven liters thee, tijdens vakanties, weekendjes en etentjes overal en nergens in het land. Jullie zijn mijn externe geweten en wat ontzettend fijn dat ik alles, maar dan ook alles met jullie kan delen en bespreken.

Maar ik wil terug naar jou, Amsterdam

Bij mijn Amsterdamse vrienden ben ik nog steeds welkom, alhoewel soms 'old school' slapend op een matje (Sander), maar gelukkig vaak ook in een echt bed (Ellen). Dank voor alle gezelligheid (bijv. Sponsterklaas) de afgelopen jaren! Diana, mijn Amsterdamse 'lotgenoot', bedankt voor het delen van ervaringen en frustraties, binnenkort ben jij aan de beurt!

Remember your name

Lieve paps en mams, jullie hebben me geleerd om open, maar toch kritisch te zijn. Ook hebben jullie me altijd de ruimte gegeven om te doen wat ik leuk vind. Een goede basis voor een promotietraject. Dank voor jullie niet aflatende (financiële) steun, interesse en liefde. Ook moet ik altijd lachen om de knipsels (mét post-its) die ik vind in de post; zeker die over de toekomstperspectieven van academici.

Johan ("*ja, met Johan*") , Marijke ("*hee zussie*") en Anders ("*and then I found out they had bokbier*"); mijn 'broers' en zusje, jullie zorgen allemaal op jullie eigen manier voor een (glim)lach op zijn tijd. Thanks!

Marieke, jaren geleden bakten we zandtaartjes samen, nu staan we schouder aan schouder te netwerken met de 'hoge' heren of drinken we bier na een gezamenlijk congres. Altijd gezellig! Ik zie uit naar jouw promotie!

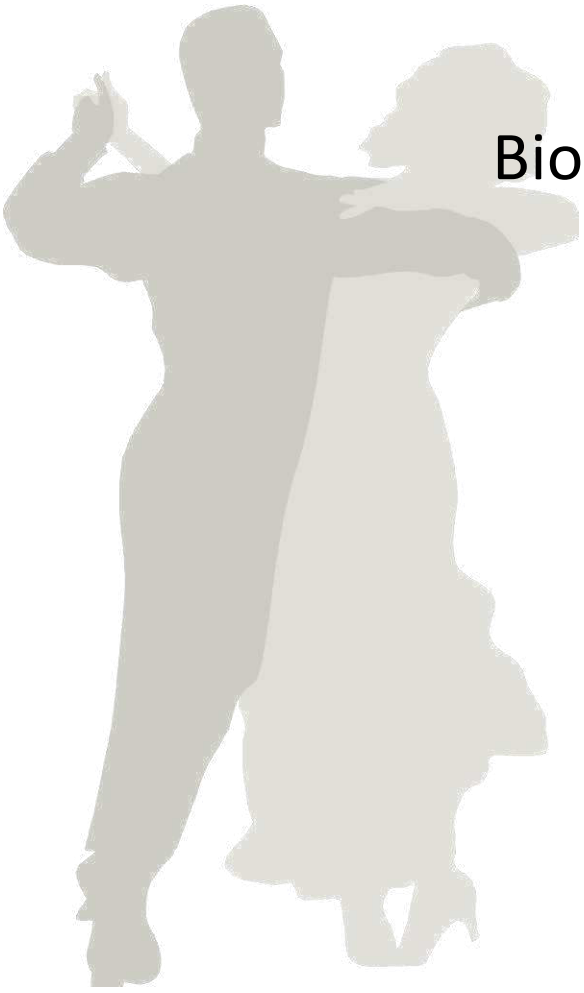
Ook wil ik mijn schoonfamilie bedanken: Henk & Joke, Lucas & Nelleke en de jongens, Steven & Benjamin. Het was vast even wennen om familie zo ver weg te hebben, maar gelukkig was er de afgelopen jaren veel te vieren, waardoor jullie vaak naar Enschede zijn gekomen. Ik hoop dat het zo blijft!

There is more than I had bargained for
Nyne, wat een geluk en plezier breng jij in het leven van mij! Je plaatst de dingen in perspectief en helpt me relativeren.

You stood up for our love
Lieve Wouter, alles begint en eindigt bij jou. De afgelopen jaren was ik was soms letterlijk én figuurlijk ver weg, maar jij altijd dichtbij. Zonder jouw onvoorwaardelijke liefde, geduld en steun had ik dit niet gekund. Je verstaat de kunst om de kleine dingen groots te beleven en dat houdt me met beide benen op de grond. Love you baby!

Verantwoording

[1] With a little help from my friends – The Beatles
[2] Push – Matchbox 20
[3] Only the young – Brandon Flowers
[4] A long time ago – Jim Croce
[5] Paperback writer – The Beatles
[6] Groot hart – De Dijk
[7] Monday Monday – The Mama's and the Papa's
[8] The distance – Live
[9] Not the doctor – Alanis Morisette
[10] 9 Crimes – Damien Rice
[11] Bitch – Meredith Brooks
[12] Amsterdam – Grof geschut
[13] Miss Celie's blues – Quincy Jones
[14] There is no greater joy - Brown Feather Sparrow
[15] vrij naar 'They stood up for love' - Live



Biography

Curriculum Vitae

Tjitske Boonstra was born in 1982, in Den Helder, The Netherlands. In 2000 she got her high school diploma from the 'Sint Antonius college' in Gouda. After a year of working and travelling, she started studying human movement science at the Free University in Amsterdam. She chose the specialization "Coordination, learning and the development of action". For her research internship she went to the Pennsylvania State University, to temporarily join the lab of prof.dr. Dagmar Sternad. At the Action Lab, she studied the acquisition and adaptation of ball bouncing. For this work she received an award for best poster and a travel grant for conference attendance. In October 2006, Tjitske graduated with a Master's degree.

Subsequently, she worked as a manager at a research institute and as move coordinator for Victory for Life (a foundation that aimed to decrease obesity in teenagers). Also, she and her husband Wouter made a beautiful and impressive six week trip to Ghana.

In February 2008, she started her PhD research at the University of Twente, as part of the Braingain consortium, resulting in this PhD thesis entitled: "The contribution of each leg to bipedal balance control", under the supervision of prof. dr. ir. H. van der Kooij and prof. dr. B.R. Bloem. In this thesis, she investigated how each leg contributes to the stabilization of upright stance, in both healthy persons and people with Parkinson's disease. Her research interests include balance control, Parkinson's disease, sensory reweighting and learning and adaptation of movements.

Currently, she is working as a Human Factors lecturer and post-doc (funded by the Dutch Parkinson Foundation) at the University of Twente.

She is married to Wouter Bokhove and they have a daughter, Nyne.

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Stellingen

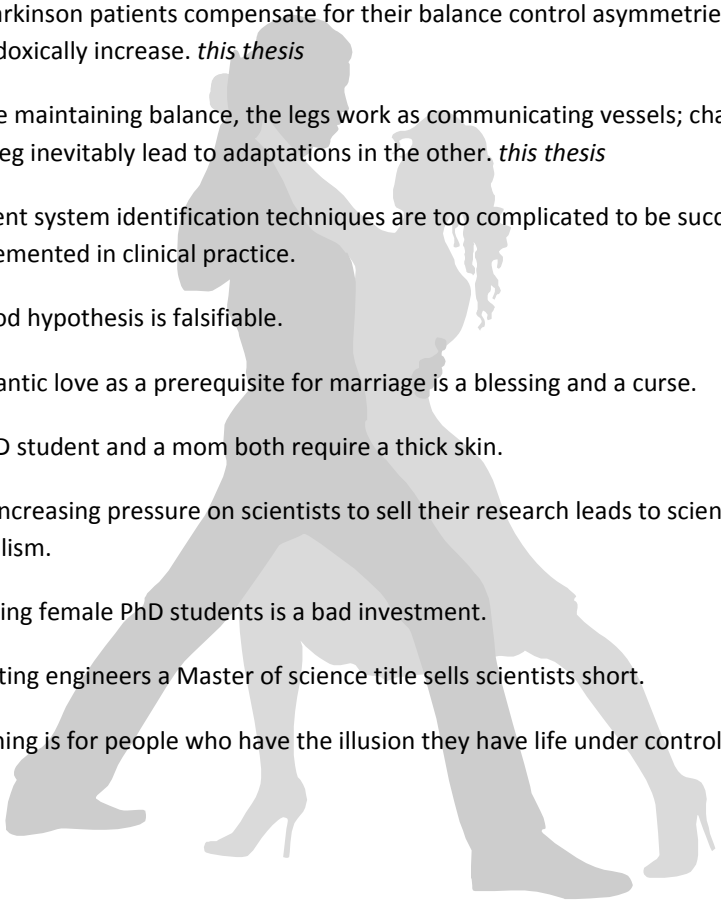
Behorende bij het proefschrift: “The contribution of each leg to bipedal balance control” te verdedigen door Tjitske Boonstra op 6 juni 2013.

1. Doordat Parkinson patiënten compenseren voor hun balansasymmetrie, wordt deze paradoxaal juist vergroot. *dit proefschrift*
2. Tijdens de balanshandhaving werken beide benen als communicerende vaten; veranderingen in het ene been leiden onvermijdelijk tot aanpassingen in het andere been. *dit proefschrift*
3. De huidige systeem identificatie technieken zijn te ingewikkeld om succesvol toegepast te worden in de kliniek.
4. Een goede hypothese moet kunnen worden ontkracht.
5. Romantische liefde als voorwaarde voor het huwelijk is een zegen én een vloek.
6. Het promovenda- en moederschap hebben met elkaar gemeen dat je er een dikke huid voor moet hebben.
7. De toenemende roep aan wetenschappers om hun onderzoek te verkopen leidt tot wetenschappelijk populisme.
8. Het opleiden van vrouwelijke promovendi is een slechte investering.
9. Het uitreiken van een ‘Master of Science’ diploma aan ingenieurs doet wetenschappers te kort.
10. Plannen maken is voor mensen die de illusie hebben het leven onder controle te hebben.

Deze stellingen zijn verdedigbaar geacht en als zodanig goedgekeurd door de promotoren: prof. dr. ir. H. van der Kooij en prof. dr. B.R. Bloem

Propositions

Belonging to the thesis: “The contribution of each leg to bipedal balance control” to be defended by Tjitske Boonstra on June 6th 2013.



1. As Parkinson patients compensate for their balance control asymmetries, they paradoxically increase. *this thesis*
2. While maintaining balance, the legs work as communicating vessels; changes in one leg inevitably lead to adaptations in the other. *this thesis*
3. Current system identification techniques are too complicated to be successfully implemented in clinical practice.
4. A good hypothesis is falsifiable.
5. Romantic love as a prerequisite for marriage is a blessing and a curse.
6. A PhD student and a mom both require a thick skin.
7. The increasing pressure on scientists to sell their research leads to scientific populism.
8. Training female PhD students is a bad investment.
9. Granting engineers a Master of science title sells scientists short.
10. Planning is for people who have the illusion they have life under control.

These propositions are deemed justifiable and have been approved by the advisors: prof. dr. ir. H. van der Kooij en prof. dr. B.R. Bloem