1 General introduction
Our ability to adopt or maintain a certain posture is an essential aspect of human movement behavior. This is inasmuch true for the posture of a small finger joint, as it is for whole-body posture, the central theme of this thesis. An inability to maintain whole-body posture, in turn, can have significant bearing on motor performance, mobility and thus on quality of life. Controlling posture and balance is compromised in Parkinson’s disease (PD). Various rehabilitative interventions aim to improve postural and balance control in this patient group. The success of such interventions is difficult to establish, not in the least because assessing the severity of postural instability can be challenging.

In this thesis, I will provide an encompassing perspective on postural control in patients with PD by combining behavioral, neurophysiological, and clinical assessments. I will demonstrate how postural instability can be assessed by means of delayed visual feedback. I will also show how this paradigm can be employed together with conventional measures to assess postural control before, during, and after a novel therapeutic intervention that includes visual feedback. The goal of this investigation was to gain insight into the effectiveness of this intervention and its potential for restoring balance capacity. Before doing so, I will introduce the general concepts and terms that are central to this thesis and describe the current understanding of postural instability in PD.

Human postural control

Balance and posture

In colloquial contexts, balance and posture are more or less generic terms that are often used interchangeably. Although they have overlapping meaning, the terms are strictly speaking not synonymous. Unfortunately, there is no commonly accepted definition of balance in the scientific literature (Berg, 1989; Pollock, Durward, Rowe, & Paul, 2000; Ragnarsdóttir, 1996). It is often defined as a state in which the vertical
projection of a body’s center-of-mass (COM) is positioned within its base of support (Winter, 2009). Used as a verb, balancing may describe the dynamics of body posture to maintain this state. Although adequate, this definition of balance seems to be too general as it does not satisfactorily cover the behavioral repertoire for ‘keeping our balance’¹. The arguably most commonly encountered definition of posture considers it as the arrangement of body parts in space (Martin, 1977).

In the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization, the terms balance and posture are mentioned only with respect to involuntary movement reactions, which are classified as body functions (b755) (World Health Organization, 2001). Instead of using the term posture, the ICF simply refers to changing (d410) and maintaining (d415) a body position. These are classified as activities related to mobility, with codes d4104 and d4154 specifically referring to the standing position (World Health Organization, 2001). In this thesis, I will consider postural control as the motor activity of maintaining and/or changing upright stance.

Postural control and postural sway

Maintaining standing posture provides a stable platform from which other tasks can be performed (Magnus, 1925; Martin, 1977; Massion, 1994). As such it affords an extraordinary range of movements and activities, including gait. At the same time, the standing posture reduces the area in which we can allow the vertical projection of the COM to move around. Bipedal stance is therefore substantially more unstable than the posture of quadrupeds. Conversely, one can contend that movements are transitions between postures (Reed, 1982).

Postural control serves to preserve or change a posture by restricting or allowing body segments to move relative to one another (Horak, 2006; Massion, 1994). Importantly, the presence of gravity requires a certain level of muscle activity to maintain a given arrangement of joint positions. The ongoing, tonic activation of postural muscles is referred to as postural tone (Magnus, 1925; Martin, 1977). For a characteristic posture like upright standing this is achieved by activating the “antigravity” musculature along the body’s axis. The innervation of axial muscles is for a large part controlled by projections from the brain stem, called the medial brain

¹ Consider for instance the state of my body after I have tripped and fallen on the ground: my body’s center of mass will be positioned within the base of support, but I would of course not argue that I successfully ‘kept my balance’.
stem pathways. Not surprisingly, these pathways are part of the phylogenetically oldest components of the descending motor system (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2000). Besides regulating muscle tone in order to maintain or change posture, a second function of postural control is to maintain a state of balance. External physical perturbations can elicit a variety of stereotypical muscle activation patterns, revealing the presence of reflex loops that serve, via postural adjustments, to stabilize the body (Horak & Nashner, 1986; Martin, 1977; Massion, 1994; Nashner, 1977). Notably, postural adjustments also occur when perturbations arise from self-generated movements. For instance, when moving the trunk and head forward, the hips will inevitably move backwards to compensate for the associated COM displacement, typically through motion (plantarflexion) in the ankle joint (Martin, 1977). In the case of such internal perturbations, postural adjustments take place prior to, that is in anticipation of, the actual goal-directed movement, and are hence named *anticipatory postural adjustments*.

Even when the intention is to stand motionless, the body’s posture will never be truly static. This is much akin to attempting to balance a stick on a single hand: the upright position can be maintained but only by applying corrective forces more or less continuously. If the restoring forces were to be removed, the equilibrium would be lost. Likewise, the human body never reaches a situation of complete static balance. Instead, it relies on the (nearly) constant modulation of postural tone to maintain its unstable equilibrium. The disturbing forces, together with the restoring forces that are applied around the ankle and hip joint result in what is referred to as *postural sway*. *Posturography*, i.e. the measurement of postural sway, offers a means for analyzing the effects of pathologies and various sensory conditions on sway. It can thereby provide a window into the mechanisms that underlie postural control (Woollacott & Shumway-Cook, 1996).

**Sensory feedback for postural control**

Closed-loop theories of motor control suggest that sensory feedback is essential for skilled performance (e.g., Adams, 1971; Shadmehr, Smith, & Krakauer, 2010). Whether this is also the case for a seemingly automatic behavior like quiet standing has been the topic of some debate (Peterka, 2002). Nonetheless, studies have revealed the unmistakable influence of visual, vestibular, and proprioceptive feedback on body sway (Diener, Dichgans, Bruzek, & Selinka, 1982; Fitzpatrick & McCloskey, 1994; Peterka, 2002). Crucially, these sources of feedback do not
Genera

contribute to the control of upright stance in a fixed fashion, but instead are
dynamically reweighted (Peterka, 2002).

Vision plays a major role in the control of any posture and this has long been
known (Romberg, 1846). One can readily experience this oneself by simply closing
the eyes while standing on one leg. The visual system can help to detect body motion
in visual environments that vary in parameters such as lighting, contrast, motion
parallax cues, etc. (Paulus, Straube, Krafczyk, & Brandt, 1989). Note that information
from the visual field itself is incomplete and must necessarily be supplemented with
afferent input (i.e. proprioceptive information) about the orientation of the eyes
(Wolsley, Sakellari, & Bronstein, 1996). Visual information is thought to play a
particularly important role in stabilizing the position of the head and trunk in space
(Buchanan & Horak, 1999). As any train traveler can affirm, changes in the visual
scene do not directly allow for a differentiation between self-motion and object
motion (Paulus et al., 1989). The simple observation of a nearby departing train from
the window of your train is powerful enough to induce the illusion of self-motion
(Lee & Aronson, 1974; Lestienne, Soechting, & Berthoz, 1977; Mach, 1875). A
particularly striking example of this influence is the so-called moving room, in which
a visually approaching wall suffices to elicit a postural adjustment in adults, and even
a fall in toddlers who just learned to walk (Lee & Aronson, 1974).

Like other motor control processes, postural control is adaptive: changes in the
environment are constantly monitored and accommodated. Maintaining posture
while standing in a bus requires different muscle activations when the bus is
accelerating than when the bus is driving at constant speed, standing still or
decelerating. As was hinted at before, sensory information in postural control is
subject to a reweighing process, which assigns more value on those sources of
feedback that are deemed more reliable (Oie, Kiemel, & Jeka, 2002; Peterka, 2002;
van der Kooij, Jacobs, Koopman, & Grootenboer, 1999). This allows to account for
changes in environmental conditions that alter the uncertainty associated with
either of the separate sources of feedback. For instance, upon turning the light off in
a room, proprioceptive and vestibular feedback can thereby take precedence over
visual feedback.

Assessments of posture

The lack of single authoritative definitions of balance and posture reflects the
difficulty of describing the rich behavior that we have come to associate with these
terms. As postural control is a complex skill involving different underlying physiological systems, simple ‘global’ balance outcomes are unsuitable to reliably assess all underlying factors (Horak, 2006). Not surprisingly, a wide variety of balance assessments are available (“Rehabilitation Measures Database,” n.d.).

Assessments of functional postural control

Functional outcome measures are indicators of a subject’s functional ability. With regard to balance they should reflect the ability to carry out one or more tasks that might challenge balance and/or posture. Subjects are asked to perform some postural task, which is observed and scored by the experimenter. For instance, the Functional Reach Test (Duncan, Weiner, Chandler, & Studenski, 1990) assesses one specific movement: reaching forward as far as one can without falling or having to take a step. The Berg Balance Scale (BBS), in contrast, assesses fourteen different tasks, ranging from picking up an item from the floor, or rising from a chair, to standing on one leg for as long as one can (Berg, 1989). In the former test, functional ability is expressed in terms of the distance reached (in cm), whereas in the latter test it is expressed in terms of a compound score based on the individual items (which are scored on a Likert scale). Noteworthy is that some functional balance measures, like the BBS, suffer from ceiling effects, i.e. a large concentration of participants score near the upper limit for a given task (Steffen & Seney, 2008). A recently suggested alternative may be the mini Balance Evaluation System Test (Mini-BESTest), which is a more dynamic test of balance control that has shown high reliability and a lower ceiling effect when compared to the BBS in people with Parkinson (King, Priest, Salarian, Pierce, & Horak, 2012).

Assessments of postural sway

Postural sway can also be assessed by means of posturography, or alternatively by analyzing the actual movement kinematics during a motor task. Given the requirement of the vertical projection of the COM to stay within the limits of stability in order to maintain standing balance, an arguably relevant variable is the position and movement of the body’s COM. The body COM is a (bio)mechanical construct representing the balancing point of the body in static equilibrium. As this parameter is solely a hypothetical point in space, however, it is not available for direct measurement. A signal that correlates strongly with the COM and can be measured directly is the center-of-pressure (COP). The COP is the point of application of the
General introduction

summed ground reaction force vector, which can be determined directly using force plates. Force plates record the forces exerted on them in three directions, and the COP can be calculated from the ratios between these forces (Winter, 2009). Forces exerted by active muscle will cause the COP to shift in position. The COP trajectory contains high-frequency components related to torques generated at the body’s joints but is otherwise the two-dimensional projection of the slowly oscillating COM. The high-frequency components in the COP are a necessary aspect to control or correct the COM position (van Emmerik & van Wegen, 2002; Winter, 2009). Note that the COP by itself does not provide direct information about the actual posture (i.e. configuration) of the body’s segments.

Posturographic paradigms are often categorized as those that address dynamic conditions (i.e. performing tasks on moving platforms), and those that focus on static conditions (i.e. quiet stance). In the latter, subjects stand quietly on a force platform. This is particularly suitable when studying individuals that suffer from postural instability as it does not require the subject to wear a safety harness and is less physically demanding than paradigms targeting dynamic stability.

Assessments of postural control

Postural sway has a seemingly erratic, dynamic structure, which has prompted many research efforts to try to describe and/or model the COP as accurately as possible. These COP measures may have a more or less direct relation to the steady-state behavior and functional interaction of the neuromuscular mechanisms underlying the maintenance of erect stance. Particularly interesting is that outcomes like the COP variance have been shown to change with pathologies such as Parkinson’s disease (van Wegen, van Emmerik, Wagenaar, & Ellis, 2001) and with aging, as well as with altered sensory and cognitive conditions (Roerdink et al., 2006). Nevertheless, it should be considered that posturographic measures as of yet largely lack the validity to be employed in the clinic, and therefore still remain part of academic dispute (see for instance Visser, Carpenter, van der Kooij, and Bloem (2008)).

Delayed visual feedback

To study the relative contributions of different forms of feedback, one may manipulate sensory information by creating altered or even conflicting sensory conditions. For instance, visual information is an important factor during postural
control (Lee & Aronson, 1974; Peterka, 2002). The extent to which subjects are utilizing visual information in controlling their posture may be analyzed by imposing visual perturbations and analyzing their impact on motor execution. Visual feedback that is incongruent corrupts the sensorimotor mapping: the predicted movement will no longer match with the visual consequences of that movement. A parameter that lends itself well for such a perturbation is a time delay (Tass, Kurths, Rosenblum, Guasti, & Hefter, 1996). Time delays can destabilize feedback loops, such as the visuomotor loop in humans (Tass et al., 1996).

Electroencephalography

The CNS comprises a number of neurophysiological structures dedicated to postural control. These structures include the vestibulocerebellum and the brainstem (Kandel et al., 2000). Their involvement might, at least in part, explain why we are able to maintain posture without much conscious effort. Posture is, however, not solely controlled by subcortical structures. For instance, under double task conditions postural control is influenced by concurrent cognitive tasks (Woollacott & Shumway-Cook, 2002). Electrophysiological techniques like encephalography (EEG) offer the possibility to perform in vivo studies on the human cortex. Though movement artifacts have until recently precluded the use of EEG recordings during whole-body movements, recent advances in data processing made the EEG a reliable tool for estimating cortical activity during the execution of postural tasks, and even gait (Bruijn, van Dieën, & Daffertshofer, 2015; Gwin, Gramann, Makeig, & Ferris, 2011).

Time-frequency analyses of neural signals can provide a window in the extent of neuronal processing. In the motor cortex, prior to and during movement, oscillations in the mu (8-13Hz) and beta ranges decrease in amplitude, whereas an increase is observed upon movement termination (Pfurtscheller & Lopes da Silva, 1999). These phenomena are referred to as event-related desynchronization (ERD) and synchronization (ERS), due to the fact that the oscillations picked up by EEG/MEG must be brought about by the synchronous activity of many (tens of thousands of) neurons.

In patients with PD, the basal ganglia show abnormally high levels of neural activity in a frequency range of 13-30 Hz. This exaggerated neural synchronization is closely associated with the motor symptoms of PD: not only does the degree of beta synchronization correlate with the degree of motor impairment (Brown, 2007; Jenkinson & Brown, 2011), beta synchronization also improves with dopamine
replacement therapy. In PD patients, ERD appears to be delayed, and both ERD and ERS are less pronounced compared to healthy controls (Devos et al., 2003). These effects are stronger in patients with advanced PD. Dopamine replacement therapy on the other hand may partially restore the lowered ERD and ERS (Devos et al., 2003).

Postural instability in Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurodegenerative disorder whose hallmark motor signs are bradykinesia (generalized slowness of movements), tremor, rigidity (stiffness of limbs), and postural instability (Davie, 2008). Estimates are that in industrialized countries PD affects about 1% of the population older than 60 years (Nussbaum & Ellis, 2003). In the Netherlands, the prevalence of parkinsonism is thought to be anywhere between 50,000 and 90,000 (Bloem et al., 2010).

Pathophysiology

Considered to be most typical for motor symptoms in idiopathic PD is the degeneration of dopaminergic cells located mainly in the pars compacta of the substantia nigra (SN), a structure that is part of a collection of nuclei known as the basal ganglia (BG). More recent perspectives have postulated that this degeneration is likely preceded by neural pathology elsewhere in the brain, and also include the noradrenergic, serotonergic, and cholinergic systems (Wolters & Braak, 2006). Symptoms of the disease may not manifest themselves until as much as 50-80% of the nigral neurons have died (Davie, 2008). While the cardinal features of PD are in essence motor-related, the first noticeable symptoms of PD are often non-motor in nature, including autonomies disturbances, olfactory dysfunction, psychiatric symptoms, and sleep disorders (Davie, 2008). The underlying cause of neural degeneration in the great majority of patients remains unknown, and hence often labeled as idiopathic.

There is no cure for PD. For this reason, the current disease management aims at reducing the symptoms. The classical view on PD as being purely a disorder of the dopamine-producing neurons of the BG has been challenged for many years (Wolters & Braak, 2006). Nonetheless, treatments mainly revolve around restoring BG function. In fact, dopamine replacement therapy (DRT) in the form of levodopa, a
dopamine precursor, is still regarded as the gold standard for the treatment of PD (Davie, 2008). However, DRT is not without drawbacks as levodopa-induced dyskinesia and wearing-off can be very disabling. In general, postural instability responds poorly to DRT (Grimbergen, Munneke, & Bloem, 2004). Its effects are limited and decline over time. Alternative treatment exists in the form of deep brain stimulation (DBS), in which electrodes that are inserted into the brain directly stimulate areas in the BG. DBS can improve motor function (in some cases exceptionally) but the elaborate surgical procedure is not suited for all patients. Moreover, DBS may promote psychiatric side effects including depression, rendering the procedure inappropriate for patients with cognitive impairments or those who are already at higher risk for depression (Davie, 2008).

In recognition of these substantial limitations the focus has recently shifted towards a more aggregated approach resulting in a multidisciplinary treatment; see for instance, Bloem & Munneke (2014). Physical training and exercise is seen as a fundamental and indispensable component of treatment (Morris, 2000), helping to induce improvements beyond those of pharmacological or surgical intervention. Evidence that physical exercise and physical therapy can positively influence mobility and mobility-related problems has accumulated (Ahlskog, 2011; de Goede, Keus, Kwakkel, & Wagenaar, 2001; Goodwin, Richards, Taylor, Taylor, & Campbell, 2008; Hirsch & Farley, 2009; Kwakkel, de Goede, & van Wegen, 2007; Tomlinson et al., 2013).

Postural instability

Despite of being considered a hallmark symptom, postural instability typically does not emerge until the later phases of PD. According to the categorization proposed by Hoehn and Yahr (1967), the onset of postural stability marks the transition between mild and moderate stages of the disease and is associated with mild to moderate disability. Postural instability has been associated with an increased risk of falling (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001). Since postural instability and falls negatively influence health-related quality of life (Morris, 2000), disease-modifying strategies may prove to be particularly valuable. Medical treatments for PD are unable to address postural instability satisfactorily (Bloem, 1992; Horak, Nutt, & Nashner, 1992).

Postural instability in PD refers to a number of deficiencies with variable origin (Schoneburg, Mancini, Horak, & Nutt, 2013). For example, patients with PD have
more difficulty with maintaining balance during destabilizing perturbations, such as an unexpected pull or push. Their responses to perturbations are generally slower and smaller than those displayed by healthy subjects, and may fail to adequately counter the loss of balance (Dimitrova, Horak, & Nutt, 2004; Horak et al., 1992). Notably, balance is not affected equally in each direction, but appears to be especially impaired in the frontal plane, i.e. lateral balance (Horak, Dimitrova, & Nutt, 2005; van Wegen et al., 2001). Patients with PD have also been shown to have poor anticipatory postural adjustments when making voluntary movements (Latash, Aruin, Neyman, & Nicholas, 1995; Mancini, Zampieri, Carlson-Kuhta, Chiari, & Horak, 2009). In addition, they appear to have impaired somatosensory integration of afferent sensory information (Brown et al., 2006; Jacobs & Horak, 2006; Keijers, Admiraal, Cools, Bloem, & Gielen, 2005; Smith, Jacobs, & Horak, 2014). It is thus not surprising that guidelines for training interventions have incorporated balance exercises as an integral part of the training routine (Bloem et al., 2010). The effects of training on balance and/or postural control have been investigated in several studies but with mixed results (Allen, Sherrington, Paul, & Canning, 2011). A Cochrane review evaluated studies on physiotherapy interventions for patients with PD with the conclusion that physiotherapy significantly improved a number of outcomes, including outcomes related to balance (Tomlinson et al., 2013). However, this review also pointed out that the quality of the included studies was not always very high and at risk of bias. In order to develop evidence-based exercise interventions it is essential to collect more high-quality data, calling for research in the form of randomized clinical trials (RCTs).

Visual-feedback based intervention

In light of the above, it is thus imperative to keep searching for superior treatment options in order to actively counter progressive functional decline. Motor learning can be described as a relatively permanent improvement of motor performance as a result of training. It is thought to result from the repeated recalibration of motor commands that is needed to meet task demands in an ever-changing world (Bastian, 2008). The constant recalibration of movement, i.e. motor adaptation, is thought to be driven by the comparison of the predicted outcome of a movement with the actual outcome (Shadmehr et al., 2010). This process can be realized through internal models called forward models, which can predict the sensory consequences of a movement, based on the motor command. Sensory prediction error is simply the
discrepancy between the sensory prediction and the actual sensory feedback. Feedback is thus an indispensable component of motor learning. Besides the here-mentioned intrinsic feedback, to which all the somatosensory stimuli belong, extrinsic, or augmented, feedback can also be made part of a task. Augmented feedback is typically characterized as either knowledge of results, giving information about the outcome of a movement, or knowledge of performance, which provides information about the movement characteristics. Augmented feedback is thought to improve the learner’s perception of their ability in a skill. Biofeedback, introduced earlier, is a form of augmented feedback. However, even a simple body-sized mirror can be considered to provide augmented visual feedback; it is not coincidental that such mirrors are applied in ballet training and certain forms of movement therapy.

With the advent of computer game consoles that can track the player’s motion and incorporate this as a controlling variable (i.e. as biofeedback) into the gameplay, there has been an increasing interest in using computer games as a gateway to exercise. These and related technologies are also increasingly adopted within therapeutic settings (Dockx et al., 2016; Huang, Wolf, & He, 2006). It allows for novel ways to engage the patient in motor and cognitive activities while at the same time enabling individualized repetitive practice of motor function (Dockx et al., 2013, 2016; Mirelman, Maidan, & Deutsch, 2013). In PD, augmented feedback may prove to be particularly valuable considering the beneficial effects of rhythmic external stimuli on motor function, in particular gait-related outcomes (Nieuwboer et al., 2007; Rubinstein, Giladi, & Hausdorff, 2002). In fact, the number of studies that show promising effects of computer-based (balance) exercises in PD is steadily increasing. Still, there is concern about the quality of the evidence regarding the efficacy of these new techniques (Barry, Galna, & Rochester, 2014; Dockx et al., 2016; Mirelman et al., 2013; Tomlinson et al., 2013).

While VF may be a useful avenue for promoting motor behavior and learning, there is also evidence that subjects with PD overly rely on visual information (see for instance, Azulay, Mesure, Amblard, & Pouget, 2002; Bronstein, Hood, Gresty, & Panagi, 1990; De Nunzio, Nardone, & Schieppati, 2007). This makes them particularly vulnerable to incongruent visual information, in which the mapping between executed movement and the visual consequences of that movement is corrupted. In other words, incongruent VF will increase the sensory prediction error, and thereby increase the uncertainty associated with that particular forward model. Highly interesting in that regard is that EEG activity in the beta band is thought to
play a role in assessing the reliability of sensory feedback. Tan, Wade, and Brown (2016) suggest that post-movement beta synchronization over the sensorimotor cortex correlates negatively with the uncertainty in feedforward estimations.

Outline of the thesis

This thesis addresses effects of augmented visual feedback (VF) on postural control. The aim is twofold:

i. to investigate the direct effects of VF on postural control, and

ii. to investigate the effects and potential benefits of providing PD patients with VF during balance tasks and after training, respectively.

The first chapters of this thesis are involved with investigating the direct effects of augmented VF. In Chapter 2, the effects of VF during quiet standing in healthy subjects are studied. Experimentally, this was realized by not only providing real-time feedback, but also by providing the subjects time-delayed feedback, probing the reliance on this kind of visual information. Building on these results, Chapter 3 is devoted at comparing task performance of individuals with PD and healthy, age-matched controls during a rhythmic weight-shifting task. In Chapter 4 I complement the behavioral results from Chapter 3 with analyses of cortical activation patterns during the weight-shifting task.

In the second half of this thesis the potential beneficial role of VF in a therapeutic setting is explored. In Chapter 5 the rationale is presented for developing a VF-based balance training program for use with PD patients, as well as a research design in order to investigate its feasibility and efficacy. The results of this pilot randomized clinical trial are subsequently reported and discussed in Chapter 6.

The epilogue, Chapter 7, provides an overview of the major findings of both the cross-sectional (PD versus healthy controls) and longitudinal (effect of training) assessments. These findings will be discussed against the background of the conceptual and methodological framework outlined in this introduction.